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 September 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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o No ☒

The number of shares of voting common stock outstanding as of November 3, 2005 was 72,201,505.

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)

	September 30, 2005 (Unaudited)	December 31, 2004 (Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 53,222	$ 27,250
Short-term investments	48,435	76,633
Contracts receivable	4,209	10,048
Inventory	917	2,722
Other current assets	7,459	8,956
Total current assets	114,242	125,609
Property, plant and equipment, net	10,181	28,454
Licenses, net	24,353	26,104
Patents, net	20,148	19,097
Deposits and other assets	3,359	3,854
Long-term investments	5,099	5,307
Total assets	$ 177,382	$ 208,425
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 2,833	$ 6,967
Accrued compensation	1,306	3,475
Accrued liabilities	10,042	8,238
Current portion of long-term obligations	8,314	10,546
Current portion of deferred contract revenue	1,410	14,190
Total current liabilities	23,905	43,416

5 1/2% convertible subordinated notes	125,000	125,000
Long-term obligations, less current portion	16,845	111,611
Long-term deferred contract revenue, less current portion	92	531
Common stock warrants	7,500	—
Total liabilities	173,342	280,558
Stockholders' equity (deficit):		
Common stock, $0.001 par value; 100,000,000 shares authorized, 72,201,505 shares and 57,447,333 shares issued and outstanding at September 30, 2005 and December 31, 2004, respectively	72	57
Additional paid-in capital	764,555	623,706
Deferred compensation	(1)	(72)
Accumulated other comprehensive income	2,349	2,623
Accumulated deficit	(762,935)	(698,447)
Total stockholders' equity (deficit)	4,040	(72,133)
Total liabilities and stockholders' equity	$ 177,382	$ 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 September 30,		Nine Months Ended September 30,	
	2005	2004	2005	2004
Revenue:				
Research and development revenue under collaborative agreements	$ 7,122	$ 9,055	$ 24,695	$ 24,270
Licensing and royalty revenue	336	38	797	6,969
Total revenue	7,458	9,093	25,492	31,239
Operating expenses:				
Research and development	18,212	29,566	61,523	90,549
General and administrative	1,724	2,373	5,771	7,394
Compensation expense (benefit) related to stock options	15	(466)	(613)	(649)
Restructuring activities	(349)	—	7,385	—
Total operating expenses	19,602	31,473	74,066	97,294
Loss from operations	(12,144)	(22,380)	(48,574)	(66,055)
Other income (expenses):				
Investment income	1,241	561	2,095	2,536
Interest expense	(4,269)	(5,832)	(18,009)	(16,387)
Loss on investments	—	(5,057)	—	(5,057)
Net loss	(15,172)	(32,708)	(64,488)	(84,963)
Accretion of dividends on preferred stock	—	—	—	(361)
Net loss applicable to common stock	$ (15,172)	$ (32,708)	$ (64,488)	$ (85,324)
Basic and diluted net loss per share	$ (0.24)	$ (0.57)	$ (1.08)	$ (1.51)
Shares used in computing basic and diluted net loss per share	64,086	57,267	59,734	56,415

See accompanying notes

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

	Nine Months Ended September 30,	
	2005	2004

Net cash used in operating activities	$ (47,373)	$ (76,974)
Investing activities:		
Purchase of short-term investments	(8,466)	(65,989)
Proceeds from the sale of short-term investments	36,778	142,668
Purchase of property, plant and equipment	(397)	(2,413)
Proceeds from the sale of property, plant and equipment	8,206	—
Other assets	(2,787)	(5,174)
Strategic investments	—	(10,000)
Net cash provided by investing activities	33,334	59,092
Financing activities:		
Net proceeds from issuance of equity	49,169	3,316
Proceeds from long-term borrowings	4,603	16,742
Principal payments on debt and capital lease obligations	(13,761)	(13,847)
Net cash provided by financing activities	40,011	6,211
Net increase (decrease) in cash and cash equivalents	25,972	(11,671)
Cash and cash equivalents at beginning of period	27,250	33,117
Cash and cash equivalents at end of period	$ 53,222	$ 21,446
Supplemental disclosures of cash flow information:		
Interest paid	$ 5,018	$ 4,858
Supplemental disclosures of non-cash investing and financing activities:		
Conversion of debt into common stock	$ 100,000	$ —
Additions to long-term investments for acquired corporate securities	$ 750	$ —
Common stock warrants	$ 7,620	$ —
Conversion of preferred stock into common stock	$ —	$ 14,935

See accompanying notes

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

1. Basis of Presentation

The unaudited interim consolidated financial statements for the three and nine month periods ended September 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., Isis USA Limited, Hepasense, Ltd., and Orasense, Ltd. On July 25, 2005, Isis dissolved the Hepasense, Ltd. subsidiary.

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 September 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 recognizes 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. In August 2005, Isis converted the loan into 2.5 million shares of its common stock according to the terms of the loan. During the term of the loan, Isis discounted the loan to its net present value by imputing interest on the amount then outstanding 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 for arrangements in which Isis is not required to provide services in the future, if collectibility is reasonably assured.

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 establish 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 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 nine months ended September 30, 2005. During the third quarter of 2004, Isis recorded a non-cash loss on investments of $5.1 million principally related to the impairment of the Company's equity investment in Alnylam Pharmaceuticals, Inc. The impairment reflected the decrease in the market value of Alnylam's common stock.

Valuation of Inventory

Isis includes in inventory material costs and related manufacturing costs for drugs that it manufactures for its partners under contractual terms, and that it uses primarily in its clinical development activities. Isis expenses these costs when it delivers it's drugs to partners, or as it provides these drugs for its own clinical trials. Isis reflects its inventory on the balance sheet at the lower of cost or market value under the first-in, first-out method. Isis reviews inventory periodically and reduces its carrying value of items considered to be slow moving or obsolete to their estimated net realizable value. The Company considers several factors in estimating the net realizable value, including shelf lives of raw materials, alternative uses for its drugs and clinical trial materials and historical write-offs. During the fourth quarter of 2004, Isis recorded a charge of approximately $21.0 million for the write-down of inventory to its estimated net realizable value related to the Company's strategic decision to reorganize and refocus its resources to advance its most promising second-generation drugs.

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

	September 30, 2005	December 31, 2004
Raw materials	$ 917	$ 1,329
Finished goods	—	1,393
Total Inventory	$ 917	$ 2,722

Licenses

Isis capitalizes the cost related to exclusive licenses obtained from third parties. Isis amortizes capitalized licenses over their estimated useful life or the term of the agreement, which for current licenses is between 7 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 relate to inventions for which Isis is pursuing patent protection. Isis evaluates costs related to inventions for which the Company is not actively pursuing patent protection for evidence of impairment. If Isis determines that an invention is impaired, it expenses the capitalized costs associated with that invention. 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 nine months 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 that Isis vacated in 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. 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 the conversion 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 September 30, 2005, Isis had collaborative arrangements with three 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. Isis expensed the payments when made. The promissory 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 promissory 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.

As part of the collaboration between Isis and iCo Therapeutics, Inc., during August 2005, Isis licensed an antisense drug to iCo in exchange for a $500,000 upfront fee consisting of a $250,000 cash payment and a $250,000 convertible promissory note. The promissory note will convert into securities that iCo issues in a financing. Isis has recognized a valuation allowance of $250,000 to offset the debt instrument, as realization of this asset is uncertain. Isis is not required to consolidate iCo'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"). 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 $15,000 and compensation benefit of $613,000 during the three and nine months ended September 30, 2005, respectively and compensation benefit of $466,000 and $649,000 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 September 30,		Nine Months Ended September 30,	
	2005	2004	2005	2004
Net loss applicable to common stock—as reported	$ (15,172)	$ (32,708)	$ (64,488)	$ (85,324)
Net loss applicable to common stock—pro forma	$ (16,562)	$ (34,775)	$ (68,724)	$ (91,289)
Basic and diluted net loss per share—as reported	$ (0.24)	$ (0.57)	$ (1.08)	$ (1.51)
Basic and diluted net loss per share—pro forma	$ (0.26)	$ (0.61)	$ (1.15)	$ (1.62)

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:

	September 30,	
	2005	2004
Risk-free interest rate	4.3%	4.1%
Dividend yield	0.0%	0.0%
Volatility	53.7%	65.3%
Expected Life	4.8 years	6.3 years

The weighted average fair values of options granted were $4.17 and $5.53 for the three and nine months ended September 30, 2005, respectively and $5.40 and $6.70 for the three and nine months ended September 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 September 30,		Nine Months Ended September 30,	
	2005	2004	2005	2004
Comprehensive loss:				
Change in unrealized gains (losses)	$ 2,515	$ 3,182	$ 33	$ (2,520)
Income tax expense	(307)	—	(307)	—
Net loss applicable to common stock	(15,172)	(32,708)	(64,488)	(85,324)
Comprehensive loss	$ (12,964)	$ (29,526)	$ (64,762)	$ (87,844)

Included in comprehensive loss at September 30, 2005 was $307,000 of income taxes incurred on the conversion of the $100.0 million loan provided by Lilly.

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 SFAS 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 it to have a material impact on its operating results and financial position.

3. Stockholders' Equity

In August 2005, the Company raised $51 million in a private placement of 12 million shares of its common stock at a price of $4.25 per share, which was a 2.3% discount from the Company's 60-day average trading price. In addition, investors in the financing received five-year warrants to purchase approximately 3 million shares of common stock at an exercise price of $5.24 per share (the "Warrants"). The net proceeds from the offering were $48.2 million. The Warrants issued in the transaction provide a call right in favor of the Company to the extent that the price per share of the Company's common stock exceeds $14.41 per share for 20 consecutive trading days, subject to certain circumstances. The Company cannot exercise this call right prior to August 2008.

Pursuant to the terms of the registration rights agreement entered into in connection with the above transaction, within defined timelines the Company was required to file with the Securities and Exchange Commission ("SEC") a registration statement under the Securities Act of 1933, as amended, covering the resale of all of the common stock purchased and the common stock underlying the Warrants. The registration rights agreement further provides that if a registration statement is not filed, or does not become effective, within the defined time period, then in addition to any other rights the holders may have, the Company would be required to pay each holder an amount in cash, as liquidated damages, equal to 1% per month of the aggregate purchase price paid by such holder in the private placement for the common stock and warrants then held. The registration statement was filed within the allowed time, and was declared effective by the SEC on November 1, 2005. As a result, the Company was not required to pay any liquidated damages in connection with the initial registration.

In accordance with EITF 00-19, *"Accounting for Derivative Financial Instruments Indexed to, and Potentially Settled in, a Company's Own Stock,"* because of the potential to pay liquidated damages, Isis has allocated a portion of the offering proceeds to the warrants based on their fair value. EITF 00-19 also requires that the Company periodically revalue the warrants as a derivative instrument by computing the value in connection with changes in the underlying stock price and other assumptions, with the change in value recorded as interest expense or interest income. On November 1, 2005, the effective date of the underlying registration statement, the warrant liability will be reclassified into stockholders' equity. Until that time, the warrant liability will be recorded at fair value based on the methodology described below. Changes in fair value during each period will be recorded as interest income.

The fair value of the warrants was estimated using the Black-Scholes option-pricing model ("Black Scholes") with the following assumptions: no dividends, a risk-free interest rate of 4.2%, a contractual life of 5 years and volatility of 54%. The fair value of the Warrants was estimated to be $7.6 million on the closing date of the transaction. Because the registration statement was not effective as of September 30, 2005, the Company re-measured the fair value of the warrants at that date and recorded a decrease in fair value of $120,000 to Interest Income in the Statement of Operations for the three and nine months ended September 30, 2005. In the fourth quarter of 2005, the warrant liability will be re-measured and the resulting amount will be reclassified into stockholders' equity. The change in the warrant liability will be recorded as interest income.

As stated above, the adjustments required by EITF 00-19 were triggered by the terms of the Company's agreements for the private placement it completed in August 2005, specifically the potential penalties if the Company did not timely register the common stock, including the common stock underlying the warrants issued in the transaction. The related registration statement was declared effective by the SEC within the contractual deadline and the Company incurred no penalties. The adjustments for EITF 00-19 had no impact on the Company's working capital, liquidity or business operations.

4. Income Taxes

As a result of the conversion of the Lilly loan, which is discussed further in the Strategic Alliances footnote below, in August 2005, the Company recognized significant cancellation of debt income for U.S. tax purposes. Isis intends to minimize its income tax payable by offsetting the taxable income with its historical net operating losses ("NOLs"). Pursuant to Sections 382 and 383 of the Internal Revenue Code, annual use of Isis' NOL carryforwards may be limited due to cumulative changes in ownership of more than 50%. Isis believes that ownership changes have occurred, but believes that such limitations will not have a material impact upon the utilization of the carryforwards. Although Isis anticipates being able to fully offset the taxable income with its NOLs, the Company is subject to alternative minimum taxes ("AMT"). For AMT purposes, even if there are sufficient NOL carryovers to offset 100 percent of the alternative minimum taxable income ("AMTI"), only 90% of the AMTI can be offset with NOLs. As of September 30, 2005, the resulting tax liability was

estimated by the Company to be $307,000. The Company based the estimated tax liability on assumptions that ultimately could change and as such the actual cash paid to the taxing authorities could be different from the amount recorded. Pursuant to SFAS 109, "*Accounting for Income Taxes*," the tax expense associated with this transaction was recorded as a component of other comprehensive income within stockholders' equity, a treatment that coincides with the book treatment of the transaction.

5. 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, in August 2005, converted into 244,300 shares of OncoGenex's series B2 preferred stock. 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 $1.0 million. To date in 2005, Isis has earned six milestone payments totaling $1.2 million under the collaboration. Pfizer will also pay Isis additional milestone payments for key research, clinical, regulatory and sales achievements and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug in the first major market, Isis will earn milestone payments totaling up to $26.1 million. 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. During 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 agreed to add a new antisense drug to Lilly's oncology drug discovery and development portfolio. The new drug targets 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 milestone payments of up to $28.0 million as this drug moves through various stages of development, and royalties on any sales of the drug. STAT-3 adds to the two other antisense oncology drugs in development at Lilly, one which targets Survivin and one which targets eIF-4E. The extended collaboration also provides Lilly access to Isis patents to support Lilly's internal antisense drug discovery and development program for a limited number of targets. In connection with the extension, Isis converted the $100.0 million loan that Lilly provided to Isis to fund its obligations under the initial collaboration. 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 its common stock. The Company reflected the conversion on its balance sheet as a reduction in long-term debt and an increase in stockholders' equity. 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.

iCo Therapeutics, Inc.

In August 2005, Isis granted a license to iCo for the development and commercialization of ISIS 13650, a second generation antisense drug. iCo will initially develop ISIS 13650 for the treatment of various eye diseases caused by the formation of new blood vessels such as age-related macular degeneration and diabetic retinopathy. iCo paid Isis a $500,000 up-front fee consisting of a $250,000 cash payment and a $250,000 debt instrument, which will convert into iCo stock upon iCo's completion of a financing. Isis has recognized a valuation allowance of $250,000 to offset the debt instrument as realization of this asset is uncertain. iCo will also pay Isis milestone payments totaling up to $23.2 million for key clinical and regulatory achievements, and royalties on any product sales of this drug. Under the terms of the agreement, iCo will be solely responsible for the clinical development and commercialization of the drug.

Alnylam Pharmaceuticals, Inc.

In March 2004, Isis entered into a strategic alliance with Alnylam to develop and commercialize RNAi therapeutics. Under the terms of the agreement, Isis exclusively licensed to Alnylam its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for double-stranded RNAi therapeutics in exchange for a $5.0 million license fee, participation in fees for Alnylam's partnering programs, as well as future milestones and royalty payments. In turn, Alnylam nonexclusively licensed Isis its patent estate relating to antisense motifs and mechanisms and oligonucleotide chemistry for single-stranded RNAi therapeutics and to a limited extent for double-stranded RNAi therapeutics. If Isis develops or commercializes an RNAi based drug using Alnylam's technology, Isis will pay Alnylam milestones and royalties.

In September 2005, Alnylam announced an alliance with Novartis for the development of RNAi therapeutics. In October 2005, Isis earned $3.7 million, which represents Isis' portion of the up front payments and equity investments under Alnylam's recent collaboration. In addition, Isis has the potential to earn additional revenue in the form of milestones and royalty payments on drugs which utilize the Isis technology sub-licensed by Alnylam to Novartis.

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 (USAMRIID), which will use the system to identify infectious agents for biowarfare defense.

6. 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 September 30, 2005				
Revenue:				
Research and development	$ 3,693	$ 3,429	$ —	$ 7,122
Licensing and royalty	336	—	—	336
Total segment revenue	$ 4,029	$ 3,429	$ —	$ 7,458
Income (Loss) from operations	$ (12,381)	$ (97)	$ 334	$ (12,144)
Three Months Ended September 30, 2004				
Revenue:				
Research and development	$ 6,866	$ 2,189	$ —	$ 9,055
Licensing and royalty	38	—	—	38
Total segment revenue	$ 6,904	$ 2,189	$ —	$ 9,093
Income (Loss) from operations	$ (22,043)	$ (803)	$ 466	$ (22,380)

	Drug Discovery and Development	Ibis	Corporate	Total
Nine Months Ended September 30, 2005				
Revenue:				
Research and development	$ 16,044	$ 8,651	$ —	$ 24,695
Licensing and royalty	797	—	—	797
Total segment revenue	$ 16,841	$ 8,651	$ —	$ 25,492
Income (Loss) from operations	$ (40,199)	$ (1,603)	$ (6,772)	$ (48,574)
Nine Months Ended September 30, 2004				
Revenue:				
Research and development	$ 15,321	$ 8,949	$ —	$ 24,270
Licensing and royalty	6,969	—	—	6,969
Total segment revenue	$ 22,290	$ 8,949	$ —	$ 31,239
Income (Loss) from operations	$ (64,432)	$ (2,272)	$ 649	$ (66,055)

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 September 30,		Nine Months Ended September 30,	
	2005	2004	2005	2004
Partner A	26%	47%	43%	33%
Partner B	25%	20%	16%	22%
Partner C	19%	0%	8%	1%
Partner D	0%	0%	0%	18%

For the three and nine months ended September 30, 2005, Isis derived approximately 46% and 35%, respectively, of its revenue directly and indirectly from agencies of the United States Government, including approximately 25% and 16% respectively, of revenue from one significant customer. For the three and nine months ended September 30, 2004, Isis derived approximately 27% and 31%, respectively, of its revenue directly or indirectly from agencies of the United States Government.

Contract receivables from three significant partners comprised approximately 49%, 15%, and 10% of contract receivables at September 30, 2005. Contract receivables from four significant partners comprised 30%, 20%, 17% and 10% of contract receivables at December 31, 2004.

7. 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, in September 2005, Isis completed the sale of two of its real properties located at 2282 and 2280 Faraday Avenue, Carlsbad, California. The real property located at 2282 Faraday Avenue, which was sold to BioMed Realty, L.P. ("BioMed"), included an approximately 28,704 square foot building, which Isis primarily uses for manufacturing. After repaying approximately $2.3 million of debt, which was secured by the property, and after deducting commissions and other expenses, Isis received net proceeds of approximately $5.9 million for the sale of the property. As part of the sale of the real property located at 2282 Faraday, Isis leased back the property from BioMed for an initial term of fifteen years. The transaction resulted in a loss of approximately $732,000. Since the book value of this property was greater than its fair value by $424,000, this amount was recognized immediately in restructuring activities in the third quarter of 2005 and the remainder will be amortized to rent expense over the term of the lease. The real property located at 2280 Faraday Avenue, which was sold to Electro Surface Technology, Inc., included an approximately 25,603 square foot building, which Isis primarily used for laboratory and office space. After repaying approximately $1.9 million of debt, which was secured by the property, and after deducting commissions and other expenses, Isis received net proceeds of approximately $1.0 million for the sale of the property. Included in the restructuring activities in the third quarter of 2005 was a gain on the sale of this building of $683,000.

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 September 30, 2005 (in thousands).

	Facility Consolidation and Closure Related Costs	Employee Separation Costs	Contract Termination Costs	Other Costs	Total
Balance at June 30, 2005	$ 1,407	$ 255	$ 977	$ 76	$ 2,715
Accrued and expensed	(384)	(14)	25	24	(349)
Charged against accrual.	(25)	(159)	(25)	(24)	(233)
Balance at September 30, 2005	$ 998	$ 82	$ 977	$ 76	$ 2,133

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' 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 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. 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. These and other risks concerning our programs are described in additional detail 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 28 of this Report.

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 12 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, cardiovascular and ocular 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 chemistry offers a number of advantages over prior chemistries. Specifically, second-generation 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 II 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 and grants 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 September 30, 2005, Ibis has earned $44.8 million in revenue from government partners. An additional $10.5 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 approximately 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 more than $75 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. To date, we have earned six milestone payments totaling $1.2 million for our research within the collaboration. Pfizer will also make additional milestone payments for key research, clinical, regulatory and sales achievements and provide research funding. Assuming that Pfizer successfully develops and commercializes the first drug in the first major market, Isis will earn milestone payments totaling up to $26.1 million. 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, Antisense Therapeutics, Ltd., Ercole, OncoGenex, Santaris Pharma A/S, Sarissa, and most recently, iCo.

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. (DRC), in exchange for aggregate payments of $24 million over the next three years. In October 2005, we received the first installment of $7.0 million from DRC.

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 12 drugs in development, of which five are in Phase II clinical development, three are in Phase I clinical development and four are in preclinical development. Our partners are developing, with our support, seven of these 12 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 August 2005, we raised $51 million in a private placement of 12 million shares of our common stock at a price of $4.25 per share, which was a 2.3% discount from our 60-day average trading price. In addition, investors in the financing received warrants to purchase approximately 3 million shares of common stock at an exercise price of $5.24 per share. The net proceeds from the offering were $48.2 million.

Also in August 2005, we extended our multi-year strategic research collaboration with Lilly. During the extension, Lilly and we will continue to advance antisense drugs identified during the initial collaboration, and continue their efforts to develop and refine antisense technologies. During the extension, our scientists will be supported by collaboration funds and Lilly scientists will be supported by Lilly. As part of the extension, the companies agreed to add a new antisense drug to Lilly's oncology drug discovery and development portfolio. This new drug targets Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death. We will be entitled to receive milestone payments of up to $28.0 million as this drug 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 targets Survivin and one which targets eIF-4E. The extended collaboration also provides Lilly access to our patents to support Lilly's internal antisense drug discovery and development program for a limited number of targets. In connection with the extension, we converted the $100.0 million loan that Lilly provided to Isis to fund its obligations under the initial collaboration. We had the option of repaying the loan in 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 into 2.5 million shares of common stock. We reflected the impact to the balance sheet as a reduction in long-term debt and an increase in stockholders' equity. 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.

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 $7.4 million during the first nine months 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, we sold three of our facilities during the first nine months of 2005. After deducting commissions, other expenses and the repayment of approximately $5.8 million of debt, we received net proceeds of approximately $7.9 million for the sales of the properties. A net gain of $1.5 million on the sales of the buildings is included in the restructuring activities for the first nine months of 2005.

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 companies' joint 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. We 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 us to help fund the research collaboration. We accounted for this difference as deferred revenue and recognized 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. To date, we have earned six milestone payments totaling $1.2 million under our Pfizer collaboration.

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. We expense these costs when we deliver our drugs to partners, or as we provide these drugs for 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 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 nine months ended September 30, 2005 was $7.5 million and $25.5 million, respectively, compared to $9.1 million and $31.2 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 September 30,		Nine Months Ended September 30,	
	2005	2004	2005	2004
Drug Discovery and Development:				
Research and development revenue	$ 3,693	$ 6,866	$ 16,044	$ 15,321
Licensing and royalty revenue	336	38	797	6,969
	$ 4,029	$ 6,904	$ 16,841	$ 22,290
Ibis Division:				
Research and development revenue	$ 3,429	2,189	8,651	8,949
Licensing and royalty revenue	—	—	—	—
	$ 3,429	$ 2,189	$ 8,651	$ 8,949
Total Revenue:				
Research and development revenue	$ 7,122	$ 9,055	$ 24,695	$ 24,270
Licensing and royalty revenue	336	38	797	6,969
	$ 7,458	$ 9,093	$ 25,492	$ 31,239

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 nine months ended September 30, 2005 was $3.7 million and $16.0 million, respectively, compared to $6.9 million and $15.3 million for the same periods in 2004. The decrease from the three months ended September 30, 2004 to the same period in 2005 was primarily due to a $2.3 million decrease in revenue generated from Lilly and $1.1 million of grant revenue from the Singapore Economic Development Board, offset by $1.5 million of upfront fees and milestones earned in the third quarter of 2005 in connection with our Pfizer collaboration. The increase from the first nine months of 2004 to the same period in 2005 reflects an increase in revenue related to additional draw downs on our loan from Lilly and revenue earned on our Pfizer collaboration offset by the amounts recognized in 2004 under our grant from the Singapore Economic Development Board. Our revenue from licensing activities and royalties for the three and nine months ended September 30, 2005 was $336,000 and $797,000, respectively, compared to $38,000 and $7.0 million for the same periods in 2004. We earned $5.5 million from Alnylam in the first nine months 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 $3.4 million and $8.7 million for the three and nine months ended September 30, 2005, respectively, compared to revenue of $2.2 million and $8.9 million for the same periods in 2004. During the first nine months of 2004, Ibis acquired equipment to build multiple TIGER systems. This resulted in $3.1 million in revenue and associated expense in the first nine months of 2004, compared to $959,000 for the same period in 2005. Ibis deployed one TIGER system in August 2005, and plans to deploy additional systems to its government partners this year. Ibis' revenue, adjusted to exclude the equipment purchases, was $7.7 million and $5.8 million for the first nine months of 2005 and 2004, respectively. The increase in Ibis' adjusted revenue from the first nine months of 2004 to the same period in 2005 is a direct result of an increase in government contracts awarded to Ibis in 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 16% and 22% of our total revenue in the first nine

months of 2005 and 2004, respectively, which represents 48% and 78% of our 2005 and 2004 Ibis division revenue, respectively. During 2004 and 2005, we entered into numerous 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 September 30, 2005, Ibis has earned $44.8 million in revenue from various government agencies to further the development of our TIGER program. An additional $10.5 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 nine months ended September 30, 2005 were $19.6 million and $74.1 million, respectively, compared to $31.5 million and $97.3 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 third 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 $7.4 million in charges we incurred during the first nine months 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.

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

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2005	2004	2005	2004
Drug Discovery and Development	$ 14,919	$ 26,838	$ 52,051	$ 80,137
Ibis Division	3,293	2,728	9,472	10,412
Total research and development expenses	$ 18,212	$ 29,566	$ 61,523	$ 90,549

For the three and nine months ended September 30, 2005, we incurred total research and development expenses of $18.2 million and $61.5 million, respectively, compared to $29.6 million and $90.5 million for the same periods in 2004. The substantial decrease of $29.0 million in research and development expenses from the first nine months 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.

Antisense drug discovery costs for the three and nine months ended September 30, 2005 were $3.8 million and $13.8 million, respectively, compared to $10.2 million and $28.5 million for the same periods in 2004. The decrease of $14.7 million from the first nine months 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. In addition, under our Lilly collaboration extension, we are no longer reimbursing Lilly for the cost of their scientists who are supporting the joint collaboration. 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 September 30,		Nine Months Ended September 30,	
	2005	2004	2005	2004
Alicaforsen for Crohn's disease	$ 60	$ 1,145	$ 403	$ 4,189
Other antisense development products	3,699	5,989	14,388	19,266
Development overhead costs	1,370	3,793	5,059	10,122
Total antisense drug development	$ 5,129	$ 10,927	$ 19,850	$ 33,577

Antisense drug development expenditures were $5.1 million and $19.9 million for the three and nine months ended September 30, 2005, respectively, compared to $10.9 million and $33.6 million for the same periods in 2004. The significant decrease of $13.7 million from the first nine months 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 clinical 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, seven of our 12 drug candidates, which substantially reduces our development costs.

We incurred development expenditures related to alicaforsen for Crohn's disease of $60,000 and $403,000 for the three and nine months ended September 30, 2005, respectively, compared to $1.1 million and $4.2 million for the same periods in 2004. The decrease of $3.8 million from the first nine months of 2004 to the same period in 2005 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 $3.7 million and $14.4 million for the three and nine months ended September 30, 2005, respectively, compared to $6.0 million and $19.3 million for the same periods in 2004. The decrease of $4.9 million from the first nine months 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 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 nine months ended September 30, 2005 were $1.6 million and $4.9 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 nine months ended September 30, 2005 were $3.3 million and $9.5 million, respectively, compared to $2.7 million and $10.4 million for the same periods in 2004. During 2004, Ibis acquired equipment to build multiple TIGER systems. This resulted in $3.1 million in expense in the first nine months of 2004 compared to $959,000 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. Ibis deployed its first TIGER system in August 2005, and plans to deploy additional systems to its government partners this year. 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 September 30,		Nine Months Ended September 30,	
	2005	2004	2005	2004
Personnel costs	$ 1,447	$ 2,640	$ 4,330	$ 8,072
Occupancy	1,600	1,622	5,318	4,732
Depreciation and amortization	1,312	1,265	3,854	4,217
Other	745	828	2,125	2,814
Total R&D Support costs	$ 5,104	$ 6,355	$ 15,627	$ 19,835

R&D Support costs for the three and nine months ended September 30, 2005 were $5.1 million and $15.6 million, respectively, compared to $6.4 million and $19.8 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 September 30,		Nine Months Ended September 30,	
	2005	2004	2005	2004
Drug Discovery and Development	$ 4,333	$ 5,565	$ 13,456	$ 17,654
Ibis Division	771	790	2,171	2,181
Total R&D Support costs	$ 5,104	$ 6,355	$ 15,627	$ 19,835

General and administrative expenses for the three and nine months ended September 30, 2005 were $1.7 million and $5.8 million, respectively, compared to $2.4 million and $7.4 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 September 30,		Nine Months Ended September 30,	
	2005	2004	2005	2004
Drug Discovery and Development	$ 1,491	$ 2,109	$ 4,988	$ 6,584

Ibis Division	233	264	783	810
Total general and administrative expenses	$ 1,724	$ 2,373	$ 5,771	$ 7,394

Total operating expenses included non-cash compensation expense related to stock options of $15,000 and a non-cash compensation benefit of $613,000 for the three and nine months ended September 30, 2005, respectively, compared to a non-cash compensation benefit of $466,000 and $649,000 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 nine months of 2005, we recorded $7.4 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 U.S. facilities, we sold three of our facilities during the first nine months of 2005. After deducting commissions, other expenses and the repayment of approximately $5.8 million of debt, we received net proceeds of approximately $7.9 million for the sales of the properties. A net gain of $1.5 million on the sales of these buildings was included in the restructuring activities for the first nine months of 2005.

Investment Income

Investment income for the three and nine months ended September 30, 2005 totaled $1.2 million and $2.1 million, respectively, compared to $561,000 and $2.5 million for the same periods in 2004. The increase in investment income from the third quarter of 2004 to the same period in 2005 was primarily due to a gain of $656,000 that was realized on the sale of a portion of the equity securities of Alnylam that Isis owned. The decrease in investment income for the first nine 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 nine months of 2005 compared to the first nine months of 2004 offset by the gain on the sale of the Alnylam stock.

Interest Expense

Interest expense for the three and nine months ended September 30, 2005 totaled $4.3 million and $18.0 million, respectively, compared to $5.8 million and $16.4 million for the same periods in 2004. The decrease from the third quarter of 2004 compared to the same period in 2005 is primarily a result of the conversion of the Lilly loan in August 2005. The increase from the first nine months of 2005 as compared to the same period in 2004 was due to the effect of a higher average debt balance during 2005 than during 2004 related to an increase in the average balance of our Lilly loan offset in part by a decrease in the carrying value of our term loan from Silicon Valley Bank. The increase was also offset by the fact that the Lilly loan was only outstanding in 2005 for a little more than seven months compared to nine months in 2004.

Net Loss Applicable to Common Stock

For the three and nine months ended September 30, 2005, we reported a net loss applicable to common stock of $15.2 million and $64.5 million, respectively, compared to a net loss applicable to common stock of $32.7 million and $85.3 million for the same periods in 2004. Our net loss applicable to common stock for the first nine months of 2004 included $361,000 of accreted dividends on preferred stock. The decrease in net loss applicable to common stock was primarily the result of the decrease in the loss from operations and the non-cash loss on investments of $5.1 million principally related to the impairment of the Company's equity investment in Alnylam that occurred in 2004. Alnylam's stock is currently trading significantly above its 2004 levels, which Isis believes reflects Alnylam's leading position in the field of RNAi. Offsetting, in part, the decrease in net lost applicable to common stock was an increase in interest expense due to the effect of a higher debt balance in 2005 compared to 2004 and a decrease in investment income due to the Company's lower average cash and short-term investments balance in 2005 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 September 30, 2005, we have earned approximately $468.6 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 $642.4 million from the sale of equity securities. We have borrowed approximately $386.7 million under long-term debt arrangements to finance a portion of our operations.

At September 30, 2005, we had cash, cash equivalents and short-term investments of $101.7 million, working capital of $90.3 million and a stockholders' equity of $4.0 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, offset by the $48.2 million of net proceeds received from the private offering in August 2005 of 12 million shares of our common stock.

As of September 30, 2005, our debt and other obligations totaled $150.2 million, compared to $258.9 million at December 31, 2004. The decrease in our debt and other obligations was primarily due to the conversion of our Lilly loan and to a lesser extent, the declining balance on our Silicon Valley Bank term loan and the payoff of the mortgages on the facilities that we sold.

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 lease line will be secured by any equipment purchased under the line. To date, we have not drawn any funds under this lease line.

Based on our current operating plan with reasonable assumptions for new sources of revenue and cash, we believe our resources will be sufficient to fund our operations at least through 2007. The following table summarizes our contractual obligations as of September 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:

Contractual Obligations (selected balances described below)	Payments Due by Period (in millions) Total	Less than 1 year	1-3 years	3-5 years	After 5 years
$5^1/_2$% Convertible Subordinated Notes	125.0	—	—	125.0	—
Standard Operating Debt	21.6	6.2	13.6	1.8	—
Capital Lease and Other Obligations	3.0	1.7	1.3	—	—
Operating Leases	23.5	3.4	5.1	3.8	11.2

Our contractual obligations consist primarily of our publicly traded convertible debt. We converted our Lilly research collaboration loan, which we converted in August 2005 into 2.5 million shares of our common stock. 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 milestones and royalties in the event of a stock price decline. The impact to the balance sheet of the loan conversion was reflected in our financial results as a reduction in long term debt and an increase in shareholders' equity. 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, and in September 2005, we repaid the remaining balance of $4.2 million when we completed the sale of the other two pieces of our real property that secured the mortgage. 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.

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 September 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 6.5% at September 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 September 30, 2005 was $21.7 million.

In connection with the sale of our 28,704 square foot manufacturing facility, we leased back the property for an initial term of fifteen years with an initial rent of $2.60 per rentable square foot. Under the terms of the lease, the monthly rent will increase five percent every two years The future contractual obligations of this lease are included in the operating lease caption of the Contractual Obligations table shown above. The lease provides us an option to extend the lease for up to two five-year periods.

In addition to contractual obligations, we had outstanding purchase orders as of September 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 September 30, 2005, we had accumulated losses of approximately $762.9 million and a stockholders' equity of approximately $4.0 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, iCo Therapeutics, Inc., 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 companies 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 at least through 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 September 30, 2005, the market price of our common stock has ranged from $2.76 to $6.63 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 which we issued to Lilly upon the conversion of outstanding convertible securities. In addition, we recently registered for resale 12,000,000 shares of our common stock and 2,999,998 shares of our common stock issuable upon the exercise of warrants, which we issued as part of our August 2005 private placement. 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 Independent Registered 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 September 30, 2005. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls subsequent to September 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. In October 2005, we filed our answering statement. A hearing date 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 24, 2005, we sold 12,000,000 shares of our common stock and warrants to purchase up to 2,999,998 shares of our common stock. The exercise price of the Warrants is $5.2395 per share. Needham & Company, LLC and Fortis Securities LLC acted as our placement agents for the Shares and Warrants issued in the Private Placement.

The offering was made only to accredited investors, as such term is defined in Rule 501 of Regulation D promulgated under the Securities Act of 1933, as amended (the "Securities Act"). A registration statement covering the resale of the Shares and the Warrant Shares was declared effective on November 1, 2005. The Company relied on the exemption from the registration requirements of the Securities Act set forth in Section 4(2) thereof and the rules and regulations promulgated thereunder.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable

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

Not applicable

ITEM 5. OTHER INFORMATION

Not applicable

ITEM 6. EXHIBITS

a. Exhibits

Exhibit Number	Description of Document
10.1	Lease Agreement dated September 6, 2005 between the Company and BMR-2282 Faraday Avenue LLC.
10.2	Restated Isis Pharmaceuticals, Inc. 10b5-1 Trading Plan dated September 30, 2005
10.3	Second Amended and Restated Collaboration Agreement dated August 5, 2005 between the Company and Eli Lilly and Company (with certain confidential information deleted).
10.4	Notice of Grant Award issued August 1, 2005 by the Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Disease (with certain confidential information deleted).
10.5	Form of Subcontract Agreement between the Company and Science Applications International Corporation.
10.6	Form of Warrant dated August 22, 2005 (1)
10.7	Securities Purchase Agreement, dated August 19, 2005, by and among the Company and the purchasers listed on Exhibit A thereto. (1)
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.

(1) Filed as an exhibit to the registrants Current Report on Form 8-K filed with the SEC on August 25, 2005 and incorporated herein by reference.

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)	November 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)	November 9, 2005

EXECUTION VERSION

LEASE AGREEMENT

THIS LEASE is entered into on September 6, 2005, by and between **BMR-2282 FARADAY AVENUE LLC**, a Delaware limited liability company (the "Landlord"), and **ISIS PHARMACEUTICALS, INC.**, a Delaware corporation, (the "Tenant").

ARTICLE 1

Description of Premises

1.1 Premises. Landlord hereby leases to Tenant and Tenant leases from Landlord, pursuant to the terms, conditions and uses herein set forth, that certain real property commonly known as 2282 Faraday Avenue, Carlsbad, California and more particularly described in Exhibit 'A' attached hereto (the "Premises"), including a building located on the Premises containing approximately 28,704 square feet of rentable space, as shown on the drawing attached hereto as Exhibit "B" (the "Building").

ARTICLE 2

Term

2.1 Lease Term. The term of this Lease will be for 180 months commencing on September [ ], 2005 (the "Commencement Date")[THE LEASE TERM WILL COMMENCE THE DATE OF THE CLOSING UNDER THE PURCHASE AGREEMENT] and ending on September [19], 2020 ("Lease Term"). Tenant has two options to extend the term, as further described in Article 36.

ARTICLE 3

Rent

3.1 Base Monthly Rental. Tenant shall pay to Landlord at the address set forth in Section 35.10, or such other address as Landlord may advise Tenant in writing, without deduction, offset or prior notice or demand, and Landlord shall accept, as rent for the Premises the sum of $74,630.40 per month, subject to adjustments pursuant to Section 3.3 below, in lawful money of the United States payable in advance on the first day of each month of the term of this Lease. Said monthly installments shall hereinafter be referred to as the "Base Monthly Rental." Tenant has delivered to Landlord the Base Monthly Rental for the first month of the term hereof upon execution and delivery of this Lease. For purposes of this Lease, "Rent" will mean the Base Monthly Rent plus the Additional Rent plus any other charges due Landlord by Tenant under this Lease.

3.2 Proration of Rent. Prior to the first day of the first full calendar month of occupancy, in lieu of the Base Monthly Rental, Tenant will pay Landlord an amount equal to the

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Base Monthly Rental multiplied by a factor having as its numerator the number of days remaining in the month from, after and including the Commencement Date and as its denominator the number thirty. Thereafter, rent shall be payable in accordance with the terms of Section 3. 1. The total consideration for the term of this Lease shall be increased by the amount of the installment required by this Section 3.2.

3.3 Biennial Adjustments. The Base Monthly Rental will be increased biennially commencing on the first day of the calendar month immediately following the second anniversary of the Commencement Date, and on each two-year anniversary thereafter, by an amount equal to 5% of the Base Monthly Rental for the preceding year.

3.4 Additional Rent, Expenses and Costs. Tenant shall pay as additional rent the cost of: insurance pursuant to Section 10, taxes pursuant to Section 12, maintenance, roof and structural repairs pursuant to Sections 11.2 and 11.3, and a management fee pursuant to Section 13.3 or other charges, expenses and cost provided for herein, ("Additional Rent") as described and in the manner provided in Article 13. Notwithstanding anything to the contrary in this Lease, in no event will Additional Rent or any other expense to be paid by Tenant include the costs and expenses listed on Schedule 3.4 attached hereto.

3.5 Late Fees. Tenant acknowledges that late payment by Tenant to Landlord of the Base Monthly Rental or other charges incurred under this Lease will cause Landlord to incur costs not contemplated by this Lease, the exact amount of such costs being extremely difficult and impracticable to fix. Such costs include, without limitation, processing, administrative and accounting charges. If any payment of Base Monthly Rental, Additional Rent, or other charges due from Tenant is not received by Landlord within 5 business days of when due, such unpaid amounts shall bear interest at the rate of eight percent (8%) per annum ("Default Rate") from the date due to the date of payment. In addition to interest, Tenant shall pay a sum of the greater of (i) 3% of the overdue rent or (ii) $15.00 as a late charge; *provided, however*, that twice but only twice in any twelve (12) month period during the Lease Term, Tenant shall be entitled to written notice of non-receipt of Base Monthly Rental or Additional Rent from Landlord, and Tenant shall not be liable for any late charge hereunder with respect thereto if such installment of Base Monthly Rental or Additional Rent is received by Landlord within five (5) days after Tenant's receipt of such notice from Landlord. Late charges shall constitute Additional Rent. The parties agree that the late charge represents a fair and reasonable estimate of the costs that Landlord will incur by reason of late payment by Tenant. Acceptance of any late charge shall not constitute a waiver of Tenant's default with respect to the overdue amount, or prevent Landlord from exercising any of the other rights and remedies available to Landlord hereunder.

3.6 Security Deposit. Tenant will pay a security deposit of $500,000 (payable in cash or in the form of a letter of credit reasonably acceptable to Landlord) (the "Security Deposit").

3.6.1 In lieu of depositing cash as the Security Deposit, Tenant shall have the right to deliver to Landlord an unconditional, irrevocable, standby letter of credit in the amount of the cash Security Deposit otherwise required hereunder, which letter of credit shall (i) be in a form reasonably acceptable to Landlord, (ii) be issued by a financial institution selected by Tenant and reasonably acceptable to Landlord, (iii) be for the benefit of Landlord, but shall be

transferable at Tenant's sole cost and expense by Landlord to any subsequent purchaser or encumbrancer of the Building, (iv) be automatically renewable from year to year throughout the Lease Term, (v) be payable by draft sight in a location reasonably acceptable to Landlord upon presentation of a certification signed by an officer of Landlord which states that Tenant has failed to perform any of its monetary or non-monetary obligations, and (vi) be payable in the event such letter of credit is not renewed on or before the date which is thirty (30) days prior to its expiration. Any amounts of cash drawn on a letter of credit Security Deposit will thereafter be treated as a cash Security Deposit hereunder.

3.6.2 Tenant shall have the right at any time during the Lease Term upon thirty (30) days prior written notice to Landlord (i) to replace a cash Security Deposit with a letter of credit which complies with all the terms of Section 3.6.1, or (ii) to replace a letter of credit Security Deposit with a corresponding amount of cash.

3.6.3 Starting with the third anniversary of the Commencement Date, this Security Deposit will be reduced by $100,000 on such third anniversary, on the sixth anniversary, on the ninth anniversary and on the twelfth anniversary of the Commencement Date, provided Tenant has not been in default after the expiration of the applicable cure periods set forth in Section 18.1 during the 36-month period prior to the date of such reduction and has had positive net income (according to US generally accepted accounting principles) for the twelve month fiscal year that ended most recently before the date of such reduction, as substantiated by financial statements that are filed with the US Securities and Exchange Commission ("SEC") or, in the event Tenant ceases to be required to file annual financial statements with the SEC, the year-end financial statements for such period that have been audited by a nationally or regionally recognized firm of certified public accountants.

3.6.4 If Tenant fails to pay Rent when required or fails to perform any other covenant contained herein, Landlord may use or retain all or any part of the Security Deposit for the payment of any sum not so paid, or for the payment of any amount which Landlord may spend or become obligated to spend by reason of Tenant's default. If any portion of said Security Deposit is so applied or used, then Tenant shall, within 5 days after written notice thereof, deposit an additional amount with Landlord sufficient to restore said Security Deposit to the amount set forth above and Tenant's failure to do so shall constitute a breach of this Lease.

3.6.5 If Tenant has performed all of its monetary and other obligations hereunder at the termination of this Lease, Landlord shall return said Security Deposit to Tenant within 30 days after termination of this Lease, less any amounts required to restore the Premises to good condition and repair, reasonable wear and tear excepted, including repairing any damage resulting from the removal by Tenant of its trade fixtures or equipment.

3.6.6 Landlord's obligation with respect to any Security Deposit is that of a debtor and not as a trustee, consequently, such sums may be commingled with rental receipts or dissipated and no interest shall accrue thereon.

3.6.7 In the event of the sale of the real property of which the Premises constitute a part, Landlord's successor in interest shall assume Landlord's obligations with respect to the sums held as security or advance rent and notify Tenant in writing setting forth the

particularity of such transfer, including the successor's name and address. Upon such assumption and written notification, Tenant shall have no further claim against Landlord with respect to any such Security Deposit and hereby waives all rights against Landlord in such regard. Notwithstanding the foregoing, Landlord will remain personally liable to the extent Landlord's successor in interest fails to assume the Landlord's obligations with respect to the deposit as specified above.

3.6.8 In the event of foreclosure by the holder of any mortgage or deed of trust encumbering the Premises, Landlord shall continue to be liable for any security deposit and any such mortgagee shall have no liability or responsibility therefore, except to the extent the Security Deposit is delivered to such mortgagee and such mortgagee assumes responsibility for such Security Deposit.

ARTICLE 4

Possession

4.1 Possession. Tenant hereby acknowledges that it currently owns and is in possession of the Premises, and is familiar with the condition thereof and accepts the Premises in its "as is" condition with all faults, and Landlord makes no representation or warranty of any kind with respect the Premises, and Landlord will have no obligation to improve, alter or repair the Premises, except as specifically set forth herein. Except as otherwise expressly provided herein, it is understood and agreed that Landlord is not obligated to install any equipment, or make any repairs, improvements or alterations to the Premises.

4.2 NOTWITHSTANDING ANYTHING TO THE CONTRARY HEREIN, IT IS EXPRESSLY UNDERSTOOD AND AGREED THAT LANDLORD IS LEASING THE PREMISES "AS IS" AND "WHERE IS," AND WITH ALL FAULTS AND THAT, LANDLORD IS MAKING NO REPRESENTATIONS AND WARRANTIES WHETHER EXPRESS OR IMPLIED, BY OPERATION OF LAW OR OTHERWISE, WITH RESPECT TO THE QUALITY OR PHYSICAL CONDITION OF THE PROPERTY, THE INCOME OR EXPENSES FROM OR OF THE PROPERTY, OR THE COMPLIANCE WITH THE PROPERTY WITH APPLICABLE BUILDING OR FIRE CODES, ENVIRONMENTAL LAWS OR OTHER LAWS, RULES, ORDERS OR REGULATIONS. WITHOUT LIMITING THE FOREGOING, IT IS UNDERSTOOD AND AGREED THAT LANDLORD MAKES NO WARRANTY OF THE HABITABILITY, SUITABILITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. TENANT AGREES THAT IT ASSUMES FULL RESPONSIBILITY FOR, AND THAT IT HAS PERFORMED EXAMINATIONS AND INVESTIGATIONS OF THE PREMISES, INCLUDING SPECIFICALLY, WITHOUT LIMITATION, EXAMINATIONS AND INVESTIGATIONS FOR THE PRESENCE OF ASBESTOS, PCBS AND OTHER HAZARDOUS SUBSTANCES, MATERIALS AND WASTES (AS THOSE TERMS MAY BE DEFINED HEREIN OR BY APPLICABLE FEDERAL OR STATE LAWS, RULES OR REGULATIONS) ON OR IN THE PREMISES. WITHOUT LIMITING THE FOREGOING, EXCEPT FOR CLAIMS ARISING UNDER THE

AGREEMENT FOR PURCHASE AND SALE DATED AS OF JULY 21, 2005, TENANT IRREVOCABLY WAIVES ALL CLAIMS AGAINST LANDLORD WITH RESPECT TO ANY ENVIRONMENTAL CONDITION, INCLUDING CONTRIBUTION AND INDEMNITY CLAIMS, WHETHER STATUTORY OR OTHERWISE, EXCEPT TO THE EXTENT ARISING OUT OF THE GROSS NEGLIGENCE OR WILLFUL MISCONDUCT OF LANDLORD.

ARTICLE 5

Use

5.1 Permitted Use of Premises. The Premises shall be used and occupied by Tenant solely for research and development and manufacture of drug candidates and substances along with associated office, lab and warehouse uses. The Premises are to be used for no other purposes without first obtaining the consent of Landlord, which consent shall not be unreasonably withheld.

5.2 Compliance with Laws. Tenant, at Tenant's sole expense, shall promptly comply, or cause compliance, with all laws, ordinances, zoning restrictions, rules, regulations, orders and requirements of any duly constituted public authorities now or hereafter affecting the Premises, including the use, safety, cleanliness and occupation of the Premises.

5.3 Prohibited Uses. Tenant shall not do, bring or keep anything in or about the Premises that will cause a cancellation of any insurance covering the Premises or the Building. Tenant shall not use the Premises in any manner that will constitute waste, nuisance or unreasonable annoyance to owners or occupants of nearby properties. Tenant shall not do anything on the Premises that will cause material damage to the Building. Tenant shall place no loads upon the floors, walls or ceiling of the Building in excess of the maximum designed load specified by Landlord or which may materially damage the Building. No machinery, apparatus, or other appliance shall be used or operated in or on the Premises that will vibrate or shake the Premises.

5.4 Rules and Regulations. Tenant shall comply with all reasonable nondiscriminatory rules and regulations (the "Rules and Regulations") from time to time adopted by Landlord with respect to the Premises. Notwithstanding anything to the contrary contained in this Lease, if any rule or regulation is in conflict with any term, covenant or condition of this Lease, this Lease shall prevail. In addition, no such rule or regulation, or any subsequent amendment thereto adopted by Landlord, shall in any way alter, reduce or adversely affect any of Tenant's rights or enlarge Tenant's obligations under this Lease.

ARTICLE 6

Alterations and Additions

6.1 Prohibited Alterations. Tenant shall not make any alterations, improvements or additions to the Premises, except for non-structural alterations not exceeding $100,000 per occurrence or an aggregate amount of $250,000 in any 12-month period, without obtaining Landlord's prior written consent, which consent shall not unreasonably be withheld. Notwithstanding the foregoing, Tenant shall not make any alterations that affect the structural elements of the Premises or require a construction or building permit without Landlord's prior written consent, which consent may be granted or withheld in Landlord's sole and absolute discretion. Any such improvements, excepting movable furniture and trade fixtures, shall become part of the realty and belong to Landlord. All alterations and improvements shall be properly permitted and installed at Tenant's sole cost, by a licensed contractor, in a good and workmanlike manner, and in conformity with the laws of all applicable duly constituted public authorities. Each such licensed contractor and any subcontractor that performs work with a cost greater than $50,000, shall be acceptable to Landlord in its reasonable discretion. Any alternations that Tenant shall desire to make and which require the consent of Landlord shall be presented to Landlord in written form with detailed plans. Tenant shall: (i) acquire all applicable governmental permits; (ii) furnish Landlord with copies of both the permits and the plans and specifications before the commencement of the work, and (iii) comply with all conditions of said permits in a prompt and expeditious manner. Any alterations shall be performed in a workmanlike manner with good and sufficient materials. Tenant shall promptly upon completion furnish Landlord with as-built plans and specifications.

6.2 Notice of Commencement. At least 20 days prior to commencing any work relating to any alterations, improvements or additions approved by Landlord, Tenant shall notify Landlord in writing of the expected date of commencement. Landlord shall have the right at any time thereafter to post and maintain on the Premises such notices as Landlord reasonably deems necessary to protect Landlord and the Premises from mechanics' liens, materialmen's liens or any other liens. Tenant shall pay, when due, all claims for labor or materials furnished to or for Tenant for use in improving the Premises. Tenant shall not permit any mechanics' or materialmen's liens to be levied against the Premises arising out of work performed, materials furnished, or obligations to have been performed on the Premises by or at the request of Tenant. Tenant hereby indemnifies and holds Landlord harmless against loss, damage, attorneys' fees and all other expenses on account of claims of lien of laborers or materialmen or others for work performed or materials or supplies furnished for Tenant or its contractors, agents or employees. If Tenant fails to remove or bond any lien(s) filed against the Premises in connection with any work performed or any work claimed to have been performed by or at the direction of Tenant within 10 days from the date of the lien(s) filing, Landlord may remove such lien(s) at Tenant's expense and Tenant shall reimburse Landlord for all costs incurred by Landlord in connection with the removal of the lien(s), which amount shall be deemed Additional Rent, and shall include, without limitation, all sums disbursed, incurred or deposited by Landlord, including Landlord's costs, expenses and actual attorneys' fees, with interest thereon, at the Default Rate from the date of expenditure.

6.3 Trade Fixtures. Tenant may install trade fixtures, machinery or other trade equipment in conformance with the ordinances of all applicable duly constituted public authorities. Tenant may remove any of such trade fixtures or machinery upon the termination of this Lease. In the event that Tenant installs improvements, machinery or trade fixtures, or makes any alterations, Tenant shall, at Landlord's option, return the Premises on termination of this

Lease to the same condition as existed at the date of entry, reasonable wear and tear excepted, including the removal of improvements or alterations approved by Landlord in Section 6.1; provided, however, if such improvements or alterations were approved by Landlord, Tenant shall only be required to remove such

improvements or alterations if Landlord's approval was conditioned upon Tenant's removal of such improvements or alterations. Tenant shall, in any event, repair any damage resulting from the removal of machinery or trade fixtures of Tenant.

ARTICLE 7

Surrender of Premises

7.1 Conditions upon Surrender. Upon the expiration, or earlier termination, of this Lease, Tenant shall surrender the Premises to Landlord in its condition existing as of the Commencement Date, normal wear and tear, casualty, condemnation and acts of God excepted, with all interior walls in good repair and repainted if marked, all carpets shampooed and cleaned, the HVAC equipment, plumbing, electrical and other mechanical installations in good operating order, and all floors cleaned and waxed, all to the reasonable satisfaction of Landlord. Tenant shall remove from Premises all of Tenant's alterations which Landlord requires Tenant to remove pursuant to Section 6.3 and all Tenant's personal property, and shall repair any damage and perform any restoration work caused by such removal. Landlord and Tenant shall each initial and attach a narrative description or floor plan of the Premises to this Lease, to be incorporated herein as Exhibit "D". Said narrative description or floor plan shall describe, among other things, those interior improvements which are to remain in the Premises upon expiration, or earlier termination, of this Lease. It is the intent of the parties that the condition of the Premises, after Tenant's removal, be in substantial conformance with the layout reflected in Exhibit "D". If Tenant fails to remove such alterations and Tenant's personal property which Tenant is authorized and obligated to remove pursuant to the above, and such failure continues after the termination of the Lease, Landlord may retain such property and all rights of Tenant with respect to it shall cease, or Landlord may place all or any portion of such property in public storage for Tenant's account. Tenant shall pay to Landlord upon demand costs of removal of such alterations and Tenant's personal property and storage and transportation costs of same, and the cost of repairing and restoring the Premises, together with attorneys' fees and interest at the Default Rate on said amounts, from the date of expenditure by Landlord. If the Premises are not so surrendered at the termination of this Lease, Landlord may, in its sole discretion, either (a) upon written notice to Tenant, treat Tenant as a month-to-month tenant at will, subject to all the terms, covenants and conditions of this Lease, or (b) proceed with an unlawful detainer action and pursue all other rights and remedies available to Landlord.

ARTICLE 8

Utilities and Services

8.1 Utilities. Tenant shall make all arrangements for and pay for all water, sewer, gas, heat, light, power, telephone service and any other service or utility Tenant requires at the Premises. Landlord shall not be liable for any failure or interruption of any utility service being

furnished to the Premises, and no such failure or interruption shall entitle Tenant to terminate this Lease; *provided, however*, that Tenant will be entitled to rent abatement in connection with any such failure or interruption to the extent Landlord receives lost rental income insurance proceeds.

8.2 Landlord Service. In the event that any utilities are furnished by Landlord, Tenant shall pay to Landlord the cost thereof in the manner set forth in Section 13.3. Tenant's cost shall be the total cost shown on utility meters servicing the Premises and any extraordinary use which may be made by Tenant.

ARTICLE 9

Indemnification

9.1 Indemnity of Landlord. Tenant hereby agrees to indemnify, defend (with attorneys approved by Landlord), protect, and hold Landlord and Landlord's agents, employees, directors, officers, managers, members, partners, affiliates, independent contractors and property managers ("Landlord's Agents"), harmless from any and all liabilities, costs, expenses and losses by reason of injury to person or property ("Losses"), caused by, arising out of, or related to, the condition of the Premises or the use or occupancy of the Premises by Tenant, its agents, directors, officers, managers, members, partners, affiliates, independent contractors and property managers, or invitees ("Tenant's Agents"), including without limitation, any liability for injury to the person or property of Tenant or Tenant's Agents, but excepting any Loss: (i) resulting from the willful breach of the Lease by Landlord or the negligence or willful misconduct of Landlord or Landlord's Agents, (ii) arising solely out of the condition of the Premises that Tenant demonstrates existed before the Commencement Date or (iii) resulting from the migration of Hazardous Materials onto the Premises from adjoining properties, except to the extent caused by Tenant or Tenant's Agents. Tenant's obligation hereunder shall survive the termination of this Lease with respect to any claims or liability arising in connection with any event occurring prior to such termination.

9.2 Waiver of Claims. Tenant, as a material part of the consideration rendered to Landlord in entering into this Lease, hereby waives all claims against Landlord for damages to goods, wares, machinery, trade fixtures, or other property of Tenant, Tenant's Agents or any other person in or about the Premises, whether such damage or injury is caused by or results from Landlord's negligence, fire, steam, electricity, gas, water or rain, or from the breakage, leakage, obstruction or other defects of pipes, fire sprinklers, wires, appliances, plumbing, HVAC or lighting fixtures, or from any other cause, whether the said injury or damage results from conditions arising upon the Premises or upon other portions of the building of which the Premises are a part, or from other sources or places, but excepting any claims resulting from the gross negligence or willful misconduct of Landlord or Landlord's Agents or breach of this Lease by Landlord. Notwithstanding Landlord's negligence or breach of this Lease, Landlord shall under no circumstances be liable for loss of profits or special, incidental or consequential damages arising therefrom.

9.3 Landlord Indemnification. Landlord agrees to indemnify Tenant and hold it harmless from any and all loss, cost, damage, expense and liability (including without limitation court costs and reasonable attorneys' fees) incurred in connection with or arising from any Losses, caused by the gross negligence or willful misconduct of Landlord and/or any of Landlord's Agents or caused by the willful breach of this Lease by Landlord. The obligations of Landlord under this Section 9.3 shall survive the termination of this Lease with respect to any claims or liability arising in connection with any event occurring prior to such termination.

9.4 Claims for Indemnification. If any indemnitee under Sections 9.2 or 9.3 above (an "Indemnitee") shall believe that such Indemnitee is entitled to indemnification pursuant to this Article 9 in respect of any Losses, such Indemnitee shall give the appropriate indemnifying party (each, as applicable, an "Indemnifying Party") prompt written notice thereof. Any such notice shall set forth in reasonable detail and to the extent then known the basis for such claim for indemnification. The failure of such Indemnitee to give notice of any claim for indemnification promptly shall not adversely affect such Indemnitee's right to indemnity hereunder except to the extent that such failure adversely affects the right of the Indemnifying Party to assert any reasonable defense to such claim.

9.5 Defense of Claims. In connection with any claim which may give rise to indemnity under this Article 9 resulting from or arising out of any claim or proceeding against an Indemnitee by a person that is not a party hereto, the Indemnifying Party shall (unless such Indemnitee elects not to seek indemnity hereunder for such claim), upon written notice to the relevant Indemnitee, assume the defense of any such claim or proceeding. The Indemnifying Party shall select counsel reasonably acceptable to such Indemnitee to conduct the defense of such claim or proceeding, shall take all steps necessary in the defense or settlement thereof and shall at all times diligently and promptly perform resolution thereof. Without the prior written consent of the Indemnitee, which consent shall not be unreasonably withheld, the Indemnifying Party will not enter into any settlement of, or any claim or proceeding which would lead to liability or create any financial or other obligation on the part of the Indemnitee for which the Indemnitee is not entitled to indemnification hereunder. Without the prior written consent of the Indemnifying Party, which consent shall not be unreasonably withheld, the Indemnitee will not enter into any settlement or any claim or proceeding which would lead to liability or create any financial or other obligation on the part of the Indemnifying Party unless the Indemnifying Party has failed or refused to acknowledge responsibility for or defend such claim or proceeding within a reasonable period of time after notice is provided pursuant to Section 9.4.

ARTICLE 10

Insurance

10.1 Landlord's Insurance. Landlord shall maintain, at Tenant's sole expense, which Tenant shall pay to Landlord as Additional Rent in the manner set forth in Section 13.3, a policy or policies of insurance protecting Landlord against the following:

10.1.1 Fire and other perils normally included within the classification of fire and extended coverage, together with insurance against vandalism and malicious mischief, to the

extent of the full replacement cost of the Premises (including, without limitation, any real property and/or fixture improvements located within the Premises existing as of the Commencement Date), but exclusive of trade fixtures, equipment and improvements insured by Tenant, with agreed value, full replacement and such other endorsements Landlord elects to maintain. Landlord may also maintain earthquake and flood coverage if available at commercially reasonable rates.

10.1.2 Eighteen (18) months of rental loss insurance and to the extent of 100% of the gross rentals from the Building of which the Premises constitute a part.

10.1.3 Public liability and property damage insurance with respect to common areas in amounts (i) not less than $1,000,000 for injury or death to any one person in any one accident or occurrence, (ii) not less than $2,000,000 for injury or death to more than one person in any one accident or occurrence, (iii) not less than $4,000,000 of excess umbrella liability insurance, and, (iv) not less than $200,000 per occurrence for damage to Premises.

10.1.4 At Landlord's sole option, environmental liability or environmental clean-up/remediation insurance in such amounts and with such deductibles and other provisions as Landlord may determine in its sole and absolute discretion.

10.2 Payment. Tenant shall pay to Landlord in the manner set forth in Section 13.3, the cost of insurance required in Section 10.1. To the extent that any such insurance is maintained pursuant to a blanket or similar policy of insurance, then the cost thereof shall be equitably allocated to the Premises by Landlord.

10.3 Tenant's Insurance. Tenant shall maintain at its sole cost and expense, in force a policy or policies of insurance protecting Landlord and Tenant against each of the following:

10.3.1 Comprehensive general liability insurance with respect to the Premises insuring against bodily injury or death and property damage in amounts (i) not less than $2,000,000 in the aggregate, (ii) not less than $2,000,000 per occurrence and (iii) not less than $5,000,000 of excess umbrella liability insurance. Landlord shall be included as additional insured. The amount of such public liability insurance shall be increased from time to time as Landlord may reasonably determine. All such bodily injury and property damage insurance shall specifically insure the performance by Tenant of the indemnity agreement as to personal injury or property damage contained in Section 9.

10.3.2 Insurance covering alterations, additions or improvements permitted under Section 6, trade fixtures and personal property made after the Commencement Date from time to time in or upon the Premises in an amount not less than 80% of their full replacement cost from time to time during the term of this Lease, providing protection against any peril included within the classification "fire and extended coverage," for the repair or replacement of the property damaged or destroyed unless this Lease shall terminate pursuant to Section 20 hereof.

10.3.3 All policies of insurance to be provided by Tenant shall be issued by insurance companies, with general policy holder's rating of not less than A- and a financial

rating of not less than Class VII as rated in the most current available "Best's" Insurance Reports, and admitted to do business in the State of California. Such policies shall be issued in the names of Landlord and Tenant. The policies provided by Tenant shall be for the mutual and joint benefit and protection of Landlord and Tenant, and executed copies of such policies of insurance or certificates thereof shall be delivered to the Landlord within 10 days after the

Commencement Date and, thereafter, within 30 days prior to the expiration of the term of each such policy. All public liability and property damage policies shall contain a provision that the Landlord, although named as an insured, shall nevertheless be entitled to recover under said policies for any loss occasioned to it or Landlord's Agents by reason of the negligence of the Tenant. Upon the expiration or termination of any such policy, renewal or additional policies shall be procured and maintained by the Tenant to provide the required coverage. All policies of insurance delivered to Landlord must contain a provision that the company writing said policy will provide to Landlord with 30 days notice in writing in advance of any cancellation or lapse or the effective date of any reduction in the amounts of insurance. All public liability, property damage and other casualty policies shall be written as primary policies, not contributing with and not in excess of coverage which Landlord may carry.

10.3.4 Notwithstanding anything to the contrary, Tenant's obligation to carry the insurance described in this Section may be brought within the coverage of a so-called blanket policy or policies of insurance carried and maintained by the Tenant, provided that (i) Landlord will be named as an additional insured thereunder as their interests may appear, (ii) the coverage afforded Landlord will not be reduced or diminished by reason of the use of such blanket policy of insurance, and (iii) the requirements set forth herein are otherwise satisfied. Tenant agrees to permit Landlord at all reasonable times to inspect the policies of insurance of Tenant covering the Premises for policies which are not required to be delivered to Landlord.

10.4 Release of Subrogation Rights. Landlord and Tenant hereby mutually release each other from liability and waive all right to recover against each other for any loss from perils insured against under their respective insurance policies, including any extended coverage and special form endorsements to said policies; provided, however, this Section shall be inapplicable if it would have the effect, but only to the extent that it would have the effect of invalidating any insurance coverage of Landlord or Tenant. The parties shall obtain, if available, from their respective insurance companies, a waiver of any right of subrogation which said insurance company may have against the Landlord or the Tenant, as the case may be.

ARTICLE 11

Care of the Premises

11.1 Care of Premises. Tenant shall, at its sole cost and expense keep the Premises and exterior and interior portions of windows, doors, and all other glass or plate glass fixtures in a working neat, clean, sanitary, safe and good condition and repair, and shall keep the Premises free from trash, rubbish and dirt. Tenant shall make all repairs or replacements thereon or thereto, whether ordinary or extraordinary.

11.2 Maintenance of Equipment. Tenant shall, at its sole cost and expense, keep and maintain all utilities, fixtures and mechanical equipment used, or available for use, by Tenant in connection with the Premises, in good working order, condition and repair. Said items shall include, but are not limited to, all plumbing or sewage facilities in the Premises, doors, locks and closing devices, windows, including glass, lights, electric systems and equipment, heating and air conditioning systems and equipment, and all other appliances and equipment of every kind necessary for the use of the Premises.

11.3 Roof, Walls, Foundation and Structural. At its cost and expense, Tenant will keep in good condition and repair the roof, foundation, load bearing walls and structural elements of the Premises to keep the Premises in the same condition and repair existing as of the Commencement Date, normal wear and tear, casualty and condemnation excepted.

11.3.1 Notwithstanding the foregoing, with respect to a Capital Structural Repair (as defined below), Tenant may elect in its sole discretion to either (i) require Landlord to complete such Capital Structural Repair with the costs and expenses of which to be paid by Tenant as set forth in Section 11.3.2 below or (ii) complete such Capital Structural Repair at Tenant's own cost and expense. For purposes of this Article 11, "Capital Structural Repair" means a repair of structural elements of the Premises or the building systems (a) that requires a construction or building permit from the City of Carlsbad to conduct such repair and (b) the estimated cost of which exceeds $250,000. The parties will use their diligent good faith efforts to mutually agree on the budget and plans for any Capital Structural Repair.

11.3.2 At Tenant's election, Tenant shall pay Landlord the cost and expense plus interest (at Landlord's actual cost of borrowing on an arms-length basis) of any Capital Structural Repairs that Landlord completes pursuant to subpart (i) of Section 11.3.1 above ("Capital Structural Expenses"): (i) in one lump sum, or (ii) as equal monthly installments over the lesser of (a) the useful life of the Capital Structural Repair for which such Capital Structural Expenses were incurred, or (b) the remaining Term of the Lease (as may be extended).

11.4 Compliance with Governmental Regulations. Tenant shall, at its sole cost and expense, promptly and properly observe and comply with, including the making by Tenant of any alterations to the Premises, all present and future orders, regulations, directions, rules, laws ordinances, and requirements of all governmental authorities (including, without limitation, state, municipal, county and federal governments and their departments, bureaus, boards and officials) arising from the use or occupy of, applicable to, the Premises.

11.5 Service Contracts. Except to the extent self-performed by Tenant's qualified and experienced personnel, as reasonably determined by Landlord, Tenant shall, at Tenant's sole cost and expense, procure and maintain contracts, with copies to Landlord, in customary form and substance for, and with contractors specializing and experienced in the maintenance of the following equipment and improvements, if any, if and when installed on the Premises: (i) HVAC equipment, (ii) boiler, and pressure vessels, (iii) fire extinguishing systems, including fire alarm and/or smoke detection, (iv) except as maintained by Faraday Court Owners' Association, landscaping and irrigation system, (v) roof covering and drains, (vi) clarifiers, (vii) basic utility feed to the perimeter of the Building, and (vii) any other equipment, if reasonably required by

Landlord. However, Landlord reserves the right, upon notice to Tenant, to procure and maintain any or all of such service contracts, and if Landlord so elects, Tenant shall reimburse Landlord, upon demand, for the cost thereof.

11.6 Action by Landlord if Tenant Fails to Maintain. If Tenant refuses or neglects to repair or maintain the Premises as required by Sections 11.1, 11.2, 11.3 and 11.4 to the reasonable satisfaction of Landlord, Landlord, at any time following 10 days from the date on which Landlord shall make written demand on Tenant to affect such repair or maintenance, may, but shall not have the obligation to, make such repair and/or maintenance with qualified and experienced contractors (without liability to Tenant for any loss or damage which may occur to Tenant's merchandise, fixtures or other personal property,

or to Tenant's business by reason thereof) and upon completion thereof, Tenant shall pay to Landlord as Additional Rent Landlord's costs for making such repairs, plus interest at the Default Rate upon demand herefore. Moreover, Tenant's failure to pay any of the charges in connection with the performance of its maintenance and repair obligations under this Lease will constitute a material default under the Lease.

ARTICLE 12

Taxes

12.1 Personal Property Taxes. Tenant shall pay prior to delinquency all taxes, assessments, license fees, and other public charges levied, assessed or imposed or which become payable during the term of this Lease upon any trade fixtures, furnishings, equipment and all other personal property of Tenant installed or located in the Premises. Whenever possible, Tenant shall cause said trade fixtures, furnishings, equipment and personal property to be separately assessed. If, however, any or all of said items shall be assessed and taxed with the real property, Tenant shall pay to Landlord such taxes as are attributable to Tenant's trade fixtures, furnishings, equipment and personal property within 15 days after receipt of an invoice from Landlord advising Tenant of the taxes applicable to Tenant's property.

12.2 Real Property Taxes. Tenant shall also pay at least 20 days before delinquent any and all real estate taxes, as defined in Section 12.3, assessed or imposed, or which become a lien upon or become chargeable against or payable in connection with the Premises. Within three business days of such payment, Tenant shall provide Landlord evidence of such payment in a form reasonably acceptable to Landlord. In the event that the Premises are not separately assessed, Tenant shall pay an equitable proportion of the real estate taxes and assessments for all the land and improvements included within the tax parcel(s) assessed, such proportion shall be determined by Landlord from the respective valuations assigned in the Assessor's worksheets and such other information as is reasonably available to Landlord, including the Building and any special improvements constructed for the benefit of Tenant. Real estate taxes for the last year of the term of this Lease shall be prorated between Landlord and Tenant as of the expiration date of the term. With respect to any assessments which may be levied against or upon the Premises, or which under the laws then in force may be evidenced by improvement or other bonds and may be paid in annual installments, only the amount of such annual installment, with appropriate

proration for any partial year, and interest thereon, shall be included within a computation of taxes and assessments levied against the Premises. To the extent tax bills are not otherwise delivered to Tenant and such tax bills are delivered to Landlord, at least 60 days prior to the applicable delinquency date, Landlord will provide Tenant with written notice detailing the amount and due date of each real estate tax Tenant is required to pay pursuant to this Section 12.2. In the event that Tenant incurs a late charge on the payment of the Base Monthly Rental or fails to pay the real property taxes within 20 days before delinquent, Landlord may estimate the current real property taxes, and require that such taxes be paid in advance to Landlord by Tenant monthly in advance with the payment of the Base Monthly Rental. Such monthly payment shall be equal to the amount of the estimated installment of taxes divided by the number of months remaining before the month in which such installment becomes delinquent. When the actual amount of the applicable tax bill is known, the amount of such equal monthly advance payments shall be adjusted as required to provide the funds needed to pay the applicable taxes. If the amount collected by Landlord is insufficient to pay such real estate taxes when due, Tenant shall pay Landlord, upon demand, such additional sum as is necessary. Upon receipt of the full amount of the real estate taxes for such period, Landlord shall, if practicable, pay such real estate taxes before they are delinquent. Advance payments may be intermingled with other moneys of Landlord and shall not bear interest. In the event of a breach by Tenant in the performance of its obligations under this Lease, then any such advance payments may be treated by Landlord as an additional security deposit; provided, however, to the extent that Landlord applies such payments to anything other than real estate taxes, then Landlord shall promptly give Tenant notice of such application.

12.3 Definition of Taxes. For purposes of this Lease, "taxes" shall also include each of the following:

12.3.1 Any form of assessment, license fee, license tax, bond or improvement bond, business license tax, commercial rental tax, levy, charge, penalty, or tax, imposed by any authority having the direct power to tax, including any city, county, state or federal government, or any school, agricultural, lighting, drainage or other improvement or special district thereof, as against any legal or equitable interest of Landlord in the Premises or the real property of which the Premises constitute a part;

12.3.2 Any tax on Landlord's right to rent or other income from the Premises or as against Landlord's business of leasing the Premises;

12.3.3 Any assessment, tax, fee, levy or charge in substitution, partially or totally, of any assessment, tax, fee, levy or charge previously included with the definition of real property tax, it being acknowledged by Tenant and Landlord that Proposition 13 was adopted by the voters of the State of California in the June 1978 election and that assessments, taxes, fees, levies and charges may be imposed by governmental agencies for such services as fire protection, street, sidewalk and road maintenance, refuse removal and for other governmental services formerly provided without charge to property owners or occupants. It is the intention of Tenant and Landlord that all such new and increased assessments, taxes, fees, levies and charges and all similar assessments, taxes, fees, levies and charges be included within the definition of real property tax for purposes of this Lease;

12.3.4 Any tax allocable to or measured by the area of the Premises or the rental payable hereunder, including without limitation, any gross income tax or excise tax levied by the State, any political subdivision thereof, city, or federal government, with respect to the receipt of such rental, or upon or with respect to the possession, leasing, operating, management, maintenance, alteration, repair, use of occupancy by Tenant of the Premises, or any portion thereof,

12.3.5 Any tax upon this transaction or any document to which Tenant is a party, creating or transferring an interest or an estate in the Premises; and

12.3.5 Any tax, fee, levy, assessment or charge, or any increase therein: (i) imposed by reason of events occurring during the term of this Lease, including but not limited to, a change in the ownership of the Premises, and (ii) levied or assessed on machinery or equipment, if any, provided by Landlord to Tenant pursuant to this Lease.

12.3.6 Notwithstanding anything contained in this Lease, “Real estate taxes” shall not include Landlord’s federal or state income, franchise, inheritance or estate taxes.

ARTICLE 13

Common Areas

13.1 Common Area. Common areas shall include all areas within the Premises outside the exterior boundaries of the buildings situated thereon, including, but not limited to, streets, driveways, parking areas, truckways, delivery passages, loading doors, sidewalks, ramps, open and closed courts and malls, landscaped and planted areas, exterior stairways, bus stops, retaining and decorative walls and planters, and other areas provided for the common use of Landlord and Tenant, their employees and invitees.

13.2 Maintenance. Except to the extent maintained by Faraday Court Owners’ Association, Landlord shall maintain said common areas in a neat, clean and orderly condition, properly lighted and landscaped as Landlord and the Faraday Court Owners’ Association shall determine, including, but not limited to, general maintenance, repairs, pest control, resurfacing, painting, restriping, cleaning, sweeping and trash removal; maintenance and repair of sidewalks and curbs; sprinkler systems, planting and landscaping; lighting, water, music and other utilities; directional signs and other markers and bumpers; maintenance and repair of any fire protection systems, automatic sprinkler systems, lighting systems, storm drainage systems and any other utility systems; personnel to implement such service and to police the common areas; and police and fire protection services. Tenant shall reimburse Landlord for all costs incurred by Landlord in connection with such maintenance of said common areas pursuant to Section 13.3, which amount shall be deemed Additional Rent.

13.3 Tenant’s Costs. Within 60 days after the Commencement Date, and within 60 days after the beginning of each calendar year, Landlord shall give Tenant a written estimate, for

such calendar year, of Tenant’s share of the cost of utilities, if not separately metered, insurance provided by Landlord and expenses in connection with maintenance of common areas. Tenant shall pay such estimated amount to Landlord in equal monthly installments, in advance. Within 90 days after the end of each calendar year, Landlord shall furnish to Tenant a statement showing in reasonable detail the costs incurred by Landlord for the operation and maintenance of the Premises during such year (the “Annual Statement”), and Tenant shall pay to Landlord Tenant’s proportionate share of the cost incurred in excess of the payments made by Tenant within 10 days of receipt of such statement. In the event that the payments made by Tenant for the operation and maintenance of the Premises exceed Tenant’s share of the cost of same, such amount shall be credited by Landlord to the rent or other charges next due and owing, provided that, if the Lease term has expired, Landlord shall accompany said statement with the amount due Tenant. At the request of Tenant, to be made within 90 days of receipt by Tenant of the Annual Statement, Landlord shall provide Tenant with copies of invoices, or other forms of payment verification, covering the costs incurred by Landlord as set forth in the Annual Statement. Tenant shall have the right, within 90 days of receipt of this additional information, to audit, through a nationally or regionally recognized firm of certified public accountants engaged on a non-contingency basis, the Landlord’s records in connection with the Annual Statement. Landlord shall make the records readily available for such examination. If any audit discloses that the Annual Statement submitted by Landlord overstates the expenses by more than 5%, Landlord shall pay Tenant within 5 days after written request the reasonable cost of such audit together with any overpayment which may have been made by Tenant. Any information obtained by Tenant pursuant to the provisions of this Section shall be treated as confidential.

13.4. Management Fee. Tenant shall pay to Landlord, as Additional Rent, a monthly fee to cover costs of property management services in an amount equal to one percent (1%) of the Base Monthly Rental due from Tenant, whether or not Landlord incurs fees payable to any third party to provide such services and without regard to the actual costs incurred by Landlord for such services.

ARTICLE 14

Signs and Advertising

14.1 Signs. Landlord shall designate the location on the Premises for one or more exterior Tenant identification sign(s) and Tenant shall not display or erect any other signs, displays, or other advertising materials that are visible from the exterior of the building. The size, design, and other physical aspects of the permitted sign(s) shall be subject to the Landlord’s written approval prior to installation, which approval will not unreasonably be withheld, any covenants, conditions, or restrictions encumbering the Premises, any applicable municipal or other governmental permits and approvals. The cost of the sign(s), including but not limited to the permitting, installation, maintenance and removal thereof shall be at Tenant’s sole cost and expense. If Tenant fails to maintain its sign(s), or if Tenant fails to remove such sign(s) upon termination of the Lease, or fails to repair any damage caused by such removal (including without limitation, painting the building, if required by Landlord), Landlord may do so at Tenant’s expense. Tenant shall on demand reimburse Landlord for all costs incurred by Landlord

to effect such removal, which amounts shall be deemed Additional Rent and shall include without limitation, all sums disbursed, incurred or deposited by Landlord, including Landlord’s costs, expenses and actual attorneys’ fees with interest thereon. By executing this Lease, Landlord hereby approves the signage currently existing on the Premises.

ARTICLE 15

Entry by Landlord

15.1 Entry by Landlord. Tenant shall permit Landlord and Landlord’s Agents, and, if accompanied by a representative of Tenant, prospective purchasers, lenders, investors and contractors to enter the Premises at all reasonable times, upon giving Tenant a 24 hour written notice, except in the event of an emergency in which case neither the 24 hour written notice nor the presence of a representative of Tenant is required: (i) for the purpose of inspecting the same, (ii) for the purpose of maintenance, repairs, alterations, or additions to any portion of the Building, including the erection and maintenance of such

scaffolding, canopies, fences, and props as may be required, (iii) for the purposes of performing any of Tenant's obligations under this Lease, or (iv) for the purpose of posting notices of non-responsibility for alterations, additions, or repairs.

15.2 Entry to Relet Premises. Landlord may, during reasonable business hours within 18 months prior to the expiration of this Lease, enter the Premises for the purpose of allowing prospective tenants to view the Premises.

15.3 No Liability. Landlord shall be permitted to enter the Premises for any of the purposes stated in and in accordance with Sections 15.1 and 15.2 above without any liability to Tenant for any loss of occupation of quiet enjoyment of the Premises resulting therefrom.

ARTICLE 16

Assignment and Subletting

16.1 Assignment and Subletting. Tenant shall neither voluntarily nor by operation of law, assign, sell, encumber, pledge or otherwise transfer all or any part of Tenant's leasehold estate hereunder, or permit the Premises to be occupied by anyone other than Tenant or Tenant's employees, or sublet the Premises or any portion thereof, without Landlord's prior written consent in each instance, which consent shall not be unreasonably withheld. Any purported assignment or subletting contrary to these provisions shall be void. Landlord's consent shall be based upon a determination that the same type, class, nature and quality of business, service, management, and financial soundness of ownership shall exist after such assignment or subletting and, provided further, that each and every covenant, condition or obligation imposed upon Tenant by this Lease is assumed by such assignee or subtenant and each and every right, remedy or benefit afforded Landlord by this Lease is not thereby impaired or diminished.

Consent by Landlord to one or more assignments of this Lease or to one or more sublettings of the Premises shall not operate to exhaust Landlord's rights under this Section.

16.2 Notice to Landlord. If Tenant desires at any time to assign this Lease or to sublet the Premises or any portion thereof, it shall first notify Landlord of its desire to do so and shall submit in writing to Landlord (the "Transfer Notice"); (i) the size and location of the space Tenant proposes to assign or sublet; (ii) the name of the proposed Subtenant or assignee; (iii) the date on which the Tenant proposes that the transfer be effective, which shall not be earlier than the date which is 10 business days after the Transfer Notice (iv) the nature of the proposed Subtenant's or assignee's business to be carried on in the Premises; (v) the terms and provisions of the proposed sublease or assignment; (vi) such reasonable financial information as Landlord may request concerning the proposed Subtenant or assignee, and (vii) such other information as Landlord may reasonably require. Tenant agrees to reimburse Landlord for Landlord's actual costs and attorneys' fees (not to exceed $5000) incurred in conjunction with the processing and documentation of any such requested assignment, subletting, transfer, change or ownership or hypothecation of this Lease.

16.3 Notwithstanding Section 16.1 and 16.2, Landlord agrees that Tenant may assign its interest in this Lease or sublet the Premises, or any portion thereof, without Landlord's prior written consent but with written notice, to any (each such assignment, a "Specially Permitted Assignment"):

(i) successor by merger or sale of substantially all of Tenant's assets to which this Lease relates in a manner such that the assignee will become liable and responsible for the performance and observance of all Tenant's duties and obligations hereunder;

(ii) corporation or other entity which controls, is controlled by, or is under common control with Tenant (a corporation or other entity will be regarded as in control of another corporation or entity if its owns or controls in excess of 50% of the voting stock or other ownership interest of the other corporation or entity); or

(iii) corporation or other entity with whom Tenant has a bona fide collaboration (by joint venture, license or otherwise) ("Other Occupants") subject to satisfaction of the following conditions:

(a) the purpose of such collaboration is to develop and/or commercialize any or all of Tenant's drug products;

(b) there shall be no separate identification of the portion of the Premises occupied by the Other Occupants visible from inside or outside the Premises,

(c) there shall be no separate entrances or partitions separating the portion of the Premises occupied by Other Occupants;

(d) there shall be no agreement purporting to transfer any part of Tenant's leasehold to any Other Occupant, and each Other Occupant (but not their

individual employees) shall affirm in writing that it is not a subtenant or other transferee of any leasehold interest; and

(e) such occupancy shall not be a subterfuge or a means to circumvent the restrictions on transfer set forth in this Section.

16.4 No Release of Liability. No subletting or assignment, even with the consent of Landlord, shall relieve Tenant of its obligation to pay the rent and perform all the other obligations to be performed by Tenant hereunder. The acceptance of rent by Landlord from any other person shall not be deemed to be a waiver by Landlord of any provision of this Lease or to be a consent to any assignment or subletting.

16.5 Transfer Premiums. If Tenant assigns or sublets its rights under this Lease, Tenant shall pay to Landlord as Additional Rent, after Tenant has recovered any relevant leasing commissions, costs of real property and/or tenant improvements and other expenses of the assignment or sublease, 50% of such excess consideration due and payable to Tenant from said assignment or sublease to the extent said consideration exceeds the Rent or a pro rata portion

of the Rent, in the event only a portion of the Premises is sublet or assigned ("Profits"); provided, however, Landlord will not be entitled to any Profits derived in connection with a Specially Permitted Assignment.

16.6 Landlord's Option. Except for Specially Permitted Assignments, if Tenant desires at any time to assign or sublet all or substantially all of the Premises, Landlord, within 15 days after Landlord's receipt of all of the information required in the Transfer Notice, may by written notice to Tenant elect to terminate this Lease as to the entire Premises. In the event the Landlord elects to terminate the Lease, the Lease shall terminate on the proposed date the transfer would be effective as specified in the Transfer Notice and Tenant shall have no furhter obligations with respect to the Premises other than to surrender and vacate the Premises on or before the effective date of termination. After any such election by Landlord, Landlord shall be entitled to re-lease the Premises in Landlord's sole and absolute discretion.

ARTICLE 17

Dispossession

17.1 No Dispossession. If Tenant shall surrender the Premises, or be disposed by process of law, or otherwise, Landlord may terminate this Lease, retake possession of the Premises, pursue its remedies provided herein, and any personal property or trade fixtures belonging to Tenant and left on the Premises shall, at the option of Landlord, be deemed abandoned. In such case, Landlord may dispose of said personal property in any manner and is hereby relieved of all liability for doing so.

ARTICLE 18

Breach by Tenant

18.1 Events of Default. The occurrence of any of the following shall constitute a breach and material default of this Lease by Tenant:

18.1.1 The failure of Tenant to pay or cause to be paid when due any Base Monthly Rental, Additional Rent, Rent, taxes, monies, or charges required by this Lease to be paid by Tenant when such failure continues for a period of 5 business days after written notice thereof from Landlord to Tenant;

18.1.2 The failure of Tenant to perform any term, covenant or condition, other than payment of rent, taxes, monies or charges, required by this Lease and Tenant shall have failed to cure such failure within 30 days after written notice from Landlord; *provided*, *however*, that where such failure cannot reasonably be cured within the 30 day period, the Tenant shall not be in default if it has commenced such cure within the same 30 day period and diligently thereafter prosecutes the same to completion;

18.1.3 Subject to the notice and cure provisions of Section 18.1.3 above, Tenant causing, permitting, or suffering, without the prior written consent of Landlord, any act when this Lease requires Landlord's prior written consent or prohibits such act; or

18.1.4 To the extent permitted by applicable law, any act of bankruptcy caused, suffered or permitted by Tenant. For purposes of this Lease, "act of bankruptcy" shall include any of the following:

18.1.4.1. Any general assignment or general arrangement for the

benefit of creditors;

18.1.4.2. The filing of any petition by or against Tenant to have Tenant adjudged a bankrupt or a petition for reorganization or arrangement under any law relating to bankruptcy, unless such petition is filed against Tenant and same is dismissed within 120 days;

18.1.4.3. The appointment of a trustee or receiver to take possession of substantially all of Tenant's assets located in the Premises or of Tenant's interest in this Lease; or,

18.1.4.4. The attachment, execution or other judicial seizure of substantially all of Tenant's assets located at the Premises or of Tenant's interest in this Lease.

18.2 Three-Day Notice. In the event that Landlord issues a three-day notice, notice of abandonment or comparable document by reason of Tenant's breach, and Tenant cures such default, Tenant agrees to pay to Landlord, the reasonable cost of preparation and delivery of same.

18.3 No Waiver. The acceptance by Landlord of rent due hereunder after breach by Tenant will not constitute a waiver of such breach, unless a written notice to that effect has been delivered to Tenant.

18.4 Replacement of Statutory Notice Requirements. When this Lease requires service of a notice, that notice shall replace rather than supplement any equivalent or similar statutory notice, including any notices required by Code of Civil Procedure section 1161 or any similar or successor statute. When a statute requires service of a notice in a particular manner, service of that notice (or a similar notice required by this Lease) in the manner required by Section 35.10 shall replace and satisfy the statutory service-of-notice procedures, including those required by Code of Civil Procedure section 1162 or any similar or successor statute.

ARTICLE 19

Remedies Upon Breach

19.1 Landlord's Remedies. If Tenant fails to perform any of its affirmative duties or obligations, within 30 days after written notice (or in the case of any facts or circumstances that create an imminent risk of damage to the Property or the Premises or injury to, or death of, persons, without written notice), Landlord may, at its option, perform such duty or obligation on Tenant's behalf, including but not limited to the obtaining of reasonable required bonds, insurance policies, or governmental licenses, permits or approvals; provided, however, in the event Tenant begins to cure within such 30 day period, Landlord shall provide Tenant a reasonable opportunity to cure such default. Tenant shall pay to Landlord an amount equal to the costs and expenses incurred by Landlord in such performance upon receipt of an invoice, with interest thereon, at the Default Rate from the date of expenditure. Upon the occurrence of any breach or material default by Tenant under Section 18.1, in addition to other rights or remedies of Landlord at law or in equity, Landlord shall have the following remedies:

19.1.1 Landlord shall have the remedy in Civil Code section 1951.4, which provides that, when a tenant has the right to sublet or assign (subject only to reasonable limitations), the landlord may continue the lease in effect after the tenant's breach and abandonment and recover Rent as it become due. Accordingly, if Landlord does not elect to terminate this Lease on account of any default by Tenant, Landlord may enforce all of Landlord's rights and remedies under this Lease, including the right to recover all Rent as it becomes due; and

19.1.2 Landlord, either as an alternative or subsequent to exercising the remedies set forth in Section 19.1.1, may terminate Tenant's right to possession of the Premises by and upon delivery to Tenant of written notice of termination. Landlord may then immediately reenter the Premises and take possession thereof pursuant to legal proceedings and remove all persons and property from the Premises; such property may be removed and stored in a public warehouse or elsewhere at the cost of and for the account of Tenant. No notice of termination shall be necessary in the event that Tenant has abandoned the Premises. In the event that Landlord elects to terminate Tenant's right of possession, Landlord may recover the following:

19.1.2.1. The worth at the time of the award of the unpaid rent which had been earned at the time of termination. "Worth at the time of award" shall be computed by allowing interest at the Default Rate from the first day the breach occurs;

19.1.2.2. The worth at the time of award of the amount by which the unpaid rent which would have been earned after termination until the time of award exceeds the amount of such rental loss that the Tenant proves could have been reasonably avoided. "Worth at the time of award" shall be determined by allowing interest at the Default Rate from the first day a breach occurs;

19.1.2.3. The worth at the time of award of the amount by which the unpaid rent for the balance of the term after the time of award exceeds the amount of such rental loss that the Tenant proves could be reasonably avoided. "Worth at the time of award" shall be computed by discounting such amount at the discount rate at the Federal Reserve Bank of San Francisco at the time of award plus 1%; and

19.1.2.4. Any other amount necessary to compensate Landlord for all the detriment proximately caused by Tenant's failure to perform its obligations under the Lease or which in the ordinary course of things would be likely to result therefrom including, but not limited to, commissions and expenses of reletting, attorneys' fees, costs of alterations and repairs, recording fees, filing fees and any other expenses customarily resulting from obtaining possession of leased premises and re-leasing.

19.2 Landlord Default. If Landlord fails to perform any of its obligations under this Lease, such failure materially interferes with the Tenant's use and operations within the Premises and Landlord fails to cure such default within twenty (20) days after written notice from Tenant specifying the nature of such default where such default could reasonably be cured within said twenty (20) day period, or fails to commence such cure within said twenty (20) day period and thereafter fails to continue with due diligence to prosecute such cure to completion where such default could not reasonably be cured with said twenty (20) day period, then (1) Tenant may proceed in equity or at law to compel Landlord to perform its obligation and/or to recover damages proximately caused by such failure to perform; and/or (2) Tenant may perform such obligations and have the right to be reimbursed for the sum it actually and reasonably expends in the performance thereof; and if Landlord does not reimburse Tenant therefore within thirty (30) days after written demand therefore from Tenant, Tenant shall have the right to withhold such sum from future Rent due hereunder until Tenant is reimbursed in full therefore; provided, however, that such right to withhold rent shall be limited to not more than one month's Base Monthly Rent in any twelve (12) month period. In the event the sum expended by Tenant exceeds one (1) month's Base Monthly Rent, Tenant by withholding such rent shall not be deemed to waive any of Tenant's rights to collect any excess proceeds pursuant to its remedies at law and/or pursue its remedies in equity. Notwithstanding the foregoing, Tenant shall have no right to terminate this Lease for any such default by Landlord.

ARTICLE 20

Damage or Destruction

20.1 Landlord's Obligation to Rebuild. If the Premises are damaged or destroyed, Landlord shall promptly and diligently repair the Premises unless it has the right to terminate this Lease as provided in Section 20.2 below and it elects to so terminate. For purposes of this Article 20, "Premises" shall include any real property and/or fixture improvements located within the Premises as of the Commencement Date.

20.2 Landlord's Right to Terminate. Landlord shall have the right to terminate this Lease following damage to or destruction of the Premises if any of the following occurs: (i) insurance proceeds together with additional amounts Tenant agrees to contribute are not confirmed to be available to Landlord, within 90 days following the date of damage, to pay 100% of the cost to fully repair the damaged Premises, excluding the deductible for which Tenant shall also be responsible; (ii) the Premises cannot, with reasonable diligence, be fully repaired by Landlord within 12 months after the date of the damage or destruction; (iii) the Premises cannot be safely repaired because of the presence of hazardous factors, including, but not limited to, earthquake faults, radiation, chemical waste and other similar dangers; (iv) the Premises are destroyed or damaged during the last 12 months of the Term; or (v) Tenant is in uncured material default under the terms of this Lease at the time of such damage or destruction.

20.3 Tenant's Right to Terminate. Tenant shall have the right to terminate this Lease following damage to or destruction of the Premises if any of the following occurs: (i) the Premises cannot, with reasonable diligence, be fully repaired by Landlord within 18 months after the date of the damage or

destruction; or (ii) the Premises are destroyed or damaged during the last 12 months of the Term.

If a party elects to terminate this Lease and has the right to so terminate, such party will give the other party written notice of its election to terminate within 30 days after it has knowledge of such damage or destruction, and this Lease will terminate 15 days after receipt of such notice. If this Lease is terminated pursuant to Section 20.2, Landlord shall, subject to the rights of its lender(s), be entitled to receive and retain all the insurance proceeds resulting from such damage, except for: (i) those proceeds payable under policies obtained by Tenant which specifically insure Tenant's personal property, trade fixtures and machinery, and (ii) that portion of the proceeds which are directly attributable to that portion of the real property and/ or fixture improvements located within the Premises and which were paid for by Tenant after the Commencement Date. If neither party elects to terminate the Lease, Landlord shall, promptly following the date of such damage or destruction and receipt of amounts required of Tenant pursuant to Section 20.2(i) above, commence the process of obtaining necessary permits and approvals, and shall diligently commence repair of the Premises as soon as practicable and thereafter prosecute the same diligently to completion, in which event this Lease will continue in full force and effect.

20.4 Limited Obligation to Repair. Landlord's obligation, should it elect or be obligated to repair or rebuild, shall be limited to the Premises (including any real property and/or

fixture improvements existing on the Premises as of the Commencement Date), Building and common areas, and Tenant shall, at its expense, replace or fully repair all Tenant's personal property and any alterations installed by Tenant existing at the time of such damage or destruction. If the Premises are to be repaired in accordance with the foregoing, Landlord shall make available to Tenant any portion of insurance proceeds it receives which are allocable to the alterations constructed by Tenant pursuant to this Lease provided Tenant is not then in default.

20.5 Abatement of Rent. Rent shall be temporarily abated in proportion to the degree to which Tenant's use of the Premises is impaired and only to the extent of any proceeds received by Landlord from the rental abatement insurance described in Section 10.1 hereof, during any period when, by reason of such damage or destruction, Landlord and Tenant reasonably determines that there is substantial interference with Tenant's use of the Building. Such abatement shall commence upon such damage or destruction and end upon substantial completion by Landlord of the repair or reconstruction which Landlord is obligated or undertakes to do. Tenant shall not be entitled to any compensation or damages from Landlord for loss of the use of the Premises, damage to Tenant's personal property or any inconvenience occasioned by such damage, repair or restoration. Tenant hereby waives the provisions of Section 1932(2) and Section 1933(4) of the California Civil Code, and the provisions of any similar law hereinafter enacted.

20.6 Replacement Cost. The determination in good faith by Landlord of the estimated cost of repair of any damage, of the replacement cost, or of the time period required for repair shall be conclusive for purposes of this Section.

ARTICLE 21

Condemnation

21.1 Total Taking – Termination. If title to all of the Premises or so much thereof is taken for any public or quasi-public use under any statute or by right of eminent domain so that reconstruction of the Premises will not result in the Premises being reasonably suitable (as reasonably determined by Landlord and Tenant) for Tenant's continued occupancy for the uses and purposes permitted by this Lease, this Lease shall terminate as of the date possession of the Premises or part thereof be taken.

21.2 Partial Taking. If any part of the Premises is taken and the remaining part after Landlord makes repairs and alterations is reasonably suitable, as reasonably determined by Landlord and Tenant, for Tenant's continued occupancy for the purposes and uses permitted by this Lease, this Lease shall, as to the part so taken terminate as of the date that possession of such part of the Premises is taken and the Base Monthly Rental shall be reduced in the same proportion that the floor area of the portion of the Building so taken (less any addition thereto by reason of any reconstruction) bears to the original floor area of the Building. Landlord shall, at its sole cost and expense, make all necessary repairs or alterations to the Building so as to make the portion of the Building not taken a complete architectural unit. Such work shall not, however, exceed the scope of the work done by Landlord in originally constructing the Building. Base

Monthly Rental due and payable hereunder shall be temporarily abated during such restoration period in proportion to the degree to which Tenant's use of Premises is impaired. Each party hereby waives the provisions of Section 1265.130 of the California Code of Civil Procedure allowing either party to petition the Superior Court to terminate in the event of a partial taking of the Building or Premises. Notwithstanding the foregoing, if more than twenty-five percent (25%) of the square footage of the Building is taken or sold under such threat, Landlord may terminate this Lease as of the date that the condemning authority takes possession by delivery of written notice of such election within twenty (20) days after Landlord has been notified of the taking or, in the absence thereof, within twenty (20) days after the condemning authority shall have taken possession.

21.3 No Apportionment of Award. No award for any partial or entire taking shall be apportioned, it being agreed and understood that Landlord shall be entitled to the entire award for any partial or entire taking. Tenant assigns to Landlord its interest in any award which may be made in such taking or condemnation, together with any and all rights of Tenant arising in or to the same or any part thereof. Nothing contained herein shall be deemed to give Landlord any interest in or require Tenant to assign to Landlord any separate award made to Tenant for the taking of Tenant's personal property, trade fixtures or machinery for the interruption of Tenant's business, or its moving costs, or for the loss of its goodwill. Notwithstanding the foregoing, Tenant shall be entitled to receive (i) an award to the extent of that portion of the award which is directly attributable to the real property and/or fixture improvements located within the Premises paid for by Tenant after the Commencement Date, and (ii) 50% of the amount attributable to any excess of the market value of the Premises for the remainder of the Lease term over the present value as of the termination date of the fixed rent and management fee payable for the remainder of the Lease term. In addition, Tenant will have the right to make a separate claim in the condemnation proceeding for (a) the taking of the unamortized or undepreciated value of any leasehold improvements that Tenant has the right to remove at the end of the Lease Term and that Tenant elects not to remove, (b) loss of goodwill, and (c) any other amount in addition to the foregoing, so long as any such claim does not reduce the amount of the award payable to Landlord.

21.4 Temporary Taking. No temporary taking of the Premises shall terminate this Lease or give Tenant any right to any abatement of Rent, except to the extent covered by insurance proceeds payable to Landlord. Any award made to Tenant by reason of such temporary taking shall belong entirely to Tenant and Landlord shall not be entitled to share therein. Each party agrees to execute and deliver to the other all instruments that may be required to effectuate the provisions of this Section.

21.5 Sale Under Threat of Condemnation. A sale made in good faith by Landlord to any authority having the power of eminent domain, either under threat of condemnation or while condemnation proceedings are pending, shall be deemed a taking under the power of eminent domain for all purposes of this Section.

ARTICLE 22

Surrender of Lease

22.1 Surrender of Lease. The voluntary or other surrender of its interest in this Lease by Tenant or a mutual cancellation of this Lease shall not work a merger, and shall, at the election of Landlord, either terminate all or any existing subleases or subtenancies or operate as an assignment to Landlord of any or all of such subleases or subtenancies. Landlord shall exercise its election within 30 days of any such surrender or cancellation.

ARTICLE 23

Attorneys' Fees

23.1 Attorneys' Fees. If either party institutes or is made a party to any action or proceeding to enforce or interpret this Lease, the prevailing party in such action or proceeding shall be entitled to recover all costs and attorneys' fees incurred in connection with such action or proceeding, or any appeal or enforcement of such action or proceeding.

ARTICLE 24

Sale of the Premises by Landlord; ROFN

24.1 Sale of Premises. Notwithstanding any provisions of this Lease to the contrary, Landlord may assign, in whole or in part, Landlord's interest in this Lease and may sell all or part of the real estate of which the Premises are a part (the "Real Property"). Should Landlord elect to sell the Real Property, Landlord agrees to notify Tenant of its intent to do so. Landlord's willingness to notify Tenant is to be considered a courtesy notice only and not an offer to sell, or an obligation of any form on the part of Landlord to sell the Real Property to Tenant. This courtesy notice is not to be construed as an option, an offer to negotiate, a right of first refusal, or any other form of agreement that would obligate Landlord to pursue a sale of the Real Property to Tenant or in any manner prohibit Landlord from its rights to sell all or part of the Real Property as it chooses.

24.2 Right of First Negotiation. If at any time during the Term, Landlord decides to sell the Real Property, Landlord shall deliver to Tenant written notice thereof (the "Sale Notice"). Tenant may, within 10 business days after its receipt of the Sale Notice, elect by written notice to Landlord to negotiate with Landlord to purchase the Premises by delivering written notice to Landlord ("Tenant's Acceptance Notice"). Promptly thereafter, the parties shall negotiate in good faith the terms and conditions of such purchase and sale of the Premises. If the parties are unable to agree on mutually acceptable terms and conditions and execute a binding commitment for the purchase and sale of the Premises within 60 days after the date of the Sale Notice ("Offer Period"), Landlord shall be deemed to have satisfied its obligation to provide Tenant with the right of first negotiation provided for herein and may offer to sell the Premises in the open market. If Landlord fails to close on the sale of the Premises with a third party within 6 months from the expiration of the Offer Period (provided such period shall be extended as

necessary to close the transaction if Landlord and such third party are in escrow within the 6-month period), the right of first negotiation provided for herein shall again apply.

ARTICLE 25

Quiet Enjoyment

25.1. Quiet Enjoyment. If Tenant is not in breach under the covenants made in this Lease, Landlord covenants that Tenant shall have peaceful and quiet enjoyment of the Premises without hindrance on the part of Landlord. Landlord will defend Tenant in the peaceful and quiet enjoyment of the Premises against claims of all persons claiming through or under Landlord.

ARTICLE 26

Estoppel Certificates and Financial Statements

26.1 Tenant Estoppel Certificate. Tenant shall at any time during the term of this Lease, within 5 business days of written notice from Landlord, execute and deliver to Landlord a statement in writing certifying that this Lease is unmodified and in full force and effect or, if modified, stating the nature of such modification. Tenant's statement shall include other details requested by Landlord, such as the date to which rent and other charges are paid, Tenant's knowledge concerning any uncured defaults with respect to Landlord's obligations under this Lease and the nature of such defaults if they are claimed, and such other matters as Landlord may reasonably request. Any such statement may be relied upon conclusively by any purchaser or lender having an interest in the Premises. Tenant's failure to deliver such statements within such time shall be conclusive upon the Tenant that this Lease is in full force and effect, except as and to the extent any modification has been represented by Landlord, and that there are no uncured defaults in Landlord's performance, and that not more than 1 month's rent has been paid in advance.

26.2 Tenant Financial Statements. Within 120 days after the end of each fiscal year, Tenant shall provide Landlord, upon Landlord's written request, a copy of the audited financial statements that have been provided to the SEC or, in the event Tenant is no longer required to deliver such financial statements to the SEC, year-end financial statements, including balance sheets and income statements, reflecting Tenant's current financial condition for such fiscal year that have been audited by a nationally or regionally recognized firm of certified public accountants. In the event Tenant is no longer required to deliver such financial statements to the SEC, Tenant will represent and warrant at the time it provides any financial statements, records or information pursuant hereto that all financial statements, records and information furnished by Tenant to Landlord in connection with this Lease are true, correct and complete in all respects.

ARTICLE 27

Subordination and Attornment

27.1 Subordination of Lease. This Lease and Tenant's rights under this Lease are subject and subordinate to any Mortgage, ground lease, and to all renewals, modifications, consolidations, replacements, or extensions thereof, now or hereafter affecting the Premises. The provisions of this Section shall be self-operative, and no further instrument of subordination shall be required. In confirmation of such subordination, however, Tenant shall within ten days execute and deliver any instruments that Landlord, the holder of any Mortgage, or the Landlord of any ground lease may request to evidence such subordination. If Tenant fails to execute and deliver any such instruments, Tenant irrevocably constitutes and appoints Landlord as Tenant's special attorney-in-fact to execute and deliver such instruments.

27.2 Attornment to Lender. If the holder of any Mortgage, or the Landlord of any ground lease affecting the Premises, shall hereafter succeed, by foreclosure or otherwise, to the rights of Landlord under this Lease, Tenant shall attorn to and recognize such successor as Tenant's Landlord under this Lease, and shall promptly execute and deliver any instruments that may be necessary to evidence such attornment, and Tenant hereby irrevocably appoints Landlord as Tenant's special attorney in fact to execute and deliver such instruments on behalf of Tenant should Tenant refuse or fail to do so. Upon such attornment, this Lease shall continue in effect as a direct lease between such successor Landlord and Tenant upon and subject to all of the provisions of this Lease. Notwithstanding the foregoing, Tenant's agreement both to subordinate and to attorn, as set forth in this Article, is contingent upon Tenant's receipt of a nondisturbance agreement from the holder of any encumbrance placed against the Premises, in a recordable, commercially reasonable form, providing that in the event of any foreclosure, sale under a power of sale, ground or master lease termination, or transfer in lieu of any of the foregoing, or the exercise of any other remedy under any such encumbrance, but subject to reasonable exceptions: (i) Tenant's use, possession, and enjoyment of the Premises will not be disturbed and this Lease will continue in full force and effect so long as Tenant is not in default; and (ii) this Lease will automatically become a lease directly between any successor to Landlord's interest, as landlord, and Tenant, as if that successor were the landlord originally named in the lease.

ARTICLE 28

Holding Over

28.1 Holding Over. If Tenant should remain in possession of the Premises after the expiration of the term of this Lease without executing a new lease or after Landlord has declared a forfeiture by reason of a default by Tenant, the such holding over shall be construed as a tenancy from month to month, subject to all the conditions, provisions and obligations of this Lease insofar as they are applicable to a month to month tenancy, including the provisions of Article 3, except that the Base Monthly Rental shall be one hundred fifty percent (150%) of the Base Monthly Rental last due, payable monthly in advance. Notwithstanding the foregoing, if Tenant fails to vacate the Premises or Tenant fulfills less than all of its obligations hereunder at the end of the Lease Term, Tenant also shall be liable for all damages incurred by Landlord by

reason of the latter's inability to deliver possession of the Premises or any portion thereof to any other person.

ARTICLE 29

Mortgagee Protection

29.1 Mortgagee Protection. In the event of any default on the part of Landlord, Tenant agrees to give notice by registered or certified mail to any beneficiary of a deed of trust or mortgage covering the Premises whose address shall have been furnished to the Tenant and shall offer such beneficiary or mortgagee a reasonable opportunity to cure such default (such cure period not to exceed 90 days after receipt of such notice).

ARTICLE 30

Liability of Successors

30.1 Successor's Liability. The covenants and conditions herein contained shall, subject to the provisions as to assignment, apply to and bind the heir, successors, executors, administrators, and permitted assigns of all the parties hereto and all of the parties hereto shall be jointly and severally liable for the covenants contained herein.

ARTICLE 31

Easements

31.1. Easements. Landlord reserves the right, from time to time, to grant such easements, rights and dedications that Landlord deems necessary or desirable, and to cause the recordation of parcel maps and restrictions, so long as such easements, rights, dedications, maps and restrictions do not unreasonably interfere with the use of the Premises by Tenant. Tenant shall sign any documents or instruments to accomplish the foregoing upon request of

Landlord, and failure to do so shall constitute a material breach of this Lease. Tenant irrevocably appoints Landlord as Tenant's special attorney in fact to execute and deliver such documents or instructions on behalf of Tenant should Tenant refuse or fail to do so.

ARTICLE 32

Covenants, Conditions and Restrictions

32.1 Compliance with Covenants, Conditions and Restrictions. In addition to requirements imposed by law, the care of the Premises and conduct of business thereupon, among other things, are restricted or subject to heightened requirements pursuant to one or more recorded Covenant, Conditions and Restrictions ("CC&R's"). The terms of all applicable

CC&R's, in their entirety, are incorporated herein by this reference. Tenant has received a copy of all applicable CC&R's prior to its execution of this Lease, and such receipt is acknowledged hereby.

32.2 Associations. Tenant shall faithfully observe and comply with the provisions of all applicable CC&R's, and all modifications and additions which may from time to time be enacted pursuant to their terms. Tenant shall similarly observe and comply with all requests, demand and orders otherwise made by any governing associations created under the authority of the CC&R's (the "Associations"). Any violation by Tenant of the CC&R's or rightful orders of the Associations created thereby after written notice to Tenant shall be a default under this Lease, subject to the cure provisions of Section 18.1.3. However, Landlord will not be responsible to Tenant for the nonperformance of any provisions of such CC&R's by its tenants occupying neighboring properties, if any.

32.3 Association Fees. All payments, charge, dues, and assessments imposed under the authority of the CC&R's and the Associations ("Association Fees") shall be the sole responsibility of Tenant, who shall timely pay such Association Fees to Landlord as Additional Rent. Each payment shall be made promptly on demand throughout the term of this Lease and shall be paid without deduction or offset.

32.4 Faraday Court Owners Association. Landlord shall not vote in favor of any matter to be voted upon by the Faraday Court Owners Association that if adopted would materially alter, reduce or adversely affect any of Tenant's rights or materially enlarge Tenant's obligations under this Lease. Landlord will promptly copy Tenant on communications from the Faraday Court Owners Association that relate to the Premises and the common areas.

ARTICLE 33

Quitclaim Deed

33.1 Quitclaim Deed. Tenant shall execute and deliver to Landlord on the expiration date or earlier termination of this Lease, promptly on Landlord's request, a quitclaim deed to the Premises, in recordable form, designating Landlord as transferee.

ARTICLE 34

Hazardous Materials

34.1 Definitions:

34.1.1 Hazardous Materials Laws. "Hazardous Materials Laws" means any and all federal, state or local laws, ordinances, rules, decrees, orders, regulations or court decisions relating to hazardous substances, hazardous materials, hazardous waste, toxic substances,

environmental conditions on, under or about the Premises, or soil and ground water conditions, including, but not limited to, California Labor Code Section 6382, California Health and Safety Code Section 25249.5, et seq., any amendments to and any regulations promulgated pursuant to the foregoing, and any similar federal, state or local laws, ordinances, rules, decrees, orders or regulations.

34.1.2 Hazardous Materials. "Hazardous Materials" means any chemical, compound, substance or other material, including, without limitation, gasoline, diesel, aviation fuels, lubricating oils, solvents and chemicals, that: (i) is defined as a hazardous substance, hazardous material, hazardous waste or toxic substance under any Hazardous Material Law; (ii) is controlled or governed by any Hazardous Materials Law, or gives rise to any reporting, notice or publication requirements thereunder, or gives rise to any liability, responsibility or duty on the part of Tenant or County with respect to any third person thereunder; or (iii) is a flammable or explosive material, asbestos, radioactive material, nuclear medicine material, drug, vaccine, bacterial, virus, hazardous waste, toxic substance, or related injurious or potentially injurious material (by itself or in combination with other materials).

34.2 Tenant's Obligations

34.2.1 Compliance with Laws. Tenant shall strictly comply with, and shall maintain the Premises in compliance with, all Hazardous Materials Laws. Tenant shall obtain and maintain in full force and effect all permits, licenses and other governmental approvals required for Tenant's operations on the Premises under any Hazardous Materials Laws and shall comply with all terms and conditions thereof. At Landlord's request, Tenant shall deliver copies of, or allow Landlord to inspect, all such permits, licenses and approvals. Tenant shall perform any monitoring, investigation, clean-up, removal, detoxification, preparation of closure or other required plans and any other remedial work (collectively, "Remedial Work') required as a result of any release or discharge of Hazardous Materials from the Premises or any violation of Hazardous Materials Laws caused by Tenant or any Subtenant of Tenant or their respective agents, contractors, employees, licensees or invitees (but not by Landlord or Landlord's Agents). Landlord shall have the right to intervene in any governmental action or proceeding involving any Remedial Work, and to approve performance of the work, in order to protect Landlord interests. Tenant

shall be solely responsible for paying all fines, damages and penalties imposed by any governmental agency resulting from Tenant's violation of any Hazardous Materials Laws.

34.2.2 Compliance with Insurance Requirements. Tenant shall comply with the requirements of Tenant's insurers regarding Hazardous Materials and with such insurers' recommendations based upon prudent industry practices regarding management of Hazardous Materials.

34.2.3 Notice; Reporting. Tenant shall notify Landlord in writing immediately after any of the following: (a) Tenant has knowledge, or has reasonable cause to believe, that any Hazardous Material has been released or discharged under or about the Premises, whether or not the Hazardous Material is in quantities that would require reporting to a public agency; (b) Tenant receives any order of a governmental agency requiring any Remedial Work pursuant to any Hazardous Materials Laws; (c) Tenant receives any warning, notice of inspection, notice of violation or alleged violation, or Tenant receives notice or knowledge of any proceeding,

investigation of enforcement action, pursuant to any Hazardous Materials Laws; or (d) Tenant receives written notice of any claims made by any third party against Tenant or the Premises relating to any loss or injury resulting from Hazardous Materials. Tenant shall deliver to Landlord copies of all test results, reports and business management plans required to be filed with any government agency pursuant to any Hazardous Materials Laws.

34.2.4 Entry and Inspection; Cure. Landlord and its agents, employees and contractors, shall have the right to enter the Premises at all reasonable times to inspect the Premises and Tenant's compliance with the terms and conditions of this Section 34, or to conduct investigations and tests. No prior notice to Tenant shall be required in the event of any emergency, or if Landlord has reasonable cause to believe that violations by Tenant of this Section 34 have occurred, or if Tenant consents at the time of entry. In all other cases, Landlord shall give at least 48 hours' prior written notice to Tenant. Landlord shall have the right, but not the obligation, to remedy any violation by Tenant of the provisions of this Section 34, or to perform any Remedial Work necessitated as a result of any discharge by Tenant of Hazardous Materials on the Premises. Tenant shall pay, upon demand, all costs incurred by Landlord in remedying such violations or performing all Remedial Work necessitated by the acts or omissions of Tenant and/or its agents or employees, plus interest thereon at the rate of 10 percent per annum from the date of demand until the date paid by the Tenant.

34.2.5 Termination/Expiration. Upon termination or expiration of this Lease, Tenant shall, at Tenant's cost, remove any equipment, improvements or storage facilities utilized in connection with any Hazardous Materials and shall clean up, detoxify, repair and otherwise restore the Premises to a condition in compliance with applicable laws governing Hazardous Materials, to the extent such condition is caused by Tenant or any Subtenant of Tenant or their respective agents, contractors, employees, licensees or invitees. Upon termination or expiration of this Lease, Tenant shall permit Landlord and Landlord's Agents to enter the Premises upon giving Tenant a 24 hour written notice for the purposes of inspecting, at Tenant's cost, the environmental condition of the Premises, including an audit of any Hazardous Materials that are located on the Premises; provided, however, Landlord shall be responsible for the cost of such inspection in the event such inspection determines that the Premises are in material compliance with this Lease.

34.2.6 Indemnification. Tenant shall indemnify, protect, defend and hold Landlord (and its employees and agents) harmless from and against any and all claims, costs, expenses, suits, judgments, actions, investigations, proceedings and liabilities arising out of or in connection with any breach of any provision of this Lease to the extent arising out of the use, generation, storage, release, disposal or transportation of Hazardous Materials by Tenant or any Subtenant, or their respective agents, contractors or employees upon the Premises (but not by Landlord or Landlord's Agents), on, under or about the Premises during the Term, including, but not limited to, all foreseeable and unforeseeable consequential damages and the cost of any Remedial Work, but excepting any loss or injury resulting from the breach of the Lease by Landlord or the gross negligence or willful misconduct of Landlord or Landlord's Agents. Neither the consent by Landlord to the use, generation, storage, release, disposal or transportation of Hazardous Materials, nor strict compliance with all Hazardous Materials Laws, shall excuse Tenant from Tenant's indemnification obligations pursuant to this Section 34.2.6.

The foregoing indemnity shall be in addition to and not a limitation of the indemnification provisions of Section 9 of this Lease. Tenant's obligations pursuant to this Section 34.2.6 shall survive the termination or expiration of the Lease. The procedures set forth in Section 9.2 also will apply to this Section.

34.2.7 Default. The release or discharge of any Hazardous Material or violation of any Hazardous Materials Law by Tenant or any Subtenant of Tenant shall be a material default by Tenant under the Lease, subject to the cure provisions set forth in 18.1.3. In addition to or in lieu of the remedies available under the Lease as a result of such default, Landlord shall have the right, without terminating the Lease, to require Tenant to suspend its operations and activities on the Premises until Landlord is satisfied that appropriate Remedial Work has been or is being adequately performed; Landlord's election of this remedy shall not constitute a waiver of Landlord's right thereafter to declare a default and pursue other remedies set forth in the Lease.

ARTICLE 35

Miscellaneous

35.1 Gender. Whenever the singular number is used in this Lease, the same shall include the plural, and the masculine gender shall include the feminine and neuter genders, and the word "person" shall include corporation, firm, or association, when required by the context.

35.2 Headings. The headings or title to the paragraphs of this Lease are for convenience only and do not in any way define, limit or construe the contents of such paragraphs.

35.3 Integration. This instrument contains all of the agreements and conditions made between the parties with respect to the hiring of the Premises and may not be modified orally or in any other manner other than by a written instrument signed by all the parties to this Lease.

35.4 Choice of Laws. The laws of the State of California as applied to contracts entered into between citizens of the State of California and to be performed within the State of California shall govern the validity, performance and enforcement of this Lease.

35.5 Severability. If any provision of this Lease is determined to be void by any court of competent jurisdiction, such determination shall not affect any other provisions of this Lease and such other provisions shall remain in full force and effect. If any provision of this Lease is capable of two constructions, one which would render the provision void and one which would render the provision valid, the provision shall be interpreted in the manner which would render it valid.

35.6 Amendment for Financing. Upon written request of Landlord, Tenant agrees to execute any lease amendments not materially altering the terms of this Lease, if required by the first mortgagee or beneficiary of a deed of trust encumbering real property of which the Premises

constitute a part ("Mortgagee") incident to the financing of the real property of which the Premises constitute a part. Any change affecting the amount or timing of the consideration to be paid by Tenant or modifying the term of this Lease shall be deemed as materially alter the terms hereof.

35.7 Payments. Except as may otherwise be expressly stated, each payment required to be made by Tenant shall be in addition to and not in substitution for other payments to be made by Tenant.

35.8 Time of Essence. Time is of the essence in this Lease.

35.9 Force Majeure. Any prevention, delay or stoppage due to strikes, lockouts, labor disputes, acts of God, inability to obtain labor or materials or reasonable substitutes thereof, governmental restrictions, regulations, or controls, enemy or hostile governmental action, civil commotion, fire or other casualty, and other causes beyond the reasonable control of the party obligated to perform, shall excuse the performance by such party for a period equal to that resulting from such prevention, delay or stoppage, except those obligations of Tenant to make payment for rental and other charges pursuant to the terms of this Lease.

35.10. Notices. All notices to be given by one party to the other under this Lease shall be in writing, mailed or delivered to the other party at the following addresses:

To Landlord:
BMR-2282 Faraday Avenue LLC
Attn: General Counsel
17140 Bernardo Center Drive, Suite 222
San Diego, California 92128
Phone: (858) 485-9840 Fax: (858) 485-9843

To Tenant:
Isis Pharmaceuticals, Inc.
Attn: Patricia Lowenstam
1896 Rutherford Road
Carlsbad, California 92008
Phone: (760) 931-9200 Fax: (760) 918-3599

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

Mailed notices shall be sent by United States Postal Service, certified or registered mail, postage prepaid and shall be deemed to have been given on the date of posting in the United States Postal Service.

Either party may, with proper notice, at any time designate a different address to which notices shall be sent.

35.11. Brokers. Landlord and Tenant each represents to the other that it has had no dealings with any real estate broker or agent in connection with the negotiation and/or execution of this Lease except as follows: CB Richard Ellis, Inc. and agree to indemnify and defend the other against all liability, costs, expenses and charges arising from any claims that may be made against them by any real estate broker, agent, finder, or other person, alleging to have acted on behalf of Landlord or Tenant.

35.12. Confidentiality. During the course of this Lease the Parties may exchange certain financial statements, accounting records and other documents that are clearly stamped "confidential" ("Confidential Information"). Landlord and Tenant hereby acknowledge and agree that the Confidential Information of each Party is to be kept strictly confidential. Accordingly, except as may be required by law or court order, neither Landlord nor Tenant will, 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 of the other party's Confidential Information to any person or entity other than such party's prospective lenders and purchasers of the Real Property and 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 35.12. The obligations of this Section 35.12 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; or (d) 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. Notwithstanding the foregoing, Landlord and Tenant may disclose on a confidential basis such information to such party's accountants, attorneys and other professional advisors in connection with the transactions contemplated by this Agreement.

ARTICLE 36

OPTION TO EXTEND

36.1 Options To Extend. Tenant shall have the option to extend the term of this Lease for two, five year periods, subject to the following provisions:

36.1.1 Tenant shall have no right to exercise an option: (i) during the period commencing with the giving of any notice of default and continuing until said default is cured, (ii) during the period of time any Rent is unpaid, or (iii) in the event that Landlord has given three or more notices of separate monetary or material non-monetary defaults, whether or not the defaults are cured, during the 12 months immediately preceding the exercise of the option.

36.1.2 The period of time within which an option may be exercised shall not be extended or enlarged by reason of Tenant's inability to exercise an option because of paragraph 36.1.1.

36.1.3 An option shall terminate and be of no further force or effect, notwithstanding Tenant's due and timely exercise of the option, if, after such exercise and prior to the commencement of the extended term, (i) Tenant fails to pay Rent for a period of 30 days after such Rent becomes due, or (ii) if Tenant commits a default under this Lease and such default is continuing after the expiration of the applicable cure periods set forth in Section 18.1.

36.1.4 Tenant shall exercise the option by delivery of written notice to Landlord not less than 12 months prior to the expiration of the initial term and, if exercised, the first option period, of this Lease. If said notice is not delivered within said time period(s), this option shall terminate.

36.2 Rent –Option.

36.2.1 Rent - - First Option. The Base Monthly Rental payable by Tenant during the first option period shall be the greater of: (a) 95% of the fair market rent for the Premises at the commencement date of such option period, and (b) the Base Monthly Rental as increased by an amount equal to 2.5% of the Base Monthly Rental for the preceding year. The Base Monthly Rental payable by Tenant would continue to be increased as of the expiration of every other year (biennially) of the option period commencing on the second anniversary of the commencement of such option period (i.e., the second anniversary of the commencement of the option period and the fourth anniversary of the commencement of the option period) by an amount equal to 5% of the Base Monthly Rental for the preceding year.

36.2.2 Rent – Second Option. The Base Monthly Rental payable by Tenant during the first year of the second option period shall be the greater of: (a) 95% of the fair market rent for the Premises at the commencement date of such option period, and (b) the Base Monthly Rental as increased by an amount equal to 2.5% of the Base Monthly Rental for the preceding year. The Base Monthly Rental payable by Tenant would continue to be increased as of the expiration of every other year (biennially) of the option period commencing on the second anniversary of the commencement of such option period (i.e., the second anniversary of the commencement of the option period and the fourth anniversary of the commencement of the option period) by an amount equal to 5% of the Base Monthly Rental for the preceding year.

36.2.3 Fair Market Rent. If Landlord and Tenant cannot agree on the fair market rent of the Premises for the extension period within 30 days after the Tenant has notified Landlord of Tenant's exercise of the option, Landlord and Tenant shall each select, within 15 days of such notification, an appraiser who must be a qualified MAI appraiser with at least 5 years experience appraising commercial properties to determine said fair market rental value. If one party fails to so designate an appraiser within the time required, the determination of fair market rental value of the one appraiser who has been designated by the other party within the time required shall be binding on both parties. The appraisers shall submit their determinations of fair market rental value to both parties within 30 days after their selection. If the difference between the two determinations is 10% or less of the higher appraisal, then the average between the determinations shall be the fair market rental value of the Premises. If said difference is greater than 10%, then the two appraisers shall within 15 days of the date the second determination is submitted to the parties designate a third appraiser who must also be a qualified

MAI appraiser. The sole responsibility of the third appraiser will be to determine which of the determinations made by the first two appraisers is most accurate. The third appraiser shall have no right to propose a middle ground or any modification of either of the determinations made by the first two appraisers. The third appraiser's choice shall be submitted to the parties within 20 days after his or her selection. Such determination shall bind both of the parties and shall establish the fair market rental value of the Premises. Each party shall pay equal shares of the fees and expenses of the third appraiser. Fair market rent for the purposes of this Lease shall mean the then prevailing rent for premises comparable in size, quality and location to the demised Premises, leased on terms comparable to the terms contained in this Lease.

36.2.4 Memorandum of Lease. Except as set forth in this Section 36.2.4, Tenant shall neither execute nor record a memorandum of this Lease. Tenant shall execute, acknowledge and deliver at any time after the date of this Lease, at the request of Landlord, a "memorandum of lease" suitable for recording. Landlord may record such a memorandum of lease.

36.2.5 Absolute Net Lease. This Lease shall be deemed and construed to be an "absolute net lease" and, except as herein expressly provided, the Landlord shall receive all payments required to be made by Tenant, free from all charges, assessments, impositions, expenses, deductions of any and every kind or nature whatsoever. Except as otherwise expressly provided in this Lease, Landlord shall not be required to furnish any services or facilities or to make any repairs, replacements, or alterations of any kind in or on the Premises. Tenant shall receive all invoices and bills relative to the Premises and, except as otherwise provided herein, shall pay for all expenses directly to the person or company submitting a bill without first having to forward payment for the expenses to Landlord. Tenant shall at Tenant's sole cost and expense be responsible for the management of the Premises, shall maintain the landscaping, parking lot and shall make all additional repairs and alterations as required to maintain the property in first class condition.

36.2.6 Waiver of Jury Trial. The parties hereby waive their respective rights to trial by jury in any action or proceeding invlving the Premises or arising out of this Agreement.

36.2.7 Americans with Disabilities Act. Since compliance with the Americans with Disabilities Act (ADA) is dependent on Tenant's specific use of the Premises, Landlord makes no warranty or representation as to whether or not the Premises comply with the ADA or any similar

legislation. In the event that Tenant's use of the Premises requires modifications or additions to the Premises in order to be in ADA compliance, subject to Section 11.3, Tenant agrees to make any such necessary modifications and/or additions at Tenant's expense.

[Signature Page Follows]

IN WITNESS WHEREOF, Landlord and Tenant have executed this Lease as of the day and year set forth at the beginning hereof.

LANDLORD:

BMR-2282 FARADAY AVENUE LLC,
a Delaware limited liability company

By: BioMed Realty, L.P.,
a Maryland limited partnership,
its Member

/s/ Gary A. Kreitzer
Name: Gary A. Kreitzer
Title: Executive Vice President

TENANT:

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall
B. Lynne Parshall,

[FARADAY LEASE SIGNATURE PAGE]

Schedule 3.4

OPERATING EXPENSE EXCLUSIONS

Notwithstanding anything contained in the Lease, the following are specifically excluded from property operating costs and Tenant shall have no obligation to pay directly or reimburse Landlord for all or any portion of the following except to the extent any of the following are caused by the actions or inactions of Tenant, or result from the failure of Tenant to comply with the terms of this Lease:

(i) costs incurred because Landlord actually violated the terms and conditions of this Lease or any other lease for premises within the Building, if any;

(ii) legal and auditing fees (other than those fees reasonably incurred in connection with the maintenance and operation of all or any portion the Building), leasing commissions, advertising expenses, and other costs incurred in connection with the original leasing of the Real Property or future re-leasing of any portion of the Building;

(iii) depreciation of the Building or any other improvements situated within the project of which the Buildings are a part;

(iv) any items for which Landlord is actually reimbursed by insurance or by direct reimbursement by Tenant or any other party;

(v) costs of repairs or other work necessitated by fire, windstorm or other casualty (excluding any deductibles) and/or costs of repair or other work necessitated by the exercise of the right of eminent domain to the extent insurance proceeds or a condemnation award, as applicable, is actually received by Landlord for such purposes;

(vi) other than any interest charges for capital improvements referred to in the Lease, any interest or payments on any financing for the Building, interest and penalties incurred as a result of Landlord's late payment of any invoice, and any bad debt loss, rent loss or reserves for same;

(vii) overhead and profit increment paid to Landlord or to subsidiaries or affiliates of Landlord for goods and/or services in the project to the extent the same exceeds the costs of such by unaffiliated third parties on a competitive basis; or any costs included in property operating expenses representing an amount paid to a person, firm, corporation or other entity related to Landlord which is in excess of the amount which would have been paid in the absence of such relationship; and

(viii) costs incurred in the investigation and/or remediation of hazardous materials which either existed on the Real Property on the Commencement Date or were brought onto the Real Property by Landlord, its agents, employee or contractors, *except* those costs caused by Tenant or Tenant's Agents whether before or after the Commencement Date.

RESTATED ISIS PHARMACEUTICALS, INC.
10B5-1 TRADING PLAN

This 10b5-1 Trading Plan, (the "Trading Plan"), between **ISIS PHARMACEUTICALS, INC.** ("Isis") and **HORWITZ & ASSOCIATES, INC** ("Broker"), is entered into effective September 30, 2005 (the "Effective Date"). Capitalized terms not otherwise defined herein will have the meanings given to them in Exhibit A attached hereto.

Recitals.

(a) This Trading Plan is entered into between Isis and Broker for the purpose of establishing a trading plan that complies with the requirements of Rule 10b5-1(c) under the Exchange Act.

(b) The purpose of this Trading Plan is to provide a mechanism by which eligible Sellers can orderly dispose of a portion of each Seller's holdings of Stock, including Stock that such Seller has the right to acquire under the Options.

(c) Isis and Broker hereby agree as follows:

Appointment. Isis hereby appoints and authorizes Broker to sell shares of Stock pursuant to the terms and conditions set forth below and in the applicable Sellers Plan. Subject to the terms and conditions set forth below, Broker hereby accepts such appointment.

Sellers Plans. Each Seller may establish up to three individual Sellers Plans with Broker in any Sales Period. In connection with such Sellers Plans, each Seller will establish an account at Broker in the name of and for the benefit of Seller (the "Plan Account"). Sales under each Sellers Plan cannot begin until the Broker receives (i) the Plan Shares, to the extent such Plan Shares are currently owned by Seller, (ii) a properly executed Seller Representation Letter and (iii) a properly completed and executed Sellers Plan, including an acknowledgment by Isis.

Obligations of Broker. With respect to each Sellers Plan, Broker will have the following obligations:

(a) Broker will sell the Plans Shares for the account of each Seller according to the terms of the Seller's Sellers Plan.

(b) Broker will not sell any Stock when broker is in possession of any material nonpublic information concerning Isis or its securities.

(c) Once a Sellers Plan becomes effective, Broker will not allow Seller to exercise, any influence over how, when or whether to effect sales of Stock pursuant to the Sellers Plan.

(d) Broker will withdraw Stock from Seller's Plan Account in order to effect sales of Stock under Seller's Sellers Plan. Broker will exercise Options to effect such sales according to the Seller's Option Priority Guidelines.

(e) Broker will deliver the proceeds from each sale of unrestricted Stock effected under a Sellers Plan to Seller's Account on a normal three-day settlement basis less any commission, commission equivalent, mark-up or differential and other expenses of sale to be paid to Broker. With respect to each sale of restricted Stock, Broker will deliver the net proceeds from such sales as soon as reasonably practicable.

(f) Broker will, in connection with the exercise of Options, remit to Isis the exercise price thereof along with such amounts as may be necessary to satisfy withholding obligations. These amounts will be deducted from the proceeds of the sale of the Stock.

(g) To the extent that any Stock remains in the Plan Account upon termination of the Sellers Plan, Broker agrees to return such Stock promptly to the Seller.

(h) Broker agrees to conduct all sales pursuant to each Sales Plan in accordance with the manner of sale requirement of Rule 144 of the Securities Act and in no event will Broker effect any sale if such sale would exceed the then-applicable amount limitation under Rule 144 or will violate the "short-swing profit" provisions of Section 16 of the Exchange Act. Broker will file Forms 144 on behalf of Seller as required by applicable law.

(i) Promptly after each Sale, Broker will advise Seller in writing as to the number of shares of Stock sold, the date of each sale and the sales price.

(j) Broker will suspend or terminate a Sellers Plan and cancel any pending sale upon notice from Isis of a Suspension Event (such notice to specify termination or suspension of the Sellers Plan). In the event of a suspension, Broker will cancel any open orders for sales of Plan Shares and will cease placing orders for Sales of Plan Shares under the Sellers Plan until Broker receives written notice from Isis stating that the relevant Suspension Event is no longer in effect. Upon Broker's receipt of notice from Isis, Broker may resume placing orders for sales of the Plan Shares in accordance with the terms and conditions of this Trading Plan and the applicable Sellers Plan; *provided*, *however*, that Broker will not reinstate any orders cancelled due to a suspension and will not place any orders that would have been placed during the suspension.

(k) Broker will not sell more than an aggregate of 30,000 shares on any single Trading Day for any individual Seller under all the Sellers Plans established by such Seller. Notwithstanding the foregoing, Broker may sell more than this specified limit if (i) such sale is reasonably necessary to facilitate the exercise of Options that will expire within three Trading Days of such sale and (ii) the Company's Chief Financial Officer has authorized such a trade according to the notice provisions below.

(l) Unless a Seller's Sellers Plan explicitly instructs Broker to do otherwise, if Broker exercises an option because such Option was about to expire, Broker must sell the shares of Stock issued upon the exercise of such Option within 5 Trading Days of exercise at the then

prevailing market price for the Stock, regardless of the Minimum Sales Prices set forth in the applicable Sellers Plan.

Termination; Amendment.

(a) Trading Plan. This Trading Plan may be Terminated by Isis at any time upon written notice to Broker. The parties hereto may amend this Trading Plan in writing by mutual written agreement.

(b) Voluntary Termination of Sellers Plan. Seller may terminate a Sellers Plan only during the last five Trading Days of a Sales Period by providing Broker and Isis advance written notice. The terminations will become effective on September 30 of the Sales Period in which proper termination notice was given.

(c) Automatic Termination of Sellers Plan. An applicable Sellers Plan will automatically terminate on any of the following dates: (i) the date Broker is required to terminate the Sellers Plan under Section 4(j) of this Trading Plan, (ii) the 90th day following the date Broker receives notice of the death of the Seller or of Seller's termination from Isis, (iii) the date Isis or any other entity publicly announces a tender or exchange offer with respect to the Stock or a merger or acquisition of Isis, or (iv) the date Broker receives notice of the commencement or impending commencement of any proceeding relating to or triggered by Seller's bankruptcy or insolvency.

(d) Termination For Breach. Isis may terminate a Sellers Plan immediately upon the breach of a representation or covenant contained in the applicable Seller's Seller Representation Letter.

(e) No Amendment of Sellers Plan. Seller may not amend a Sellers Plan.

General.

(f) The prices and share amounts set forth in this Trading Plan and in each Sellers Plan will be automatically adjusted on a proportionate basis to take into account any stock split, stock dividend or any change in the capitalization similarly affecting the Stock of the Isis that occurs during the Sales Period.

(g) This Trading Plan, including exhibits, constitutes the entire agreement between the parties with respect to this Trading Plan and supercedes any prior agreements or understandings between the parties with regard to the Trading Plan.

(h) Any notice required to be given under this Trading Plan or a Sellers Plan will be addressed to the relevant party at the address set forth below.

To Broker:

Horwitz & Associates, Inc
2511 Garden Road, Suite C-225
Monterey, CA 93940
Attn: Peter Albano
Fax: (831) 648-1951

Phone: (866) 648-8010

w/copy to:

Horwitz & Associates, Inc
630 Dundee Road
Northbrook, IL 60062
Attn: Executive office

To Isis:

Isis Pharmaceuticals, Inc.
1896 Rutherford Road
Carlsbad, CA 92008
Attn: Executive Vice President
Fax: 760-268-4922
Phone: 760-603-2460

with copies to:

Linda Powell
Fax: 760-918-3593

To Seller:

The contact information specified in the applicable Seller Representation Letter.

Notice will be deemed sufficiently given for all purposes upon the earlier of: (a) the date of actual receipt; (b) if mailed, three (3) calendar days after the date of postmark; (c) if delivered by overnight courier, the next business day such overnight courier regularly makes deliveries; or (d) if sent by facsimile, when the sender's facsimile system generates a message confirming successful transmission of the total number of pages of the notice unless, within one business day after the transmission, the recipient informs the sender that the recipient has not received the entire notice.

(i) This Trading Plan may be signed in counterparts, each of which will be an original, with the same effect as if the signatures thereto and hereto were upon the same instrument.

(j) If any provision of this Trading Plan is or becomes inconsistent with any applicable present or future law, rule or regulation, that provision will be deemed modified or, if necessary, rescinded in order to comply with the relevant law, rule or regulation. All other provisions of this Trading Plan will continue and remain in full force and effect.

(k) This Trading Plan and any Sellers Plan is not an employment contract and nothing in such plans will create in any way whatsoever any obligation on a Seller's part to continue in the employ of Isis, or of Isis to continue Seller's employment with Isis.

(l) In the event of any conflict between the provisions of a Sellers Plan and those of this Trading Plan, the provisions of this Trading Plan will control.

(m) The parties' rights and obligations under this Trading Plan will bind and inure to the benefit of their respective successors, heirs, executors, and administrators and permitted assigns.

IN WITNESS WHEREOF, the undersigned have entered into this Trading Plan as of the date first written above.

ISIS PHARMACEUTICALS, INC.

/s/ B. Lynne Parshall
B. Lynne Parshall
Executive Vice President

HORWITZ & ASSOCIATES, INC

/s/ Gerald A. Horwitz
Gerald A. Horwitz
Chief Executive Officer

EXHIBIT A
DEFINITIONS

"Daily Sales Amount" has the meaning set forth in the applicable Sellers Plan.

"Effective Date" means, with respect to a Sellers Plan, the date the Seller Representation Letter was executed by Seller and accepted by Broker.

"Exchange Act" means the Securities Exchange Act of 1934, as amended.

"Options" means the outstanding stock options issued by Isis listed in the applicable Sellers Plan.

"Option Priority Guidelines" has the meaning set forth in the applicable Sellers Plan.

"Minimum Sales Price" has the meaning set forth in the applicable Sellers Plan.

"Plan Shares" means (i) the Stock and (ii) the Stock issuable upon exercise of the Options, to be sold pursuant to the Sellers Plan.

"Rule 144" means Rule 144 under the Securities Act.

"Sales Period" The first Sales Period will begin on the effective date of this Trading Plan and will end on September 30, 2002. Thereafter, Sales Periods will begin every year on October 1 (beginning with October 1, 2002) and will end on September 30 of the following year until this Trading Plan or the applicable Sellers Plan is terminated.

"Sellers Plan" means a Sellers Plan in the form attached hereto as Exhibit B entered into between Broker and a Seller.

"Securities Act" means the Securities Act of 1933, as amended.

"Seller Representation Letter" is the seller representation letter, a form of which is attached hereto as Exhibit C.

"Seller" means Isis' executive officers, members of its Board of Directors and other individuals specified by Isis who participate in the Trading Plan and who have agreed to only sell Stock under the Trading Plan.

"Stock" means the common stock, $0.001 par value per share, of Isis.

"Suspension Event" means a legal, contractual or regulatory restriction that is applicable to Seller or Seller's affiliates that does not permit the execution of sales made under a Sellers Plan (other than any such restriction relating to Seller's possession or alleged possession of material nonpublic information about

Isis or its securities subsequent to the execution of the Sellers Plan), including, without limitation, (i) any restriction related to a merger or acquisition, (ii) a stock

offering requiring an affiliate lock-up, that would prohibit any sale pursuant to the Trading Plan, or (iii) a potential violation of Section 16 of the Exchange Act.

“Trading Day” means any day during the Sales Period that (i) the Nasdaq Stock Market is open for business and the Stock trades regularly on such day and (ii) Isis is open for business as a corporation.

EXHIBIT B

SELLERS PLAN

Effective Date:

Seller’s Name:

Seller’s Account Number:

Commissions:

Plan Shares:

shares of Stock owned by Seller; and

shares of Stock issuable upon the exercise of the Options listed on the last page of this Sellers Plan.

Option Priority Guidelines:

(Please Check Only One of The Following)

o Exercise first those Options with the earliest expiration date; or

o Exercise first those Options with the lowest exercise price.

(Please Check Only One of The Following)

o To complete sales under this Sellers Plan, Broker will sell the Plan Shares owned by Seller first, before exercising any Options (except if such Options are about to expire); or

o To complete sales under this Sellers Plan, Broker will sell the shares issuable upon exercise of the Options first, before selling the Plan Shares owned by Seller.

No Expiration of In-the-Money Options:

In the event that unexercised Options are about to expire, Broker will exercise such Options at its discretion during the last:

(Please Check Only One of The Following)

o 5 Trading Days prior to the expiration date of the Options

o 30 Trading Days prior to the expiration date of the Options

o 60 Trading Days prior to the expiration date of the Options

o Trading Days prior to the expiration date of the Options

Broker will in no event exercise any Option if at the time of exercise the exercise price of the Option is equal to or higher than then current market price of the Stock.

Instructions:

During the Sales Period, Broker will sell the Daily Sales Amount, if any, for the account of Seller on each Trading Day under ordinary principles of best execution at the then-prevailing market price; provided that Broker will not sell any shares of Stock under a Sellers Plan at a price of less than the Minimum

Sales Price.

If, consistent with ordinary principles of best execution, Broker cannot sell the Daily Sales Amount on any Trading Day, then the amount of such shortfall may be sold as soon as practicable on the immediately succeeding Trading Day and on each subsequent Trading Day as is necessary to sell such shortfall consistent with the ordinary principals of best execution. If any shortfall exists after the close of trading on the last Trading Day prior to the termination of this Trading Plan or the applicable Sellers Plan, Broker's obligation and authorization to sell such shares will terminate.

Minimum Sales Price:

- o $ per share (before deducting any commission, commission equivalent, mark-up or differential and other expenses of sale); or
- o The greater of (i) the 20-day trailing average closing sale price of the Stock, as reported by Bloomberg (or, if such trailing average price is not reported by Bloomberg, the 20-day trailing average closing sale price as calculated by Broker, whose calculation shall be final and binding absent gross error), or (ii) $ per share (before deducting any commission, commission equivalent, mark-up or differential and other expenses of sale); or
- o For each number of shares listed on the table below, the Minimum Sales Price will be the price opposite such number of shares.

Number of Shares	Minimum Sales Price

Daily Sales Amount *(please check only one of the following)***:**

- o Broker will set the Daily Sales Amount in its sole discretion; or
- o shares of Stock; or
- o an amount of Stock resulting in aggregate proceeds (after deducting any commission, commission equivalent, mark-up or differential, other expenses of sale, exercise prices (if any), withholding taxes and other expenses of exercise) of $; or
- o shares of Stock, *except* if or more shares of Stock have been sold under this Sellers Plan within the days preceding the current Trading Day, then the Daily Sales Amount will be zero shares.

Reload Feature

- o On the first day of each Sales Period, unless this Sellers Plan is otherwise terminated, new shares of stock will be added as Plan Shares to this Sellers Plan equal to the greater of (i) the number of Plan Shares in the preceding Sales Period minus any shares not sold pursuant to the Sellers Plan during the preceding Sales Period or (ii) the number of shares of Stock subject to stock options held by Seller that will expire during the then current Sales Period. If necessary to reload the Plan Shares (as described above), the Options will be updated to add the earliest to expire stock options of the Seller until the Plan Shares have been reloaded. Notwithstanding the foregoing, Options will not be added to this Sellers Plan that will not vest within the then current Sales Period.

ESPP Shares

o If Seller purchases shares through the Isis Employee Stock Purchase Plan at any time during the Sales Period, the newly purchased shares will automatically become part of this Sellers Plan as Plan Shares and Broker will sell such shares according to the following instructions:

Other Instructions:

Options:

Option Number	Number of Shares	Exercise Price	Expiration Date

EXHIBIT C
SELLER REPRESENTATION LETTER
Seller Representation and Covenant Letter

Date:

Horwitz & Associates, Inc.
2511 Garden Road, Suite C-225
Monterey, CA 93940
Attn: Peter Albano

Dear Peter:

In consideration of your accepting orders to sell the Stock of Isis Pharmaceuticals, Inc. ("Isis") under the Isis Pharmaceuticals 10b5-1 Trading Plan (the "Trading Plan") and the Sellers Plan (as defined below), the Seller makes the representations and agrees to the covenants set forth below.

All capitalized terms that are not otherwise defined herein shall have the meanings ascribed to them in the Trading Plan. The terms of the Trading Plan are incorporated herein by reference. In the event of any conflict between the provisions of this letter and the Trading Plan, the provisions of the Trading Plan will control.

Seller hereby appoints and authorizes Broker to sell shares of Stock pursuant to the terms and conditions of the Trading Plan and the Sellers Plan attached hereto and incorporated herein by reference as Exhibit I (the "Sellers Plan"). Broker hereby accepts such appointment.

Seller Representations.

1. Sales of Stock under the Sellers Plan have been approved by an authorized representative of Isis.

2. As of the date hereof, Seller is not aware of any material nonpublic information concerning Isis or its securities. Seller is entering into the Sellers Plan in good faith and not as part of a plan or scheme to evade compliance with the federal securities laws.

3. The Stock to be sold under the Sellers Plan is owned free and clear by Seller (subject, in the case of shares underlying Options, only to the compliance by Seller with the exercise provisions of such options) and is not subject to any agreement granting any pledge, lien, mortgage, hypothecation, security interest, charge, option or encumbrance or any other limitation on disposition, other than those which may have been entered into between Seller and Broker or imposed by Rules 144 or 145 under the Securities Act.

4. Seller has had an opportunity to discuss the Sellers Plan with his or her own advisors as to the legal, tax, business, financial and related aspects of the Sellers Plan and has determined that the Sellers Plan meets the affirmative defense criteria set forth in Rule 10b5-1(c).

Seller has not relied upon Broker or Isis (or any person affiliated with Broker or Isis) in connection with, Seller's adoption and implementation of the Sellers Plan.

5. Seller acknowledges and agrees that, once the Sellers Plan becomes effective, Seller does not have, and shall not attempt to exercise, any influence over how, when or whether to effect sales of Stock pursuant to the Sellers Plan.

Seller Covenants.

1. While the Sellers Plan is in effect, Seller agrees not to (i) buy or sell any securities of Isis outside of the transactions contemplated by the Trading Plan and purchases pursuant to Isis' Employee Stock Purchase Plan, (ii) enter into or alter any corresponding or hedging transaction or position with respect to the Stock covered by the Sellers Plan (including, without limitation, with respect to any securities convertible or exchangeable into the Stock), and (iii) alter or deviate from the terms of the Sellers Plan.

2. Seller agrees to deliver to Broker the Plan Shares pursuant to the Sellers Plan to be placed into Seller's Plan Account prior to the commencement of sales under the Sellers Plan.

3. Seller agrees to make appropriate arrangements with Isis and its transfer agent and stock plan administrator to permit Broker to furnish notice to Isis of the exercise of the Options and to have underlying shares delivered to Broker as necessary to effect sales under the Sellers Plan. Seller hereby authorizes Broker to serve as Seller's agent and attorney-in-fact and, in accordance with the terms of the Sellers Plan, to exercise the Options. Seller agrees to complete, execute and deliver to Broker cashless exercise forms, in sufficient form to allow for the exercise of Options pursuant to the Sellers Plan at such times and in such numbers as Broker may reasonably request.

4. Seller will not, directly or indirectly, communicate any information relating to the Stock or Isis to any employee of Broker or its affiliates who is involved, directly or indirectly, in executing the Sellers Plan at any time while the Sellers Plan is in effect.

5. Seller agrees to notify Broker's compliance office by telephone or facsimile as soon as practicable if Seller becomes aware of the occurrence of any Suspension Event. Such notice will indicate the anticipated duration of the restriction, but will not include any other information about the nature of the restriction or its applicability to Seller and will not in any way communicate any material nonpublic information about Isis or its securities to Broker.

6. Seller understands and agrees that so long as it is an "affiliate" of Isis for purposes of Rule 144 under the Securities Act, all sales under the Plan will be in accordance with Rule 144. Seller agrees not to take any action that would cause Seller to aggregate sales under the Sellers Plan with sales of

other securities of the issuer pursuant to Rule 144, and not to take any action that would cause the sales under the Plan not to comply with Rule 144.

7. Seller agrees to complete, execute and deliver to Broker Forms 144 for the sales to be effected under the Sellers Plan at such times and in such numbers as Broker reasonably requests. The "Remarks" section of each Form 144 will state that the sale is being made

pursuant to a previously adopted plan intended to comply with Rule 10b5-1(c) and will indicate the date the Sellers Plan was adopted and that the representation is made as of such date.

8. Seller agrees to make all filings, if any, required under Sections 13(d), 13(g) and 16 of the Exchange Act in a timely manner, to the extent any such filings are applicable to Seller.

9. Seller agrees that Seller will at all times during the Sales Period, in connection with the performance of the Sellers Plan, comply with all applicable laws, including, without limitation, Section 16 of the Exchange Act and the rules and regulations promulgated thereunder.

10. Seller will notify Broker and Isis of any other purchase or sale transactions involving securities of Isis that are not contemplated by the Trading Plan.

Very truly yours,

_____

[name]
[address]
[telephone]
[fax]

Agreed:

Horwitz & Associates, Inc

By: _____

Its: _____

Acknowledged:

Isis Pharmaceuticals, Inc.

B. Lynne Parshall
Executive Vice President

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

SECOND AMENDED AND RESTATED COLLABORATION AGREEMENT

BETWEEN

ELI LILLY AND COMPANY

AND

ISIS PHARMACEUTICALS, INC.

August 5, 2005

SECOND AMENDED AND RESTATED COLLABORATION AGREEMENT

THIS SECOND AMENDED AND RESTATED COLLABORATION AGREEMENT (the ***"Agreement"***) executed on August 5, 2005 (the *"Second Restatement Execution Date"*) and effective as of August 25, 2005 (the ***"Second Restatement Date"***), by and between **ELI LILLY AND COMPANY**, a corporation organized and existing under the laws of Indiana and its Affiliates (together ***"Lilly"***), and **ISIS PHARMACEUTICALS, INC.,** a corporation organized and existing under the laws of Delaware (***"Isis"***).

RECITALS

A. Isis is engaged in the research and development of antisense oligonucleotides and has accumulated considerable knowledge in the field of antisense technology, including processes and techniques relating to the design, synthesis and research of antisense oligonucleotides for use in gene functionalization and target validation and as therapeutic products.

B. Lilly has expertise in the research, development, distribution and sale of prophylactic and therapeutic products for human use.

C. Lilly and Isis entered into a collaboration agreement (the ***"Original Agreement"***) effective as of the Effective Date to identify, characterize and/or develop antisense oligonucleotides that modulate the expression of biological molecules and to characterize the effect of such modulation to validate gene targets for drug discovery, including antisense drug discovery.

D. Lilly and Isis amended and restated the Original Agreement effective as of the Restatement Date (including all amendments thereto, the ***"Amended and Restated Agreement"***).

E. Lilly and Isis amended the Amended and Restated Agreement by agreement dated June 17, 2002.

F. Lilly and Isis extended the Oncology Term and further amended the Amended and Restated Agreement by agreement dated May 3, 2004 (the ***"May 3, 2004 Agreement"***).

G. Lilly and Isis now desire to extend the Collaboration Term with respect to the Antisense Drug Discovery Program and the drug discovery Target Validation Program, both in the Collaboration Therapeutic Area of oncology, and to amend and restate certain terms of the Amended and Restated Agreement.

AGREEMENT

NOW, THEREFORE, in consideration of the mutual covenants contained in this Agreement, the Parties agree as follows:

ARTICLE 1

DEFINITIONS; AMENDMENT AND RESTATEMENT

1.1 **Definitions.** Capitalized terms used in this Agreement, whether in the singular or plural, have the meanings set forth in Schedule 1.1 which is attached hereto and made part of this Agreement, or as otherwise specifically defined in this Agreement.

1.2 **Amendment and Restatement.** Effective as of the Second Restatement Date, this Agreement restates and supersedes the Original Agreement and the Amended and Restated Agreement as each has been amended through the Second Restatement Date. The terms and conditions of the Original Agreement shall apply for the period from the Effective Date until the Restatement Date unless otherwise provided by the Amended and Restated Agreement (and any amendment thereto) or this Second Amended and Restated Agreement. The terms and conditions of the Amended and Restated Agreement (and any amendment thereto) shall apply for the period from the Restatement Effective Date until the Second Restatement Date unless otherwise provided by this Second Amended and Restated Agreement.

ARTICLE 2

COLLABORATION OVERVIEW AND GOVERNANCE

2.1 **The Collaboration.** Lilly and Isis hereby agree to undertake the Collaboration during the Extended Collaboration Term under the terms and conditions set forth in this Agreement. The Collaboration shall consist of the Target Validation Program and the Antisense Drug Discovery Program during the Extended Collaboration Term as directed by the Collaborative Research Plan.

2.2 **[DELETED].**

2.3 **[DELETED].**

2.4 **[DELETED].**

2.5 **Governance - - Executive Committee.** The strategic direction and overall management of the Collaboration during the Extended Collaboration Term shall be the responsibility of the Executive Committee. The Executive Committee shall consist of the three (3) members from each Party listed in Schedule 2.5. The Executive Committee may name additional members to the Executive Committee from time to time so long as each Party has an equal number of members. Each Party will designate a member who will be the primary contact on the Executive Committee for that Party. The designated Lilly representative shall be responsible for scheduling the meeting of the Executive Committee for that purpose. Either

Party can change its representatives on the Executive Committee by written notice to the other Party.

2.5.1 **Executive Committee Meetings.** During the Extended Collaboration Term and for one (1) year thereafter the Executive Committee shall meet at least every three (3) months to review the research carried out under the Collaboration and to consider modifications to the strategy and goals of the Target Validation Program and the Antisense Drug Discovery Program. In addition, the Executive Committee may meet on an ad hoc basis. The Parties shall mutually agree upon the times and places for such meetings, alternating between Indianapolis, Indiana and Carlsbad, California, or such other location as members of the Executive Committee shall agree. Each Party shall bear its own costs associated with holding and attending such meetings. If mutually agreed by the Parties, such meetings may be held by videoconference or teleconference. An agenda shall be agreed upon by the Executive Committee members and be distributed to the Parties no less than one (1) week before any semiannual meeting. If a representative of a Party on the Executive Committee is unable to attend a meeting of the Executive Committee, such Party may designate an alternate to attend such meeting and vote on behalf of such missing representative. In addition, each Party may, at its discretion, invite nonvoting employees, consultants or advisors (which consultants and advisors shall be under an obligation of confidentiality no less stringent than those terms set forth herein) to attend any meeting of the Executive Committee. Minutes shall be kept of all Executive Committee meetings by the hosting Party and sent to all members of the Executive Committee for review and approval within seven (7) days after each meeting. Minutes shall be deemed approved unless any member of the Executive Committee objects to the accuracy of such minutes by providing written notice to the other members of the Executive Committee within ten (10) days of receipt of the minutes; provided, however, that in the event of any such objection by a Party that the Parties are unable to resolve, such minutes shall reflect such unresolved dispute.

2.5.2 **Executive Committee Responsibilities.** The Executive Committee shall have the following responsibilities:

(a) to review the Collaborative Research Plan from a strategic perspective;

(b) to review the progress and results of the Collaboration to ensure that the Parties are meeting their commitments for both human and financial support and are each fulfilling all of their respective contractual obligations;

(c) to attempt to resolve any disagreements between the Parties with respect to the research conducted under the Collaboration;

(d) to optimize the value of the intellectual property arising from the Collaboration.

(e) to review the Collaborative Research Plan from a scientific and operational perspective;

(f) to make changes to the portions of the Collaborative Research Plan relating to the Target Validation Program and the Antisense Drug Discovery Program as it deems necessary to accomplish the purpose of the Collaboration;

(g) to prioritize and monitor progress of antisense lead identification for the Target Validation Program and Drug Discovery Program; *provided, however,* that if there is a disagreement concerning the prioritization of a Validation Target, such disagreement shall be decided by Lilly;

(h) to review the qualifications of the Collaboration FTEs to ensure that the Parties are meeting the intent of the Collaborative Research Plan;

(i) to approve changes to the allocation of Collaboration Funds set forth in the Collaborative Research Plan between the Target Validation Program and the Antisense Drug Discovery Program;

(j) to review and approve the use of any Third Party in the Collaboration and expenses related thereto, including review and approval of any related Third Party contract;

(k) to review and monitor all results of the work performed under Collaboration, including scientific efforts of both Parties, and providing prioritization, oversight and direction regarding such work in accordance with the Collaborative Research Plan;

(l) to adopt and modify the Critical Success Factors related to a Collaboration Therapeutic Area either generally or specifically with respect to a Validation Target or a Drug Discovery Target as documented by approved Executive Committee minutes;

(m) to determine whether a Validation Target is an Accepted Validation Target or Rejected Validation Target or Abandoned Validation Target;

(n) to designate Drug Discovery Targets and Validation Targets; and

(o) to make a determination of whether a Drug Discovery ASO Compound meets the criteria for designation as a Development Candidate and making such designations.

2.5.3 **Executive Committee Decisions.** Decisions of the Executive Committee shall be made by unanimous vote, with each member having one (1) vote. No vote of the Executive Committee may be taken unless all members of the Executive Committee vote. If the Executive Committee is unable to reach a unanimous vote on any matter, then the matter shall be referred to [***].

2.5.4 **Executive Committee Quarterly Status Reports.** During the Extended Collaboration Term and upon expiration thereof the Executive Committee will prepare a quarterly status report that generally summarizes the research and development efforts conducted by each Party under the Collaboration during the two (2) previous Calendar Quarters. The report shall include, without limitation, a general summary of important events, progress on critical

success objectives, any milestones reached, personnel changes, learning points and other matters that the Executive Committee may deem appropriate. The Executive Committee shall establish goals and objectives for the Collaboration.

2.6 [DELETED].

2.6.1 **[DELETED]**.

2.6.2 **[DELETED]** .

2.6.3 **[DELETED]**.

2.7 [DELETED] ..

2.7.1 **[DELETED].**

2.7.2 **[DELETED].**

2.8 **Dissolution of the Committees.** Upon expiration of the Initial Collaboration Term all committees other than the Executive Committee shall dissolve. The Executive Committee shall cease having regular meetings twelve (12) months after expiration or termination of the Extended Collaboration Term but shall meet on an *ad hoc* basis for so long thereafter as is necessary

2.9 **Alliance Managers.** Each Party shall designate one (1) representative to coordinate the activities of the Parties under the Collaboration (the ***"Alliance Managers"***). The Alliance Managers are listed on ***Schedule 2.9***. The Alliance Managers' responsibilities shall include maintenance of a current list of Validation Targets (including Rejected Validation Targets and Accepted Validation Targets), Drug Discovery Targets and Reserved Targets, coordinating meetings of the Executive Committee and otherwise facilitating the activities of the Parties in the course of the Collaboration under this Agreement. Each Party may change its Alliance Manager by written notice to the other Party.

ARTICLE 3

THE COLLABORATION

3.1 **Collaboration Staffing.** Isis and Lilly employees involved in the Collaboration will conduct the research activities in a manner as required to maintain progress on the objectives of the Collaboration as set forth herein and in the Collaborative Research Plan. To achieve these objectives, Isis and Lilly will assign qualified employees as set forth in the Collaborative Research Plan. During the Extended Collaboration Term, Isis shall commit the number of Isis Collaboration FTEs to the Antisense Drug Discovery Program as specified in the Collaborative Research Plan. By unanimous decision of the Executive Committee the number of FTEs committed to the Collaboration may be increased or decreased from the levels specified in the Collaborative Research Plan. Lilly shall apply an appropriate number of FTEs to achieve the objectives set out for Lilly in the Collaborative Research Plan. FTEs applied by Lilly to carry

out the work set forth in the Collaborative Research Plan shall not be considered to be Lilly Collaboration FTEs and such FTEs shall not be reimbursed with Collaboration Funds.

3.2 **Subcontracting.** Except to the extent approved by the Executive Committee or as otherwise expressly permitted in the Collaborative Research Plan, neither Party shall subcontract to a Third Party any portion of the activities assigned to it under the Collaborative Research Plan, other than through the use of on site contract employees. To the extent such subcontracting is approved, prior to engaging a Third Party, Isis or Lilly, as applicable, shall first obtain a written agreement with such Third Party containing appropriate confidentiality and non-use provisions as determined by the Parties and written assignments to Isis or Lilly, as applicable, of all Patent Rights and Know-How that such subcontractors may develop by reason of work performed under such contract. Moreover, any Third Party subcontractor shall be required to perform its services in accordance with any applicable generally accepted professional standards as well as standards designated by the Executive Committee (if any) and with any applicable codes, rules and regulations.

3.3 **Staff Availability.** Each Party shall make its employees, and permitted subcontractors engaged in the Collaboration reasonably available upon reasonable notice during normal business hours at their respective places of employment to consult with the other Party on issues arising during Collaboration and in connection with any request from any regulatory agency, including those relating to regulatory, scientific, and technical issues.

3.4 **Facility Visits.** Representatives of Lilly and Isis may, upon reasonable notice during normal business hours, (a) visit the facilities where the Collaboration is being conducted, including by Third Parties, (b) consult informally, during such visits and by telephone, with personnel for the other Party performing work on the Collaboration, and (c) with the other Party's prior approval, which approval shall not be unreasonably withheld, visit the sites of any experiments or tests being conducted by, or on behalf of, such other Party in connection with the Collaboration. On such visits, an employee of the Party being visited shall accompany the employee(s) of the visiting Party. If requested by a Party, the other Party shall cause appropriate individuals working on the Collaboration to be reasonably available for meetings at times and places reasonably convenient to the Party subject to such request.

3.5 **Exchange of Information.** Isis will promptly make available and disclose to Lilly such information regarding the sequence, design, synthesis and screening of Validation ASO Compounds and Drug Discovery ASO Compounds generated by Isis in carrying out the Collaboration as set forth in the Collaborative Research Plan. All discoveries or inventions made in the course of the Collaboration by a Party will be promptly disclosed to the other Party. At a Party's request, the other Party will provide written reports of any studies performed by such other Party as part of the Collaboration required to support regulatory submissions relating to Products to be made by such first Party or its Sublicensees and will allow such first Party and its Sublicensees to use the data included in such reports to support such submissions. The Parties are encouraged to communicate often by telephone, electronic mail or other mechanisms to keep each Party fully advised of the activities being carried out by a Party under the Collaboration.

3.6 **Records.** Isis and Lilly will each maintain records in sufficient detail and in good scientific and business manner appropriate for purposes such as patent and regulatory

matters, which will be complete and accurate and will fully and properly reflect all work done and results achieved in the performance of the Collaboration including prompt signing and corroboration of laboratory notebooks and conception documents.

3.7 **Compliance.** All studies done in connection with the Collaboration shall be carried out in compliance with any applicable laws, regulations, or guidelines governing the conduct of research at the site where such studies are being conducted. All animals involved in the Collaboration shall be provided humane care and treatment in accordance with generally acceptable current veterinary practices.

ARTICLE 4
THE REAGENT PROVISION PROGRAM

4.1 **[DELETED].**

4.2 **[DELETED].**

4.3 **[DELETED]**.

4.4 **[DELETED]**.

4.5 **[DELETED]**.

4.6 **[DELETED]**.

4.7 **[DELETED].**

ARTICLE 5

THE DRUG DISCOVERY TARGET VALIDATION PROGRAM

5.1 **Description and Term.** The drug discovery Target Validation Program commenced on the Effective Date and shall continue to be conducted by Lilly and Isis during the Extended Collaboration Term in accordance with the Collaborative Research Plan.

5.2 **Target Designation.** Targets to be analyzed in the course of the drug discovery Target Validation Program shall be selected by Lilly in the Collaboration Therapeutic Area of oncology and designated as Validation Targets in accordance with this Section 5.2. Lilly shall provide written notice to Isis identifying each Target that it wishes to designate as a Validation Target (a ***"Proposed Validation Target"***). Within [***] days after such notice, Isis shall provide written notice to Lilly indicating whether such Proposed Validation Target is subject to any agreement between Isis and a Third Party under which such Third Party has or may acquire rights to ASO Products directed to such Proposed Validation Target, or whether Isis has an Isis Internal Program with respect to such Proposed Validation Target or ASO Products directed thereto.

5.2.1 If a Proposed Validation Target is not subject to an agreement between Isis and a Third Party under which such Third Party has or may acquire rights to ASO Products directed to such Proposed Validation Target and Isis does not have an Isis Internal Program with respect to such Proposed Validation Target or ASO Products directed thereto, then such Proposed Validation Target shall be deemed a Validation Target and shall be made part of the Target Validation Program.

5.2.2 If a Proposed Validation Target is subject to an agreement between Isis and a Third Party under which such Third Party has or may acquire rights to ASO Products directed to such Proposed Validation Target [***].

5.2.3 [***]

5.3 **Target Validation Program.** Validation Targets and Validation ASO Compounds directed thereto shall be analyzed under the Target Validation Program with the aim of achieving the applicable Critical Success Factors agreed to by the Executive Committee. All results generated in the course of Target Validation Program shall be promptly provided to a member of the Executive Committee for the other Party by means of a written report generated by the Parties and by placing such results in a shared database. [***].

5.3.1 As of the Second Restatement Date there are no Validation Targets under evaluation in the Target Validation Program in any of the Collaboration Therapeutic Areas. The Executive Committee may agree to add Validation Targets to the Collaborative Research Plan according to the procedure set forth in Section 5.2 but only in the Collaboration Therapeutic Area of oncology.

5.4 **Executive Committee Review.** At the next Executive Committee meeting following the completion of the evaluation of a Validation Target under the Target Validation Program, the Executive Committee shall review the results generated with respect to such Validation Target and shall determine whether such Validation Target has achieved the Critical Success Factors for such Validation Target. If the Executive Committee determines that a Validation Target meets the Critical Success Factors, such Validation Target shall be deemed an ***"Accepted Validation Target."*** If the Executive Committee determines that a Validation Target does not meet the Critical Success Factors, such Validation Target shall be deemed a ***"Rejected Validation Target."***

5.5 **Accepted Validation Targets.** [***].

5.5.1 Isis shall provide written notice to Lilly [***].

5.5.2 Isis shall provide written notice to Lilly if [***].

5.5.3 The Accepted Validation Targets as of the Second Restatement Execution Date are listed in ***Schedule 5.5.3***.

5.6 **Rejected Validation Targets.** [***].

5.6.1 [***].

5.6.2 [***].

5.6.3 The Rejected Validation Targets as of the Second Restatement Execution Date are listed in ***Schedule 5.6.3***.

5.7 **Lilly Rights Regarding Other Targets.** [***]

5.8 **Exclusive Targets.** During the Target Validation Program Term Lilly may elect to designate any Validation Target, respectively, an ***"Exclusive Target"*** as described in this Section 5.8. Lilly shall provide Isis with a written description of each Target that Lilly desires to designate as an Exclusive Target. The date upon which Isis receives such notice from Lilly shall be the ***"Target Notice Date."*** [***]

5.9 **Validation ASO Products.** Lilly shall have an option to obtain one or more licenses with respect to Validation ASO Products in accordance with Section 8.2.2.

5.10 **Lilly Confidential Information.** All information provided to Isis by Lilly with respect to a Validation Target shall be considered the Confidential Information of Lilly and shall be subject to the obligations of Article 10 of this Agreement, including any nucleic acid or amino acid sequence of a Validation Target that is provided to Isis by Lilly. As long as such information is Confidential Information, Isis shall use such Confidential Information of Lilly only (a) in the course of the Collaboration, (b) in Isis' internal antisense drug discovery efforts as expressly permitted by this Agreement, or (c) as otherwise expressly permitted by this Agreement, but for no other purpose.

5.11 **Use and Disclosure.** Use of Validation ASO Compounds or Validation Targets by a Party as expressly permitted by this Agreement shall not be considered part of the Collaboration unless such use is carried out as specifically provided in the Collaborative Research Plan. Know-How generated outside the course of the Collaboration by Lilly or Isis as expressly permitted by this Agreement, including through use of Validation ASO Compounds, Validation Non-ASO Compounds, or Validation Targets, shall not be Lilly Collaboration Know-How or Isis Collaboration Know-How, respectively, and any resulting Patent Rights shall not be Lilly Collaboration Patent Rights or Isis Collaboration Patent Rights, respectively.

5.12 **Abandoned Validation Targets.** The Executive Committee shall have the authority to designate one or more Validation Target(s) as ***"Abandoned Validation Target(s)"*** if the Executive Committee determines that no further work aimed at achieving the applicable Critical Success Factors for any such Validation Target should be carried out under the Target Validation Program. Upon designation of a Validation Target as an Abandoned Validation Target no further work shall be conducted under the Validation Program on such Abandoned Validation Target. Abandoned Validation Targets shall not be considered to be Validation Targets for purposes of the Agreement. The terms of the Agreement with respect to Validation Targets, including ASO Compounds and Non-ASO Compounds directed thereto, shall not be applicable to any such Abandoned Validation Targets, including ASO Compounds and Non-ASO Compounds directed thereto, except as specifically provided otherwise in this Section 5.12. The terms of Section 5.6.2 of the Agreement with respect to Rejected Validation Targets and ASO Compounds directed thereto shall be applicable to all Abandoned Validation Targets and

ASO Compounds directed thereto. Lilly will have the right to designate any Abandoned Validation Target as an Exclusive Target, Reserved Target, or Validation Target in accordance with the terms of Sections 5.8, 6.8 and 5.2, respectively, of the Agreement (a ***"Designation Event"***). For purposes of clarity, (i) there are no residual milestone or royalty payment obligations owing either Party to the other with respect to Abandoned Validation Targets, including ASO Compounds and Non-ASO Compounds directed thereto, unless a Designation Event occurs and only if specifically required by this Agreement and

(ii) the LillyRight of First Negotiation under Section 8.3.3 will not apply to Abandoned Validation Targets, including ASO Compounds and Non-ASO Compounds directed thereto. The Abandoned Validation Targets as of the Second Restatement Execution Date are listed in ***Schedule 5.12***.

ARTICLE 6

THE ANTISENSE DRUG DISCOVERY PROGRAM

6.1 **Description and Term.** The Antisense Drug Discovery Program shall continue to be conducted by Isis and Lilly during the Antisense Drug Discovery Term in accordance with the Collaborative Research Plan. The Antisense Drug Discovery Term commenced on the Effective Date and shall continue until the expiration of the Extended Collaboration Term, unless Lilly exercises its option to extend the Antisense Drug Discovery Term, as provided in Section 13.1, the Parties otherwise mutually agree to extend or terminate the Antisense Drug Discovery Program, or the Collaboration is terminated in accordance with Article 13. Lilly and Isis shall use commercially reasonable efforts to develop Drug Discovery ASO Compounds into Development Candidates in accordance with the Collaborative Research Plan. The Collaborative Research Plan includes the Critical Success Factors for the Antisense Drug Discovery Program. By execution of this Agreement the Critical Success Factors are approved by each Party. The Executive Committee is responsible for implementing the Collaborative Research Plan, and any modifications or amendments thereto, consistent with the terms of this Agreement.

6.2 **Drug Discovery Target Designation.**

6.2.1 **Targets Available for Designation as Drug Discovery Targets.** During the Antisense Drug Discovery Term, the Executive Committee shall designate the Drug Discovery Targets to be analyzed under the Antisense Drug Discovery Program in the Collaboration Therapeutic Area of oncology. [***] Targets designated as Drug Discovery Targets during the Antisense Drug Discovery Term may include any Target that is suspected of playing a role in the Collaboration Therapeutic Area of oncology, including Reserved Targets, Reagent Targets, Accepted Validation Targets, Exclusive Targets, Rejected Validation Targets, and other Targets that the Executive Committee determines to be of interest based on the scientific merits of applying Antisense Technology to modulate such Target; [***]. The Drug Discovery Targets provided by Isis for the Collaboration Therapeutic Area of oncology and the stage of development of such Targets as of the Second Restatement Date (i.e., whether such Target is a Stage 1, Stage 2 or Stage 3 Drug Discovery Target) are identified in ***Schedule 6.2***, which may be amended from time to time by agreement of the Parties.

6.2.2 **Disagreements Regarding Drug Discovery Target Designation.** If the Executive Committee cannot agree on whether to designate a Target a Drug Discovery Target, [***].

6.2.3 **Restriction on Isis' Right to Use Drug Discovery Targets.** Except as otherwise expressly permitted by this Agreement, Isis shall not (i) conduct any research on any Drug Discovery Target or any ASO Compound directed thereto, outside the course of the Collaboration either on its own or for a Third Party or (ii) grant or assign any rights to a Third Party with respect to any Drug Discovery Target or ASO Compound directed thereto, in each case, while such Drug Discovery Target is the subject of an Active Program.

6.3 **Further Designation as Stage 1, 2 or 3 Drug Discovery Target.** Concurrently with the designation by the Executive Committee of a Target as a Drug Discovery Target, the Executive Committee shall also designate such Target as a Stage 1 Drug Discovery Target, Stage 2 Drug Discovery Target, or Stage 3 Drug Discovery Target, as appropriate.

6.4 Development Candidate Designation.

6.4.1 **During the Antisense Drug Discovery Term.** During the Antisense Drug Discovery Term if in the opinion of a Party, a Drug Discovery ASO Compound has met the Critical Success Factors set out in the Collaborative Research Plan and such Drug Discovery ASO Compound is ready for IND-enabling toxicology studies, such Party may recommend to the Executive Committee that such Drug Discovery ASO Compound be designated a Development Candidate and, at the next meeting of such Committee, the Committee shall vote on such matter. If the Executive Committee determines that a Drug Discovery ASO Compound has met the Critical Success Factors, then such Drug Discovery ASO Compound shall be considered to be a ***"Development Candidate."*** Lilly shall have the option to license each Development Candidate in accordance with Section 8.2.3.

6.4.2 **After the Antisense Drug Discovery Term.** Subject to Section 6.5, after the Antisense Drug Discovery Term Lilly shall make the decision of whether a Drug Discovery ASO Compound corresponding to a Drug Discovery Target that is the subject of an Active Program shall be designated a Development Candidate, using criteria substantially similar to those used by the Executive Committee during the Antisense Drug Discovery Term and the Extended Collaboration Term. Lilly shall have the option to license each Development Candidate in accordance with Section 8.2.3.

6.5 **Continued Development of Drug Discovery Targets After the Antisense Drug Discovery Term.** Within ten (10) days following expiration or termination (subject to Article 13) of the Antisense Drug Discovery Term and again on the [***] anniversary of such expiration or termination, Lilly shall provide Isis with written notice of those Drug Discovery Targets with respect to which Lilly intends to continue an Active Program. In addition, from the date that is [***] months following such expiration or termination of the Antisense Drug Discovery Term until the [***] anniversary of the expiration or termination (subject to Article 13) of the Antisense Drug Discovery Term Lilly shall provide Isis with semiannual written reports describing the work conducted in the previous six (6) months on each such Drug Discovery Target and Drug Discovery ASO Compounds directed thereto in sufficient detail to

permit Isis to verify that Lilly is maintaining an Active Program with respect thereto and notifying Isis of any such Drug Discovery Target with respect to which Lilly has discontinued an Active Program; *provided, however,* such reports shall be given annually once such Drug Discovery Target has been licensed by Lilly under Section 8.2.3. Subject to the provisions of Article 13, for so long as Lilly maintains an Active Program with respect to a Drug Discovery Target after the expiration or termination of the Antisense Drug Discovery Term (but in no event to exceed [***] years after such expiration or termination), Lilly shall have the right to continue to perform research and development on such Drug Discovery Target and Drug Discovery ASO Compounds directed thereto.

6.5.1 **Active Programs.** As of the Second Restatement Execution Date there are no Active Programs in any of the Collaboration Therapeutic Areas other than those in the Collaboration Therapeutic Area of oncology. As of the Second Restatement Date the Active Programs in the Collaboration Therapeutic Area of oncology are listed in ***Schedule 6.5.1***.

6.6 **Development and Commercialization of Development Candidates.** Unless agreed otherwise by the Executive Committee and subject to Section 8.2.3, Lilly shall be solely responsible for all development and commercialization activities relating to Development Candidates.

6.7 **Abandoned Drug Discovery Targets.** During the Antisense Drug Discovery Term, the Executive Committee may designate a Drug Discovery Target as an ***"Abandoned Drug Discovery Target"*** if such committee concludes that such Drug Discovery Target should no longer be the subject of an Active Program as part of the Collaboration. [***].

6.7.1 Effective as of Second Restatement Date, the [***] metabolics Targets listed ***Schedule 6.7.1*** shall be deemed Abandoned Drug Discovery Targets.

6.7.2 The Abandoned Drug Discovery Targets as of the Second Restatement Execution Date (including the [***] metabolics Targets listed ***Schedule 6.7.1***) are listed in ***Schedule 6.7.2***.

6.8 **Reserved Targets.** During the Extended Collaboration Term Lilly may designate any Target related to a Collaboration Therapeutic Area as a ***"Reserved Target,"*** [***]. Lilly shall provide written notice to Isis identifying each Target that Lilly desires to designate as a Reserved Target. The date upon which Isis receives such notice shall be deemed the ***"Reserved Target Notice Date."*** [***]

6.9 **Limitation on Number of Drug Discovery Targets and Reserved Targets.** During the Extended Collaboration Term, the total number of Reserved Targets shall not [***]. Within [***] days after the expiration of the Extended Collaboration Term, Lilly shall decrease the total number of Reserved Targets to [***] and such [***]. Reserved Targets shall be limited to Targets in the Collaboration Therapeutic Area of oncology. Effective as of the [***] anniversary of the expiration of the Extended Collaboration Term, no Target shall be deemed a Reserved Target for purposes of this Agreement.

6.9.1 The Reserved Targets as of the Second Restatement Execution Date are listed in ***Schedule 6.9.1***.

ARTICLE 7

DEVELOPMENT, COMMERCIALIZATION, MANUFACTURING AND SUPPLY

7.1 **Research Supply.** Isis shall supply Validation ASO Compounds and Drug Discovery ASO Compounds to Lilly as set forth in the Collaborative Research Plan. In the event that Lilly elects to obtain additional quantities of a Validation ASO Compound and/or Drug Discovery ASO Compound for use outside of the Collaboration, Lilly shall so inform Isis in writing specifying the additional quantity desired by Lilly. Isis shall promptly provide Lilly such additional quantities of such Validation ASO Compound and/or Drug Discovery ASO Compound in accordance with the specifications set out in the Collaborative Research Plan. Within [***] days after receipt of such Validation ASO Compound, and/or Drug Discovery ASO Compound, Lilly shall pay Isis [***] (inclusive of all shipping, freight and other delivery charges) for the first gram (or fraction thereof) of such additional Validation ASO Compound or Drug Discovery ASO Compound requested by and delivered to Lilly in any one order. For any quantities of Validation ASO Compound or Drug Discovery ASO Compound requested by and delivered to Lilly above [***] in any one order Lilly shall pay for such extra quantity in an amount equal to [***] per gram or fraction thereof within [***] after receipt of such additional quantities of Validation ASO Compound, and/or Drug Discovery ASO Compound.

7.2 **Clinical Supply.** Upon request by Lilly, Isis will supply all of Lilly's requirements of any Validation ASO Compound and/or Drug Discovery ASO Compound required by Lilly (not to exceed [***] such ASO Compounds per year, nor to exceed [***] kilograms of all ASO Compounds provided under this Section 7.2 per year) through the completion of Phase II Clinical Trials on such Validation ASO Compound or Drug Discovery ASO Compound. Isis will also provide any information and documentation on such Validation ASO Compound or Drug Discovery ASO Compound that is required by regulatory authorities. Isis will supply any such Validation ASO Compound or Drug Discovery ASO Compound pursuant to mutually agreed upon specifications. The Parties will negotiate in good faith on the terms of a clinical supply agreement containing these and other customary terms. If Isis is not able to supply a Validation ASO Compound or Drug Discovery ASO Compound to Lilly or if Lilly determines to obtain supply of any such Validation ASO Compound or Drug Discovery ASO Compounds from a Third Party, then Isis will, at Lilly's request and expense, promptly transfer all necessary technology and technical assistance and grant all necessary rights and licenses to permit Lilly, a Lilly Sublicensee, or Third Parties on behalf of Lilly or a Lilly Sublicensee, to manufacture and supply such Validation ASO Compound and Drug Discovery ASO Compounds (a ***"Supply Transfer"***). Notwithstanding the foregoing, for every Supply Transfer by Lilly or a Lilly Sublicensee, the following conditions apply (A) Lilly will obtain an agreement from any Lilly Sublicensee or Third Party that receives Isis' technology as part of a Supply Transfer that such Lilly Sublicensee or Third Party can only use such technology on behalf of Lilly in connection with the relevant Validation ASO Compound and Drug Discovery ASO Compounds, and will keep such technology confidential and (B) Lilly will promptly notify Isis in writing identifying the Isis technology disclosed to a Lilly Sublicensee or Third Party as part of a Supply Transfer and identifying by name each such Lilly Sublicensee or Third Party and (C) Lilly will enforce the obligations of confidentiality and nonuse set forth in the agreement referred to above in Section 7.2(A).

7.3 **Development and Commercialization.** Lilly shall be solely responsible for all development and commercialization of Lilly Products, including toxicology, clinical development, regulatory, manufacturing and commercialization efforts, except as agreed otherwise by the Parties. Lilly and its Sublicensees shall have the sole right and responsibility for the preparation of any regulatory filings required in order to conduct clinical trials on Lilly Products in the Territory, together with the preparation of suitable applications for marketing approval in the Territory and shall be the owner and party of record of all such regulatory filings. Isis shall cooperate with Lilly, at Lilly's expense, as Lilly reasonably requires in preparing such regulatory filings including, without limitation, any and all data contained therein.

7.4 **STAT3 Material Supply.** Upon request by Lilly, Isis will supply Lilly with up to [***] grams of the ASO Compound directed to the STAT3 Target which was produced in accordance with Good Manufacturing Practices and is located at Isis' facilities as of the Second Restatement Execution Date (***"STAT3 ASO Compound")***. Isis will supply all such STAT3 ASO Compound in amounts requested by Lilly (not to exceed a total of [***] grams) through the initiation of [***] on such STAT3 ASO Compound; *provided, however*, that Lilly may purchase such STAT3 ASO Compound in no more than [***] installments, the last installment of which may be requested by Lilly no later than sixty (60) days after such STAT3 ASO Compound achieves [***]. Lilly shall pay Isis [***]gram [***] for the amount of STAT3 ASO Compound requested by Lilly. Isis will also provide any information and documentation on such STAT3 ASO Compound that is requested by Lilly and that is required by, or useful to, regulatory authorities at no additional cost to Lilly; *provided, however*, that Isis shall not be required to create any such documentation for Lilly, unless otherwise agreed by the Parties. Lilly acknowledges that the STAT3 ASO Compound is provided "AS IS," without any warranty of any kind, express or implied, including any warranty of merchantability or fitness for a particular purpose.

ARTICLE 8

GRANT OF RIGHTS

8.1 **Licenses to Lilly.**

8.1.1 **Research Licenses.** Subject to the terms and conditions of this Agreement, Isis hereby grants to Lilly:

(a) a co-exclusive (with Isis), nonsublicensable, royalty free license during the Collaboration Term under the Isis Collaboration Technology solely to the extent necessary or appropriate to carry out Lilly's responsibilities under the Collaborative Research Plan;

(b) a non-exclusive, nonsublicensable, royalty free license, under the Isis Technology (i) solely to the extent necessary or appropriate to carry out Lilly's responsibilities under the Collaborative Research Plan and (ii) to use Reagent ASO Compounds for internal research purposes (which shall include, without limitation, research conducted in connection with *bona fide* collaboration arrangements between Lilly and Third Parties); and

(c) an exclusive, nonsublicensable, royalty free license under the Isis Collaboration Blocking Patents, and a non-exclusive, nonsublicensable, royalty free license under the Isis Collaboration Technology other than the Isis Collaboration Blocking Patent Rights, in each case to conduct research outside the course of the Collaboration in the Non-ASO Field in the Territory.

8.1.2 **Product Licenses.** Subject to the terms and conditions of this Agreement, Isis hereby grants to Lilly (i) an exclusive license, including the right to sublicense, under the Isis Collaboration Blocking Patents, and (ii) a non-exclusive license, including the right to sublicense, under the Isis Collaboration Technology other than the Isis Collaboration Blocking Patents, in each case to make, use, import, sell and offer to sell Reagent Non-ASO Products, Validation Non-ASO Products, and Drug Discovery Non-ASO Products in the Territory. Such licenses shall be royalty-bearing as expressly provided by this Agreement.

8.2 **Lilly Product Options.**

8.2.1 **Option to Isis Blocking Patent Rights for Reagent Non-ASO Products.** Subject to the terms and conditions of this Agreement, Isis hereby grants to Lilly an option, exercisable on a Reagent Non-ASO Compound-by-Reagent Non-ASO Compound basis, to obtain a non-exclusive royalty-bearing licenses under the Isis Blocking Patent Rights to develop, make, use, import, offer for sale and sell Reagent Non-ASO Products in the Territory; such license(s) shall include the right to grant sublicenses solely for the purpose of developing, making, using, importing, offering for sale and selling the applicable Reagent Non-ASO Product. Lilly may exercise an option granted pursuant to this Section 8.2.1 at any time during the term of this Agreement by providing written notice to Isis that includes a description of the Isis Blocking Patent Rights for which Lilly desires to obtain such non-exclusive license. Any license granted to Lilly pursuant to exercise of an option under this Section 8.2.1 shall be royalty-bearing in accordance with Section 9.3.1(b) hereof.

8.2.2 **Option to Reagent Targets and Validation Targets and Exclusive Targets.**

(a) **Grant of Option.** Subject to the terms and conditions of this Agreement, Isis hereby grants to Lilly an option, exercisable on a Reagent Target-by-Reagent Target or Validation Target-by-Validation Target basis, as applicable, to obtain an exclusive, royalty-bearing license, including the right to sublicense, under the Isis Collaboration Technology and the Isis Technology to develop, make, use, import, offer for sale and sell Reagent ASO Products containing one or more Reagent ASO Compounds directed to such Reagent Target or Validation ASO Products containing one or more Validation ASO Compounds directed to such Validation Target, as applicable, in the Territory.

(b) **Exercise of Option.** Lilly may exercise an option granted pursuant to this Section 8.2.2 with respect to (i) any Reagent Target during the [***] year period commencing upon delivery to Lilly of a Reagent ASO Compound directed to such Reagent Target and (ii) any Validation Target, except Abandoned Validation Targets, during the Initial Collaboration Term and [***] year thereafter for Validation Targets in Collaboration Therapeutic Areas other than oncology and during the Target Validation Program Term and

[***] year thereafter for Validation Targets in the Collaboration Therapeutic Area of oncology, in each case, by providing written notice to Isis that includes a description of such Reagent Target or Validation Target, as applicable. The date that Isis receives such notice shall be deemed the ***"Section 8.2.2 Exercise Notice Date."*** Within [***] days following the Section 8.2.2 Exercise Notice Date for a Reagent Target or Validation Target, Isis shall notify Lilly whether or not Isis has granted or assigned any rights to any Third Party as permitted by this Agreement with respect to such Reagent Target or Validation Target, or any ASO Compounds directed thereto as of the Section 8.2.2 Exercise Notice Date and the nature of the rights so granted, if any, or whether Isis has an Isis Internal Program with respect to such Reagent Target or Validation Target. Isis shall have no obligation to disclose to Lilly the identity of any such Third Party to which rights or licenses have been granted. If Isis has not granted any such rights or license and does not have an Isis Internal Program with respect to such Target as of the Section 8.2.2 Exercise Notice Date, then Isis shall grant to Lilly, and is hereby deemed to grant to Lilly, the license described above in

this Section 8.2.2 with respect to such Reagent Target or Validation Target as of the Section 8.2.2 Exercise Notice Date and Lilly shall be obligated to make payments to Isis with respect to such Reagent ASO Product or Validation ASO Product directed to such Reagent Target or Validation Target, as applicable, in accordance with Section 9.3.3. It is understood and agreed that a Reagent Target or Validation Target may not be available to be licensed by Lilly under this Section 8.2.2 if: (i) Isis has previously granted a Third Party exclusive rights with respect to such Reagent Target and all ASO Compounds directed thereto or Validation Target and all ASO Compounds directed thereto, or (ii) Isis has an Isis Internal Program with respect to the Reagent Target or Validation Target. The Reagent Targets and the date of delivery to Lilly of a Reagent ASO Compound directed to each such Reagent Target are listed in ***Schedule 8.2.2***.

(c) **Diligence and Reporting.** In order to maintain any license granted to Lilly under this Section 8.2.2 with respect to a Reagent Target or Validation Target, Lilly must (i) maintain an Active Program with respect to such Reagent Target or Validation Target, (ii) achieve Program Sanction Approval on Reagent ASO Compounds or Validation ASO Compounds directed to such Reagent Target or Validation Target, as applicable, in no more than [***] months from the time of licensing of such Target by Lilly and (iii) consider a Reagent ASO Compound directed to such Reagent Target or a Validation ASO Compound directed to such Validation Target under Lilly's formal review process for Candidate Selection in no more than [***] months from Program Sanction Approval. In the event that any of the foregoing diligence obligations is not met by Lilly with respect to a Reagent Target or Validation Target or ASO Compound directed thereto, the license granted to Lilly under this Section 8.2.2 with respect to such Reagent Target or Validation Target and ASO Compounds directed thereto shall terminate. Lilly shall provide Isis with annual written reports that include a description of the research, development and commercialization activities by Lilly on any Reagent Target or Validation Target (and ASO Compounds directed thereto) licensed by Lilly under this Section 8.2.2. Lilly shall provide prompt written notice to Isis when it ceases to have an Active Program on any Reagent Target or Validation Target licensed by Lilly pursuant to this Section 8.2.2 and thereafter such license shall terminate. Within [***] months of such notice from Lilly, or within [***] months of termination of this Agreement by Isis pursuant to Section 13.4 or 13.5, Isis shall provide written notice to Lilly if it desires to develop an ASO Product to such Reagent Target or Validation Target and receive from Lilly summary reports on completed IND-enabling toxicology studies and completed clinical trials for the ASO Compound

related to such Reagent Target or Validation Target. Lilly shall provide such summary reports promptly after receiving such notice from Isis. If Isis fails to provide such notice within such [***] month period Lilly shall have no obligation to provide such summary reports to Isis. For purposes of clarity, if Isis fails to request such summary reports from Lilly for a Reagent Target or Validation Target for which Lilly ceases to have an Active Program, Isis may still develop an Isis Drug Discovery ASO Product to such Reagent Target or Validation Target, subject to the Lilly Right of First Negotiation under Section 8.3 and other applicable terms of this Agreement.

8.2.3 **Option to Drug Discovery ASO Targets.**

(a) **Grant of Option.** Subject to the terms and conditions of this Agreement, Isis hereby grants to Lilly an exclusive option, exercisable on a Drug Discovery Target-by-Drug Discovery Target basis, to obtain an exclusive, royalty-bearing license, including the right to sublicense, under the Isis Collaboration Technology and the Isis Technology to develop, make, use, import, offer for sale and sell Drug Discovery ASO Products containing one or more Drug Discovery ASO Compounds directed to such Drug Discovery Target in the Territory.

(b) **Exercise of Option.** Lilly's option under this Section 8.2.3 with respect to any Drug Discovery Target shall be exercisable during the Antisense Drug Discovery Term and for so long thereafter (not to exceed [***] as Lilly has an Active Program with respect thereto or to the Drug Discovery Target, *provided, however*, that such option shall, in any event, expire upon the earliest to occur of (i) [***] days after a Drug Discovery ASO Compound directed to such Drug Discovery Target achieves Candidate Selection or (ii) [***] after the date that a Drug Discovery ASO Compound directed to such Drug Discovery Target was designated a Development Candidate. Lilly may exercise an option granted pursuant to this Section 8.2.3 by providing written notice to Isis that includes a description of the Drug Discovery Target for which Lilly desires to obtain such exclusive license. The date that Isis receives such notice shall be deemed the ***"Section 8.2.3 Exercise Notice Date."*** The exclusive license described above in this Section 8.2.3 shall be deemed granted to Lilly on the Section 8.2.3 Exercise Notice Date and Lilly shall be obligated to make payments to Isis with respect to Drug Discovery ASO Products directed to such Drug Discovery Target in accordance with Section 9.3.4. If Lilly fails to timely exercise its option under this Section 8.2.3, then thereafter the Drug Discovery Target corresponding to such the Drug Discovery ASO Compound shall be deemed an Abandoned Drug Discovery Target; *provided, however,* that prior to the expiration of Lilly's option under this Section 8.2.3 with respect to such Drug Discovery Target, Lilly shall have the right to designate such Drug Discovery Target as a Reserved Target for no more than [***], subject to the provisions of Sections 6.8 and 6.9.

(c) **Diligence and Reporting.** In order to maintain any license granted to Lilly under this Section 8.2.3 with respect to a Drug Discovery Target, Lilly must maintain an Active Program on such Drug Discovery Target, and as long as Lilly has an Active Program with respect to a Drug Discovery Target Isis shall not conduct any research on its own or with a Third Party on such Drug Discovery Target or any ASO Compound directed to such Drug Discovery Target. In the event that the foregoing diligence obligation is not met by Lilly with respect to a Drug Discovery Target or Drug Discovery ASO Compounds directed thereto, the license granted to Lilly under this Section 8.2.3 with respect to such Drug Discovery Target

shall terminate. Lilly shall provide Isis with annual written reports that include a description of the research, development and commercialization activities by Lilly on any Drug Discovery Target and Drug Discovery ASO Compounds related thereto licensed by Lilly under this Section 8.2.3. Lilly shall provide prompt written notice to Isis when it ceases to have an Active Program on any Drug Discovery Target or Drug Discovery ASO Compounds directed thereto licensed by Lilly pursuant to this Section 8.2.3 and thereafter such license shall terminate. Within [***] months of such notice from Lilly, or within [***] months of termination of this Agreement by Isis pursuant to Section 13.4 or 13.5, Isis shall provide written notice to Lilly if it desires to develop an ASO Product to such Drug Discovery Target and whether it desires to receive from Lilly summary reports on completed IND-enabling toxicology studies and completed clinical trials for the ASO Compound related to such Drug Discovery Target. Lilly shall provide such summary reports promptly after receiving such notice from Isis. If Isis fails to provide such notice within such [***] month period Lilly shall have no obligation to provide such summary reports to Isis. For purposes of clarity, if Isis fails to requests such summary reports from Lilly for a Drug Discovery Target or Drug Discovery ASO Compounds the license to which is terminated as described above in this Section 8.2.3(c), Isis may develop an Isis Drug Discovery ASO Product to such Drug Discovery Target, subject to the Lilly Right of First Negotiation under Section 8.3 and other applicable terms of this Agreement.

8.3 **Lilly's Right of First Negotiation.** Isis hereby grants to Lilly a right of first negotiation (the ***"Lilly Right of First Negotiation"***) to obtain from Isis an exclusive, worldwide, license under the Isis Collaboration Technology and the Isis Technology regarding (a) Isis Products directed to

Abandoned Drug Discovery Targets, Exclusive Targets, Lilly-Blocked Targets (subject to Section 6.2.2) or Accepted Validation Targets that (i) Isis elects to partner or develop or commercialize in collaboration with a Third Party or (ii) are developed by Isis and achieve Phase III Study Initiation. The Lilly Right of First Negotiation shall be exercisable by Lilly during the term of this Agreement and shall operate as follows:

8.3.1 Isis shall promptly notify Lilly in writing (the ***"Isis Notification"***) of (i) its intention to negotiate with or seek a collaborator for the commercialization of any Isis Product directed to an Abandoned Drug Discovery Target or Accepted Validation Target or any Isis Reagent ASO Products and/or (ii) when any Isis Product directed to an Abandoned Drug Discovery Target, Exclusive Targets, Lilly-Blocked Targets or Accepted Validation Target achieves Phase III Study Initiation. The Isis Notification shall include a description of the Isis Product that includes summaries of preclinical, toxicological and available clinical data and patent information of the level of detail included in a Clinical Investigators Brochure and, for Isis Products that achieve Phase III Study Initiation, a written report setting out the Phase II Clinical Trial Protocol and the Clinical Investigative Brochure for the Phase III Clinical Trials, in order to permit Lilly to evaluate its interest in exercising its rights under this Section 8.3. All information contained in the Isis Notification shall be considered Confidential Information of Isis and subject to Article 10 and shall be used by Lilly solely for the purpose of evaluating its interest in exercising its rights under this Section 8.3.

8.3.2 Lilly shall notify Isis within [***] days after receipt of the Isis Notification (the ***"Lilly Response Period"***), indicating its interest, if any, in initiating discussions regarding an agreement with Isis with respect to the commercialization of such Isis Product.

8.3.3 In the event that Lilly notifies Isis prior to the termination of the Lilly Response Period that it has an interest in the commercialization of such Isis Product (a ***"Lilly Expression of Interest"***), then the Parties shall negotiate exclusively in good faith reasonable terms that are intended to form the basis of a final agreement for a period of up to the longer of (i) [***] days from the date of Isis's receipt of the Lilly Expression of Interest or (ii) [***] days from the Isis Notification.

8.3.4 In the event that (i) Lilly fails to notify Isis prior to the termination of the Lilly Response Period, or (ii) Lilly notifies Isis prior to the termination of the Lilly Response Period that it has no interest in collaborating with Isis in the commercialization of such Isis Product, or (iii) the Parties fail to reach agreement on the terms that are intended to form the basis of a final agreement within [***] days of the Isis Notification, or (iv) the Parties fail to reach a final agreement within [***] days following the date on which the Parties reach agreement on the terms that are intended to form the basis of a final agreement, then Isis shall thereafter be free to develop such Isis Product on its own or to initiate discussions with potential alternative partners with respect to the commercialization of such Isis Product; *provided, however,* that in the event Isis enters into discussions with alternative partner the following provisions shall apply:

(a) [***] For the purpose of calculating net present value under this Section 8.3.4 the following timing definitions will apply:

(i) [***] and

(ii) [***] and

(b) [***]

8.3.5 Isis shall disclose the terms of any such proposed Third Party agreement terms to Lilly, and in the event that Lilly disputes that such terms meet the requirements of this Section 8.3, then an independent Third Party with the requisite expertise, selected by the Parties, shall make such determination. The expense of such independent Third Party shall be shared equally by the Parties. In the event that any Third Party terms include non-monetary consideration (e.g., licensing of patent rights), then such independent Third Party shall value such non-monetary consideration as well as any other terms offered by such Third Party and decide whether as a whole the Third Party offer exceeds the Lilly offer as set forth above.

8.3.6 If a Third Party offer for the Isis Product exceeds the Lilly offer by the guidelines outlined in Section 8.3.4 and is accepted by Isis, Lilly shall receive from Isis the milestones and running royalty that would be owed by Isis to Lilly under Section 9.6.

8.3.7 In the event that Lilly provides Isis with a timely offer of terms, pursuant to Section 8.3.3 (the ***"Lilly Offered Terms"***), but Isis does not enter into an agreement with Lilly or reach a mutually agreed-upon term sheet that represents a firm commitment from a Third Party approved by an officer of the company of such Third Party with respect to the commercialization of such ASO Product pursuant to the provisions of Section 8.3.4 within [***] months of the receipt by Isis of the Lilly Offered Terms, then the Lilly Right of First Negotiation with respect to such ASO Product shall be revived.

8.3.8 For each of the [***] Abandoned Drug Discovery Targets listed in ***Schedule 6.7.1*** of this Agreement, the Lilly Right of First Negotiation shall not be applicable for a period of [***] months from the Second Restatement Date. All other terms and conditions of this Agreement with respect to any Abandoned Drug Discovery Target shall remain in effect. If Isis fails to enter into an agreement with a Third Party whereby Isis exclusively licenses the Isis right to commercialize ASO Products directed to any such Abandoned Drug Discovery Target listed in ***Schedule 6.7.1*** of this Agreement within [***] months from the Second Restatement Date, the Lilly Right of First Negotiation and all other terms of this Section 8.3, other than this Section 8.3.8, shall immediately become effective and applicable to any such unlicensed Abandoned Drug Discovery Targets.

8.4 **Licenses to Isis.**

8.4.1 **Research Licenses.** Subject to the terms and conditions of this Agreement, Lilly hereby grants to Isis:

(a) a co-exclusive (with Lilly), nonsublicensable, royalty free license during the Collaboration Term under the Lilly Collaboration Technology solely to the extent necessary or appropriate to carry out Isis' responsibilities under the Collaborative Research Plan;

(b) an exclusive, nonsublicensable, royalty-free license under the Lilly Collaboration Technology in the ASO Field in the Territory to conduct research outside the course of the Collaboration; *provided, however,* that such license shall automatically terminate for any particular Lilly Collaboration Patent Right that covers a Reagent ASO Product, Validation ASO Product, or Drug Discovery ASO Product upon the licensing of the related Reagent Target, Validation Target or Drug Discovery Target by Lilly under Sections 8.2.1, 8.2.2 or 8.2.3.

8.4.2 **Product Licenses.** Subject to the terms and conditions of this Agreement, Lilly hereby grants to Isis an exclusive, royalty-bearing license, including the right to sublicense, under Lilly Collaboration Technology to develop, make, have made, use, import, offer for sale and sell Isis Validation ASO Products and Isis Drug Discovery ASO Products in the Territory. Isis shall provide Lilly with annual written reports that include a description of the research, development and commercialization activities by Isis on any Isis Validation ASO Products or Isis Drug Discovery ASO Products licensed by Isis under this Section 8.4.2.

8.5 **Isis Option to License Lilly Non-Collaboration ASO Patent Rights.** Subject to the terms and conditions of this Agreement, including this Section 8.5, [***]. During the Reagent Provision Term plus [***] years thereafter Isis may acquire the Isis Option with respect to any such Reagent Target as set forth below:

(i) [***].

(ii) [***] Isis shall be limited as to the number of Reagent Targets with respect to which it may make such inquiries as follows:

(1) Until the expiration of [***] months after the Effective Date, Isis may not make any such inquiries;

(2) During the [***] months following the period described in Section 8.5(ii)(1), Isis may inquire on the status of up to [***]. Reagent Targets;

(3) During the [***] months following the period described in Section 8.5(ii)(2), Isis may inquire on the status of up to [***]. Reagent Targets; and

(4) During the [***] months following the period described in Section 8.5(ii)(3) and during each successive twelve [***] month period thereafter until the expiration of the [***] year following expiration of the Reagent Provision Term, Isis may inquire on the status of up to [***] Reagent Targets per [***] month period.

Isis may make such inquiries under this Section 8.5(ii) no more than [***] times per year; *provided, however,* [***]. Within five (5) days of receipt of any such notice from Isis under this Section 8.5(ii), the Third Party Reviewer shall notify Isis in writing whether such Reagent Target is an Excluded Reagent Target.

(iii) On or after such time as any Reagent Target validated and functionalized by Isis in its own internal drug discovery programs has reached [***].

(iv) Isis may exercise each Isis Option granted under Section 8.5(iii) at any time following such grant during the Reagent Provision Term plus [***] years upon written notice to Lilly. Any license granted to Isis pursuant to exercise of an Isis Option under this Section 8.5 shall be royalty-bearing in accordance with Section 9.6.1 hereof.

(v) Isis shall provide Lilly with annual written reports that include a description of the research, development and commercialization activities by Isis on any Isis Validation ASO Products or Isis Non-Collaboration ASO Products licensed by Isis under this Section 8.5.

8.6 **No Implied Licenses.** Except as expressly provided otherwise herein, neither Party hereto will be deemed by this Agreement to have been granted any license or other rights to the other Party's intellectual property rights including any Third Party patent rights.

8.7 [DELETED]**.**

8.8 [DELETED]**.**

8.9 **Manufacturing Improvements.** During the first [***] years of the term of this Agreement, the Parties will meet at least annually to review Manufacturing Improvements developed by either of the Parties outside of the course of the Collaboration. [***].

8.9.1 The entire right, title, and interest in and to all Manufacturing Improvements developed or invented solely by employees or consultants of Lilly during the term of this Agreement will be the sole and exclusive property of Lilly. [***].

8.9.2 The entire right, title, and interest in and to all Manufacturing Improvements developed or invented solely by employees or consultants of Isis during the term of this Agreement will be the sole and exclusive property of Isis. [***].

8.9.3 The entire right, title, and interest in and to all Manufacturing Improvements developed or invented jointly by employees or consultants of Isis and Lilly during the term of this Agreement will be the joint property of Isis and Lilly. Each Party will have an undivided joint ownership interest in such Manufacturing Improvements, and may license its rights under such Manufacturing Improvements for its own account and without the consent of the other Party, subject to the licenses granted to Lilly under Sections 8.1 and 8.2.

8.10 **Negative Covenant of Isis.** Isis hereby agrees that, for so long as a particular Validation Target or Drug Discovery Target is subject to restrictions on Isis' use of such Target outside the Collaboration pursuant to Section 5.3, 5.5, 5.6, 5.8, 6.2.3 or 6.8, as applicable, or is subject to an exclusive license granted to Lilly under Section 8.2.2, 8.2.3, 8.3, 8.11 or 8.12 Isis shall not [***]. Upon mutual written agreement of the Parties during the Extended Collaboration Term, the Target Validation Program and/or Antisense Drug Discovery Program, as applicable, may be expanded to include activities directed to [***].

8.11 **STAT3 License Grant.**

8.11.1 Subject to the terms and conditions of this Agreement, Isis hereby grants to Lilly an exclusive, royalty-bearing license, including the right to sublicense, under the Isis Collaboration Technology and the Isis Technology to develop, make, use, import, offer for sale and sell ASO Products containing one or more ASO Compounds directed to the Target known as STAT3 (the ***"STAT3 Target")*** in the Territory. Effective as of the Second Restatement Execution Date, the STAT3 Target shall be deemed a [***] licensed by Lilly under Section 8.2.3(b) and subject to all applicable terms of this Agreement, except as otherwise expressly permitted in this Agreement.

8.11.2 Notwithstanding anything to the contrary in Section 9.3.4(a) of this Agreement, [***] license fee shall be payable by Lilly to Isis for the license granted to Lilly under Section 8.11.1.

8.11.3 In addition to any milestone payments payable by Lilly to Isis under Section 9.3.4(b), and subject to all other terms and conditions thereof, Lilly will pay to Isis a milestone payment in the amount of [***] within thirty (30) days after achievement of Candidate Selection for the first Drug Discovery ASO Compound being developed as a Drug Discovery ASO Product that is directed to the STAT3 Target.

8.11.4 If a Drug Discovery ASO Compound being developed as a Drug Discovery ASO Product that is directed to the STAT3 Target does not achieve [***] on or before [***] (the "STAT3 [***] Target Date"), the license granted to Lilly under Section 8.11.1 shall terminate; *provided, however,* that if such [***] will not be achieved by the STAT3 Candidate Selection Target Date due to scientific or regulatory issues, including but not limited to: [***], Lilly shall so inform Isis before the STAT3 [***] Target Date and the license granted to Lilly under Section 8.11.1 shall not terminate. The Executive Committee shall thereafter promptly

determine (i) a course of action including a detailed timetable of activities required to resolve such scientific or regulatory issue and (ii) an appropriate extension of time for STAT3 Candidate Selection Target Date. This Agreement shall be amended to reflect the determination of the Executive Committee with regard to the extension of the STAT3 Candidate Selection Target Date.

8.11.5 In addition to any extension of the STAT3 [***] Target Date under Section 8.11.6, Lilly shall have the option of extending the STAT3 [***] Target Date for up to [***] consecutive [***] day periods by paying Isis [***] for each such [***] day period. All such fees shall be fully creditable against any payment later due from Lilly under Section 8.11.3 and Section 8.11.6. Lilly may exercise each such option under this Section 8.11.5 by providing written notice to Isis before the STAT3 [***] Target Date or the expiration of any extensions thereof under Section 8.11.4 or this Section 8.11.5. Any fee that becomes payable by Lilly to Isis under this Section 8.11.5 shall be paid by Lilly within [***] days of the written notice provided to Isis under this Section 8.11.5.

8.11.6 Lilly shall have the right to eliminate the requirement to achieve Candidate Selection for the first Drug Discovery ASO Compound being developed as a Drug Discovery ASO Product that is directed to the STAT3 Target by the STAT3 [***] Target Date or any extension thereof by providing written notice to Isis and paying Isis the amount that would otherwise become payable to Isis under Section 8.11.3 as if the first Drug Discovery ASO Compound being developed as a Drug Discovery ASO Product that is directed to the STAT3 Target achieved [***]. Such amount shall be paid by Lilly within [***] days of the written notice provided to Isis under this Section 8.11.5. Any payment made by Lilly to Isis under this Section 8.11.6 shall be fully creditable against the milestone payment that becomes payable by Lilly to Isis under Section 8.11.3.

8.11.7 Isis shall allow Lilly to conduct reasonable due diligence (***e.g.,*** intellectual property, regulatory and scientific due diligence) on the STAT3 Target and the STAT3 ASO Compound following the Second Restatement Effective Date.

8.12 **Target Option**

8.12.1 Subject to the terms and conditions of this Agreement, and in addition to the options granted in Section 8.2 of this Agreement, Isis hereby grants to Lilly the right to obtain up to [***] exclusive options, on a Target-by-Target basis, to obtain an exclusive, royalty-bearing license, under (i) the Isis Collaboration Technology and the Isis Technology and (ii) the Isis Special Technology (subject to 8.12.4), to develop, make, use, import, offer for sale and sell ASO Products containing one or more ASO Compounds directed to the applicable Target in the Territory.

8.12.2 Lilly's may obtain one or more options under Section 8.12 for a period of [***] years after the expiration of Initial Collaboration Term. Lilly may inquire of Isis whether an option is available under this Section 8.12 by providing written notice to an Isis designee (the ***"Isis Designee"***) that includes a description of up to [***] Targets for which Lilly may desire to obtain such option (the ***"Section 8.12.2 Option Notice"***). The date that the Isis Designee receives such notice shall be deemed the ***"Section 8.12.2 Option Notice Date."*** Within ten (10)

business days following the Section 8.12.3 Option Notice Date for a particular Target, the Isis Designee will determine whether or not Isis has [***]. Within twenty (20) business days following the Section 8.12.2 Option Notice Date, but no sooner than of (10) business days thereafter, Lilly shall contact the Isis Designee and identify which of the [***] Targets described in the Section 8.12.2 Option Notice(each a ***"Potential Optioned Target"***) Lilly desires to obtain an option on under Section 8.12. If Isis has not [***] as of the Section 8.12.2 Option Notice Date, then any such Potential Optioned Target shall be deemed an ***"Optioned Target"*** as of the Section 8.12.2 Option Notice Date. Each Party shall confirm the identity of each Optioned Target by written notice to the other Party. The Isis Designee shall be an attorney in the Isis legal department or outside counsel representing Isis and shall sign a confidentiality agreement whereby such Isis Designee shall be obligated not to disclose to any other person or Party or to use for any purpose other than the purpose of providing notice to Lilly under this Section 8.12.2, all information provided by Lilly in its written notice to Isis under this Section 8.12.2.

8.12.3 An option obtained by Lilly under this Section 8.12 shall be exercisable only during a period of [***] for all other Optioned Targets. During such option period Isis shall allow Lilly to conduct intellectual property due diligence on Patent Rights (if any) that Isis has filed on such Optioned Target or ASO compounds directed thereto. Lilly may exercise an option granted pursuant to this Section 8.12 by providing written notice to Isis that includes a description of the Optioned Target for which Lilly desires to obtain the exclusive license described in Section 8.12.1. The date that Isis receives such notice shall be deemed the ***"Section 8.12 Exercise Notice Date."*** The exclusive license described above in this Section 8.12 shall be deemed granted to Lilly on the Section 8.12 Exercise Notice Date. Any Target licensed by Lilly pursuant to this Section 8.12 shall be deemed a [***] licensed by Lilly under Section 8.2.3(b) and thereafter subject to all of the applicable terms of this Agreement; *provided, however,* notwithstanding anything to the contrary in Section 9.3.4(a) of this Agreement, the license fee payable by Lilly to Isis for a license granted to Lilly under Section 8.12 shall be [***]. Any option granted to Lilly under this Section 8.12 that is not exercised in accordance with Section 8.12.3 shall count against the [***] options that Lilly has a right to obtain under Section 8.12.1. Any license granted pursuant to the exercise of an option under this Section 8.12.3 by Lilly shall be sublicensable by Lilly solely in connection with the grant of a license to develop, make, use, import, offer for sale and sell an ASO Product discovered and optimized by Isis and/or Lilly directed to the applicable Optioned Target.

8.12.4 Isis Special Technology shall only be included in the license granted to Lilly pursuant to Section 8.12 if Lilly and Isis negotiate an agreement to license such Isis Special Technology as follows:

(a) If Isis would have no financial obligations to a Third Party arising from the grant to Lilly and/or the practice by Lilly, its Affiliates, or Sublicensees, of the Isis Special Technology then any such agreement between Isis and Lilly under this Section 8.12.4 shall include terms providing that for the development and sale by Lilly of an ASO Product directed to an Optioned Target licensed by Lilly under this Section 8.12, [***].

(b) If Isis would have financial obligations to a Third Party arising from the grant to Lilly and/or the practice by Lilly, its Affiliates, or Sublicensees, of the Isis

Special Technology then any such agreement between Isis and Lilly under this Section 8.12.4 shall include terms providing that [***].

(c) In addition to Section 8.12.4(a) and Section 8.12.4(b), as applicable:

(i) Lilly will compensate Isis for an [***]; and

(ii) if Isis' access to such Isis Special Technology is limited to [***]; and

(iii) Lilly will abide by all of the terms of the agreement with a Third Party under which Isis has obtained Control of such Isis Special Technology.

(d) Notwithstanding anything to the contrary in this Section 8.12.4, any agreement negotiated between Isis and Lilly under this Section 8.12.4 shall contain terms that are [***]. The terms of Section 9.5 (Access to Third Party Rights) will not apply to any Isis Special Technology licensed to Lilly under this Section 8.12.

ARTICLE 9

PAYMENTS AND ACCOUNTING

9.1 **Collaboration Funding.** The Collaboration Funds shall be applied by Isis solely towards the Collaboration and in accordance with the Collaborative Research Plan. All remaining Collaboration Funds as of the end of the Initial Collaboration Term shall be used to fund Isis Collaboration FTEs during the Extended Collaboration Term for those activities set forth in the Collaborative Research Plan, or as otherwise agreed upon in writing by the Parties, and for no other purpose. Notwithstanding anything to the contrary in the Agreement or the Collaborative Research Plan, all Collaboration Funds designated in the Collaborative Research Plan to fund [***]. Isis shall be reimbursed from the Collaboration Funds for [***] Isis Collaboration FTEs dedicated to the [***] for the period of [***] as provided under the Collaborative Research Plan; *provided, however*, that an equivalent number of Isis Collaboration FTEs shall be dedicated to research on the Abandoned Drug Discovery Targets listed in ***Schedule 6.7.1*** through the end of the Initial Collaboration Term. Research and development conducted by Isis through the end of the Initial Collaboration Term on such on Abandoned Drug Discovery Targets shall be [***]. At Lilly's request, Isis shall provide Lilly semiannual written reports on the research and development of the Abandoned Drug Discovery Targets listed in ***Schedule 6.7.1*** and any Isis Internal Programs in the area of [***] for a period that is the longer of [***].

9.1.1 **Collaboration FTEs.** Isis shall maintain complete and accurate records of all monies expended by it for research under the Collaboration and the Collaboration FTEs applied in the course of the Collaboration. During the Extended Collaboration Term, Isis will be obligated to report to Lilly only the number of Collaboration FTEs dedicated to work on the Collaboration for the previous Calendar Quarter.

9.1.2 [DELETED]

9.1.3 [DELETED]

9.1.4 **Audits.** If a Party desires to audit the other Party's records regarding Collaboration Funds and Collaboration FTEs, it shall utilize the independent, certified public accountant of the other Party to examine such records. Such accountant shall be instructed to provide the Party desiring the audit a report on the findings of the agreed upon procedures which verifies any previous report made or payment submitted by the audited Party during such period. The expense of such audit shall be borne by the auditing Party; *provided, however,* that if an error in favor of the auditing Party of more than the greater of [***] of the amount reported or paid or [***] is discovered, then such expenses shall be paid by the audited Party. Any information received by a

Party pursuant to this Section 9.1.4 shall be deemed to be the Confidential Information of the other Party. This right to audit shall remain during the Collaboration Term and for a period of [***] years thereafter, but no more often than [***] per year.

9.1.5 [DELETED]

9.1.6 [DELETED]

9.1.7 [DELETED]

9.1.8 **Payment of Royalty Reduction Fee.** Lilly paid to Isis [***] within thirty (30) days after the Restatement Date, which payment shall be applied to reduce the royalty rate payable under this Agreement with respect to a Drug Discovery ASO Product directed to the Drug Discovery Target known as [***].

9.2 **Technology Access Fee.**

9.2.1 If Lilly is conducting any research, development or commercialization activities relating to any Lilly Product as of the [***] anniversary of the Effective Date, Lilly shall commence making the first of [***] equal installments of the Technology Access Fee to Isis. For a period of [***] years thereafter, if Lilly continues to conducting any research, development or commercialization activities relating to any Lilly Product as of each anniversary of the Effective Date then Lilly shall pay the next installment of the Technology Access Fee. Technology Access Fee installments shall be paid by Lilly within [***] days after the [***] anniversary of the Effective Date and each anniversary date thereafter until a total [***] such Technology Access Fee installments have been made by Lilly. The total amount of each such Technology Access Fee installment shall be calculated by:

(a) subtracting from the Collaboration Funds both:

(i) [***]; and

(ii) [***]; and

(b) [***] pursuant to this Section 9.2.

9.2.2 As of the Second Restatement Execution Date the Parties acknowledge and agree that the total amount of the Technology Access Fee and each installment thereof that shall be payable by Lilly is zero.

9.2.3 Capitalized terms used in Section 9.2.1 and Section 9.2.2 that are not defined in this Agreement shall have the meanings set forth in the Loan Agreement.

9.2.4 Credits Against Technology Access Fee. [***].

9.3 **License, Milestone and Royalty Payments - Lilly.**

9.3.1 **Reagent Non-ASO Products.**

(a) **Milestone Payments.** Lilly will pay to Isis the following milestone payments for a Reagent Non-ASO Product within [***] days after achievement of each of the following events in the first Major Market Country; *provided, however,* that no milestone payment shall be due or owing for any Reagent Non-ASO Compound being developed as a Reagent ASO Product that has as its site of activity the same Target that is the site of activity of any Lilly Product with respect to which such milestone payment has already been paid:

Milestone Event	Milestone Payment
[***]	[***]
[***]	[***]
[***]	[***]

Lilly shall be obligated to pay milestone payments with respect to a Reagent Non-ASO Compound under this Section 9.3.1 only if such Reagent Non-ASO Compound achieves Program Sanction Approval within [***] years of the date that Lilly performs the Lilly First Pass In Vitro Assay with respect to the related Reagent ASO Compound delivered to Lilly by Isis under this Agreement that is directed to the same Target as such Reagent Non-ASO Compound, as reasonably evidenced by Lilly's laboratory notebooks or other scientific records.

(b) **Royalties.** Lilly will pay to Isis [***] on the annual Net Sales of a Reagent Non-ASO Product on a country-by-country basis from the date of the First Commercial Sale in each such country of a Reagent Non-ASO Product until the expiration of the last to expire Isis Blocking Patent Right licensed by Lilly under Section 8.2.1 that includes a Valid Claim that Covers such Reagent Non-ASO Product.

9.3.2 **Validation Non-ASO Products and Drug Discovery Non-ASO Products.**

(a) **Milestone Payments.** Lilly will pay to Isis the following milestone payments for a Validation Non-ASO Product or Drug Discovery Non-ASO Product

within thirty (30) days after achievement of each of the following events in the first Major Market Country; *provided, however,* that no milestone payment shall be due or owing for any Validation Non-ASO Compound being developed as a Validation Non-ASO Product or Drug Discovery Non-ASO Compound

being developed as a Drug Discovery Non-ASO Product that has as its site of activity the same Target that is the site of activity of any Lilly Product with respect to which such milestone payment has already been paid:

Milestone Event	Milestone Payment
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

Lilly shall be obligated to make only those milestone payments for the events listed above in this Section 9.3.2 that occur after the Validation Target or Drug Discovery Target that is targeted by the Validation Non-ASO Compound being developed as a Validation Non-ASO Product or Drug Discovery Non-ASO Compound being developed as a Drug Discovery Non-ASO Product is designated [***].

Lilly shall be obligated to pay milestone payments with respect to a Validation Non-ASO Compound being developed as a Validation Non-ASO Product or Drug Discovery Non-ASO Compound being developed as a Drug Discovery Non-ASO Product under this Section 9.3.2 only if such Validation Non-ASO Compound or Drug Discovery Non-ASO Compound achieves Program Sanction Approval within [***] years and [***] months of the date that the related Validation ASO Compound or Drug Discovery ASO Compound that is directed to the same Target as the Validation Non-ASO Compound or Drug Discovery Non-ASO Compound is delivered to Lilly or the Collaboration for use thereunder, as applicable.

(b) **Royalties.** Lilly will pay the following royalties to Isis on a country-by-country basis from the date of the First Commercial Sale in each such country of a Validation Non-ASO Product or Drug Discovery Non-ASO Product:

(i) [***] on the annual Net Sales of Validation Non-ASO Product or Drug Discovery Non-ASO Product for a period of [***] years if there is no Isis Collaboration Patent Right or Isis Patent Right that includes a Valid Claim that Covers such Validation Non-ASO Product or Drug Discovery Non-ASO Product; *provided, however,* that no royalty payment shall be owed by Lilly under this Section 9.3.2(b) for a Validation Non-ASO Product or Drug Discovery Non-ASO Product that is [***] or

(ii) [***] on the annual Net Sales of a Validation Non-ASO Product or Drug Discovery Non-ASO Product until the expiration of the last to expire Isis

Collaboration Patent Right or Isis Patent Right that includes a Valid Claim that Covers such Validation Non-ASO Product or Drug Discovery Non-ASO Product.

9.3.3 **Reagent ASO Products and Validation ASO Products.**

(a) **License Fees.** In the event that Lilly exercises its option to license a Reagent Target or a Validation Target in accordance with Section 8.2.2, Lilly shall pay Isis a one time license fee of [***] within [***] days after the Section 8.2.2 Exercise Notice Date for each such licensed Reagent Target or Validation Target.

(b) **Milestone Payments.** Lilly will pay to Isis the following milestone payments for a Reagent ASO Compound being developed as a Reagent ASO Product or a Validation ASO Compound being developed as a Validation ASO Product within thirty (30) days after achievement of each of the following events in the first Major Market Country; *provided, however,* that no milestone payment shall be due or owing for any Reagent ASO Compound or a Validation ASO Compound that has as its site of activity the same Target that is the site of activity of any Lilly Product with respect to which such milestone payment has already been paid:

Milestone Event	Milestone Payment
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

Provided, however, that with respect to any Combination Product that contains more than one (1) Reagent ASO Compound and/or Validation ASO Compound, Lilly shall be obligated to the milestones set forth in the foregoing table for Phase III Study Initiation, Registration and First Commercial Sale only once for such Combination Product.

(c) **Royalties.** Lilly will pay to Isis the following royalties on a country-by-country basis from the date of the First Commercial Sale in each such country of a Reagent ASO Product or a Validation ASO Product until the expiration of the last to expire Isis Collaboration Patent Right or Isis Patent Right that includes a Valid Claim that Covers such Reagent ASO Product or Validation ASO Product, as applicable:

Worldwide Annual Sales of the Product	Royalty Rate
[***]	[***]
[***]	[***]
[***]	[***]

Provided, however, that the royalty rate payable by Lilly under this Section 9.3.3(c) shall be increased by the amount of any pass through royalties payable by Isis to a Third Party on Lilly's sale of such Reagent ASO Product or Validation ASO Product but in no event shall the royalty rate payable by Lilly under this Section be increased to amount greater than [***].

9.3.4 **Drug Discovery ASO Products.**

(a) **License Fees.** In the event that Lilly exercises an option to license a Drug Discovery ASO Target in accordance with Section 8.2.3, Lilly shall pay the following applicable one-time license fee [***] days after the Section 8.2.3 Exercise Notice Date for each such Drug Discovery ASO Target:

Drug Discovery ASO Target	License Fee
[***]	[***]
[***]	[***]
[***]	[***]

(b) **Milestone Payments.** Lilly will pay to Isis the following milestone payments for a Drug Discovery ASO Compound being developed as a Drug Discovery ASO Product within [***] days after achievement of each of the following events in the first Major Market Country; *provided, however,* that no milestone payment shall be due or owing for any Drug Discovery ASO Compound that has as its site of activity the same Target that is the site of activity of any Drug Discovery ASO Product with respect to which such milestone payment has already been paid:

MILESTONE PAYMENT

Milestone Event	Stage 1 Drug Discovery Target	Stage 2 Drug Discovery Target	Stage 3 Drug Discovery Target
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]

Provided, however, that with respect to any Combination Product that contains more than one (1) Drug Discovery ASO Compound, Lilly shall be obligated to the milestones set forth in the foregoing table for Phase III Study Initiation, Registration and First Commercial Sale only once for such Combination Product.

(c) **Royalties.** Subject to Section 9.4, Lilly will pay to Isis the following royalties on a country-by-country basis from the date of the First Commercial Sale in each such country of a Drug Discovery ASO Product until the expiration of the last to expire Isis Collaboration Patent Right or Isis Patent Right that includes a Valid Claim that Covers such Drug Discovery ASO Product:

Royalty Rates

Worldwide Annual Net Sales of the Product	Stage 1 Drug Discovery Target	Stage 2 Drug Discovery Target	Stage 3 Drug Discovery Target
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]

9.3.5 **Lilly Sublicensing Obligations.** In the event that Lilly elects to sublicense its rights to a Reagent ASO Compound, a Drug Discovery ASO Product or a Validation ASO Product, as permitted by this Agreement, Lilly shall be obligated to pay to Isis, at Lilly's option, either (i) [***] of any and all Sublicense Income received by Lilly pursuant to a sublicense agreement entered into by Lilly with respect to such Reagent ASO Compound, a Drug Discovery ASO Product or a Validation ASO Product or (ii) any payments as set forth in this Article 9 that would be owed by Lilly if Lilly were selling such Reagent ASO Product, Drug Discovery ASO Product or Validation ASO Product; *provided, however,* [***].

9.3.6 [***] **Payments.**

(a) **Milestone Payments**. For any Validation ASO Product or Drug Discovery ASO Product developed by Lilly that is directed to [***] (and in addition to the milestone payments specified in Section 9.3.3(b) and Section 9.3.4(b) of the Agreement, as applicable) Lilly shall pay to Isis the applicable milestone payments payable by Isis to [***] under the [***] Agreement for an "Isis Antisense Product" (as defined in the [***] Agreement) directed to [***]. Such milestone payments are set forth in ***Schedule 9.4.3*** of this Agreement. Lilly shall pay each such milestone payment to Isis only if Isis remains obligated to pay such to [***] under the [***] Agreement at the time the applicable milestone is achieved.

(b) [***] **Royalties.** The royalty rates specified in Sections 9.3.3(c) and Section 9.3.4(c) of the Agreement for Validation ASO Products or Drug Discovery ASO Products directed to [***] shall be increased by [***] in view of the pass through royalties of the same amount payable by Isis to [***] under the [***] Agreement for an "Isis Antisense Product" directed [***]. Lilly shall pay such pass through royalty to Isis for so long as such royalty is payable by Isis to [***] under the [***] Agreement. As of the date of this letter, such royalty payment is payable by Isis to [***] for a period of [***] years following the "First Commercial Sale" in a "Major Country" of the first "Isis Antisense Product" directed to [***]. For a second or subsequent "Isis Antisense Product" directed to [***], royalties are payable by Isis in a "Major Country" only during the [***] year period initiated by the "First Commercial Sale" of the first such "Isis Antisense Product". For the purposes of this paragraph, the terms "Isis Antisense Product", "First Commercial Sale", and "Major Country" have the meanings set forth in the [***] Agreement.

(c) [***] **Non-ASO Products**. Lilly shall not be obligated to pay any milestone or royalty payments to Isis under the Agreement, including Sections 9.3.1 or 9.3.2 thereof, for any Reagent Non-ASO Product, Validation Non-ASO Product or Drug Discovery Non-ASO Product directed to the target known as [***].

9.4 **Pass Through Royalties.** [***].

9.4.1 [***].

9.4.2 [***]

9.4.3 [***]

9.4.4 [***]

9.4.5 **Royalty Reduction.** In addition to those rights specified in Section 9.4.2, Lilly shall have the right to reduce the royalty rate for any present or future Lilly ASO Product payable to Isis under this Agreement by [***] by paying Isis [***] on or before [***]. The applicable Lilly ASO Product shall be designated by Lilly at any time during the term of this Agreement.

9.5 **Access to Third Party Rights.**

9.5.1 **Third Party Licenses.** If, after the Effective Date access to a Third Party's intellectual property rights becomes necessary to make, use, import, or offer to sell, or

sell a Reagent ASO Product, Validation ASO Product or Drug Discovery ASO Product in the Territory, Lilly shall have the right to acquire such access. [***] of the acquisition cost paid by Lilly (*i.e.*, all consideration paid by Lilly in connection with such acquisition including, without limitation up-front payments, milestones payments and royalties) shall be credited against future royalties owed to Isis by Lilly under this Agreement for a Reagent ASO Product, Validation ASO Product or Drug Discovery ASO Product. Except as the Parties may otherwise agree in writing, under no circumstance shall Lilly acquisitions of Third Party intellectual property rights under the provisions of this Section 9.5 result in a reduction of Net Royalties payable to Isis under this Agreement by more than [***] percent of the royalty otherwise due to Isis.

9.5.2 **Oral Preparation or Formulation Technology.** Any oral preparation or formulation technology that is applicable to Reagent ASO Products, Validation ASO Products or Drug Discovery ASO Products that is obtained by Isis from any Affiliate or Third Party, including [***], shall be made available to Lilly for use at a cost (including royalties, milestones and other payments) that is no greater than the amount payable by Isis to such Third Party. Any oral preparation or formulation technology developed by Isis during the term of the Agreement that is applicable to Reagent ASO Products, Validation ASO Products or Drug Discovery ASO Products shall be made available to Lilly hereunder as Isis Technology.

9.6 **Payments by Isis.** Subject to the terms and conditions of this Agreement, Isis shall pay to Lilly royalties on a country-by-country basis from the date of the First Commercial Sale of an Isis Product in each such country as follows:

9.6.1 **Isis Non-Collaboration ASO Products.** For Isis Non-Collaboration ASO Products, Isis shall pay Lilly [***] on Isis' annual Net Sales of each Isis Non-Collaboration ASO Product until the expiration of the last to expire Lilly Non-Collaboration ASO Patent Right that includes a Valid Claim that Covers such Isis Non-Collaboration ASO Product;

9.6.2 **Isis Validation ASO Products**. For Isis Validation ASO Products, Isis shall pay Lilly [***] on Isis' annual Net Sales of each Isis Validation ASO Product until the expiration of the last to expire Isis Collaboration Patent Right or Lilly Collaboration Patent Right that includes a Valid Claim that Covers such Isis Validation ASO Product; *provided, however,* that the total royalty payable by Isis with respect to any Isis Product under Sections 9.6.1 and 9.6.2 shall not exceed [***] of Net Sales in the aggregate; and

9.6.3 **Isis Drug Discovery ASO Products**. For an Isis Drug Discovery ASO Product that is not directed to a Stage 2 Drug Discovery Target or a Stage 3 Drug Discovery Target, Isis shall pay to Lilly the applicable percentage of Net Sales set forth below for each such Isis Drug Discovery ASO Product until the expiration of the last to expire Isis Collaboration Patent Right or Lilly Collaboration Patent Right that includes a Valid Claim that Covers such Isis Drug Discovery ASO Product:

Stage at which Lilly's license to a Isis Drug Discovery ASO Product was terminated	**Royalty Rate**
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

9.6.4 **Isis Drug Discovery ASO Products**. For Isis Drug Discovery ASO Products that are directed to Stage 2 Drug Discovery Targets or Stage 3 Drug Discovery Targets, Isis will pay to Lilly the applicable percentage of Net Sales set forth below for each such a Isis Drug Discovery ASO Product until the expiration of the last to expire Isis Collaboration Patent Right or Lilly Collaboration Patent Right that includes a Valid Claim that Covers such Isis Drug Discovery ASO Product:

Stage at which Lilly's license to a Isis Drug Discovery ASO Product was terminated	**Royalty Rate**
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

9.6.5 **Lilly Summary Reports.** If Isis elects to receive a summary report from Lilly under Section 8.2.2(c) or 8.2.3(c) with respect to an ASO Compound, Isis shall make the applicable payment set forth below to Lilly with respect to any Isis Reagent ASO Product, Isis Validation Product or Isis Drug Discovery Product based thereon, as applicable within [***] after receipt of such report from Lilly:

(a) If Isis acquires rights to an Isis Reagent ASO Product, Isis Validation ASO Product or Isis Drug Discovery ASO Product pursuant to Section 8.2.2(c) or 8.2.3(c) prior to completion of IND-enabling toxicology studies, then Isis shall pay Lilly [***];

(b) If Isis acquires rights to an Isis Reagent ASO Product, Isis Validation ASO Product or Isis Drug Discovery ASO Product pursuant to Section 8.2.2(c) or 8.2.3(c) after completion of IND-enabling toxicology studies but before completion of Phase I Clinical Trials, then Isis shall pay Lilly [***];

(c) If Isis acquires rights to an Isis Reagent ASO Product, Isis Validation ASO Product or Isis Drug Discovery ASO Product pursuant to Section 8.2.2(c) or

8.2.3(c) after completion of Phase I Clinical Trials but prior to completion of Phase II Clinical Trials, then Isis shall pay Lilly [***]; and

(d) If Isis acquires rights to an Isis Reagent ASO Product, Isis Validation ASO Product or Isis Drug Discovery ASO Product pursuant to Section 8.2.2(c) or 8.2.3(c) after completion of Phase II Clinical Trials, then Isis shall pay Lilly [***].

9.6.6 **ASO Product Competition.** In the event that during the term of this Agreement, Isis develops or commercializes an ASO Product not subject to payment obligations under any other provision of this Section 9.6 that:

(a) selectively modulates a Target that has [***]; and

(b) [***].

then Isis shall pay to Lilly royalties on the Net Sales of such ASO Product being developed or commercialized by Isis for such same indication(s) that is equal to [***] of the Net Royalty payable by Lilly to Isis for such competing Lilly ASO Product.

9.7 **Royalty Obligations.** Except as otherwise provided in this Agreement both Parties acknowledge and agree that each is solely responsible for any and all royalty obligations that have accrued or may accrue in the future with respect to any agreements and/or arrangement that such Party may have agreed to prior to the Effective Date. Except as otherwise provided in this Agreement, any Third Party technology acquired by Isis that is applicable to Reagent ASO Products, Validation ASO Products or Drug Discovery ASO Products shall be made available to Lilly at the cost (including royalties, milestones and other payments) payable by Isis to such Third Party.

9.8 **COPS Protection.** Isis and Lilly agree to discuss in good faith a royalty reduction for any Lilly Product or Isis Product for which the COPS is greater than [***].

9.9 **Compulsory License.** If in any country a Third Party obtains a Compulsory License to sell a Lilly Product or Isis Product, then Lilly or Isis, respectively, shall promptly notify the other Party. If the royalty rate payable by the grantee of the Compulsory License is less than the then-current royalty rate paid under this Agreement, then the royalty rate, payable under this Agreement with respect to such Lilly Product or Isis Product, as applicable, shall be reduced to such lower rate in the subject country for so long as sales are made pursuant to the Compulsory License; *provided*, *however,* [***].

9.10 **Inflation.** The increments of annual Net Sales tiers set forth in Sections 9.3.3(c) and 9.3.4(c) will be adjusted on a Calendar Year basis commencing January 1, 2002 (and on January 1 of each year thereafter during the term of this Agreement) by an amount equal to the percentage change, if any, in the CPI for the preceding year.

9.11 **Accounting Reports; Payment of Royalty.** Each Party (including its Affiliates) and its Sublicensees shall keep complete and accurate books and records which may be necessary to ascertain properly and to verify the payments owed hereunder. [***] Each Party will make royalty payments to the other Party for Products sold by such Party, its Affiliates and

Sublicensees during the Calendar Quarter within [***] days of the last day of that Calendar Quarter. Each royalty payment will be accompanied by a written report for that Calendar Quarter showing the Net Sales of the Products sold by such Party, its Affiliates and Sublicensees worldwide during the quarterly reporting period and the calculation of the royalties payable under this Agreement.

9.12 **Audits.** Upon the written request of a Party (the ***"Auditing Party"***), and not more than once in each Calendar Year, the other Party (the ***"Audited Party"***) will permit the Audited Party's independent certified public accountant to have access during normal business hours to such of the records of the Audited Party as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for the current year and the preceding two (2) years prior to the date of such request. The Auditing Party shall submit an audit plan, including audit scope, to the Audited Party for the Audited Party's approval, which shall not be unreasonably withheld, prior to audit implementation. The independent certified public accountants shall keep confidential any information obtained during such inspection and shall report to the Auditing Party only the amounts of Net Sales and royalties due and payable. Upon the expiration of two (2) years following the end of any Calendar Year, the calculation of royalties payable with respect to such year will be binding and conclusive upon the Auditing Party, and the Audited Party and its Affiliates and Sublicensees will be released from any liability or accountability with respect to royalties for such year. If such accounting firm concludes that additional royalties were owed, or that the Audited Party overpaid royalties, during such period, the Audited Party will pay the additional royalties, or the Auditing Party shall return any overpaid royalties, within ninety (90) days of the date the Auditing Party delivers to the Audited Party such accounting firm's written report. The fees charged by such accounting firm will be paid by the Auditing Party unless the additional royalties owed by the Audited Party exceed [***] of the royalties paid for the royalty period subject to the audit, in which case the Audited Party will pay the reasonable fees of the accounting firm. The Audited Party will include in each sublicense granted by it pursuant to this Agreement a provision requiring the Sublicensee to make reports to the Audited Party, to keep and maintain records of sales made pursuant to such sublicense and to grant access to such records by a mutually agreed upon independent accountant to the same extent required of the Audited Party under this Agreement. The Auditing Party will treat all financial information subject to review under this Section 9.12 or under any sublicense agreement in accordance with the

confidentiality provisions of this Agreement, and will cause its accounting firm to enter into an acceptable confidentiality agreement with the Audited Party obligating it to retain all such financial information in confidence pursuant to such confidentiality agreement.

9.13 **Payment.** All payments to a Party under this Agreement will be made in United States Dollars by bank wire transfer in next day available funds to such bank account in the United States designated in writing by the other Party from time to time. Each Party will pay a late payment service charge of [***] per month (or the highest amount allowed by law, if lower than [***]) on all past-due amounts owed by such Party under this Agreement.

9.14 **Income Tax Withholding.** Each Party will be responsible for its own tax liabilities resulting from the payments received from the other Party under this Agreement. If laws, rules or regulations require withholding of income taxes or other taxes imposed upon payments set forth in this Article 9, the paying Party will make such withholding payments as

required and subtract such withholding payments from the payments set forth in this Article 9. The paying Party will submit appropriate proof of payment of the withholding taxes to the other Party within a reasonable period of time.

ARTICLE 10

CONFIDENTIALITY

10.1 **Nondisclosure and Nonuse Obligations.** All (i) Confidential Information disclosed by one Party to the other Party hereunder and (ii) Collaboration Know-How will be maintained in confidence and will not be disclosed to any Third Party or used for any purpose except as expressly permitted herein without the prior written consent of the other Party.

10.2 **Permitted Disclosure of Confidential Information.** Notwithstanding Section 10.1, a Party may disclose Confidential Information of the other Party or Collaboration Know-How as follows:

10.2.1 to appropriate U.S. and/or foreign tax authorities, appropriate patent agencies in order to obtain Patent Rights pursuant to this Agreement, appropriate regulatory authorities to gain approval to conduct clinical trials or to market Lilly Products or Isis Products pursuant to this Agreement, but such disclosure, may be only to the extent reasonably necessary to obtain such Patent Rights or authorizations;

10.2.2 if required by any governmental authority other than under Section 10.2.1, provided that prior to such disclosure, the Party subject to the request for such disclosure (the ***"Notifying Party"***) promptly notifies the other Party of such requirement so that such other Party may seek a protective order or other appropriate remedy; and *provided, further*, that in the event that no such protective order or other remedy is obtained, or that such other Party waives compliance with this Article 10, the Notifying Party will furnish only that portion of the other Party's Confidential Information or of the Collaboration Know-How that it is advised by counsel it is legally required to furnish and will exercise all reasonable efforts to obtain reasonable assurance that confidential treatment will be accorded the other Party's Confidential Information or Collaboration Know-How so furnished.

10.2.3 by a Party to its permitted Sublicensees, agents, consultants, Affiliates and/or other Third Parties for the research and development, manufacturing and/or marketing of Lilly Products or Isis Products (or for such Parties to determine their interest in performing such activities) in accordance with this Agreement on the condition that such Affiliates and Third Parties agree to be bound by the confidentiality and non-use obligations contained in this Agreement; or

10.2.4 if required to be disclosed by law or court order, provided that notice is promptly delivered to the non-disclosing Party in order to provide an opportunity to challenge or limit the disclosure obligations.

ARTICLE 11

DISCLAIMERS, REPRESENTATIONS, WARRANTIES AND INDEMNIFICATIONS

11.1 **Isis Representations and Warranties.** Isis represents and warrants to Lilly as follows:

11.1.1 **Corporate Existence and Authority.** As of the Effective Date, Isis: (a) is a corporation duly organized, validly existing and in good standing under the laws of the state in which it is incorporated, (b) has full corporate power and authority and the legal right to own and operate its property and assets and to carry on its business as it is now being conducted and as contemplated in this Agreement, including the right to grant the options to license and licenses granted hereunder, (c) has the corporate power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, (d) has taken all necessary corporate action on its part required to authorize the execution and delivery of the Agreement and the performance of its obligations hereunder, and (e) has delivered an Agreement that has been duly executed and constitutes a legal, valid, binding obligation of Isis and is enforceable against it in accordance with its terms;

11.1.2 **Patents, Prior Art.** As of the Effective Date and to the best of Isis' knowledge, it has the sufficient legal and/or beneficial title and ownership under the Isis Technology as is necessary to fulfill its obligations under this Agreement and to grant the licenses and options to license to Lilly pursuant to this Agreement. Isis is not aware of any communications alleging that it has violated or, by conducting its business as currently proposed under this Agreement, would violate any of the intellectual property rights of any Third Party;

11.1.3 **Absence of Litigation, Infringement, Misappropriation**. As of the Effective Date and to the best of Isis' knowledge, there is no pending or threatened litigation (and Isis has not received any communication relating thereto) which alleges that Isis' activities in the field of Antisense Technology or under this Agreement would infringe or misappropriate any intellectual property rights of any Third Party. To the best of Isis' knowledge,

there is no material unauthorized use, infringement or misappropriation of any of its intellectual property rights that are the subject of the licenses or options to license granted hereunder;

11.1.4 **Full Disclosures.** Isis has provided Lilly with all information that Lilly has requested for deciding the merits of entering into this Agreement and all information reasonably useful or necessary to enable Lilly to make an informed decision regarding entering into this Agreement;

11.1.5 **Employee Obligations**. All Isis employees who will conduct research under this Agreement have legal obligations requiring assignment to Isis of all inventions made in the course of and as a result of their association with Isis and obligating the individual to maintain as confidential the Confidential Information of Isis, as well as the Confidential Information of Lilly which Isis may receive;

11.1.6 **Compliance with Laws.** In carrying out its work under this Agreement, all Isis work shall be carried out in compliance with any applicable laws including, without limitation, federal, state, or local laws, regulations, or guidelines governing the work at the site where such work is being conducted. Moreover, Isis will carry out all work under the Collaboration in accordance with current Good Laboratory Practices, Good Clinical Practices, and Good Manufacturing Practices, if applicable based on the specific work to be conducted;

11.1.7 **No Debarment.** Isis will comply at all times with the provisions of the Generic Drug Enforcement Act of 1992 and will upon request certify in writing to Lilly that none of its employees nor any person providing services to Isis in connection with the Collaboration have been debarred under the provisions of such Act;

11.1.8 **Licenses**. Isis has not taken nor will it take any action which would, in Isis' good faith judgment, interfere with any obligations of Isis set forth in this Agreement, including but not limited to the obligation to grant Lilly the licenses and options to license described in Article 8; and

11.1.9 **Target Availability.** Isis agrees not to enter into any collaboration with, or render services for, a Third Party wherein Antisense Technology is applied to Targets in the Collaboration Therapeutic Area of oncology whereby such collaboration or service with or for a Third Party will negatively impact the timely accomplishment of the objectives of the Collaboration.

11.2 **Lilly Representations and Warranties.** Lilly represents and warrants to Isis as follows:

11.2.1 **Corporate Existence and Authority.** As of the Effective Date, Lilly: (a) is a corporation duly organized, validly existing and in good standing under the laws of the state in which it is incorporated, (b) has full corporate power and authority and the legal right to own and operate its property and assets and to carry on its business as it is now being conducted and as contemplated in this Agreement, including the right to grant the options to license and licenses granted hereunder, (c) has the corporate power and authority and the legal right to enter into this Agreement and perform its obligations hereunder, (d) has taken all necessary corporate action on its part required to authorize the execution and delivery of the Agreement and the performance of its obligations hereunder, and (e) has delivered an Agreement that has been duly executed and constitutes a legal, valid, binding obligation of Lilly and is enforceable against it in accordance with its terms;

11.2.2 **Employee Obligations**. All Lilly personnel who will conduct research under this Agreement have legal obligations requiring assignment to Lilly of all inventions made in the course of and as a result of their association with Lilly and obligating the individual to maintain as confidential the confidential information of Lilly, as well as the confidential information of Isis which Lilly may receive;

11.2.3 **Compliance with Laws**. In carrying out its work under this Agreement, all Lilly work shall be carried out in compliance with any applicable laws including, without limitation, federal, state, or local laws, regulations, or guidelines governing the work at the site

where such work is being conducted. Moreover, Lilly will carry out all work under the Collaboration in accordance with current Good Laboratory Practices, Good Clinical Practices, Good Manufacturing Practices, if applicable based on the specific work to be conducted;

11.2.4 **No Debarment.** Lilly will comply at all times with the provisions of the Generic Drug Enforcement Act of 1992 and will upon request certify in writing to Isis that none of its employees nor any person providing services to Lilly in connection with this Collaboration or this Agreement have been debarred under the provisions of such Act; and

11.2.5 **Licenses.** Lilly has not taken nor will it take any action which would, in Lilly's good faith judgment, interfere with any obligations of Lilly set forth in this Agreement, including but not limited to the obligation to grant Isis the licenses and options to license described in Article 8.

11.3 **Disclaimer.** EXCEPT AS EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY MAKES ANY REPRESENTATION OR WARRANTY TO THE OTHER PARTY OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING, WITHOUT LIMITATION, ANY WARRANTY OF NON-INFRINGEMENT, MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. Without limiting the generality of the foregoing, each Party expressly does not warrant (a) the success of any research undertaken in the course of the Collaboration or (b) the safety for any purpose of the technology it provides hereunder.

11.4 **Responsibility and Control.** Lilly and Isis shall each be solely responsible for the safety of their respective employees, agents, licensees or Sublicensees with respect to efforts employed under this Agreement and each shall hold the other harmless with regard to any liability for damages or personal injuries resulting from acts of its respective employees, agents, licensees or Sublicensees.

11.5 **Isis' Right to Indemnification.** Lilly shall indemnify each of Isis, its Affiliates, Sublicensees, permitted successors and assigns, and the directors, officers, employees, agents and counsel thereof (the ***"Isis Indemnitees"***), and defend and hold each Isis Indemnitee harmless from and against any and all liabilities, damages, losses, settlements, claims, actions, suits, penalties, fines, costs or expenses (including, without limitation reasonable attorneys' fees) (any of the foregoing, ***"Damages"***) incurred by or asserted against any Isis Indemnitee of whatever kind or nature, including, without

limitation, any claim or liability based upon negligence, warranty, strict liability, or violation of government regulation but only to the extent arising from or occurring as a result of a claim or demand made by a Third Party (a ***"Third Party Claim"***) against any Isis Indemnitee arising because of: (a) breach of any representation or warranty made by Lilly pursuant to this Article 11; (b) any material breach of this Agreement by Lilly; (c) the manufacture, use, handling, storage, sale or other disposition of a Lilly Product that is sold by Lilly, its Affiliates, agents or Sublicensees; (d) violation of the trade secrets of any Third Party by Lilly; (e) any Third Party Claim that any Lilly Collaboration Technology or Lilly Non-Collaboration ASO Patent Right should not have been disclosed or made available to Isis; (f) a Third Party Claim for payment under the Yale Agreement with respect to the development and/or commercialization by Lilly, its Affiliates and/or Sublicensees of Drug Discovery ASO Products directed to Survivin; *provided*, *however*, that such indemnification by Lilly under this Section 11.5(f) shall apply only to Third Party Claims for payment because such Drug Discovery

ASO Product is alleged to be a Licensed Product (as defined in the Yale Agreement) under Section 1.7(i) of the Yale Agreement; or (g) any Third Party Claim that either Party's use of a Target designated by Lilly for use in the Collaboration infringes the intellectual property rights of such Third Party; except, in each such case in subparagraphs (a) through (g) above, to the extent that such Damages are finally determined to have resulted from the negligence or misconduct of an Isis Indemnitee, or the breach of any representation or warranty under Section 11.1 by Isis.

11.6 **Lilly's Right to Indemnification.** Isis shall indemnify each of Lilly, its Affiliates, Sublicensees, successors and assigns, and the directors, officers, employees, agents and counsel thereof (the ***"Lilly Indemnitees"***), and defend and hold each Lilly Indemnitee harmless from and against any and all Damages incurred by or asserted against any Lilly Indemnitee of whatever kind or nature, including, without limitation, any claim or liability based upon negligence, warranty, strict liability, violation of government regulation but only to the extent arising from or occurring as a result of a Third Party Claim against any Lilly Indemnitee arising because of: (a) breach of any representation or warranty made by Isis pursuant to this Article 11; (b) any material breach of this Agreement by Isis; (c) the manufacture, use, handling, storage, sale or other disposition of an Isis Product that is sold by Isis, its Affiliates, agents or Sublicensees; (d) violation of the trade secrets of any Third Party by Isis; (e) any Third Party Claim that any Isis Technology or Isis Collaboration Technology should not have been disclosed or made available to Lilly; (f) any Third Party Claim for payments under the Yale Agreement with respect to the development and/or commercialization by Lilly, its Affiliates and/or Sublicensees of Drug Discovery ASO Products directed to Survivin; *provided*, *however*, that such indemnification by Isis under this Section 11.6(f) shall apply only to Third Party Claims for payment because such Drug Discovery ASO Product is alleged to be a Licensed Product (as defined in the Yale Agreement) under Section 1.7(ii) of the Yale Agreement as a result of any invention made by Isis using the technology licensed under the Yale Agreement; or (g) any Third Party Claim that either Party's use of a Target designated by Isis for use in the Collaboration infringes the intellectual property rights of such Third Party; except, in each such case, in subparagraphs (a) through (g) above, to the extent that such Damages are finally determined to have resulted from the negligence or misconduct of a Lilly Indemnitee, or the breach of any representation or warranty under Section 11.2 by Lilly.

11.7 **Indemnification Procedures.** Promptly after a Party entitled to indemnification under Section 11.5 or 11.6 (an ***"Indemnitee"***) receives notice of any pending or threatened claim against it (an ***"Action"***), such Indemnitee shall give written notice to the Party to whom the Indemnitee is entitled to look for indemnification pursuant to Section 11.5 or 11.6, as applicable (the ***"Indemnifying Party"***), of the commencement thereof, provided that the failure so to notify the Indemnifying Party shall not relieve it of any liability that it may have to any Indemnitee hereunder, except to the extent the Indemnifying Party demonstrates that it is prejudiced thereby. In case any Action that is subject to indemnification under this Article 11, shall be brought against an Indemnitee and it shall give written notice to the Indemnifying Party of the commencement thereof, the Indemnifying Party shall be entitled to participate therein and, if it so desires, to assume the defense thereof with counsel reasonably satisfactory to such Indemnitee and, after notice from the Indemnifying Party to the Indemnitee of its election to assume the defense thereof, the Indemnifying Party shall not be liable to such Indemnitee under this Article 11 for any fees of other counsel or any other expenses, in each case subsequently

incurred by such Indemnitee in connection with the defense thereof, other than reasonable costs of investigation. Notwithstanding an Indemnifying Party's election to assume the defense of any such Action that is subject to indemnification under this Article 11, the Indemnitee shall have the right to employ separate counsel and to participate in the defense of such Action, and the Indemnifying Party shall bear the reasonable fees, costs and expenses of such separate counsel if: (i) the use of counsel chosen by the Indemnifying Party to represent the Indemnitee would present such counsel with a conflict of interest; (ii) the actual or potential defendants in, or targets of, any such Action include both the Indemnifying Party and the Indemnitee, and the Indemnitee shall have reasonably concluded that there may be legal defenses available to it which are different from or additional to those available to the Indemnifying Party (in which case the Indemnifying Party shall not have the right to assume the defense of such Action on the Indemnitee's behalf); (iii) the Indemnifying Party shall not have employed counsel satisfactory to the Indemnitee to represent the Indemnitee within a reasonable time after notice of the institution of such Action; or (iv) the Indemnifying Party shall authorize the Indemnitee to employ separate counsel at the Indemnifying Party's expense. If an Indemnifying Party assumes the defense of such Action, no compromise or settlement thereof may be effected by the Indemnifying Party without the Indemnitee's written consent, which consent shall not be unreasonably withheld or delayed, unless (1) there is no finding or admission of any violation of law or any violation of the rights of any other Party and no effect on any other claims that may be made against the Indemnitee and (2) the sole relief provided is monetary damages that are paid in full by the Indemnifying Party.

ARTICLE 12

INTELLECTUAL PROPERTY

12.1 **Disclosures and Reports.** During the Collaboration Term, each Party shall promptly disclose to the other in writing all Know-How generated in the course of the Collaboration. Such disclosure shall be in sufficient detail to permit the other Party to employ such Know-How as provided herein. Within ninety (90) days after of the expiration of the Collaboration Term, each Party shall provide the other Party with a comprehensive final written report with respect to the Know-How generated by such Party in the course of the Collaboration.

12.2 **Ownership.** Lilly shall own all inventions within the scope of the Collaboration made solely by its employees and Isis shall own all inventions within the scope of the Collaboration made solely by its employees. All inventions made jointly by employees of Lilly and employees of Isis pursuant to 35 USC 116 within the scope of the Collaboration shall be owned jointly by Isis and Lilly (the ***"Joint Collaboration Patent Rights***"). All Patent Rights covering any invention made within the scope of the Collaboration shall be owned by the Parties or Party, as the case may be, that own(s) said invention.

12.3 **Patent Filing and Prosecution**. Lilly and Isis shall work closely to ensure that, when appropriate, Patent Rights are obtained for inventions arising in the course of the Collaboration. Each Party shall use its commercially reasonable efforts in filing and prosecuting Patent Rights claiming inventions arising in the course of the Collaboration under this Section 12.3. When appropriate, the Parties shall file Collaboration ASO Compound Patent Rights separately from patent applications containing all other claims, including, without

limitation, non-ASO Compound composition of matter claims and claims directed to the use of such non-ASO Compound. Lilly shall not be responsible for reimbursement under Section 12.6 of any of Isis' external costs of filing, prosecuting, maintaining and extending any Isis Collaboration ASO Compound Patent Right; *provided, however,* that Lilly shall reimburse [***] of Isis' external costs of filing, prosecuting, maintaining and extending Isis Collaboration ASO Compound Patent Rights claiming Drug Discovery ASO Compounds and/or the use of Drug Discovery ASO Compounds directed to a Drug Discovery Target until the earlier to occur of the time (i) such Target becomes an Abandoned Drug Discovery Target or otherwise ceases to be a Drug Discovery Target for purposes of this Agreement, (ii) Lilly assumes responsibility for such Isis Collaboration ASO Compound Patent Rights as provided in Section 12.3.1 (in which case the terms of Section 12.3.1 will apply), or (iii) Lilly elects to discontinue such reimbursement pursuant to Section 12.6. Except as provided in Section 12.3.1, Isis shall be responsible for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to the Isis Collaboration Patent Rights and the Isis Patent Rights. Lilly shall be responsible for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to the (i) Lilly Collaboration Patent Rights and (ii) Isis Collaboration ASO Compound Patent Rights and Isis ASO Compound Patent Rights as provided by Section 12.3.1. The Executive Committee shall designate one of the Parties as being the responsible Party for preparing, filing, prosecuting, maintaining and taking such other actions as are reasonably necessary or appropriate with respect to the Joint Collaboration Patent Rights. Allocation of external costs for preparing, filing, prosecuting, maintaining such Joint Collaboration Patent Rights shall be determined by the Executive Committee. Each Party shall provide the other Party with a copy of any patent application that first discloses an invention arising in the course of the Collaboration or any Collaboration Know-How, prior to filing the first of such applications in any jurisdiction, for review and comment by the other Party. Each Party shall keep the other Party continuously informed of all significant matters relating to the preparation, filing, prosecution and maintenance of Collaboration Patent Rights. Each Party shall provide the other Party with copies of any substantial prosecution papers relating to Collaboration Patent Rights within thirty (30) days of receipt. Each Party shall endeavor in good faith to coordinate its efforts with those of the other Party to minimize or avoid interference with the prosecution of the other Party's patent applications. The Executive Committee shall review and have oversight responsibility for all patent matters pertaining to the Collaboration.

12.3.1 Lilly at its own expense, will prepare, file, prosecute and/or maintain the (i) Isis Collaboration ASO Compound Patent Rights and (ii) Isis ASO Compound Patent Rights that are exclusively licensed by Lilly pursuant to Article 8. Lilly shall be responsible for [***] of the cost of filing, prosecuting, and maintaining (i) Isis Collaboration ASO Compound Patent Rights and (ii) Isis ASO Compound Patent Rights, that are incurred on and after such time as any such Patent Right is exclusively licensed to Lilly under Article 8. In the event of termination under Section 13.4 or 13.5, or upon written agreement of the Parties, such responsibility and expense for preparation, filing, prosecuting and maintenance shall revert back to Isis; *provided*, *however*, such responsibility and expense for preparation, filing, prosecuting and maintenance shall not revert to Isis for those (i) Isis Collaboration ASO Compound Patent Rights and (ii) Isis ASO Compound Patent Rights that continue to be exclusively licensed by Lilly as provided by Article 13.6. Lilly may use in-house patent counsel or outside patent counsel that is acceptable to Isis for the filing, prosecution and maintenance of Isis Collaboration ASO Compound Patent

Rights and Isis ASO Compound Patent Rights for which Lilly assumes responsibility for under this Section 12.3.1. Upon licensing of Isis Collaboration ASO Compound Patent Rights and Isis ASO Compound Patent Rights by Lilly under Article 8, Isis will promptly transfer the subject patent files to Lilly and shall execute such documents and perform such acts as may be reasonably necessary for Lilly to take control of the such patent filing, prosecution and maintenance and will provide all necessary assistance in the prosecution and maintenance thereof. Lilly will, in a timely manner, provide Isis with copies of all draft applications, responses and other substantive papers relating to the filing, prosecution and maintenance (including the verification of all fees and annuities) of such Isis Collaboration ASO Compound Patent Rights and Isis ASO Compound Patent Rights and shall provide Isis with an opportunity to comment on any draft applications, responses or amendments at least 3 days prior to filing and to the extent practicable incorporate such comments. Isis hereby acknowledges a possible conflict of interest between Lilly and Isis relating to the Isis Collaboration ASO Compound Patent Rights and Isis ASO Compound Patent Rights for which Lilly assumes responsibility for filing, prosecution and maintenance under this Section 12.3.1. So long as Lilly complies with provisions of this Section 12.3.1, Isis hereby grants Lilly and Lilly's patent counsel a conflict waiver, to the limited extent of any conflict of interest arising from the fact that (a) Lilly has the right to prepare, file, prosecute and maintain the Isis Collaboration ASO Compound Patent Rights and Isis ASO Compound Patent Rights pursuant to this Section 12.3.1 and (b) Isis owns or Controls such Patent Rights.

12.4 **Election Not to File, Prosecute or Maintain.** If the responsible Party under Section 12.3 elects (a) not to file a patent application claiming an invention made in the course of the Collaboration in a particular country, or (b) to discontinue prosecution or maintenance of any Patent Right in a particular country that is (i) Controlled by such Party Covering a Product being developed or commercialized by the other Party hereunder or (ii) of any Collaboration Patent Right or (iii) with respect to Lilly, an Isis Collaboration ASO Compound Patent Right or Isis ASO Compound Patent Right for which Lilly assumes responsibility for filing, prosecution and maintenance under Section 12.3.1 that Party (the ***"Initial Responsible Party"***) shall give thirty (30) days advance written notice to the other Party of any decision to cease preparation, filing, prosecution and maintenance of that Patent Right (a ***"Discontinued Patent"***); *provided, however,* that abandonment of a patent application in favor of a continuation or a continuation-in-part thereof shall not constitute discontinuance of the patent application. In such case, the other Party may elect at its sole discretion to continue preparation, filing, prosecution or maintenance of the Discontinued Patent at its sole expense. The Party so continuing shall own any such patent application and patents maturing therefrom and be solely responsible for all costs, and the Initial Responsible Party shall have a non-exclusive, worldwide, irrevocable, perpetual, fully-paid license to continue to practice such Discontinued Patent, including the right to sublicense solely in connection with the grant of a license to develop, make, use, import, offer for sale and sell a product of the Initial Responsible Party; *provided, however*, with respect to an Isis Collaboration ASO Compound Patent Right or Isis ASO Compound Patent Right for which Lilly assumes responsibility for filing, prosecution and maintenance under Section 12.3.1 that becomes a Discontinued Patent under this Section 12.4, the license granted under this Agreement with respect to each such Discontinued Patent shall terminate on the date of receipt of such written notification from Lilly and Lilly shall cease to have any obligation to pay royalties to Isis under this Agreement with respect to such Discontinued Patent. In addition, such Party so continuing shall cease to have any obligation to pay royalties to the Initial Responsible Party under this

Agreement with respect to the Discontinued Patent. The Initial Responsible Party shall execute such documents and perform such acts as may be reasonably necessary for the other Party to file or to continue prosecution or maintenance, including assigning ownership of such patents and inventions to such electing Party. Discontinuance may be on a country-by-country basis or for a patent application or patent series in total.

12.5 **Inventions Otherwise Unpatentable in the United States.** Any invention made by a Party in the course of the Target Validation Program or Drug Discovery Program hereto that would be rendered unpatentable in the United States solely on account of prior art under one or more of subsections 102(e), (f), or (g) of Title 35, U.S.C., but for the absence of an obligation of assignment of said invention (or an undivided interest therein) to the other Party hereto, is hereby subjected to an obligation of assignment to such other Party of such interest in the invention as renders the invention patentable in the United States. Such assignment shall have force and effect only with respect to patents granted in the United States. The rights of the Parties with respect to any invention subject to an obligation of assignment under this Section 12.5, except for subject matter patentable to the assignee in the absence of the assignment, shall be the same as the rights that would have applied under this Agreement had no obligation to assign under this Section 12.5 existed. If and only if required to give force and effect to the immediately preceding sentence and, in such case, only to the extent required to give such force and effect, each assignee under this Section 12.5 hereby grants to each of the assignors under this Section 12.5 such licenses, if any, as are required to vest in the assignor rights to make, have made, use, sell and import the assigned invention, except for subject matter patentable to the assignee in the absence of the assignment.

12.6 **Costs and Expenses.** Lilly shall bear its own costs and expenses in filing, prosecuting, maintaining and extending Lilly Collaboration Patent Rights and, subject to Section 12.3 (including 12.3.1), shall reimburse Isis for [***] of Isis' external costs of filing, prosecuting, maintaining and extending any Isis Collaboration Patent Rights for which costs are incurred after the Effective Date of this Agreement. Lilly and Isis patent costs and expenses shall not be paid from the Collaboration Funds. Lilly may at any time, and in its sole discretion, discontinue reimbursement of the external costs incurred by Isis in filing, prosecuting (including any interference), maintaining, and extending any Isis Collaboration Patent Right, on an Isis Collaboration Patent Right-by-Isis Collaboration Patent Right and country-by-country basis. Lilly shall provide Isis with written notice designating each Isis Collaboration Patent Right and country for which Lilly has decided to discontinue such reimbursement. Lilly's obligation to reimburse Isis for any external costs with respect to any such Isis Collaboration Patent Right shall cease on the date of receipt of such notification; *provided, however,* that Lilly shall remain responsible for [***] (or [***] in the case Section 12.3.1 applies) of the external costs incurred up to the date of receipt of such notification. The license granted under this Agreement with respect to each Isis Collaboration Patent Right in each country that is specified in the written notice provided by Lilly to Isis pursuant to this Section 12.6 shall terminate on the date of receipt of such written notification and Lilly shall cease to have any obligation to pay royalties to Isis under this Agreement with respect to such Isis Collaboration Patent Right.

12.7 **Patent Term Extensions.** The Parties shall cooperate with each other in gaining patent term extension wherever applicable to any Lilly Product or Isis Product. The Party selling such Lilly Product or Isis Product shall determine which patents shall be extended.

All filings for such extension shall be made by the Party to whom the patent is assigned; *provided, however,* that in the event that the Party to whom the patent is assigned elects not to file for an extension, such Party shall (i) inform the other Party of its intention not to file, (ii) grant the other Party the right to file for such extension, and (iii) cooperate as necessary to assist the other Party in filing such extension.

12.8 **Audit of Costs.** Upon written notice, Lilly and Isis shall each have the right at its own expense and not more than annually in or in respect of any Calendar Year, and during normal business hours, to audit those books and records as may be reasonably necessary to verify the accuracy and reasonableness of any costs incurred by the other Party and for which the other Party is seeking or has received partial reimbursement pursuant to Section 12.6 in respect of any Calendar Year ending not more than [***] year prior to the date of such notice. Any information received or obtained in connection with an audit under this Section 12.8 is Confidential Information and both Parties shall retain all such information in confidence.

12.9 **Notice of Certification.** Isis and Lilly each shall immediately upon receiving notice give notice to the other of any certification filed under the U.S. "Drug Price Competition and Patent Term Restoration Act of 1984" claiming that (a) a Collaboration Patent Right or Isis Patent Right Covering a Lilly Product being developed or commercialized by Lilly hereunder, or (b) a Collaboration Patent Right Covering an Isis Product being developed or commercialized by Isis hereunder, is invalid or that any infringement will not arise from the manufacture, use, sale, offer for sale or import of any product by a Third Party. If Lilly decides not to bring infringement proceedings against the entity making such a certification with respect to a Collaboration Patent Right or Isis Patent Right Covering a Lilly Product being developed or commercialized by Lilly hereunder, Lilly shall give notice to Isis of its decision not to bring suit within twenty-one (21) days after receipt of notice of such certification. Isis may then, but is not required to, bring suit against the entity that filed the certification. If Isis decides not to bring infringement proceedings against the entity making such a certification with respect to a Collaboration Patent Right Covering an Isis Product being developed or commercialized by Isis hereunder, Isis shall give notice to Lilly of its decision not to bring suit within twenty-one (21) days after receipt of notice of such certification. Lilly may then, but is not required to, bring suit against the Third Party that filed the certification. Any suit by Lilly or Isis shall either be in the name of Lilly or in the name of Isis, or jointly by Lilly and Isis, as may be required by law. For this purpose, the Party not bringing suit shall execute such legal papers necessary for the prosecution of such suit as may be reasonably requested by the Party bringing suit. Any costs incurred or benefits received as a result of proceeding under this Section 12.9 shall be paid or received entirely by the Party who pursued the action.

12.10 **Notice of Infringement Claim.** If the practice of a license granted to a Party under this Agreement results in a claim against a Party for patent infringement or for inducing or contributing to patent infringement (***"Infringement Claim"***), the Party first having notice of an Infringement Claim shall promptly notify the other in writing. The notice shall set forth the facts of the Infringement Claim in reasonable detail.

12.10.1 **Responsibilities.** Isis shall have the sole right to control any defense of any Infringement Claim involving alleged infringement of Third Party rights by Isis' activities at its own expense and by counsel of its own choice, and Lilly shall have the right, at its own

expense, to be represented in any such action by counsel of its own choice. Lilly shall have the sole right to control any defense of any Infringement Claim involving alleged infringement of Third Party rights by Lilly's activities at its own expense and by counsel of its own choice, and Isis shall have the right, at its own expense, to be represented in any such action by counsel of its own choice. Notwithstanding the foregoing, if the claim involves an allegation of a

violation of the trade secret rights of a Third Party, the Party accused of such violation shall have the obligation to defend against such claim and shall indemnify the other Party against all costs associated with such claim. Neither Party shall have the right to settle any patent infringement litigation under this Section 12.10 relating to any Patent Rights owned by or exclusively licensed to the other Party hereunder without the consent of such other Party. Each Party shall also keep the other Party continually informed of all significant matters relating to Infringement Claims of Third Parties.

12.11 **Infringement Claims Against Third Parties.**

12.11.1 **Protection Against Infringement.** Isis and Lilly each agree to take reasonable actions to protect their respective patents and technology from infringement and from unauthorized possession or use.

12.11.2 **Notice of Infringement.** If any Collaboration Know-How, Collaboration Patent Right or any other Patent Right licensed by one Party to the other under this Agreement is infringed or misappropriated, as the case may be, by a Third Party, the Party to this Agreement first having knowledge of such infringement or misappropriation, shall promptly notify the other in writing. The notice shall set forth the facts of such infringement or misappropriation in reasonable detail. The exclusive licensee of the Collaboration Know-How Collaboration Patent Right or other Patent Right shall have the primary right, but not the obligation, to institute, prosecute, and control any action or proceeding with respect to infringement or misappropriation of such Collaboration Patent Right, other Patent Right or Collaboration Know-How by its own counsel. The other Party shall have the right, at its own expense, to be represented in such action by its own counsel. The Parties shall promptly determine which Party shall have the primary responsibility to institute, prosecute, and control any action or proceeding with respect to infringement or misappropriation of Joint Collaboration Patent Rights, and the other Party shall have the right, at its expense, to be represented in such action by its counsel. During the Collaboration Term, such determination may be made by the Executive Committee. Except as otherwise agreed to by the Parties as part of a cost-sharing arrangement, any recovery realized as a result of such litigation, after reimbursement of any litigation expenses of Isis and Lilly, shall be retained by the Party that brought and controlled such litigation for purposes of this Agreement, except that any recovery realized by Isis or Lilly as a result of such litigation, after reimbursement of the Parties' litigation expenses, shall, to the extent attributable to lost sales of Isis Products or Lilly Products, respectively, be treated as Net Sales of Isis Products by Isis or Net Sales of Lilly Products by Lilly, respectively.

12.11.3 **Expenses of Bringing Infringement Action.** Lilly shall bear the costs and expenses of all infringement or misappropriation actions on Collaboration Know-How, Collaboration Patent Rights, or any other Patent Right licensed to Lilly under this Agreement to the extent such Collaboration Know-How, Collaboration Patent Rights or any other Patent Right licensed to Lilly under this Agreement Cover a Lilly Product. Isis shall bear the costs and

expenses of all infringement or misappropriation actions on Collaboration Know-How, Collaboration Patent Rights, or any other Patent Right licensed to Isis under this Agreement to the extent such Collaboration Know-How, Collaboration Patent Rights, or any other Patent Right licensed to Isis under this Agreement Cover an Isis Product.

12.11.4 **Lilly's Failure to Institute, Prosecute and Control.** If Lilly fails to institute, prosecute, and control such action or prosecution within a period of one hundred twenty (120) days after receiving notice of the infringement, Isis, subject to the prior rights of any Third Party, shall have the right to bring and control any such action by counsel of its own choice, and Lilly shall have the right, at its own expense, to be represented in any such action by counsel of its own choice. Except as otherwise agreed to by the Parties as part of a cost-sharing arrangement, any recovery realized as a result of such litigation, after reimbursement of 100% of any litigation expenses of Isis and 100% of any litigation expenses of Lilly (including the costs and expenses incurred by Lilly in providing reasonable assistance to Isis), shall be shared equally by the Parties. No settlement or consent judgment or other voluntary final disposition of a suit under this Section 12.11.4 may be entered into without the joint consent of Isis and Lilly (which consent shall not be unreasonably withheld or delayed).

12.11.5 **Isis' Failure to Institute, Prosecute and Control.** If Isis fails to institute, prosecute, and control such action or prosecution within a period of one hundred twenty (120) days after receiving notice of the infringement, Lilly, subject to the prior rights of any Third Party, shall have the right to bring and control any such action by counsel of its own choice, and Isis shall have the right, at its own expense, to be represented in any such action by counsel of its own choice. Except as otherwise agreed to by the Parties as part of a cost-sharing arrangement, any recovery realized as a result of such litigation, after reimbursement of 100% of any litigation expenses of Lilly and 100% of any litigation expenses of Isis (including the costs and expenses incurred by Isis in providing reasonable assistance to Lilly), shall be shared equally by the Parties. No settlement or consent judgment or other voluntary final disposition of a suit under this Section 12.11.5 may be entered into without the joint consent of Isis and Lilly (which consent shall not be unreasonably withheld or delayed).

12.11.6 **Settlement Approval.** Neither Party shall settle any such proceeding under this Section 12.11 without the approval of the other Party, which approval shall not be unreasonably withheld or delayed.

12.12 The Collaboration Targets on which exist Collaboration Patent Rights as of the Second Restatement Date are listed in ***Schedule 12.12***.

ARTICLE 13

TERM AND TERMINATION

13.1 **Term of Collaboration.**

13.1.1 **The Collaboration Term.** The Collaboration Term became effective on the Effective Date and shall continue in effect in accordance with this Article 13. Prior to the close of the Collaboration Term, Lilly shall have the option to extend each or both of the Target

Validation Program Term, and/or the Antisense Drug Discovery Program Term for two (2) consecutive two year periods provided that Lilly gives notice to Isis at least nine (9) months prior to the expiration of the Collaboration Term or any extension period of the Target Validation Program Term, and/or the

Antisense Drug Discovery Program Term. However, Lilly and Isis shall begin discussions concerning the expiration or extension of Collaboration at least twelve (12) months prior to the end of the Collaboration Term or any extension period of the Target Validation Program Term, and/or the Antisense Drug Discovery Program Term. If the Target Validation Program Term, and/or the Antisense Drug Discovery Program Term are extended, any such extension shall be on terms that are the same as those provided herein; *provided, however,* that (i) the funding amount paid by Lilly for any such extension shall be paid by Lilly in cash, unless agreed otherwise, disbursed on a schedule substantially the same as the disbursement schedule of Collaboration Funds under the Loan Agreement and (ii) unless agreed otherwise, such funding amount shall be the same as provided in this Agreement for the Target Validation Program, and/or the Antisense Drug Discovery Program, as applicable, such funding amount adjusted for the reduction in the duration of the extension period as compared to the Initial Collaboration Term.

13.1.2 [DELETED]

13.1.3 **Extension of the Collaboration Term**. Having extended the Oncology Term to the end of the Initial Collaboration Term pursuant to the May 3, 2004 Agreement, the Parties now hereby agree to extend the Collaboration Term with respect to the (i) Antisense Drug Discovery Program in the Collaboration Therapeutic Area of oncology and (ii) the Target Validation Program with respect to the Collaboration Therapeutic Area of oncology. The Collaboration Term shall expire on the later of (a) December 31, 2006 or (b) when the last of the Collaboration Funds are expended in accordance with the Collaborative Research Plan. Such extension of the Collaboration Term is deemed an extension of the Antisense Drug Discovery Term and the Target Validation Program Term. If the last of the Collaboration Funds are expended after December 31, 2006, the Executive Committee shall make a written determination of the exact date when the last of the Collaboration Funds were expended in order to establish the date of expiration of the Extended Collaboration Term. During the Extended Collaboration Term, the Antisense Drug Discovery Program and Target Validation Program shall be subject to the terms and conditions of this Second Restated and Amended Agreement and shall be conducted in accordance with the Collaborative Research Plan, which is attached hereto as Schedule 13.1.3 and made part of this Agreement. The Parties agree that the Reagent Provision Term shall expire on August 24, 2005 and that all activities conducted under the Reagent Provision Program shall cease on or before such date. The Parties agree that all activities conducted under the Target Validation Program with respect to all Collaboration Therapeutic Areas other than oncology, and the Antisense Drug Discovery Program with respect to all Collaboration Therapeutic Areas other than oncology, shall cease on or before August 24, 2005.

13.2 **Term of Agreement.** This Agreement shall commence on the Effective Date and shall continue until no payments are due or are capable of becoming due hereinunder, unless the Agreement is terminated earlier. All licenses granted hereunder that are in effect at expiration of this Agreement shall be deemed fully paid-up and perpetual, except as provided otherwise by this Agreement.

13.3 **Termination of Collaboration Upon Change of Control.** Lilly has the right to terminate the Collaboration during the Collaboration Term as set forth in this Section 13.3. In the event of a Change of Control of Isis, Isis shall notify Lilly of such change specifying the effective date of the change and the name(s) of the controlling Party or Parties. Lilly has the right to terminate either or both of the Target Validation Program and the Antisense Drug Discovery Program and transfer all research and development activities to Lilly as a result of such Change of Control at any time within ninety (90) days following such Change of Control, effective upon thirty (30) days written notice by Lilly. The Parties shall treat a termination under this Section 13.3 as an expiration of the Target Validation Program and/or Antisense Drug Discovery Program, as applicable. Lilly shall receive a non-exclusive license from Isis under Isis Technology and Isis Collaboration Technology to carry out all activities that would have otherwise been carried out under the Collaboration Agreement if there were no such termination by Lilly under this Section 13.3. In the alternative, Lilly may elect to continue either or both of the Target Validation Program and the Antisense Drug Discovery Program pursuant to the terms of this Agreement.

13.4 **Termination for Breach.** Either Party may terminate this Agreement by notice to the other Party at any time during the term of this Agreement if the other Party is in breach of any material obligations hereunder and has not cured such breach within ninety (90) days after notice requesting cure of the breach or such longer period of time as is required to cure such breach as long as the breaching Party is proceeding in good faith to cure; *provided, however,* that in any case when a breach is alleged regarding the payment of money hereunder, the time period will be thirty (30) days and undisputed amounts must be paid prior to such time to avoid breach. Lilly shall have the right to terminate this Agreement upon written notice to Isis in the event Isis is in breach of its obligation to pay the debt on the Payment Date as required by the Loan Agreement, which breach has not been cured within thirty (30) days of such notice. Upon material breach by a Party of its obligations hereunder, if such Party decides not to terminate this Agreement, such Party shall have the right to offset any costs it may incur as a result of curing such breach against the amounts payable to the breaching Party for the performance of such obligations. Further, to the extent that a Party prevails in a lawsuit brought against the other Party for material breach of this Agreement, such prevailing Party shall be entitled to collect from the other Party reasonable attorneys' fees and legal costs incurred in connection with such law suit. If the non-breaching Party terminates this Agreement under Section 13.4 following material breach by the breaching Party, the breaching Party shall return to the non-Breaching Party all of the non-breaching Party's Confidential Information and all materials received from the non-breaching Party during the Agreement, and the breaching Party shall cease all use of the non-breaching Party's Confidential Information and materials received from the non-breaching Party for any purpose except as provided in Sections 13.6 and 13.7, and except that the breaching Party may (1) keep a copy of all documents for record keeping purposes only and (2) keep and use any Confidential Information and materials received from the non-breaching Party that are necessary for the breaching Party to exercise those of its rights and fulfill those of its obligations that survive the termination of this Agreement.

13.5 **Termination Upon Insolvency.** Either Party may terminate this Agreement upon notice to the other should the other Party become insolvent or file or consent to the filing of a petition under any bankruptcy or insolvency law or have any such petition filed against it which has not been stayed within sixty (60) days of such filing. During the term of this

Agreement, all rights and licenses granted under or pursuant to this Agreement by Isis or Lilly are, and will otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code, licenses of right to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code. The Parties agree that, during the term of this Agreement, the Parties, as licensees of such rights under this Agreement, will retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code. The Parties further agree that, in the event of the commencement of a bankruptcy proceeding-by or against either Party under the U.S. Bankruptcy Code, the Party hereto that is not a party to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, and same, if not already in their possession, will be promptly delivered to them (i) upon any such commencement of a bankruptcy proceeding upon their written request therefor, unless the

Party subject to such proceeding elects to continue to perform all of its obligations under this Agreement, or (ii) if not delivered under (i) above, following the rejection of this Agreement by or on behalf of the Party subject to such proceeding upon written request therefor by the non-subject Party.

13.6 **Effect of Termination Due to Lilly Breach or Insolvency.** If Isis terminates the Agreement based on material breach by or insolvency of Lilly, then:

(a) licenses granted by Lilly to Isis pursuant to Sections 8.4.1(b) and 8.4.2, and all licenses granted under Section 8.5 prior to such termination, shall survive;

(b) Isis payment obligations set forth in Article 9 shall continue; *provided, however,* that the amounts of the payments shall be decreased to reflect the nature of Lilly's breach and the damages caused thereby by amounts to be agreed upon by the Parties or, if the Parties are unable to reach agreement, by an independent Third Party with the requisite expertise selected by the Parties, the expense of which shall be borne by Lilly;

(c) Lilly's payment obligations set forth in Article 9 shall continue; *provided, however,* that the amounts of the payments shall be increased to reflect the nature of Lilly's breach and the damages caused thereby by amounts to be agreed upon by the Parties or, if the Parties are unable to reach agreement, by an independent Third Party with the requisite expertise selected by the Parties, the expense of which shall be borne by Lilly;

(d) the licenses granted by Isis to Lilly pursuant to Sections 8.1.1(a) and 8.1.1(b) shall terminate;

(e) the licenses granted by Isis to Lilly pursuant to Sections 8.1.1(c) and 8.1.2 shall survive and the option under Sections 8.2.1, 8.2.2, and 8.2.3 shall terminate; *provided, however,* that any license granted to Lilly under Sections 8.2.1, 8.2.2, and 8.2.3 before termination under Section 13.4 or 13.5 by Isis shall survive;

(f) the Lilly Right of First Negotiation granted by Isis to Lilly pursuant to Section 8.3 shall terminate;

(g) Isis shall retain all rights to Validation Targets, Reserved Targets and Drug Discovery Targets not licensed by Lilly before such termination with no obligation to Lilly with respect to such to Validation Targets, Reserved Targets and Drug Discovery Targets;

provided, however, that Lilly shall have the right to license any such Validation Targets, Reserved Targets or Drug Discovery Targets within ninety (90) days of the date of termination under Section 13.4 or 13.5 and thereafter Lilly shall pay the applicable license fees;

(h) any sublicense granted by either Party to any Sublicensee under a license hereunder that terminates as a result of termination of this Agreement by Isis pursuant to Section 13.4 or 13.5 shall continue in full force and effect but be assigned by such Party to the other Party, and such Party shall provide the other Party with complete and accurate copies of such sublicense agreements within thirty (30) days following the effective date of such termination;

(i) the license granted by Isis to Lilly pursuant to Sections 8.11 shall survive; *provided, however*, on a product-by product basis, any such license for a Lilly Product shall not survive if Lilly has breached its obligation to pay milestone payments and/or royalties to Isis for such Lilly Product as required by Article 9.

(j) the options under Sections 8.12 shall terminate; *provided, however,* that any license granted to Lilly under Sections 8.12 before termination under Section 13.4 or 13.5 by Isis shall survive; and *further provided, however*, on a product-by product basis, any such license for a Lilly Product shall not survive if Lilly has breached its obligation to pay milestone payments and/or royalties to Isis for such Lilly Product as required by Article 9.

13.7 **Effect of Termination Due to Isis Breach or Insolvency.** If Lilly terminates the Agreement based on material breach by or insolvency of Isis, then:

(a) licenses granted by Isis to Lilly pursuant to Sections 8.1.1(c), 8.1.2, 8.2.1, 8.2.2, 8.2.3, 8.3, 8.11 and 8.12 and options granted pursuant to Section 8.12 shall survive;

(b) the Lilly Right of First Negotiation granted by Isis to Lilly pursuant to Section 8.3 shall survive;

(c) Lilly's payment obligations set forth in Article 9 shall continue, *provided, however,* that the amounts of the payments shall be decreased to reflect the nature of Isis's breach and the damages caused thereby by amounts to be agreed upon by the Parties or, if the Parties are unable to reach agreement, by an independent Third Party with the requisite expertise selected by the Parties, the expense of which shall be borne by Isis;

(d) Isis' payment obligations set forth in Article 9 shall continue, *provided, however,* that the amounts of the payments shall be increased to reflect the nature of Isis' breach and the damages caused thereby by amounts to be agreed upon by the Parties or, if the Parties are unable to reach agreement, by an independent Third Party with the requisite expertise selected by the Parties, the expense of which shall be borne by Isis;

(e) all Drug Discovery Targets and the Reserved Targets on the date of such termination of this Agreement by Lilly under Section 13.4 or 13.5 shall be deemed to be licensed by Lilly under Section 8.2.3 as Drug Discovery Targets; *provided, however,* that: (i) with respect to each such Drug Discovery Target and Reserved Target, no license fee shall be payable under Section 9.3.4(a) until the date that is [***] years after the Effective Date and, prior

to such date, Lilly may terminate its license with respect to any Drug Discovery Target or Reserved Target by providing written notice to Isis and no license fee shall be owed by Lilly with respect to such Drug Discovery Target or Reserved Target; (ii) the provision regarding diligence set forth in Section 8.2.3(c) shall not apply until [***] years after the Effective Date; and (iii) Lilly's milestone payment obligations set forth in Section 9.3.4(b) and

royalty payment obligations set forth in Section 9.3.4(c) shall continue; *provided, however,* that the amounts of the milestone and royalty payments shall be decreased to reflect the nature of Isis' breach and the damages caused thereby by amounts to be agreed upon by the Parties or, if the Parties are unable to reach agreement, by an independent Third Party with the requisite expertise selected by the Parties, the expense of which shall be borne by Isis;

(f) Lilly shall have the right to select [***] Validation Targets, to be identified by Lilly within [***] days following the date of termination of this Agreement by Lilly under Section 13.4 or 13.5, and such Validation Targets shall be deemed licensed by Lilly under Section 8.2.2; *provided, however,* that: (i) with respect to each such Validation Target, no license fee shall be payable by Lilly under Section 9.3.2(a) until the date that is [***] years after the Effective Date and, prior to such date, Lilly may terminate its license with respect to any such Validation Target by providing written notice to Isis and no license fee shall be owed by Lilly with respect to such Validation Target; (ii) the provision regarding diligence set forth in Section 8.2.2(c) shall not apply until [***] years after the Effective Date; and (iii) Lilly's milestone payment obligations set forth in Section 9.3.3(b) and royalty payment obligations set forth in Section 9.3.3(c) shall continue; *provided, however,* that the amounts of the milestone and royalty payments shall be decreased to reflect the nature of Isis' breach and the damages caused thereby by amounts to be agreed upon by the Parties or, if the Parties are unable to reach agreement, by an independent Third Party with the requisite expertise selected by the Parties, the expense of which shall be borne by Isis;

(g) the licenses granted by Lilly to Isis pursuant to Section 8.4.1 shall terminate;

the option granted by Lilly to Isis pursuant to Section 8.5 and all of Lilly's obligation under Section 8.5 shall terminate; *provided, however,* that any license granted to Isis under Section 8.5 before termination of this Agreement under Section 13.4 or 13.5 by Lilly shall survive;

(h) any sublicense granted by either Party to any Sublicensee under a license hereunder that terminates as a result of termination of this Agreement by Lilly pursuant to Section 13.4 or 13.5 shall continue in full force and effect but be assigned by such Party to the other Party, and such Party shall provide the other Party with complete and accurate copies of such sublicense agreements within thirty (30) days following the effective date of such termination; and

(i) any milestone payments that are paid by Lilly between the date that this Agreement is terminated under Section 13.4 or 13.5 and the date that is four (4) years after the Effective Date shall be fully creditable towards any Technology Access Fee payable by Lilly under Section 9.2.

13.8 **Accrued Rights/Surviving Obligations.** Except as expressly provided in this Agreement, expiration or termination of this Agreement will not relieve the Parties of any obligation that accrued prior to such expiration or termination, and Lilly will be obligated to pay and will pay to Isis, within thirty (30) days of such expiration or termination, all payments and royalties due or accrued pursuant to the terms of Article 9 and Isis will be obligated to pay and will pay to Lilly, within thirty (30) days of such expiration or termination, all payments and royalties due or accrued pursuant to the terms of Article 9. Upon expiration or early termination of this Agreement, all rights and obligations of the Parties shall cease, except as follows:

(a) In the case of expiration of this Agreement only (and, for purposes of clarification, not in the case of termination of this Agreement pursuant to Section 13.4 or 13.5), each of the licenses set forth in Sections 8.1, 8.4, 8.5 and 8.11, or granted pursuant to 8.2 or 8.12, shall survive and shall be deemed to be perpetual and fully paid up, provided that all payment and other obligations with respect to such licenses have been fulfilled;

(b) The obligations to pay royalties and other sums accruing hereunder up to the date of termination or expiration shall survive;

(c) The obligations of confidentiality set forth in Article 10 shall survive;

(d) The obligations for record keeping and accounting reports set forth in Article 9 shall survive for so long as Lilly Products or Isis Products are sold. At such time after termination or expiration of this Agreement when sales or other dispositions of Lilly Products or Isis Products have ceased, the Party selling such Product shall render a final report along with any royalty payment due;

(e) Isis' and Lilly's rights to inspect books and records as described in Article 9 shall survive;

(f) The obligations of defense and indemnity set forth in Article 11 shall survive;

(g) Any cause of action or claim of Isis or Lilly accrued or to accrue because of any breach or default by the other Party hereunder shall survive; and

(h) All other terms, provisions, representations, rights and obligations contained in this Agreement that are intended to survive as specifically set forth elsewhere in this Agreement shall survive.

13.9 **Limitation of Liability.** No Party shall be liable to another for indirect, incidental, consequential or special damages, including but not limited to lost profits, arising from or relating to any breach of this Agreement, regardless of any notice of the possibility of such damages. Nothing in this Section is intended to limit or restrict the indemnification rights or obligations of any Party under Article 11.

ARTICLE 14

PUBLICITY

14.1 **Disclosure of Agreement.** Neither Party to this Agreement may release any information to any Third Party regarding the terms or existence of this Agreement or the reasons for any termination hereof, without the prior written consent of the other Party. Without limitation, this prohibition applies to press releases, educational and scientific conferences, quarterly investor updates, promotional materials, governmental filings and discussions with

public officials, the media, security analysts and investors. However, this provision does not apply to any disclosures regarding this Agreement or related information to regulatory agencies such as the FDA or Federal Trade Commission and/or Department of Justice for such disclosures which may be required by law, including requests for a copy of this Agreement or related information by tax authorities. If any Party to this Agreement determines a release of information regarding the existence or terms of this Agreement is required by law (including releases a may be required to be filed through the Securities Exchange Commission or other government agency), that Party will notify the other Party as soon as practicable and give as much detail as possible in relation to the disclosure required. The Parties will then cooperate with respect to determining what information should actually be released. The Parties hereby agree that release of a press release upon complete execution of this Agreement is appropriate and such press release shall be mutually agreed upon by the Parties.

14.2 **Use of Names, Logos or Symbols.** No Party hereto shall use the name, trademarks, logos, physical likeness, employee names or owner symbol of any other Party for any purpose, including, without limitation, private or public securities placements, without the prior written consent of the affected Party, such consent not to be unreasonably withheld or delayed so long as such use of name is limited to objective statements of fact, rather than for endorsement purposes. Nothing contained herein shall be construed as granting either Party any rights or license to use any of the other Party's trademarks or tradenames without separate, express written permission of the owner of such trademark or tradename.

14.3 **Publication.** The Parties acknowledge and agree that scientific lead time is a key element of the value of the research to be performed under this Agreement. The Parties also acknowledge and agree that the ability to publish selected results of the research to be performed under this Agreement in the course of the Collaboration is essential for the recruitment and retention of scientific talent by the Parties. In order to ensure that scientific publications are strictly monitored to prevent any adverse effect of premature publication, the Executive Committee shall establish a procedure for publication review and approval and each Party shall first submit to the Executive Committee an early draft of all such publications, whether they are to be presented orally or in written form, at least sixty (60) days prior to submission for publication. The Executive Committee shall review each such proposed publication in order to avoid the unauthorized disclosure of any Confidential Information and to preserve the patentability of inventions arising from the research performed in the course of the Collaboration. If, within thirty (30) days following

receipt of an advance copy of a Party's proposed publication, the Executive Committee informs such Party that its proposed publication contains the other Party's Confidential Information, then such Party shall delete such Confidential Information from its proposed publication. If, within thirty (30) days following receipt of an advance copy of a Party's proposed publication, the Executive Committee informs such Party that its proposed publication contains Collaboration Know-How, the publication of which could be expected to have a material adverse effect on any Collaboration Patent Rights or Collaboration Know-How, then such Party shall at the election of the Executive Committee either (1) delete such Confidential Information from such Party's proposed publication or (2) delay such proposed publication sufficiently long to permit the timely preparation and filing of a patent application(s) on the information involved. If, within forty five (45) days following receipt of an advance copy of a Party's proposed publication, the Executive Committee fails to approve of such Party's proposed publication, then such proposed publication shall be regarded as denied by the Executive Committee and shall not be published.

ARTICLE 15

HART-SCOTT RODINO FILING

15.1 **[DELETED].**

15.2 **[DELETED].**

ARTICLE 16

MISCELLANEOUS

16.1 **Key Personnel.** During the Extended Collaboration Term, Isis shall inform Lilly if [***] leaves the employ of Isis. In each such case, Lilly shall have the right to suggest replacements and interview any potential replacement in order to provide feedback to Isis regarding any such potential replacement, but, for purposes of clarification, Lilly shall not have the right to terminate this Agreement or the Collaboration as a result of the events described in this Section 16.1.

16.2 **Force Majeure.** No Party will be held liable or responsible to the other Party nor be deemed to have defaulted under or breached the Agreement for failure or delay in fulfilling or performing any term of the Agreement (except payment obligations) when such failure or delay is caused by or results from causes beyond the reasonable control of the affected Party including, but not limited to, fire, flood, embargo, war, acts of war (whether war be declared or not), insurrection, riot, civil commotion, strike, lockout or other labor disturbance, act of God or act, omission or delay in acting by any governmental authority or the other Party. The affected Party will notify the other Party of such force majeure circumstances as soon as reasonably practical.

16.3 **Assignment.** This Agreement may not be assigned or otherwise transferred, nor, except as expressly provided hereunder, may any right or obligations hereunder be assigned or transferred, by a Party without the written consent of the other Party; *provided, however,* that either Party may, without such consent, assign the Agreement and its rights and obligations hereunder to (i) any wholly-owned subsidiary in a manner such that the assignor (if it continues as a separate entity) shall remain liable and responsible for the performance and observance of all its duties and obligations hereunder or (ii) subject to Section 13.3 to any successor by merger

or sale of substantially all of its business unit to which this Agreement relates, or in the event of its merger or consolidation or change in control or similar transaction. This Agreement shall be binding upon the permitted successors and permitted assigns of the Parties. Any assignment not in accordance with this Section 16.3 shall be void.

16.4 **Severability.** In the event that any of the provisions contained in this Agreement are held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein will not in any way be affected or impaired thereby, unless the

absence of the invalidated provision(s) adversely affect the substantive rights of the Parties. The Parties will replace the invalid, illegal or unenforceable provision(s) with valid, legal and enforceable provision(s), which, insofar as practical, implement the purposes of this Agreement.

16.5 **Notices.** All notices or other communications which are required or permitted hereunder will be in writing and deemed to be effective (a) on the date of delivery if delivered in person and written confirmation of delivery is provided, (b) on the date sent by facsimile or other electronic transmission, provided such receipt is verified, (c) on the day following date of deposit with an overnight courier if a receipt confirming delivery by overnight courier is provided, or (d) three days after mailing if mailed by first-class certified mail, postage paid, to the respective addresses given below, or to another address as it will designate by written notice given to the other Party.

if to Isis, to:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
Attention: Chief Executive Officer
Telephone: 760-931-9200
Facsimile: 760-931-0265

with a copy to:

Attention: Chief Financial Officer
Telephone: 760-931-9200
Facsimile: 760-931-9639

if to Lilly, to:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
Attention: Group Vice President, Lilly Research Laboratories
Telephone: 317-276-5624
Facsimile: 317-277-7979

with a copy to:

Attention: General Patent Counsel/TGP
Telephone: 317-276-2958
Facsimile: 317-277-1917

16.6 **Dispute Resolution.** In the event of any controversy or claim arising from or relating to any provision of this Agreement, or any term or condition hereof, or the performance by a Party of its obligations hereunder, or its construction or its actual or alleged breach, the Parties will try to settle their differences amicably between themselves. All disputes relating to the implementation of the Collaborative Research Plan shall be handled in accordance with Article 2.

16.7 **Choice of Law.** This Agreement will be governed by and construed in accordance with the laws of the State of New York and the United States without reference to any rules of conflict of laws.

16.8 **Entire Agreement.** This Agreement (including all Schedules hereto), together with the Original Agreement, the Amended and Restated Agreement, the Loan Agreement, the Registration Rights Agreement and the Securities Purchase Agreement, including all amendments to any of the foregoing, constitute the entire agreement between the Parties with respect to the subject matter hereof, and supersedes all previous arrangement with respect to the subject matter hereof, whether written or oral. Any amendment or modification to this Agreement shall be made in writing signed by both Parties. In the event of any conflict between the terms of this Agreement and the Collaborative Research Plan, the terms of this Agreement shall govern.

16.9 **Headings.** The captions to the several Articles and Sections hereof are not a part of the Agreement, but are merely guides or labels to assist in locating and reading the several Articles and Sections hereof.

16.10 **Independent Contractors.** It is expressly agreed that the Parties will be independent contractors and that the relationship between the Parties will not constitute a partnership, joint venture or agency. No Party will have the authority to make any statements, representations or commitments of any kind, or to take any action, which will be binding on the other Parties, without the prior consent of such other Parties. Members of the Executive Committee shall be and shall remain employees of Isis or Lilly as the case may be. Lilly shall not incur any liability for any act or failure to act by employees of Isis, including members of the Executive Committee who are employees of Isis. Isis shall not incur any liability for any act or failure to act by employees of Lilly, including members of the Executive Committee who are employees of Lilly.

16.11 **Non-Solicitation of Employees.** During the Collaboration Term and for a period of six (6) months thereafter, each Party agrees that it will not directly recruit, solicit or induce any employee of the other Party who is directly associated with the Collaboration to terminate his or her employment with such other Party. However, nothing set forth in this Section 16.11 shall prohibit a Party from indirectly recruiting, soliciting or inducing such

employees to leave the other Party through the use of advertisements in trade journals and the like or from discussing employment opportunities with such employees to the extent such employees contact such Party first.

16.12 **Further Actions.** Each Party agrees to execute, acknowledge and deliver such further instruments, and to do all such other acts, as may be necessary or appropriate in order to carry out the purposes and intent of the Agreement.

16.13 **Waiver.** The waiver by a Party hereto of any right hereunder or the failure to perform or of a breach by another Party will not be deemed a waiver of any other right hereunder or of any other breach or failure by said other Party whether of a similar nature or otherwise.

16.14 **Jointly Prepared.** This Agreement has been prepared jointly and shall not be strictly construed against either Party.

16.15 **Counterparts.** This Agreement may be executed in two or more counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

[THIS SPACE INTENTIONALLY LEFT BLANK]

IN WITNESS WHEREOF, the Parties have executed this Agreement as of the date first set forth above.

ELI LILLY AND COMPANY	**ISIS PHARMACEUTICALS, INC.**
By: /s/ Steven M. Paul	By: /s/ B. Lynne Parshall
Steven M. Paul	B. Lynne Parshall
Executive Vice President	Executive Vice President and
Science and Technology	Chief Financial Officer

[SIGNATURE PAGE TO COLLABORATION AGREEMENT]

List of Schedules

Schedule 1.1	Definitions
Schedule 2.2	Collaborative Research Plan
Schedule 2.5	Members of Executive Committee During the Extended Collaboration Term
Schedule 2.6	[DELETED]
Schedule 2.9	Alliance Managers
Schedule 5.5.3	Accepted Validation Targets as of the Second Restatement Execution Date
Schedule 5.6.3	Rejected Validation Targets as of the Second Restatement Execution Date
Schedule 5.12	Abandoned Validation Targets as of the Second Restatement Execution Date
Schedule 6.2	Development Stages of Drug Discovery Targets as of the Second Restatement Execution Date
Schedule 6.5.1	Active Programs as of the Second Restatement Execution Date
Schedule 6.7.1	[***] Abandoned Drug Discovery Targets in the Metabolic Collaboration Therapeutic Area
Schedule 6.7.2	Abandoned Drug Discovery Targets as of the Second Restatement Execution Date
Schedule 6.9.1	Reserved Targets as of the Second Restatement Execution Date
Schedule 8.2.2	The Reagent Targets and the Date of Delivery to Lilly of a Reagent ASO Compound Directed to Each Such Reagent Target
Schedule 8.7	[DELETED]
Schedule 9.4.3	Milestones and Royalties under Section 9.4.3 and 9.4.4
Schedule 12.12	Collaboration Patent Rights as of the Second Restatement Execution Date
Schedule A	[DELETED]
Schedule B	Isis Manufacturing Patent Rights as of the Second Restatement Execution Date

SCHEDULE 1.1

DEFINITIONS

"Abandoned Drug Discovery Target" means any Drug Discovery Target following termination by Lilly of an Active Program for such Drug Discovery Target, as more fully described in Section 6.7.

[***]

"Abandoned Validation Target" has the meaning set forth in Section 5.12.

"Accepted Validation Targets" has the meaning set forth in Section 5.4.

"Active Program" means:

(a) with respect to a Drug Discovery Target, any reasonable (as defined below) ongoing research, development, or commercialization, including sublicensing efforts, of a Drug Discovery ASO Compound directed to such Drug Discovery Target that occurs (i) in the course of the Collaboration or (ii) by Lilly outside the course of the Collaboration during the Collaboration Term plus [***] years thereafter; and

(b) with respect to a Reagent Target, Validation Target or a Drug Discovery Target licensed by Lilly under Article 8 or an Isis-Blocked Target pursuant to Section 6.2, any reasonable (as defined below) ongoing research, development, or commercialization, including sublicensing efforts, of an ASO Compound directed to such Target.

For purposes of clarification, research, development and commercialization efforts with respect to a Target or ASO Compound shall be deemed reasonable if Lilly's research and development efforts with respect to such Target or ASO Compound are reasonably comparable with other projects in Lilly's portfolio at a similar stage of development and of similar market potential.

"Affiliate" means any person, organization, corporation or other business entity that controls, directly or indirectly, the power to direct, or cause the direction of, the management and policies of another person, organization, corporation or entity, whether through the ownership of voting securities or by contract or court order or otherwise. For purposes of this definition, an entity will be deemed to control another entity if it owns or controls, directly or indirectly, at least fifty percent (50%) of the outstanding stock or other voting rights entitled to elect directors or their equivalent of such other entity.

"Alliance Managers" has the meaning set forth in Section 2.9.

"Amended and Restated Agreement" has the meaning set forth in Recital D of this Agreement.

"Antisense Drug Discovery Program" means the program of research and development of Drug Discovery ASO Compounds and Products in the Collaborative Therapeutic Areas under this Agreement, as described in Section 2.4, Article 6 and the Collaborative Research Plan.

"Antisense Drug Discovery Term" means the term of the Antisense Drug Discovery Program carried out pursuant to this Agreement and any extension thereof, including during the Extended Collaboration Term. The Antisense Drug Discovery Term shall include the Oncology Term.

"Antisense Technology" means the selective modulation of protein synthesis at the nucleic acid level caused by the binding of an oligonucleotide or an analog thereof (an ***"oligonucleotide"***) to a complementary sequence.

"ASO Compound" means an oligonucleotide or an analog thereof (an ***"oligonucleotide"***) that selectively modulates protein synthesis at the nucleic acid level through the binding of such oligonucleotide to a complementary sequence.

"ASO Field" means the development, manufacture and sale of ASO Products as therapeutic or prophylactic pharmaceutical products.

"ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more ASO Compounds.

"Calendar Quarter" shall mean the respective three month periods ending on March 31, June 30, September 30, or December 31 for so long as the Agreement is in effect.

"Calendar Year" shall mean each successive twelve month period commencing on January 1 and ending on December 31 for so long as the Agreement is in effect.

"Candidate Selection" means the designation of a potential drug candidate within Lilly's portfolio by Lilly's Lead Development Committee, or its successor, for advancement to clinical development based on pharmacology, chemistry, patent status, toxicology, ADME, biopharmaceutics, medical and marketing considerations.

"Change of Control" means any of the following events: (i) the acquisition by any Person or group, other than a Person or group controlling such Party as of the Effective Date, of "beneficial ownership" (as defined in Rule 13d-3 under the United States Securities Exchange Act of 1934, as amended), directly or indirectly, of fifty percent (50%) or more of the shares of such Party's capital stock the holders of which have general voting power under ordinary circumstances to elect at least a majority of such Party's Board of Directors or equivalent body (the ***"Board of Directors"***) (the ***"Voting Stock"***); (ii) the first

day of which less than two-thirds of the total membership of such Party's Board of Directors shall be Continuing Directors (as such term is defined below); (iii) the approval by the shareholders of such Party of a merger, share exchange, reorganization, consolidation or similar transaction of such Party (a ***"Transaction"***), other than a Transaction which would result in the Voting Stock of such Party outstanding immediately prior thereto continuing to represent (either by remaining outstanding or by being converted into voting securities of the surviving entity) more than fifty percent

(50%) of the Voting Stock of such Party or such surviving entity immediately after such Transaction; or (iv) approval by the shareholders of such Party of a complete liquidation of such Party or a sale or disposition of all or substantially all of the assets of such Party. For purposes of this definition, "Continuing Directors" means individuals serving as of the Second Restatement Date hereof on such Party's Board of Directors and any individuals elected after the date hereof whose election or nomination was approved by at least a majority of the Continuing Directors serving at the time.

"Collaboration" means, (i) during the Initial Collaboration Term, collectively, the Reagent Provision Program, the Target Validation Program and the Antisense Drug Discovery Program or (ii) During the Extended Collaboration Term, the Antisense Drug Discovery Program and the Target Validation Program both in the Collaboration Therapeutic Area of oncology.

"Collaboration ASO Compound Patent Right" means a Patent Right that claims inventions conceived in the course of the Target Validation Program or the Antisense Drug Discovery Program and that Cover the composition of matter of an ASO Compound and/or the use of such ASO Compound.

"Collaboration FTE" means a Lilly Collaboration FTE or an FTE applied by Isis in conducting the research under the Target Validation Program or Antisense Drug Discovery Program.

"Collaboration Funds" means the funds provided to Isis by Lilly pursuant to the Loan Agreement.

"Collaboration Know-How" means Isis Collaboration Know-How and Lilly Collaboration Know-How.

"Collaboration Patent Rights" means the Isis Collaboration Patent Rights, the Lilly Collaboration Patent Rights and the Joint Collaboration Patent Rights.

"***Collaborative Research Plan***" means the Research Plan describing the research collaboration to be carried out pursuant this Agreement, which is attached hereto as ***Schedule 2.2***, including all amendments thereto.

"Collaboration Term" means the term of the collaborative research efforts carried out pursuant to this Agreement and any extension thereof, including the Initial Collaboration Term and the Extended Collaboration Term. Collaboration Term shall include the Reagent Provision Term, the Target Validation Term, the Antisense Drug Discovery Term, the Oncology Term and any extensions of any of the foregoing.

"Collaboration Therapeutic Areas" means (a) with respect to the Target Validation Program, inflammation, bone and metabolism (*e.g.*, diabetes and obesity), *provided*, *however*, that Parties may agree to include oncology in the Target Validation Program as provided in Section 3.1; and (b) with respect to the Antisense Drug Discovery Program, inflammation, bone, metabolism and oncology.

"Compulsory License" means, in the case of a Lilly Product or Isis Product, a compulsory license under the a Party's technology obtained by a Third Party through the order, decree or grant of a governmental authority having competent jurisdiction, authorizing such Third Party to manufacture, use, sell, offer for sale or import such Lilly Product or Isis Product in a particular country.

"Confidential Information" means any and all inventions, know-any, and data and shall include, without limitation, information relating to research and development plans, experiments, results and plans, compounds, therapeutic leads, candidates and products, clinical and preclinical data, trade secrets and manufacturing, marketing, financial, regulatory, personnel and other business information and plans, all scientific, clinical, regulatory, marketing, financial and commercial information or data, all whether communicated in writing, orally or by any other means, and which is provided by one Party to the other Party in connection with this Agreement. Confidential Information will not include information that:

(a) is known by the receiving Party at the time of its receipt, and not through a prior disclosure by the disclosing Party, as documented by written records;

(b) is properly in the public domain through no fault of the receiving Party;

(c) is subsequently disclosed to the receiving Party by a Third Party who may lawfully do so and is not under an obligation of confidentiality to the disclosing Party; or

(d) is developed by the receiving Party independently of Confidential Information received from the other Party, as documented by written records.

"Control" or ***"Controlled"*** means with respect to any intellectual property right, that the Party owns or has a license to such intellectual property right and has the ability to grant access, a license, or a sublicense to such intellectual property right to the other Party as provided for in this Agreement without violating an agreement with, or infringing any rights of, a Third Party as of the time the Party would be first required under this Agreement to grant the other Party such access, license or sublicense.

"Cost of Products" or ***"COPS"*** means costs of supplying Products calculated in accordance with a Party's accounting methods consistently applied which methodology shall be calculated in compliance with U.S. generally accepted accounting principles (GAAP). For the purposes of this Agreement, COPS shall include Third Party royalty burdens, royalties due to the other Party, final filling/finishing and packaging of the Product.

"Cover" (including variations thereof such as ***"Covering"***, ***"Covered"***, and ***"Coverage"***) means that the manufacture, use, import, offer for sale or sale of a Lilly Product or Isis Product would infringe a Valid Claim; provided, with respect to a process or manufacturing patent, that such a Valid Claim therein effectively precludes a Third Party from manufacturing, using, importing, offering for sale, or selling such Lilly Product or Isis Product. The determination of whether a Lilly Product or Isis Product is Covered by a particular Valid Claim shall be made on a country-by-country basis. A Valid Claim shall be deemed to provide effective preclusion hereunder where (i) there is no competing product being marketed or (ii) if a product is being

marketed by a competitor, it infringes the Valid Claim (including any period in which, and provided that, the Valid Claim is being litigated).

"CPI" or ***"Consumer Price Index"*** means the consumer price index for all urban consumer series ID CUUR0000SAO as published from time to time by the US Bureau of Labor Statistics, where the CPI for June, 2001 was 178.

"Critical Success Factor" has the meaning set forth in the Collaborative Research Plan as applicable to Reagent Targets, Validation Targets and Drug Discovery Targets.

"Development Candidate" means a Drug Discovery ASO Compound that is directed to a Drug Discovery Target, that is ready for IND supporting toxicology studies and that is designated as a Development Candidate by the Executive Committee, as described in Section 6.4.1 or by Lilly in accordance with Section 6.4.2.

"Drug Discovery ASO Compound" means an ASO Compound that selectively modulates protein synthesis of a Drug Discovery Target.

"Drug Discovery ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more Drug Discovery ASO Compounds.

"Drug Discovery Non-ASO Compound" means a compound that (a) is developed by Lilly through the use of Collaboration Know-How and (b) is not an ASO Compound and (c) is either (i) an agonist or antagonist of a Drug Discovery Target or (ii) is a Drug Discovery Target.

"Drug Discovery Non-ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more Drug Discovery Non-ASO Compounds.

"Drug Discovery Target" means any Target included in the Antisense Drug Discovery Program by the Executive Committee.

"Effective Date" means August 25, 2001.

"Exclusive Target" has the meaning set forth in Section 5.8.

"Executive Committee" means the committee established pursuant to Section 2.5.

"Extended Collaboration Term" means the period from August 25, 2005 until the completion of the Collaboration Term as set forth in Section 13.1.3.

"FDA" means the United States Food and Drug Administration or any successor agency having the administrative authority to regulate the approval for marketing of new human pharmaceutical or biological therapeutic products in the United States.

"First Commercial Sale" means with respect to any Lilly Product or Isis Product the first sale to a Third Party by (i) Lilly or its Sublicensees, or (ii) Isis, its Affiliates or Sublicensees.

First Commercial Sale shall not include transfer of reasonable quantities of any free samples of a Lilly Product or Isis Product or reasonable quantities of a Lilly Product or Isis Product solely for development purposes, such as for use in experimental studies or clinical trials.

"FTE" means the equivalent of the work of one (1) employee full time for one (1) year (consisting of at least a total of [***] weeks or [***] (excluding vacations and holidays) of work on or directly related to the Collaboration), carried out by an Isis employee or a Lilly Collaboration FTE, or Third Party mutually agreed upon by the Executive Committee. Overtime shall not be counted toward the number of hours that are used to calculate the FTE contribution. No one person shall be permitted to account for more than one (1) FTE. Scientific work on the Collaboration to be performed by Isis employees, Lilly Collaboration FTEs, or mutually agreeable Third Parties can include, but is not limited to, experimental laboratory work, recording and writing up results, reviewing literature and references, and holding scientific discussions.

[***]

"IND" means an Investigational New Drug application as defined in 21 C.F.R. 312 and any versions thereof governing the FDA as may be amended from time to time.

"Initial Collaboration Term" means the period from August 25, 2001 until August 24, 2005.

"Isis ASO Compound Patent Rights" means Patent Rights Controlled by Isis on or after the Effective Date that claim inventions that are conceived outside the course of the Target Validation Program or Drug Discovery Program and that that Cover the composition of matter of an ASO Compound or the method of using such ASO Compound per se, including Patent Rights that Cover inventions made in the course of the Reagent Provision Program and Patent Rights that Cover the composition of matter or use of an antisense oligonucleotide(s) directed to Stage 2 Drug Discovery Targets and Stage 3 Drug Discovery Targets included in the Research Plan on the Effective Date or thereafter.

"Isis-Blocked Target" has the meaning set forth in Section 6.2.2.

"Isis Blocking Patent Rights" means Patent Rights Controlled by Isis on the Effective Date or come into Isis' Control during the Collaboration Term that claim inventions that are conceived outside the course of the Validation Program or Drug Discovery Program and that Cover the method of treating a condition by modulating a Target through the use of a non-ASO Compound.

"Isis Collaboration ASO Compound Patent Rights" means Patent Rights Controlled by Isis that claim inventions conceived in the course of the Target Validation Program or the Antisense Drug Discovery Program and that Cover the composition of matter of an ASO Compound or the use of such ASO Compound.

"Isis Collaboration Blocking Patent Rights" means Patent Rights Controlled by Isis that claim inventions conceived in the course of the Target Validation Program or the Antisense Drug

Discovery Program that Cover the method of treating a condition by modulating a Target through the use of a non-ASO Compound.

"Isis Collaboration Core Technology Patent Rights" means Patent Rights Controlled by Isis that claim inventions conceived in the course of the Target Validation Program or the Antisense Drug Discovery Program that Cover the practice of Isis Standard Chemistry including Patent Rights that Cover chemistries, motifs (patterns of arranging the chemical building blocks of an antisense oligonucleotides) and/or cellular mechanism of action by which an oligonucleotide promotes RNA cleavage.

"Isis Collaboration Know-How" means Know-How Controlled by Isis that is conceived in the course of the Target Validation Program or the Antisense Drug Discovery Program.

"Isis Collaboration Manufacturing Patent Rights" means Patents Controlled by Isis that claim inventions conceived in the course of the Target Validation Program or the Antisense Drug Discovery Program that Cover the practice of the Isis Standard Chemistry Manufacturing Process.

"Isis Collaboration Patent Rights" means the Isis Collaboration ASO Compound Patent Rights, Isis Collaboration Manufacturing Patent Rights, Isis Collaboration Core Technology Patent Rights and Isis Collaboration Blocking Patent Rights.

"Isis Collaboration Technology" means Isis Collaboration Know-How and Isis Collaboration Patent Rights.

"Isis Core Technology Patent Rights" means Patent Rights Controlled by Isis on or after the Effective Date that claim inventions that are conceived outside the course of the Validation Program or Drug Discovery Program and that Cover the practice of Isis Standard Chemistry including Patent Rights that Cover chemistries, motifs (patterns of arranging the chemical building blocks of an antisense oligonucleotides) and/or cellular mechanism of action by which an oligonucleotide promotes RNA cleavage. The Isis Core Technology Patent Rights that exist as of the Second Restatement Date of this Agreement are listed in ***Schedule C***.

"Isis Drug Discovery ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more ASO Compounds directed against a Drug Discovery Target that is developed by Isis as permitted by Section 8.2.3(c).

"Isis Internal Program" means an internal research effort on the development of ASO Compounds directed to a Target for use as ASO Products conducted by Isis conducted outside the course of the Collaboration whereby such internal research effort on such Target has advanced to a stage that is equivalent to the achievement of the Critical Success Factors for a Validation Target as reasonably evidenced to Lilly by written documentation of Isis; *provided, however,* that if there is a disagreement as to whether such Target has advanced to a stage that is equivalent to the achievement of the Critical Success Factors for a Validation Target such matter shall be referred to the Executive Committee for resolution, and lacking resolution by the Executive Committee such internal research effort shall be deemed an Isis Internal Program.

"Isis Know-How" means all Know-How that is either (i) Controlled by Isis as of the Effective Date or (ii) that becomes Controlled by Isis after the Effective Date that is not Collaboration Know-How that is reasonably necessary or useful for research, development, manufacture, use and sale of Lilly Products, including Know-How that is discovered or developed by employees or agents of Isis in the course of the Reagent Provision Program.

"Isis Manufacturing Patent Rights" means Patent Rights Controlled by Isis on or after the Effective Date that claim inventions that are conceived outside the course of the Target Validation Program or Antisense Drug Discovery Program that Cover the practice of the Isis Standard Chemistry Manufacturing Process. The Isis Manufacturing Patent Rights as of the date of this Agreement are listed in ***Schedule B***.

"Isis Non-Collaboration ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more ASO Compounds directed against a Target that not designated as a Validation Target or Drug Discovery Target pursuant to this Agreement and that is developed by Isis as permitted by this Agreement.

"Isis Patent Rights" means the Isis Core Technology Patent Rights, the Isis Manufacturing Patent Rights, the Isis Blocking Patent Rights and Isis ASO Compound Patent Rights. To the extent Isis Controls Patent Rights as of the Effective Date or during the Collaboration Term and one (1) year thereafter other than the Isis Manufacturing Patents, Isis Core Technology Patent Rights, Isis Blocking Patent Rights and the Isis ASO Compound Patent Rights, and such Patent Rights would Cover a Lilly ASO Product, such Patent Rights will be included in the definition of Isis Patent Rights automatically if they can be licensed to Lilly with no obligation (financial or otherwise) to any Third Party with respect to a particular Lilly ASO Product at the time the Lilly ASO Product is licensed from Isis, or if the relevant invention is made subsequent to such license, at the time such invention is made. To the extent Isis Controls Patent Rights as of the Effective Date or during the Collaboration Term, other than the Isis Manufacturing Patent Rights, the Isis Core Technology Patent

Rights, Isis Blocking Patent Rights and Isis ASO Compound Patent Rights that would Cover a Lilly ASO Product, and such Patent Rights were acquired by Isis from a Third Party and/or Isis has obligations (financial or otherwise) to a Third Party in connection with the practice of such Patent Rights, such Patent Rights will only be included in the definition of Isis Patent Rights if Isis and Lilly negotiate an agreement to license such Patent Rights which includes (1) the assumption by Lilly of all financial obligations of Isis arising from the grant to Lilly and the practice by Lilly, its Affiliates of Sublicensees, of the Patent Rights, (2) the compensation of an appropriate portion of any acquisition costs incurred by Isis in connection with obtaining Control of such Patent Rights, and (3) an agreement by Lilly to abide by all of the terms of the agreement under which Isis has obtained Control of such Patent Right.

"Isis Product" means an Isis Drug Discovery ASO Product, Isis Non-Collaboration ASO Product, and/or an Isis Validation ASO Product.

"Isis Reagent ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal

use, which contains one or more ASO Compounds directed against a Reagent Target that is developed by Isis as permitted by Section 8.2.2(c).

"Isis Special Technology" means Patent Rights that Isis Controls on or after the Effective Date that Cover both (1) chemistries, motifs (patterns of arranging the chemical building blocks of antisense oligonucleotides) and/or cellular mechanism of action by which an oligonucleotide promotes nucleic acid cleavage in the field of Antisense Technology and (2) an ASO Product licensed by Lilly pursuant to Section 8.12, but does not include Isis Collaboration Patent Rights and Isis Patent Rights.

"Isis Standard Chemistry" means "2´MOE Gapmers" or an antisense phosphothioate oligonucleotide of 15-30 nucleotides wherein all of the backbone linkages are modified by adding a sulfur at the non-bridging oxygen (phosphorothioate) and a stretch of at least 10 consecutive nucleotides remain unmodified (deoxy sugars) and the remaining nucleotides contain an O´-methyl O´-ethyl substitution at the 2´ position (MOE).

"Isis Standard Chemistry Manufacturing Process" means the manufacturing process as of the Effective Date represented by the batch record for Isis 113715. Manufacturing for this purpose includes synthesis, purification and analysis.

"Isis Technology" means Isis Know-How and Isis Patent Rights.

"Isis Validation ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more ASO Compounds directed against a Validation Target that is developed by Isis as permitted Isis as permitted by Section 8.2.2(c).

"Joint Collaboration Patent Rights" has the meaning set forth in Section 12.2.

"Know-How" means all tangible or intangible know-how, inventions (whether patentable or not), discoveries, processes, formulas, data, clinical and preclinical results, non-patented inventions, trade secrets, and any physical, chemical, or biological material or any replication of any such material in whole or in part.

"Lilly ASO Product" means a Reagent ASO Product, Validation ASO Product or a Drug Discovery ASO Product that is developed and sold by Lilly.

"Lilly-Blocked Target" has the meaning set forth in Section 6.2.2.

"Lilly Collaboration ASO Compound Patent Rights" means Patent Rights Controlled by Lilly that claim inventions conceived in the course of the Target Validation Program or the Antisense Drug Discovery Program that Cover the composition of matter of an ASO Compound or the use of such ASO Compound.

"Lilly Collaboration Blocking Patent Rights" means Patent Rights Controlled by Lilly that claim inventions conceived in the course of the Target Validation Program or the Antisense Drug Discovery Program that Cover the method of treating a condition by modulating a Target through the use of a non-ASO Compound.

"Lilly Collaboration FTE" means an FTE that is applied by Lilly in carrying out work in the course of the Target Validation Program or Antisense Drug Discovery Program in accordance with the Collaborative Research Plan and reimbursed with Collaboration Funds.

"Lilly Collaboration Know-How" means Know-How Controlled by Lilly that is conceived in the course of the Target Validation Program or the Antisense Drug Discovery Program.

"Lilly Collaboration Patent Rights" means the Lilly Collaboration ASO Compound Patent Rights and the Lilly Collaboration Blocking Patent Rights.

"Lilly Collaboration Technology" means Lilly Collaboration Know-How and Lilly Collaboration Patent Rights.

"Lilly Non-ASO Product" means a Validation Non-ASO Product, Drug Discovery Non-ASO Product, or Reagent Non-ASO Product that is developed and sold by Lilly.

"Lilly Non-Collaboration ASO Patent Right" means all Patent Rights that are Controlled by Lilly, or any Sublicensees to whom Lilly provides data generated from the use of a Reagent ASO Compound provided to Lilly by Isis pursuant to this Agreement and that [***]

"Lilly Product" means a Lilly ASO Product or a Lilly Non-ASO Product.

"Lilly Right of First Negotiation" has the meaning set forth in Section 8.3.

"Loan Agreement" means that certain loan agreement by and between Lilly and Isis signed concurrently with the Original Agreement.

"Major Market Country" means the United States, Japan, Germany, the United Kingdom, France, Spain or Italy.

"Manufacturing Improvements" means any and all scientific and technical data, information, methods, techniques, protocols, and processes that are useful in the manufacture of ASO Compounds developed by or coming under Control of a Party outside the course of the Collaboration after the Effective Date.

"May 3, 2004 Agreement" has the meaning set forth in Recital F of this Agreement.

"NDA" means a new drug application or other application filed with the FDA to obtain approval for marketing a Lilly Product or Isis Product in the United States, or any future equivalent process.

"Net Royalty" means [***].

"Net Sales" means, with respect to a Product, the gross amount invoiced by a Party, its Affiliates or Sublicensees thereof to unrelated Third Parties, excluding any Sublicensee, for the Product, less:

(a) Trade, quantity and cash discounts allowed;

(b) Commissions, discounts, refunds, rebates, chargebacks, retroactive price adjustments, and any other allowances which effectively reduce the net selling price;

(c) Product returns and allowances;

(d) That portion of the value associated with the cost of the drug delivery systems;

(e) Any tax imposed on the production, sale, delivery or use of the Product, including, without limitation, sales, use, excise or value added taxes;

(f) Allowance for distribution expenses; and

(g) Any other similar and customary deductions.

Net Sales will be calculated in U.S. Dollars. Such amounts shall be determined from the books and records of a Party, its Affiliate or Sublicensee, maintained in accordance with U.S. Generally Accepted Accounting Principles or, in the case of Sublicensees, such similar accounting principles, consistently applied. Each Party further agrees in determining such amounts, it will use its then current standard procedures and methodology, including its then current standard exchange rate methodology for the translation of foreign currency sales into U.S. Dollars or, in the case of Sublicensees, such similar methodology, consistently applied.

Net Sales excludes:

(i) The transfer of reasonable and customary quantities of free samples of Product(s) and the transfer of Product(s) as clinical trial materials, other than for subsequent resale;

(ii) Sales or transfers of Product(s) among a Party and its Affiliates unless the receiving Party is the consumer or user of the Product(s); and

(ii) Use by a Party or its Affiliates or Sublicensees of Product for any use connected with the securing of regulatory approval or validating of a manufacturing process or the obtaining of other necessary marketing approvals for Product (unless such Product is subsequently sold).

In the event that the Product(s) is sold as part of a Combination Product (where ***"Combination Product"*** means any pharmaceutical product which comprises the Product(s) and at least one other active compound(s) and/or ingredients), the Net Sales of the Product(s), for the purposes of determining royalty payments, shall be determined by multiplying the Net Sales of Combination Product (as defined in the standard Net Sales definition) by the fraction, A / (A+B) where A is the weighted average sale price of the Product(s) when sold separately in finished form, and B is the weighted average sale price of the other product(s) sold separately in finished form.

In the event that the weighted average sale price of the Product(s) can be determined but the weighted average sale price of the other product(s) cannot be determined, Net Sales for

purposes of determining royalty payments shall be calculated by multiplying the Net Sales of the Combination Product by the fraction A / C where A is the weighted average sale price of the Product(s) when sold separately in finished form and C is the weighted average selling price of the Combination Product. In the event that the weighted average sale price of the other product(s) can be determined but the weighted average sale price of the Product cannot be determined, Net Sales for purposes of determining royalty payments shall be calculated by multiplying the Net Sales of the Combination Product by the following formula: one (1) minus B / C where B is the weighted average sale price of the other product(s) when sold separately in finished form and C is the weighted average selling price of the Combination Product. In the event that the weighted average sale price of both the Product(s) and the other product(s)

in the Combination Product cannot be determined, the Parties will attempt to agree on an appropriate weighted average sale price of both the Product(s) and the other product(s) in the Combination Product, and lacking such agreement the Net Sales of the Product(s) shall be deemed to be equal to fifty percent (50%) of the Net Sales of the Combination Product.

The weighted average sale price for a Product, other product(s), or Combination Product shall be calculated once each Calendar Year and such price shall be used during all applicable royalty reporting periods for the entire Calendar Year. When determining the weighted average sale price of a Product, other product(s), or Combination Product, the weighted average sale price shall be calculated by dividing the sales dollars (translated into U.S. Dollars) by the units of active ingredient sold during the twelve (12) months (or the number of months sold in a partial Calendar Year) for the respective Product(s), other product(s), or Combination Product. In the initial Calendar Year, a forecasted weighted average sale price will be used for Product(s), other product(s), or Combination Product. Any over or under payment due to a difference between forecasted and actual weighted average sale prices will be paid or credited in the first royalty payment of the following Calendar Year.

"Non-ASO Field" means the research, development, manufacture and sale of compounds other than ASO Compounds as therapeutic or prophylactic pharmaceutical products.

[***]

"Original Agreement" has the meaning provided in Recital C of this Agreement.

"Oncology Term" means the period of time during which the Parties will conduct the Antisense Drug Discovery Program and, subject to Section 3.1, the Target Validation Program in the Collaboration Therapeutic Area of oncology. ***"Party"*** means Lilly or Isis. ***"Parties"*** means Lilly and Isis.

"Patent Rights" means: (a) patent applications (including provisional applications and applications for certificates of invention); (b) any patents issuing from such patent applications (including certificates of invention); (c) all patents and patent applications based on, corresponding to, or claiming the priority date(s) of any of the foregoing; (d) any reissues, substitutions, confirmations, registrations, validations, re-examinations, additions, continuations, continued prosecutions, continuations-in-part, or divisions of or to any of the foregoing; and (e) term extension or other governmental action which provide exclusive rights beyond the original patent expiration date.

"Phase I Study Initiation" means the first human clinical trial conducted on normal volunteers and designed to evaluate safety of a product; *provided, however,* with respect to oncology, "Phase I Study Initiation" means the first human clinical trial conducted on patients with cancer who have no therapeutic options other than experimental therapy or normal volunteers.

"Phase II Study Initiation" means the first human clinical trial conducted in patients and designed to indicate a statistically significant level of efficacy for product in the desired indication, as well as to obtain some indication of the dosage regimen required; *provided*, *however*, with respect to oncology, "Phase II Study Initiation" means the first human clinical trial conducted on a series of patients with the same type and stage of cancer.

"Phase III Study Initiation" means the first human clinical trial conducted in patients and designed to establish Product safety and efficacy and required to obtain clinical registration of a product with health regulatory authorities such as the FDA.

"Product" shall mean a Lilly Product or an Isis Product, as applicable.

"Program Sanction Approval" means [***]

"Project Sanction Approval" means [***]

"Proposed Validation Target" has the meaning set forth in Section 5.2.

"Reagent ASO Compound" means all ASO Compounds that selectively modulate protein synthesis of a Reagent Target.

"Reagent ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more Reagent ASO Compounds.

"Reagent Non-ASO Compound" means a compound that (a) is developed by Lilly through the use of Collaboration Know-How and (b) is not an ASO Compound and (c) is either (i) an agonist or antagonist of a Reagent Target or (ii) is a Reagent Target.

"Reagent Non-ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more Reagent Non-ASO Compounds.

"Reagent Provision Program" means the program of identification, and delivery to Lilly, of ASO Compounds directed to Targets identified by Lilly under the Original Agreement and the Amended and Restated Agreement.

"Reagent Provision Term" means the term of the Reagent Provision Program carried out pursuant to the Original Agreement and the Amended and Restated Agreement..

"Reagent Target" means a Target that is designated a Reagent Target by Lilly; *provided, however,* that a Reagent Target that is later designated a Validation Target or a Drug Discovery Target shall not be considered a Reagent Target after the date of such designation.

"Registration" means (a) in the United States, approval by the FDA of an NDA, or similar application for marketing approval, and satisfaction of any related applicable FDA registration and notification requirements (if any), and (b) in any Major Market Country other than the United States, approval by regulatory authorities having jurisdiction over such country of a single application or set of applications comparable to an NDA and satisfaction of any related applicable regulatory and notification requirements, if any, together with any other approval necessary to make and sell pharmaceuticals and medical devices commercially in such country.

"Rejected Validation Target" has the meaning provided in Section 5.4.

"Reserved Target" has the meaning set forth in Section 6.8.

"***Restatement Date***" means the June 17, 2002, the effective date of the Amended and Restated Agreement.

"***RNAi Compound***" means a double-stranded RNA or DNA oligonucleotide or an analog thereof, including RNAi, that selectively modulates protein synthesis at the nucleic acid level through the binding of such oligonucleotide to a complementary sequence.

"Second Restatement Execution Date" means August 5, 2005, the date on which this Agreement was executed by the Parties.

"Second Restatement Date" means August 25, 2005, the effective date of this Agreement.

"Stage I Drug Discovery Target" means a Target that is designated a Drug Discovery Target under Section 6.3 that (i) has not reached the status of a Stage II Drug Discovery Target or Stage III Drug Discovery Target outside the course of the Collaboration prior to the designation of such target as a Drug Discovery Target or (ii) any Accepted Validation Target that enters the Antisense Drug Discovery Program under Section 6.3.

"Stage II Drug Discovery Target" means a Target that Isis moves to the status that is equivalent to Accepted Validation Target outside the course of the Collaboration (but that has not reached the status of a Stage III Drug Discovery Target) prior to the designation of such Target as a Drug Discovery Target.

"Stage III Drug Discovery Target" means a Target for which Isis has developed ASO Compounds and has analyzed such ASO Compounds in at least one (1) animal model in two (2) different species outside the course of the Collaboration and prior to the designation of such Target as a Drug Discovery Target.

"STAT3 Target" has the meaning set forth in Section 8.11.1

"Sublicense Income" means all consideration received by Lilly from a Sublicensee of Lilly pursuant to a sublicense agreement permitted under Section 9.3.5 excluding (a) payments made by such Sublicensee in consideration for the issuance of equity or debt securities of Lilly at fair market value, and (b) payments made by such Sublicensee to support or fund research activities to be undertaken by Lilly at cost.

"Sublicensees" means any Third Party to which Lilly or any of its Affiliates or Isis or any of its Affiliates grants any right to manufacture, market and sell a Lilly Product or an Isis Product, as applicable. A Third Party who is granted only the right to sell a Lilly Product or an Isis Product (such as a wholesaler) will not be considered a Sublicensee.

"Target" means a transcriptional unit of a gene, and any protein product of such transcriptional unit, including all splice variants.

"Target Validation Program" means the program of Target functionalization and validation under this Agreement, as described in Section 2.3, Article 5 and the Collaborative Research Plan.

"Target Validation Program Term" means the term of the Target Validation Program any extensions thereof.

"Territory" means the entire world.

"Third Party" means any Party other than Isis or Lilly and their respective Affiliates.

"Valid Claim" means any claim in an issued and unexpired patent which has not been held unenforceable, unpatentable or invalid by a decision of a court or other governmental agency of competent jurisdiction following exhaustion of all possible appeal processes and which has not been admitted to be invalid or unenforceable through reissue, reexamination or disclaimer, or otherwise.

"Validation ASO Compound" means all ASO Compounds that selectively modulate protein synthesis of a Validation Target.

"Validation ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more Validation ASO Compounds.

"Validation Non-ASO Compound" means a compound that (a) is developed by Lilly through the use of Collaboration Know-How and (b) is not an ASO Compound and (c) is either (i) an agonist or antagonist of a Validation Target or (ii) is a Validation Target.

"Validation Non-ASO Product" means any preparation in final form for sale by prescription, over-the-counter or any other method for any indication, including human or animal use, which contains one or more Validation Non-ASO Compounds.

"Validation Target" means any Target designated by Lilly for inclusion in the Target Validation Program; *provided, however,* that a Validation Target that is later designated a Drug

Discovery Target, shall be considered a Drug Discovery Target and not a Validation Target. Validation Targets includes Accepted Validation Targets and Rejected Validation Targets.

[***]

SCHEDULE 2.2

COLLABORATIVE RESEARCH PLAN

[***]

SCHEDULE 2.5

MEMBERS OF THE EXECUTIVE COMMITTEE AS OF THE SECOND RESTATEMENT EXECUTION DATE

Lilly	Isis
[***]	[***]

SCHEDULE 2.9

ALLIANCE MANAGERS AS OF THE SECOND RESTATEMENT EXECUTION DATE

Lilly	Isis
[***]	[***]

Schedule 5.5.3

Accepted Validation Targets as of the Second Restatement Execution Date

Submission Record ID	Gene Name
[***]	[***]

Schedule 5.6.3

Rejected Validation Targets as of the Second Restatement Execution Date

Submission Record ID	Gene Name
[***]	[***]

Schedule 5.12

Abandoned Validation Targets as of the Second Restatement Execution Date

Submission Record ID	Gene Name
[***]	[***]

Submission Record ID	Gene Name
[***]	[***]

Submission Record ID	Gene Name
[***]	[***]

Submission Record ID	Gene Name
[***]	[***]

Schedule 6.2

Development Stages of Drug Discovery Targets as of the Second Restatement Execution Date

Stage 1 Drug Discovery Targets

[***]

[***]

[***]

Stage 2 Drug Discovery Targets

[***]

[***]

Stage 3 Drug Discovery Targets

[***]

Schedule 6.5.1

Active Programs as of as of the Second Restatement Execution Date

1. [***]

Schedule 6.7.1

[***] **Abandoned Drug Discovery Targets in the Metabolic Collaboration Therapeutic Area**

1. [***]

Schedule 6.7.2

Abandoned Drug Discovery Targets as of the Second Restatement Execution Date

Submission Record ID	Gene Name	Development Stage at Time of Designation as Drug Discovery Target
[***]	[***]	[***]

Schedule 6.9.1

Reserved Targets as of the Second Restatement Execution Date

1. [***]

SCHEDULE 8.2.2

The Reagent Targets and the Date of Delivery to Lilly of a Reagent ASO Compound Directed to Each Such Reagent Target

Submission Record ID	Gene Name	Submitted Species	Date Delivered
[***]	[***]	[***]	[***]

SCHEDULE 9.4.3

Milestones and Royalties under Section 9.4.3 and 9.4.4

MILESTONE PAYMENTS

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

[***]

Schedule 12.12

Collaboration Patent Rights as of the Second Restatement Execution Date

1. Isis Collaboration Patent Rights

Docket/Serial Number	Gene Name
[***]	[***]

---

2. Lilly Collaboration Patent Rights

[***]

3. Joint Collaboration Patent Rights

[***]

SCHEDULE A

[DELETED]

SCHEDULE B

ISIS MANUFACTURING PATENT RIGHTS AS OF THE SECOND RESTATEMENT EXECUTION DATE

[***]

SCHEDULE C

ISIS CORE TECHNOLOGY PATENT RIGHTS AS OF THE SECOND RESTATEMENT EXECUTION DATE

1. [***]

Exhibit 10.4

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

NOTICE OF GRANT AWARD

NIH CHALLENGE GRANTS AND PARTNERSHIP Issue Date:08/01/2005

Department of Health and Human Services
National Institutes of Health
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Grant Number: 1 UC1 AI067232-01
Principal Investigator: PHD
Project Title: Multivariate pathogen diagnostic products based upon de*

DIRECTOR
IBIS THERAPEUTICS, INC.
1891 RUTHERFORD ROAD
CARLSBAD, CA 92008
UNITED STATES

Budget Period: 08/01/2005 - 07/31/2008
Project Period: 08/01/2005 - 07/31/2008

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $4,873,632(see ''Award Calculation'' in Section I) to ISIS PHARMACEUTICALS, INC. in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 P.L. 106 - 113 and is subject to terms and conditions referenced below. Acceptance of this award including the Terms and Conditions is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Award recipients are responsible for reporting inventions derived or reduced to practice in the performance of work under this grant. Rights to inventions vest with the grantee organization provided certain requirements are met and there is acknowledgement of NIH support. In addition, recipients must ensure that patent and license activities are consistent with their responsibility to make unique research resources developed under this award available to the scientific community, in accordance with NIH policy. For additional information, please visit http://www.iedison.gov.

If you have any questions about this award, please contact the individual(s) referenced in the information below.

Sincerely yours,

/s/ Pamela G. Fleming

Pamela G. Fleming
Grants Management Officer
NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

See additional information below

SECTION I - - AWARD DATA - 1 UC1 AI067232-01

AWARD CALCULATION (U.S. Dollars):

Salaries and Wages	$	***
Fringe Benefits	$	***
Personnel Costs	$	***
Consultant Services	$	***
Equipment	$	***
Supplies	$	***
Travel Costs	$	***
Other Costs	$	***
Federal Direct Costs	$	***
Federal F&A Costs	$	***
APPROVED BUDGET	$	4,873,632

TOTAL FEDERAL AWARD AMOUNT	$	4,873,632

FISCAL INFORMATION:
CFDA Number: 93.856
EIN: 1330336973A1
Document Number: UAI067232A

IC/ CAN / FY2005
AI/8460938/ 4,873,632

NIH ADMINISTRATIVE DATA:
PCC: M63 B / OC: 41.4L /Processed: PFLEMING 050728 0957

SECTION II - - PAYMENT/HOTLINE INFORMATION - 1 UC1 AI067232-01

For Payment and HHS Office of Inspector General Hotline Information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III - - TERMS AND CONDITIONS - 1 UC1 AI067232-01

This award is based on the application submitted to, and as approved by, the NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Grant Award.
b. The restrictions on the expenditure of federal funds in appropriations acts, to the extent those restrictions are pertinent to the award.
c. 45 CFR Part 74 or 45 CFR Part 92 as applicable.

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d. The NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(see NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

Treatment of Program Income:
Additional Costs

SECTION IV - - NIAID SPECIFIC TERMS OF AWARD -

THIS AWARD CONTAINS GRANT SPECIFIC RESTRICTIONS. THESE RESTRICTIONS MAY ONLY BE LIFTED BY A REVISED NOTICE OF GRANT AWARD.

This award is made under the initiative, “Challenge Grants: Biodefense and SARS Product Development”, RFA AI-04-029, and is awarded at the NIAID Institute’s recommended level of $4,873,632 total costs.

This award is subject to the Terms and Conditions of Award as set forth in the SPECIAL REQUIREMENTS section of RFA/PA AI-04-029, NIH Guide to Grants and Contracts, 06/15/04. These special terms and conditions are incorporated in this award by reference.

Copies of the RFA may be accessed at the following Internet address: http://grants2.nih.gov/grants/guide/rfa-files/RFA-AI-03-016.html

The conditions of award incorporate the details of the specific milestone and timelines for achieving each milestone as described in the original grant application dated 01/15/05, and include any modifications submitted by the applicant on 06/15/05.

Milestone Breakout (Time and Amount):

MILESTONE 1: 08/01/05 - 07/31/06		$	***		
MILESTONE 2: 08/01/06 - 07/31/07		$	***		
MILESTONE 3: 08/01/06 - 07/31/07				$	***
MILESTONE 4: 08/01/07 - 07/31/08				$	***
TOTAL	36 MONTHS	$	4,873,632		

FUNDS AVAILABLE ARE THOSE FOR THE ACHIEVEMENT OF MILESTONE #1 ($***) ALL FUNDS FOR FUTURE MILESTONES ARE RESTRICTED FROM EXPENDITURE UNTIL DETERMINATION THAT MILESTONE #1 GOALS ARE ACHIEVED. RESTRICTED FUNDS MAY ONLY BE USED UPON RECEIPT OF A REVISED AWARD LIFTING THE RESTRICTIONS.

To achieve consideration of future milestones, the following information must be submitted to NIAID Grants Management two months prior to the completion of the next milestone: 1) 2590 application - that includes a progress report; 2) Updated Product Development plans; 3) updated information regarding assurances, budget and key personnel changes.

This information should be sent to:

Mary Ledford, Grants Management Specialist
DEA, NIAID, NIH, DHHS
Room 2129
6700-B Rockledge Drive, MSC 7614
Bethesda, MD 20892-7614 (Regular Mail)
Bethesda, MD 20817 (Express Mail)

This award may be adjusted in time or funding, as necessary, if the grantee fails to meet the agreed upon milestones. Any changes in these items from the Notice of Grant Award will require concurrence of NIH.

RESTRICTION: Pending the establishment of a negotiated facilities and administrative (F&A) cost rate, this award has been issued at the requested level, however, only F&A costs of ***% salaries and wages for the achievement of the first milestone ($***) may be expended/obligated at this time. All other F&A costs are restricted from drawdown. The timeline to establish this rate is *** days from the issuance of this Notice of Grant Award. Immediately contact Ms. Ruth Bishop, Office of Financial Management/NIH at (301) 496-2444 for assistance.

RESTRICTION: The present award is being made without a currently valid certification of Institutional Review Board (IRB) approval for this project with the following restriction: Only activities that are clearly severable and independent from activities that involve human subjects may be conducted under this award until the project has received IRB approval consistent with 45 CFR Part 46 and certification of IRB approval has been submitted to and accepted by the NIH awarding component.

No funds may be drawn down from the payment system and no obligations may be made against Federal funds for research involving human subjects by the grantee or any other site engaged in such research for any period not covered by an OHRP-approved Assurance and IRB approval consistent with 45 CFR Part 46.

Failure to comply with the above requirements may result in suspension and/or termination of this award, withholding of support, audit disallowances, and/or other appropriate action.

See the NIH Grants Policy Statement, December 2003, (http://grants2.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part5.htm), pages 54-56 for specific requirements related to the protection of human subjects, which are applicable to and a term and condition of this award.

This award is subject to the Clinical Terms of Award included in Monitoring of Clinical Trials and Studies - NIAID (see NIH Guide for Grants and Contracts, July 8, 2002, NOT AI-02-032). These terms and conditions are hereby incorporated by reference, and can be accessed via the following World Wide Web address: http://www.niaid.nih.gov/ncn/pdf/clinterm.pdf All submissions required by the NIAID Clinical Terms of Award must be forwarded electronically or by mail to the responsible NIAID Program Official identified on this Notice of Grant Award.

Awardees who conduct research involving Select Agents (see 42 CFR 73 for the Select Agent list; and 7 CFR 331 and 9 CFR 121 for the relevant animal and plant pathogens) must complete registration with CDC (or USDA, depending on the agent) before using NIH funds. No funds can be used for research involving Select Agents if the final registration certificate is denied.

The proposed research has been identified as involving an infectious agent that may warrant a biocontainment safety level of BSL3 or higher, according to the current edition of Biosafety in Microbiological and Biomedical Laboratories (BMBL; http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm). It is the responsibility of the Grantee Organization to assure that ALL Personnel, including those at associated institutions, handling these highly pathogenic infectious agents have received appropriate training and are working in appropriate biocontainment safety level facilities, as recommended in the current edition of BMBL.

In addition, it is a term and condition of NIH funding that all recombinant DNA research must be reviewed and approved by local Institutional Biosafety Committees, as described in the NIH Guidelines for Research Involving Recombinant DNA Molecules (http://www4.od.nih.gov/oba/rac/guidelines_02/NIH_Gdlnes_lnk_2002z.pdf).

None of the funds in this award shall be used to pay the salary of an individual at a rate in excess of $180,100 per year. Therefore, this award and/or future years are adjusted accordingly, if applicable.

Maria Y. Giovanni, Program Official
Phone: 301-496-1884 Email: mg37u@nih.gov Fax: 301-480-4528

Mary K. Ledford, Grants Specialist
Phone: 301-402-6446 Email: mledford@niaid.nih.gov Fax: 301-480-3780

SPREADSHEET
GRANT NUMBER: 1 UC1 AI067232-01

P.I.: ***
INSTITUTION: ISIS PHARMACEUTICALS, INC.

	YEAR 01
Salaries and Wages	***
Fringe Benefits	***
Personnel Costs	***
Consultant Services	***
Equipment	***

Supplies	***
Travel Costs	***
Other Costs	***
TOTAL FEDERAL DC	***
TOTAL FEDERAL F&A	***
TOTAL COST	4,873,632

	YEAR 01
F&A Cost Rate 1	***%
F&A Cost Base 1	***
F&A Costs 1	***
F&A Cost Rate 2	***%
F&A Cost Base 2	***
F&A Costs 2	***
F&A Cost Rate 3	***%
F&A Cost Base 3	***
F&A Costs 3	***

SUBCONTRACT AGREEMENT
Time and Material / Labor Hour

SUBCONTRACTOR:
Ibis Therapeutics, A Division of Isis Pharmaceuticals, Inc.
ADDRESS:
1891 Rutherford Road
Carlsbad, CA 92008

SUBCONTRACT #: [ ]
DPAS RATING: [ ]
TYPE: Time and Material/Labor Hour
NOT-TO-EXCEED CEILING PRICE: $[ ]

INTRODUCTION

This Subcontract Agreement, effective **[ ]** is made between SCIENCE APPLICATIONS INTERNATIONAL CORPORATION (hereinafter known as "Buyer"), a Delaware corporation with principal offices in San Diego, California, and Isis Pharmaceuticals, Inc. (hereinafter known as "Seller"), a corporation, with principal offices in Carlsbad, California. The effort to be performed by Seller under this Subcontract will be part of Buyer's Prime Contract # **[ ]** that has been issued by **[ ]**. The work, defined in Attachment I (Statement of Work and Schedule) will be performed on a Time and Material/Labor Hour basis, in accordance with Schedule A (Specific Terms and Conditions), and any referenced document in **18.0 Order of Precedence** clause of this agreement.

SCHEDULE A
SPECIFIC TERMS AND CONDITIONS

1.0 PERIOD OF PERFORMANCE

The period of performance for this Subcontract is **[ ]** through **[ ]**, unless amended in writing by mutual agreement of the parties. Seller is not obligated to continue work or provide services and Buyer is not obligated to compensate Seller for expenses incurred or commitments made before or after these dates.

1.1 LABOR RATES

The following are the Seller's fixed hourly labor rates effective for the period of performance identified in paragraph 1.0 of this Subcontract:

LABOR CATEGORY	BILLING RATE GFY 05 (12/16/04-09/30/05)	BILLING RATE GFY 06 (10/01/05-09/30/06)
Executive	$ [ ] Per hour	$ [ ] Per hour
Scientist II	$ [ ] Per hour	$ [ ] Per hour
Scientist I	$ [ ] Per hour	$ [ ] Per hour
Scientist	$ [ ] Per hour	$ [ ] Per hour

1.2 FUNDING

This Subcontract may be incrementally or fully funded. The Subcontract Ceiling Price of $**[ ]** is currently fully funded in the amount of $**[ ]** ($**[ ]** Labor / $**[ ]** Consumables), which is anticipated to cover expenses through **[ ]**. And, unless amended in writing by mutual agreement of the parties, Seller is not obligated to incur expenses or make commitments in excess of the Subcontract funded amount, and Buyer is not obligated to compensate Seller beyond the funded amount of the Subcontract. If at any time the Seller has reason to believe that the hourly rate payments and material costs that will accrue in performing this Subcontract in the next succeeding 30 days, if added to all other payments and cost previously accrued will exceed eighty-five percent (85%) of the of the total funded amount of this Subcontract, the Seller shall immediately notify the Buyer in writing providing supporting rationale for additional funds. It is mutually agreed and understood that the above 85% notification requirement applies to each increment of funds provided to Seller under this Subcontract.

1.3 INSPECTION

All materials furnished and services performed pursuant hereto shall be subject to inspection and test by Buyer and its agents and by its customers at all times and places, during the period of performance, and in any event before acceptance. In the event that material furnished or services supplied are not performed in accordance with the statement of work requirements, Buyer may require Seller to replace or correct services or materials. The cost of replacement or correction shall be determined under the Payment clause of this subcontract, but the "hourly rate" for labor hours incurred in the replacement or correction shall be reduced to exclude that portion of the rate attributable to profit. If the Seller fails to proceed with reasonable promptness to perform required replacement or correction, and if the replacement or correction cannot be performed within the Not-To-Exceed ceiling price, the Buyer may terminate the subcontract for default.

1.4 INVOICES

Invoices shall be prepared in duplicate and contain the following information; subcontract number, labor categories, hourly rates, labor hours, extended totals by category, material and other direct costs detail shall be separated from labor costs. Invoices will be mailed to:

Science Applications International Corporation
Attention: Josh Houser, M/S 700
4001 North Fairfax Drive, Suite 375
Arlington, VA 22203

Invoices shall clearly reference a unique invoice number on each invoice, period of incurred costs, and the date of the invoice. Invoices shall include the "Amount Previously Billed," the "Amount of this Invoice," and the "Total Amount Billed to Date" for each labor category. Seller shall submit invoices for the full amount stating the amount of withhold/retention if any for each line item billed.

Invoices shall be signed and dated by the cognizant Contractual Representative of the Seller, verifying the costs included are correct. The following statement will be executed for all invoices whose billing rates are based on fixed hourly rates tied to labor categories that contain minimum education and experience qualifications for assigned personnel:

"I have reviewed the qualifications of the individuals whose labor costs are being invoiced hereunder and hereby confirm that all individuals meet the minimum labor category education and experience requirements for the specific labor categories for which his or her work is being billed."

1.5 PAYMENT

The Buyer shall pay the Seller upon the submission of invoices approved by the Buyer as follows:

(a) *Hourly rate*. The amounts shall be computed by multiplying the appropriate hourly rates in Section 1.1 by the number of direct labor hours performed. Invoices may be submitted once each month to the Buyer. The Seller shall substantiate invoices by evidence of actual payment and by individual daily job time cards, or other substantiation approved by the Buyer. The Buyer shall pay the invoice within 30 days after receipt of proper invoice.

(b) Unless specifically authorized in writing by the Buyer, the Seller is not authorized to perform and the Buyer is not obligated to reimburse the Seller for work performed on an Overtime, Extended Work Week, Shift Premium, or Uncompensated Time basis.

(c) *Materials and other direct costs*. Authorized material and other direct costs, such as travel, will be reimbursed on an actual cost basis in accordance with Generally Accepted Accounting Principles applied on a consistent basis. Where materials are withdrawn from inventories, cost must be determined in accordance with proper accounting practices consistently followed by Seller. Seller shall support all material cost claims by submitting invoices, storeroom requisitions, expense reports, or other substantiation acceptable to Buyer. Reasonable and allocable materials handling costs may be included in the charge for material at cost to the extent they are clearly excluded from hourly rates. The material handling cost shall be 15% of direct material and other direct costs.

(d) *Total cost*. To the extent the Ceiling Price of this Subcontract is fully funded, it is estimated that the total cost to the Buyer for the performance of this subcontract shall not exceed the ceiling price. The Seller agrees to use its best efforts to perform the work within the ceiling price. If at any time the Seller has reason to believe that the total price to the Buyer will be substantially greater or less than the ceiling price, the Seller shall immediately notify the Buyer in writing and provide a revised estimate for performing the work.

1.6 AUDIT

At any time before final payment the Buyer may request and perform an audit of the invoices and substantiating material. Each payment previously made shall be subject to reduction to the extent of amounts that are found by the Buyer not to have been properly payable in accordance with the payment terms of this subcontract. Audit will include, but not be limited to, individual daily job time cards, invoices for material, storeroom requisitions, expense reports, and other substantiation supporting invoiced amounts.

1.7 WARRANTY

Seller represents and warrants (1) that all goods and services delivered pursuant hereto will be new, unless otherwise specified, and free from defects in material and workmanship; (2) that all goods and services will conform to applicable specifications, drawings, and standards of quality and performance, and that all items will be free from defects in design and suitable for their intended purpose; and (3) that the goods covered by this order are fit and safe for consumer use, if so intended. All representations and warranties of Seller together with its service warranties and guarantees, if any, shall run to Buyer and Buyer's customers. The foregoing warranties shall survive any delivery, inspection, acceptance, or payment by Buyer.

2.0 TECHNICAL AND CONTRACTUAL REPRESENTATIVES

The following authorized representatives are hereby designated for this Subcontract:

SELLER:
TECHNICAL: **[ ]**
Phone: **[ ]**
Fax: **[ ]**
Email: **[ ]**
CONTRACTUAL: **[ ]**
Phone: **[ ]**
Fax: **[ ]**
Email: **[ ]**

BUYER:
TECHNICAL: **[ ]**
Phone: **[ ]**
Fax: **[ ]**
Email: **[ ]**
CONTRACTUAL: **[ ]**
Phone: **[ ]**
Fax: **[ ]**
Email: **[ ]**

2.1 CONTACTS

Contacts with Buyer that affect the subcontract prices, schedule, statement of work, and subcontract terms and conditions shall be made with the authorized contractual representative. No changes to this Subcontract shall be binding upon Buyer unless incorporated in a written modification to the Subcontract and signed by Buyer's contractual representative.

2.2 CHANGES

Buyer may, by written notice to Seller at any time before completion of this subcontract, make changes within the general scope of this subcontract in any one of the following: (a) drawings, designs, or specifications; (b) quantity; (c) delivery; (d) method of shipment or routing; and (e) make changes in the amount of Buyer furnished property. If any such change causes a material increase or decrease in any hourly rate or the not-to-exceed ceiling price, or the time required for the performance of any part of the work under this subcontract, the Buyer shall make an equitable adjustment in the hourly rates or delivery schedule, or both, and shall modify the subcontract not-to-exceed ceiling price. As a condition precedent to any equitable adjustment, the Seller must notify Buyer in writing of any request for adjustment within twenty (20) days from the date Seller receives notice from Buyer of a change, or from the date of any act of Buyer, which Seller considers to constitute a change. Failure to agree to any adjustment shall be a dispute under the Disputes clause of this subcontract. However, Seller shall proceed with the work as changed without interruption and without awaiting settlement of any such claim.

3.0 DISCLOSURE

The parties shall not disclose information concerning work under this Subcontract to any third party, unless such disclosure is necessary for the performance of the subcontract effort. No news releases, public announcement, denial or confirmation of any part of the subject matter of this Subcontract or any phase of any program hereunder shall be made without prior written consent of Parties, which consent will not be unreasonably withheld. The restrictions of this paragraph shall continue in effect upon completion or the parties may mutually agree upon termination of this Subcontract for such period of time as in writing. In the absence of a written established period, no disclosure is authorized. Failure to comply with the provisions of this clause may be cause for termination of this subcontract. The obligations of Paragraph 3.0 will not apply to information that the receiving party can establish by written records was disclosed by the receiving party pursuant to any judicial, government or stock exchange request, requirement or order, so long as the receiving party provides the disclosing party with sufficient prior written notice in order to allow the disclosing party to contest such request, requirement or order.

4.0 KEY PERSONNEL

(a) For purposes of this clause, Buyer and Seller define "Key Personnel" as those individuals who are mutually recognized as essential to the successful completion and execution of this Subcontract.

(b) Personnel designated as "Key Personnel" shall be assigned to the extent necessary for the timely completion of the task to which assigned. Any substitution or reassignment involving Seller's "Key Personnel" assigned to this work shall be made only with persons of equal abilities and qualifications and is subject to prior approval of Buyer, in writing.

(c) Buyer reserves the right to direct the removal of any individual assigned to this Subcontract.

(d) Seller's Key Personnel is **[ ]**.

4.1 IP RIGHTS

Subject to the rights reserved to the U.S. Government under the referenced FAR's, Isis will retain all rights, including commercial rights, to any technology, software and inventions created by Isis during the performance of this Subcontract Agreement ("ISIS Technology"). Inventorship of any invention created hereunder will be determined in accordance with U.S. Patent Law, including joint inventorship, if any, between SAIC and Isis. The ISIS Technology disclosed to SAIC hereunder is disclosed solely for use in performance of SAIC's obligations to the U.S. Government under Prime Contract # **[ ]**. Any other use of Isis Technology by SAIC, including the pursuit of commercial opportunities, will be subject to separate agreements.

5.0 ASSIGNMENTS AND SUBCONTRACTS

This Subcontract is not assignable and shall not be assigned by Seller without the prior written consent of Buyer. Further, Seller agrees to obtain Buyer's approval before subcontracting this order or any substantial portion thereof; provided, however, that this limitation shall not apply to the purchase of standard commercial supplies or raw materials.

6.0 INSURANCE PROVISION FOR PROCUREMENT CONTRACTS

Without prejudice to Seller's liability to indemnify Buyer as stated in the indemnification provision of this Agreement, Seller shall procure, at its expense, and maintain for the duration of the Agreement, the insurance policies described below with financially responsible insurance companies, reasonably acceptable to Buyer, with policy limits not less than those indicated below. Notwithstanding any provision contained herein, the Seller, and its employees, agents, representatives, consultants and lower-tier subcontractors and suppliers, are not insured by Buyer, and are not covered under any policy of insurance that Buyer has obtained or has in place.

Special Provisions Applicable to Seller's Insurance coverage:

1. Additional Insured - Seller shall have all policies, except Workers' Compensation and Employer's Liability, endorsed to name Buyer as an Additional Insured with respect to the work to be performed by the Seller.

2. Waiver of Subrogation - Seller shall have all policies endorsed to waive the insurer's rights of subrogation in favor of Buyer except for Workers Compensation.

3. Deductibles - - Subject to the reasonable review and approval of Buyer, the Seller may arrange deductibles or self-insured retention's as part of the required insurance coverage's. However, it is expressly agreed that all deductibles or self-insured retention's are the sole responsibility of the Seller.

4. Adequacy of Insurance Limits - The insurance coverage limits stated below are minimum coverage requirements, not limits of liability, and shall not be construed in any way as Buyer's acceptance of responsibility of the Seller.

5. Certificates of Insurance - Prior to commencement of any work under this Agreement, the Seller shall furnish Buyer with Certificates of Insurance covering the current period of performance of this Subcontract, in a format acceptable to Buyer, evidencing the insurance coverage required in this Agreement and containing the following information:

   a. Identify Buyer as an "Additional Insured" with respect to all policies except Workers' Compensation and employers' liability.

   b. State that all policies have been endorsed to waive subrogation in favor of Buyer except for Workers Compensation.

   c. State that the underwriters agree to provide Buyer with at least 30 days prior written notice of any cancellation in the coverage.

In addition, the Seller shall furnish the Buyer revised Certificates of Insurance covering any and all subsequent extensions to the initial period of performance of this Subcontract.

6.1 COVERAGE

A. Workers' Compensation - Insurance for statutory obligations imposed by law including, where applicable, coverage under United States Longshoremen's and Harbor Workers' Act and Jones Act. (if applicable, Defense Base Act for those employees working on a U.S. Military installation outside of the United States).

B. Employers Liability - Insurance with limits of $1,000,000 for bodily injury by accident and $1,000,000 for bodily injury by disease, including, if applicable, maritime coverage endorsement.

C. Commercial General Liability - (Standard ISO occurrence form) - including full fire legal liability and contractual liability, with a per occurrence limit of $1,000,000.

D. Business Auto Liability - Coverage for bodily injury and property damage liability for all owned, hired or non-owned vehicles, with an each accident limit of $1,000,000.

The following clauses are applicable to this Agreement if checked:

E. Professional Liability - $1,000,000 per occurrence and aggregate providing coverage for claims arising out of the performance of professional services, resulting from any error, omission or negligent act of the Seller.

7.0 INDEMNIFICATION

(a) Seller shall indemnify, defend and hold SAIC and SAIC's customers harmless from and against any and all damages, losses, liabilities and expenses (including reasonable attorneys' fees) arising out of or relating to any claims, causes of action, lawsuits or other proceedings, regardless of legal theory, that result, in whole or in part, from Seller's (or any of Seller's subcontractors, suppliers, employees, agents or representatives): (i) intentional misconduct, negligence, or fraud, (ii) breach of any representation, warranty or covenant made herein, or (iii) products or services including, without limitation, any claims that such products or services infringe any United States patent, copyright, trademark, trade secret or any other proprietary right of any third party.

(b) Buyer shall promptly notify Seller of any claim against Buyer that is covered by this indemnification provision and shall authorize representatives of Seller to settle or defend any such claim or suit and to represent Buyer in, or to take charge of, any litigation in connection therewith.

8.0 INFRINGEMENT INDEMNITY

(a) In lieu of any warranty by Buyer or Seller against infringement, statutory or otherwise, it is agreed that Seller shall defend, at its expense, any suit against Buyer or its customers based on a claim that any item furnished under this order or the normal use or sale thereof infringes any U.S. Letters patent or copyright, and shall pay costs and damages finally awarded in any such suit, provided that Seller is notified in writing of the suit and given authority, information, and assistance at Seller's expense for the defense of same. If the use or sale of said item is enjoined as a result of such suit, Seller, at no expense to Buyer, shall use commercially

reasonable efforts to obtain for Buyer and its customers the right to use and sell said item or shall substitute an equivalent item acceptable to Buyer and extend this patent indemnity thereto.

(b) Notwithstanding the foregoing paragraph, when this order is performed under the Authorization and Consent of the U.S. Government to infringe U.S. Patents, Seller's liability for infringement of such Patents in such performance shall be limited to the extent of the obligation of Buyer to indemnify the U.S. Government.

9.0 CONFIDENTIALITY AND USE OF BUYER FURNISHED ITEMS/INFORMATION

Seller agrees that it will keep confidential the features of any equipment, tools, gauges, patterns, designs, drawings, engineering data or other technical or proprietary information furnished by Buyer and use such items only in the performance of this Subcontract or other orders from Buyer and not otherwise, unless Buyer's written consent is first obtained. Seller also agrees to use any designs or data in accordance with any restrictive legends placed on such items by the Buyer or any third party. Upon completion or termination of this Order, Seller shall return all such items to Buyer or make such other disposition thereof as may be directed or approved by Buyer.

10.0 DISPUTES

Any dispute not disposed of in accordance with the "Disputes Clause" of Schedule B, if any, shall be determined in the following manner.

(a) Buyer and Seller agree to enter into Negotiation to resolve any dispute. Both parties agree to negotiate in good faith to reach a mutually agreeable settlement within a reasonable amount of time.

(b) If negotiation is unsuccessful, Buyer and Seller agree to enter into binding Arbitration. The American Arbitration Association (AAA) Commercial Arbitration Rules (most recent edition) are to govern this Arbitration. The Arbitration shall take place in the County of San Diego, State of California. The Arbitrator shall be bound to follow the applicable subcontract provisions and California law in adjudicating the dispute. It is agreed by both parties that the Arbitrator's decision is final, and that no party may take any action, judicial or administrative, to overturn this decision. The judgment rendered by the Arbitrator may be entered in any court having jurisdiction thereof.

Pending any decision, appeal or judgment referred to in this provision or the settlement of any dispute arising under this Subcontract, Seller shall proceed diligently with the performance of this Subcontract.

11.0 DEFAULT

(a) The Buyer may, by written notice of default to the Seller, terminate the whole or any part of this Subcontract in any one of the following circumstances: (i) if Seller fails to make progress in the work so as to endanger performance delivery of the supplies or to perform the services within the time specified herein or any extension thereof; or (ii) if Seller fails to perform any of the other provisions of this Subcontract in accordance with its terms, and in either of these two circumstances does not cure such failure within a period of 10 days (or such longer period as Buyer may authorize in writing) after receipt of notice from the Buyer specifying such failure; or (iii) Seller becomes insolvent or the subject of proceedings under any law relating to bankruptcy or the relief of debtors or admits in writing its inability to pay its debts as they become due.

(b) If this Subcontract is so terminated, Seller shall submit a final termination settlement proposal to the Buyer. The Seller shall submit the proposal promptly but no later than six (6) months from the effective date of the termination. If Seller fails to submit the proposal within the time allowed, the Buyer may determine the amount, if any, due the Seller because of the termination. The amount will be determined as follows; (i) An amount for direct labor hours determined by multiplying the number of direct labor hours expended before the effective date of termination by the hourly rates, less profit, in the Schedule, less any hourly rate payments already made to the Seller; (ii) An amount for material expenses incurred before the effective date of termination, not previously paid to the Seller. Buyer may procure or otherwise obtain, upon such terms and in such manner as Buyer may deem appropriate, supplies or services similar to those terminated, Seller, subject to the exceptions set forth below, shall be liable to Buyer for any excess costs of such similar supplies or services.

(c) Seller shall transfer title and deliver to Buyer, in the manner and to the extent requested in writing by Buyer at or after termination such complete articles, partially completed articles and materials, parts, tools, dies, patterns, jigs, fixtures, plans, drawings, information and contract rights as Seller has produced or acquired for the performance of the terminated part of this Subcontract, and Buyer will pay Seller the contract price for

complete articles delivered to and accepted by Buyer and the fair value of the other property of Seller so requested and delivered.

(d) Seller shall continue performance of this Subcontract to the extent not terminated. Buyer shall have no obligations to Seller with respect to the terminated part of this Subcontract except as herein provided. In case of Seller's default, Buyer's rights as set forth herein shall be in addition to Buyer's other rights although not set forth in this Subcontract.

(e) Seller shall not be liable for damages resulting from default due to causes beyond the Seller's control and without Seller's fault or negligence, provided, however, that if Seller's default is caused by the default of a subcontractor or supplier, such default must arise out of causes beyond the control of both Seller and subcontractor or supplier, and without the fault or negligence of either of them and, provided further, the supplies or services to be furnished by the subcontractor or supplier were not obtainable from other sources.

12.0 SUBCONTRACT CLOSEOUT

Within sixty-calendar days after the end of the period of performance for the services to be procured herein, as described in the Attachment I Statement of Work and the satisfactory performance of which shall be solely determined by Buyer, Buyer will issue to Seller a Subcontract Closeout Package. The Package will include, as applicable, Subcontractor Release of Claims; Subcontractor's Assignment of Refunds, Rebates, Credits, and Other Amounts; Subcontract Patents Report; and any other documentation or request for information considered necessary by Buyer to closeout this Subcontract Agreement.

Seller agrees to submit all information and documentation, including a FINAL invoice bearing the statement, "*This FINAL invoice was prepared using final audited rates*" as required by the Subcontract Closeout Package within thirty-calendar days of the date of the Package. The parties further agree if the information and documentation submitted by Buyer, finds Seller acceptable with or without negotiations (the necessity for which shall be solely determined by Buyer), to be bound by Seller's closeout submission as the final agreement between the parties with respect thereto.

In the event Seller fails to submit the required closeout information and documentation in a timely manner, such failure shall constitute Seller's express agreement that the amounts paid to date by Buyer pursuant to this Agreement, as determined by Buyer's records, constitute the full, complete and final extent of Buyer's financial obligation to Seller, that Seller does forever fully and finally remise, release, and discharge Buyer, its officers, agents and employees, of and from any and all liabilities, obligations, claims, and demands whatsoever arising under or relating to this Subcontract Agreement, and that Seller expressly authorizes Buyer to rely on the foregoing representations and release in connection with Buyer's closeout of or other actions taken with respect to

Buyer's contract with the Government. Furthermore, such failure is considered to be a material breach of the terms of this subcontract, and may subject seller to forfeiture of all or part of the fee withhold prescribed by Article 1.4.

13.0 GENERAL RELATIONSHIP

The Subcontractor is not an employee of SAIC for any purpose whatsoever. Seller agrees that in all matters relating to this Subcontract it shall be acting as an independent contractor and shall assume and pay all liabilities and perform all obligations imposed with respect to the performance of this Subcontract. Seller shall have no right, power or authority to create any obligation, expressed or implied, on behalf of Buyer and/or the Government and shall have no authority to represent Buyer as an agent.

14.0 NON-WAIVER OF RIGHTS

The failure of Buyer to insist upon strict performance of any of the terms and conditions in the Subcontract, or to exercise any rights or remedies, shall not be construed as a waiver of its rights to assert any of the same or to rely on any such terms or conditions at any time thereafter. The invalidity in whole or in part of any term or condition of this subcontract shall not affect the validity of other parts hereof.

15.0 APPLICABLE STATE LAW AND COMPLIANCE

This Subcontract shall be governed by and construed in accordance with the laws of the State of California. Seller agrees to comply with the applicable provisions of any federal, state or local law or ordinance and all orders, rules and regulations issued there under.

16.0 EXPORT CONTROL COMPLIANCE FOR FOREIGN PERSONS

The subject technology of this Subcontract (together including data, services, and hardware provided hereunder) may be controlled for export purposes under the International Traffic in Arms Regulations (ITAR) controlled by the U.S. Department of State or the Export Administration Regulations ("EAR") controlled by the U.S. Department of Commerce. ITAR controlled technology may not be exported without prior written authorization and certain EAR technology requires a prior license depending upon its categorization, destination, end-user and end-use. Exports or re-exports of any U.S. technology to [any destination under U.S. sanction or embargo are forbidden.

Access to certain technology ("Controlled Technology") by Foreign Persons (working legally in the U.S.), as defined below, may require an export license if the Controlled Technology would require a license prior to delivery to the Foreign Person's country of origin. SELLER is bound by U.S. export statutes and regulations and shall comply with all U.S. export laws. SELLER shall have full responsibility for obtaining any export licenses or authorization required to fulfill its obligations under this Subcontract.

SELLER hereby certifies that all SELLER employees who have access to the Controlled Technology are U.S. citizens, have permanent U.S. residency or have been granted political asylum or refugee status in accordance with 8 U.S.C. 1324b(a)(3). Any non-citizens who do not meet one of these criteria are "Foreign Persons" within the meaning of this clause but have been authorized under export licenses to perform their work hereunder.

17.0 STANDARDS OF BUSINESS ETHICS & CONDUCT

SAIC believes in fair and open competition and is committed to conducting its business fairly, impartially and in an ethical and proper manner. SAIC is owned and controlled by its employee owners. These characteristics make it imperative that SAIC employees adhere to a particularly high ethical standard. Employee ownership both demands and fosters highly ethical conduct because SAIC can be successful only when employees look after long-term interests of the company and resist pressures to compromise SAIC standards. Buyer's expectation is that Seller also will conduct its business fairly, impartially and in an ethical and proper manner. If Seller has cause to believe that Buyer or any employee or agent of Buyer has acted improperly or unethically under this agreement/order, Seller shall report such behavior to the SAIC Ethics Hotline (800) 435-4234. Copies of The Science Applications International Corporation (SAIC) code of Ethics and contacts for such reports are available on www.saic.com under Corporate Governance.

18.0 ORDER OF PRECEDENCE

The documents listed below are hereby incorporated by reference. In the event of an inconsistency or conflict between or among the provisions of this Subcontract, the inconsistency shall be resolved by giving precedence in the following order:

1. Attachment I: Statement of Work dated **[ ]**, entitled "**[ ]**"
2. Schedule A: Specific Terms and Conditions Form 9-932-025 (Rev. 9/20/04)
3. Schedule B Part I: U.S. Government Terms and Conditions Form 9-932-031 (Rev. 7/1/02)
4. Schedule B Part II: Contract Clauses Department of Defense (DOD) (Rev. 12/5/03)

19.0 ENTIRE AGREEMENT

The parties hereby agree that this Subcontract, including all documents incorporated herein by reference, shall constitute the entire agreement and understanding between the parties hereto and shall supersede and replace any and all prior or contemporaneous representations, agreements or understandings of any kind, whether written or oral, relating to the subject matter hereof.

In witness whereof, the duly authorized representatives of Buyer and the Seller have executed this Subcontract on the dates shown.

SELLER:
IBIS THERAPEUTICS
A DIVISION OF ISIS PHARMACEUTICALS, INC.

SCIENCE APPLICATIONS INTERNATIONAL CORPORATION

(Company Name)

(Signature)

NAME: [ ]
(Type or Print)

TITLE: [ ]

DATE: [ ]

(Signature)

NAME: [ ]
(Type or Print)

TITLE: [ ]

DATE: [ ]

Attachment I

Statement of Work

[ ]

[ ]

Science Applications International Corporation
An Employee-Owned Company

SCHEDULE B - U.S. GOVERNMENT TERMS AND CONDITIONS

Applicable to all U.S. Government subcontracts
PART I - FAR CLAUSES

1. DEFINITIONS

In all such clauses, unless the context of the clause requires otherwise, the term "Contractor" shall mean Seller, the term "Contract" shall mean this Order, and the terms "Government," "Contracting Officer" and equivalent phrases shall mean Buyer and Buyer's Purchasing Representative (except with respect to [ ], in which the term "Government," "Contracting Officer" and equivalent phrases will retain their respective meanings as set forth in such FARs), respectively. It is intended that the referenced clauses shall apply to Seller in such manner as is necessary to reflect the position of Seller as a subcontractor to Buyer, to insure Seller's obligations to Buyer and to the United States Government, and to enable Buyer to meet its obligations under its Prime Contract or Subcontract.

The following definitions apply unless otherwise specifically stated:

"Buyer" - the legal entity issuing this Order.
"Purchasing Representative" - Buyer's authorized representative.
"Seller" - the legal entity which contracts with the Buyer.
"This Order" - this contractual instrument, including changes.
"Prime Contract" - the Government contract under which this Order is issued.
"FAR" - the Federal Acquisition Regulation.

2. IDENTIFICATION OF CONTRACT NUMBERS

Government contract numbers shown on this Order shall be included in subcontracts and purchase orders issued by Seller hereunder.

3. DISPUTES

(a) Notwithstanding any provisions herein to the contrary:

(1) If a decision relating to the Prime Contract is made by the Contracting Officer and such decision is also related to this Order, said decision, if binding upon Buyer under the Prime Contract shall in turn be binding upon Buyer and Seller with respect to such matter; provided, however, that if Seller disagrees with any such decision made by the Contracting Officer and Buyer elects not to appeal such decision, Seller shall have the right reserved to Buyer under the Prime Contract with the Government to prosecute a timely appeal in the name of Buyer, as permitted by the contract or by law, Seller to bear its own legal and other costs. If Buyer elects not to appeal any such decision, Buyer agrees to notify Seller in a timely fashion after receipt of such decision and to assist Seller in its prosecution of any such appeal in every reasonable manner. If Buyer elects to appeal any such

decision of the Contracting Officer, Buyer agrees to furnish Seller promptly with a copy of such appeal. Any decision upon appeal, if binding upon Buyer, shall in turn be binding upon Seller. Pending the making of any decision, either by the Contracting Officer or on appeal, Seller shall proceed diligently with performance of this Order.

(2) If, as a result of any decision or judgment which is binding upon Seller and Buyer, as provided above, Buyer is unable to obtain payment or reimbursement from the Government under the Prime Contract for, or is required to refund or credit to the Government, any amount with respect to any item or matter for which Buyer has reimbursed or paid Seller, Seller shall, on demand, promptly repay such amount to Buyer. Additionally, pending the final conclusion of any appeal hereunder, Seller shall, on demand, promptly repay any such amount to Buyer. Buyer's maximum liability for any matter connected with or related to this Order which was properly the subject of a claim against the Government under the Prime Contract shall not exceed the amount of Buyer's recovery from the Government.

(3) If this Order is issued by Buyer under a Government Subcontract rather than a Prime Contract, and if Buyer has the right under such Subcontract to appeal a decision made by the Contracting Officer under the Prime Contract in the name of the Prime Contractor (or if Buyer is subject to any arbitrator's decision under the terms of its subcontract), and said decision is also related to this Order, this Disputes Clause shall also apply to Seller in a manner consistent with its intent and similar to its application had this Order been issued by Buyer under a Prime Contract with the Government.

(4) Seller agrees to provide certification that data supporting any claim made by Seller hereunder is made in good faith and that the supporting data is accurate and complete to the best of Seller's knowledge or belief, all in accordance with the requirements of the Contract Disputes Act of 1978 (41USC601-613) and implementing regulations. If any claim of Seller is determined to be based upon fraud or misrepresentation, Seller agrees to defend, indemnify and hold Buyer harmless for any and all liability, loss, cost or expense resulting therefrom.

(b) Any dispute not addressed in paragraph (a) above, will be subject to the disputes clause of Schedule A of this subcontract agreement.

4. OTHER GOVERNMENT PROCUREMENT

Nothing contained herein shall be construed as precluding the Seller from producing items for direct sale to the Government, utilizing therefore all hardware and/or software, including designs, drawings, engineering data or other technical or proprietary information furnished Seller by Buyer, provided the Government has the unrestricted right to permit the use thereof for such purpose.

5. INDEMNIFICATION - COST OR PRICING DATA - COST ACCOUNTING STANDARDS

Seller agrees to indemnify and hold Buyer harmless to the full extent of any cost or price reduction effected by Buyer's customer, which may result from (i) certified cost or pricing data submitted by Seller or its lower-tier subcontractors which is not accurate, current or complete as certified by Seller; (ii) the failure by Seller or its lower-tier subcontractors to disclose and consistently follow applicable cost accounting practices and standards or otherwise comply with pertinent parts of the FAR, applicable agency supplements thereto, and regulations promulgated by the Cost Accounting Standards Board.

6. TERMINATION FOR CONVENIENCE

The Buyer may terminate performance of work under this subcontract in whole, or in part if the Purchasing Representative determines that a termination is in the Buyer's interest. The Buyer shall terminate by delivering to the Seller a Notice of Termination specifying the extent of termination and the effective date. If this is a Fixed Price subcontract, the termination will be in accordance with FAR 52.249-2 and FAR 52.249-4. If this is a Cost Reimbursable subcontract, the termination will be in accordance with FAR 52.249-6. If this is a Cost Reimbursement subcontract for Educational or Other Nonprofit Institutions, then termination will be in accordance with FAR 52.249-5.

7. GOVERNMENT PROPERTY

Seller shall comply with the Government Property requirements contained in FAR clause 52.245-2 if this is a fixed priced contract and FAR clause 52.245-5 (substituting 52.245-2 subparagraph (g) for 52.245-5 subparagraphs (g) (1), (2), and (3) if this is a cost reimbursement contract.

8. CONTRACT COST PRINCIPLES AND PROCEDURES

Seller agrees that to the extent applicable, costs allocated to this contract shall be in full compliance with Subpart 31.2 of FAR (Subpart 31.3 for Educational Institutions) and the applicable agency supplements thereto, if any, set forth in Part II hereof. In the event such compliance is not maintained, Seller agrees to compensate Buyer to the full extent of any prices or costs, including any penalties or interest, which are determined by Buyer's customer to be unallowable or unreasonable or not allocable, under Buyer's contract with its customer.

9. FAR CLAUSES APPLICABLE TO THIS ORDER

The clauses in FAR Subpart 52.2 referenced in subparagraph (a), the clauses applicable at the dollar thresholds in subparagraph (b), and those clauses referenced and checked in subparagraph (c) below, in effect on the date of this Order, are incorporated herein and made a part of this Order. To the extent that an earlier version of any such clause is included in the Prime Contract or Subcontract under which this Order is issued, the date of the clause as it appears in such Prime Contract or Subcontract shall be controlling and said version shall be incorporated herein.

(a) The following clauses are applicable to this Order:

Clause # & FAR Ref.	Title of Clause
52.203-3	Gratuities
52.211-5	Material Requirements

52.211-15	Defense Priority and Allocation Requirements
52.222-1	Notice to the Government of Labor Disputes
52.222-26	Equal Opportunity (Only Paragraphs (b)(1) through (b)(11)
52.223-3	Hazardous Material Identification and Material Safety Data
52.225-13	Restrictions on Certain Foreign Purchases
52.229-3	Federal, State, and Local Taxes

(b) The following clauses are applicable to this Order at the indicated dollar values:

Clause # & FAR Ref.	Title of Clause
52.203-5	Covenant Against Contingent Fees***** (**if order exceeds $50,000*)
52.203-6	Restrictions on Subcontractor Sales to the Government* (**if order exceeds $100,000*)
52.203-7	Anti-Kickback Procedures* (**if order exceeds $100,000*)
52.203-8	Cancellation, Rescission, and Recovery of Funds for Illegal or Improper Activity
52.203-10	Price or Fee Adjustment for Illegal or Improper Activity * (**If order exceeds $50,000*)
52.203-11	Certification and Disclosure Regarding Payments to Influence Certain Federal Transactions* (**if order exceeds or is expected to exceed $100,000*)
52.203-12	Limitation on Payments to Influence Certain Federal Transactions***** (**if order exceeds or is expected to exceed $100,000*)
52.209-6	Protecting the Governments Interest when Subcontracting with Contractors Debarred, Suspended, or Proposed for Debarment* (**if Order exceeds $25,000*)
52.215-2	Audit and Records-Negotiation* (**if Order exceeds $50,000*)
52.219-8	Utilization of Small Business Concerns* (**if Order exceeds $100,000*)
52.219-9	Small Business Subcontracting Plan* (**if Subcontract exceeds or is expected to exceed $500,000*)
52.222-4	Contract Work Hours & Safety Standards Act - Overtime Compensation* (**if Order exceeds $100,000*)
52.222-35	Affirmative Action for Disabled Veterans & Veterans of the Vietnam Era* (**if Order exceeds $10,000*)
52.222-36	Affirmative Action for Workers with Disabilities* (**if Order exceeds $2,500*)
52.222-37	Employment Reports on Special Disabled Veterans and Veterans of the Vietnam Era* (**if Order exceeds $10,000*)
52.227-2	Notice and Assistance Regarding Patent and Copyright Infringement* (**if Order exceeds $50,000*)
52.246-16	Responsibility for Supplies* (**if order exceeds $50,000*)
52.247-63	Preference for U.S. Flag Air Carriers* (**if order exceeds $50,000*)

(c) The following clauses are applicable to this Order if checked:

Clause # & FAR Ref.	Title of Clause
o52.203-10	Price or Fee Adjustment for Illegal or Improper Activity* (**If Order exceeds $50,000*)
o52.204-2	Security Requirements
o52.204-4	Printing/Copying Double Sided on Recycled Paper
o52.207-3	Right of First Refusal of Employment Openings
o52.214-26	Audit and Records-Sealed Bidding
o52.214-27	Price Reduction for Defective Cost or Pricing Data Modifications - Sealed Bidding
o52.214-28	Subcontractor Cost or Pricing Data - Modifications - Sealed Bidding
o52.215-10	Price Reduction for Defective Cost or Pricing Data
o52.215-11	Price Reduction for Defective Cost or Pricing Data -Modifications
o52.215-12	Subcontractor Cost or Pricing Data
o52.215-13	Subcontractor Cost or Pricing Data - Modifications
o52.215-15	Pension Adjustments and Asset Reversions
o52.215-16	Facilities Capital Cost of Money
o52.215-18	Reversion or Adjustment of Plans for Post-Retirement Benefits Other Than Pensions
o52.215-19	Notification of Ownership Changes
o52.215-20	Requirements for Cost or Pricing Data or Information Other Than Cost or Pricing Data
o52.215-21	Requirements for Cost or Pricing Data or Information Other Than Cost or Pricing Data - Modifications
o52.216-7	Allowable Cost and Payment
o52.216-8	Fixed Fee
o52.216-18	Ordering
o52.216-22	Indefinite Quantity
o52.217-8	Option to Extend Services
o52.217-9	Option to Extend the Term of the Contract
	(a) within the current contract year
	(b) not to exceed 60 months or 5 years
o52.219-16	Liquidated Damages – Subcontracting Plan
o52.222-2	Payment for Overtime Premiums -Subparagraph (a) Add “0”
o52.222-3	Convict Labor
o52.222-6	Davis-Bacon Act (if order is for construction exceeding $2,000)
o52.222-11	Subcontracts (Labor Standards)
o52.222-20	Walsh-Healy Public Contracts Act (if Order exceeds $10,000)
o52.222-21	Prohibition of Segregated Facilities
o52.222-29	Notification of Visa Denial
o52-222-41	Service Contract Act of 1965, as Amended* (**if Order exceeds $2,500*)
o52.222-42	Statement of Equivalent Rates by Federal Hires
o52.222-43	Fair Labor Standards Act and Service Contract Act - Price Adjustment* (**Multiple Year and Option Contracts*)
o52.222-46	Evaluation of Compensation for Professional Employees
o52.223-5	Pollution Prevention and Right-to-Know Information

o52.223-6	Drug-Free Workplace
o52.223-7	Notice of Radioactive Materials
o52.223-14	Toxic Chemical Release Reporting
o52.224-2	Privacy Act

Clause # & FAR Ref.	Title of Clause
o52.225-1	Buy American Act -Balance of Payments Program - Supplies
o52.225-5	Trade Agreements
o52.225-8	Duty-Free Entry
o52.226-1	Utilization of Indian Organizations and Indian -Owned Economic Enterprises
o52.227-1	Authorization and Consent (if order exceeds $50,000)
o52.227-1	Authorization and Consent -Alternate I
o52.227-3	Patent Indemnity (if order exceeds $50,000)
o52.227-9	Refund of Royalties
o52.227-10	Filing of Patent Applications - Classified Subject Matter
o52.227-11	Patent Rights - Retention by the Contractor (Short Form)
o52.227-12	Patent Rights - Retention by the Contractor (Long Form)
o52.227-13	Patent Rights - Acquisition by the Government
o52.227-14	Rights in Data - General (Alternate I, II, III, IV, or V)
o52.227-16	Additional Data Requirements
o52.227-17	Rights in Data - Special Works
o52.227-18	Rights in Data - Existing Works
o52.227-19	Commercial Computer Software - Restricted Rights
o52.227-20	Rights in Data SBIR Program
o52.227-21	Technical Data, Certification, Revision and Withholding of Payment - Major Systems
o52.227-22	Major System - Minimum Rights
o52.227-23	Rights to Proposal Data (Technical)
o52.228-3	Worker’s Compensation Insurance (Defense Base Act)
o52.228-4	Worker’s Compensation and War-Hazard Insurance Overseas
o52.228-5	Insurance - Work on a Government Installation
o52.228-7	Insurance - Liability to Third Persons
o52.229-6	Taxes - Foreign Fixed-Price Contracts
o52.229-7	Taxes - Fixed-Price Contracts with Foreign Governments
o52.229-8	Taxes - Foreign Cost-Reimbursement Contracts
o52.229-9	Taxes - Cost-Reimbursement Contracts with Foreign Governments
o52.229-10	State of New Mexico Gross Receipts and Compensating Tax
o52.230-2	Cost Accounting Standards
o52.230-3	Disclosure and Consistency of Cost Accounting Practices
o52.230-5	Cost Accounting Standards -Educational Institution
o52.230-6	Administration of Cost Accounting Standards
o52.232-7	Payments Under Time-and-Materials and Labor-Hour Contracts
o52.232-16	Progress Payments (Notwithstanding paragraph 8 above, in paragraph (d),”Government” means the “U.S. Government” except in subdivision (d)(2)(iv).
o52.232-17	Interest
o52.232-18	Availability of Funds
o52.232-19	Availability of Funds for the Next Fiscal Year
o52.232-20	Limitation of Cost
o52.232-22	Limitation of Funds
o52.232-23	Assignment of Claims
o52.232-23	Assignment of Claims Alternate 1
o52.232-32	Performance-Based Payments
o52.236-2	Differing Site Conditions
o52.236-13	Accident Prevention

Clause # & FAR Ref.	Title of Clause
o52.237-2	Protection of Government Buildings, Equipment & Vegetation
o52.237-3	Continuity of Services
o52.237-7	Indemnification and Medical Liability Insurance
o52.237-10	Identification of Uncompensated Overtime
o52.239-1	Privacy or Security Safeguards
o52.242-1	Notice of Intent to Disallow Costs
o52.242-3	Penalties for Unallowable Costs
o52.242-4	Certification of Final Indirect Costs
o52.242-12	Report of Shipment
o52.242-13	Bankruptcy
o52.242-15	Stop-Work Order
o52.242-15	Stop-Work Order Alternate 1
o52.243-1	Changes - Fixed-Price
o52.243-1	Changes - Fixed- Price - Alternate I

o52.243-2	Changes - Cost-Reimbursement
o52.243-2	Changes - Cost-Reimbursement - Alternate I
o52.243-2	Changes - Cost-Reimbursement - Alternate II
o52.243-2	Changes - Cost-Reimbursement - Alternate V
o52.243-3	Changes - Changes - Time-and-Materials or Labor-Hours
o52.243-6	Change Order Accounting
o52.244-2	Subcontracts
o52.244-5	Competition in Subcontracting
o52.244-6	Subcontracts for Commercial Items and Commercial Components
o52.245-4	Government-Furnished Property (Short Form)
o52.245-8	Liability for the Facilities
o52.245-16	Facilities Equipment Modernization
o52.245-17	Special Tooling
o52.245-18	Special Test Equipment
o52.245-19	Government Property Furnished “As Is”
o52.246-1	Contractor Inspection Requirements
o52.246-2	Inspection of Supplies - Fixed Price
o52.246-3	Inspection of Supplies - Cost-Reimbursement
o52.246-4	Inspection of Services - Fixed-Price
o52.246-5	Inspection of Services - Cost-Reimbursement
o52.246-6	Inspection of Time-and- Material and Labor-Hour
o52.246-8	Inspection of Research and Development - Cost-Reimbursement
o52.246-20	Warranty of Services
o52.246-23	Limitation of Liability
o52.246-24	Limitation of Liability - High-Value Items
o52.246-25	Limitation of Liability – Services
o52.247-1	Commercial Bill of Lading Notation
o52.247-55	F.O.B. Point for Delivery of Government-Furnished Property
o52.247-64	Preference for Privately Owned U.S. Flag Commercial Vessels
o52.248-1	Value Engineering
o52.249-8	Default -(Fixed-Price Supply and Services)
o52.249-14	Excusable Delays
o52.253-1	Computer Generated Forms

Clause # & FAR Ref.	Title of Clause
o52.242-17	Government Delay of Work
o52.247-34	FOB Destination
o52.202-1	Definitions
o52.219-14	Limitations on Subcontracting
o52.219-23	Notice of Price Evaluation Adjustment for SDB Concerns
o52.225-16	Sanctioned European Union Country Services
o52.227-5	Waiver of Indemnity
o52.229-3	Federal, State and Local Taxes
o52.232-9	Limitation on Withholding of Payments
o52.232-25	Prompt Payment
o52.232-33	Payment by Electronic Funds Transfer
o52.233-1	Disputes
o52.233-3	Protest after Award
o52.252-2	Clauses Incorporated by Reference
o52.252-6	Authorized Deviation in Clauses

SCHEDULE B - CONTRACT CLAUSES

Department OF Defense (DOD) PART II DFAR CLAUSES

1. REFERENCES TO DFAR SUPPLEMENT

All references herein to “DFAR Supplement” or “DFAR SUPP” shall mean the Department of Defense Supplement to the Federal Acquisition Regulation.

2. DFAR SUPPLEMENT CLAUSES APPLICABLE TO THIS ORDER

The clauses in DFAR Supplement Subpart 252.2 referenced in subparagraph (a) and those clauses referenced and checked in subparagraph (b), below, in effect on the date of this Order, are incorporated herein and made a part of this Order. To the extent that an earlier version of any such clause is included in the Prime Contract or Subcontract under which this Order is issued, the date of the clause as it appears in such Prime Contract or Subcontract shall be controlling and said version shall be incorporated therein. In all such clauses, unless the context of a clause requires otherwise, the term “Contractor” shall mean Seller, the term “Contract” shall mean this Order, and the terms “Government,” “Contracting Officer” and equivalent phrases shall mean Buyer and Buyer’s Purchasing Representative (except with respect to [ ], in which the term “Government” will retain its meaning as set forth in such DFARs), respectively. It is intended that the referenced clause shall apply to Seller in such manner as is necessary to reflect the position of Seller as a subcontractor to

Buyer, to insure Seller's obligations to Buyer and to the United States Government, and to enable Buyer to meet its obligations under its Prime Contract or Subcontract.

(a) The following clauses are applicable to this Order:

DFAR Reference	Title of Clause
252.203-7001	Prohibition on Persons Convicted of Fraud or Other Defense-Contract-Related Felonies
252.204-7000	Disclosure of Information
252.208-7000	Intent to Furnish Precious Metals as Government-Furnished Material
252.209-7000	Acquisitions From Subcontractors Subject to On-Site Inspection under the Intermediate-Range Nuclear Forces (INF) Treaty (If Subcontract exceeds $25,000)
252.211-7000	Acquisition Streamlining (If Subcontract exceeds $1,000,000)
252.215-7000	Pricing Adjustments
252.219-7003	Small, Small Disadvantaged and Women-Owned Small Business Subcontracting Plan (DOD Contracts) (If Order exceeds $500,000)
252.225-7026	Reporting of Contract Performance Outside the United States
252-226-7001	Utilization of Indian Organizations and Indian-Owned Economic Enterprises – DoD Contracts
252.227-7034	Patents – Subcontracts
252.227-7037	Validation of Restrictive Markings on Technical Data
252.231-7000	Supplemental Cost Principles

(b) DFAR Supplement clauses applicable to this Order if checked:

DFAR Reference	Title of Clause
o252.203-7002	Display of DoD Hotline Poster
o252.204-7003	Control of Government Personnel Work Product
o252.206-7000	Domestic Source Restriction
o252.209-7001	Disclosure of Ownership or Control by the Government of a Terrorist Country

DFAR Reference	Title of Clause
o252.209-7002	Disclosure of Ownership or Control by a Foreign Government
o252.209-7004	Subcontracting w/Firms that are Owned or Controlled by the Government of a Terrorist Country
o252.217-7003	Changes
o252.217-7026	Identification of Sources of Supply
o252.222-7000	Restrictions on Employment of Personnel
o252.223-7001	Hazard Warning Labels
o252.223-7002	Safety Precautions for Ammunition and Explosives
o252.223-7003	Change in Place of Performance - Ammunition and Explosives
o252.223-7004	Drug-Free Work Force
o252.223-7006	Prohibition on Storage and Disposal of Toxic and Hazardous Materials
o252.225.7000	Buy American Act - Balance of Payments Program Certificate
o252.225-7001	Buy American Act and Balance of Payments Program
o252.225-7002	Qualifying Country Sources as Subcontractors
o252.225-7005	Identification of Expenditures in the United States
o252.225-7006	Buy American Act, Trade Agreement Act, and the Balance of Payments Program Certificate
o252.225-7007	Trade Agreements
o252.225-7009	Duty Free Entry - Qualifying Country (End Products & Components)
o252.225-7010	Duty Free Entry - Additional Provisions
o252.225-7012	Preference for Certain Domestic Commodities
o252.225-7014	Preference for Domestic Specialty Metals
o252.225-7015	Preference for Domestic Hand or Measuring Tools
o252.225-7031	Secondary Arab Boycott of Israel
o252.225-7043	Antiterrorism/Force Protection Policy for Defense Contractors Outside the U.S.
o252.227-7013	Rights in Technical Data Noncommercial Items
o252.227-7014	Rights in Non-commercial Computer Software and Non-commercial Computer Software Documentation
o252.227-7015	Technical Data – Commercial Items
o252.227-7016	Rights in Bid or Proposal Information
o252.227-7017	Identification and Assertion of Use, Release, or Disclosure Restrictions
o252.227-7018	Rights in Noncommercial Technical Data and Computer Software -Small Business Innovation Research (SBIR) Program
o252.227-7019	Validation of Asserted Restrictions -Computer Software
o252.227-7020	Rights in Special Works
o252.227-7021	Rights in Data - Existing Works
o252.227-7022	Government Rights (Unlimited)
o252.227-7023	Drawings and Other Data to Become Property of Government
o252.227-7025	Limitations on the Use or Disclosure of Government-Furnished Information Marked w/ Restrictive Legends
o252.227-7026	Deferred Delivery of Technical Data or Computer Software
o252.227-7027	Deferred Ordering of Technical Data or Computer Software
o252.227-7028	Technical Data or Computer Software Previously Delivered to the Government
o252.227-7030	Technical Data - Withholding of Payment

DFAR Reference	Title of Clause
o252.227-7032	Rights in technical data and computer software (Foreign)
o252.227-7033	Rights in Shop Drawings
o252.227-7036	Declaration of Technical Data Conformity
o252.227-7039	Patents – Reporting of Subject Inventions
o252.228-7005	Accident Reporting & Investigation Involving Aircraft, Missiles, and Space Launch Vehicles
o252.232-7006	Reduction or Suspension of Contract Payments Upon Finding of Fraud
o252.235-7002	Animal Welfare
o252.235-7003	Frequency Authorization
o252.235-7010	Acknowledgment of Support and Disclaimer
o252.236-7000	Modification Proposals - Price Breakdown
o252.239-7000	Protection Against Compromising Emanations
o252.239-7016	Telecommunications Security Equipment, Devices, Techniques and Services
o252.245-7001	Reports of Government Property
o252.246-7001	Warranty of Data
o252.247-7001	Price Adjustment (NOTE: Amsec may need to do)
o252.247-7023	Transportation of Supplies by Sea (If Order exceeds $25,000)
o252.247-7024	Notification of Transportation of Supplies by Sea
o252.232-7003	Electronic Submission of Payment Requests
o252.235-7011	Final Scientific or Technical Report
o252.243-7001	Pricing of Contract Modifications
o252.244-7000	Subcontracts for Commercial Items/Components

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: November 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: November 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 September 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: November 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.