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SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

FORM 10-Q

(Mark One)

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

For the quarterly period ended June 30, 2002

OR

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

For the transition period from to

Commission file number 0-19125

Isis Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**33-0336973**
(State or other jurisdiction of incorporations or organization)	(I.R.S. Employer Identification No.)

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

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

(1) Yes ☒ No o (2) Yes ☒ No o

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

Common stock $.001 par value	**54,296,723**
(Class)	(Outstanding at August 1, 2002)

ISIS PHARMACEUTICALS, INC.
FORM 10-Q

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

	June 30, 2002 (Unaudited)	December 31, 2001 (Note)
ASSETS		
Current assets:		
Cash and cash equivalents	$ 110,017	$ 127,011
Short-term investments	215,119	185,007
Contracts receivable	12,010	10,360
Other current assets	11,310	6,438
Total current assets	348,456	328,816
Property, plant and equipment, net	37,946	28,245
Licenses, net	31,148	32,361
Patents, net	18,186	16,735
Deposits and other assets	5,168	6,605
Long-term investments	2,322	4,299
Total assets	$ 443,226	$ 417,061
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,197	$ 6,126
Accrued compensation	3,734	5,646
Accrued liabilities	4,677	3,942
Amount due to affiliates	4,729	—
Current portion of deferred revenues	21,220	22,696
Current portion of long-term obligations	9,737	9,837
Total current liabilities	47,294	48,247
Long-term deferred revenue, less current portion	17,900	20,005
Long-term obligations, less current portion	191,661	125,710
Stockholders' equity:		
Series A Convertible Exchangeable 5% Preferred stock, $.001 par value, 120,150 shares	12,015	12,015

authorized, issued and outstanding at June 30, 2002 and December 31, 2001		
Accretion of Series A Preferred stock dividends	2,050	1,711
Series B Convertible Exchangeable 5% Preferred stock, $.001 par value, 16,620 shares authorized, 12,015 shares issued and outstanding at June 30, 2002 and December 31, 2001	12,015	12,015
Accretion of Series B Preferred stock dividends	1,553	1,222
Common stock, $.001 par value, 100,000,000 shares authorized, 54,191,776 and 53,750,318 shares issued and outstanding at June 30, 2002 and December 31, 2001, respectively	54	54
Additional paid-in capital	585,404	582,258
Deferred compensation	(22)	(245)
Accumulated other comprehensive income (loss)	(600)	660
Accumulated deficit	(426,098)	(386,591)
Total stockholders' equity	186,371	223,099
Total liabilities and stockholders' equity	$ 443,226	$ 417,061

Note: The balance sheet at December 31, 2001 has been derived from the audited financial statements at that date.

See accompanying notes.

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

	Three months ended June 30,		Six months ended June 30,	
	2002	2001	2002	2001
Revenue:				
Research and development revenue under collaborative agreements	$ 17,889	$ 5,114	$ 32,603	$ 7,903
Research and development revenue from affiliates	2,087	2,432	5,121	4,148
Licensing and royalty revenue	85	46	296	174
Total revenue	20,061	7,592	38,020	12,225
Expenses:				
Research and development	31,530	19,924	58,513	39,059
General and administrative	2,444	2,778	4,671	5,593
Compensation related to stock options	(1,574)	1,354	(3,106)	1,271
Total operating expenses	32,400	24,056	60,078	45,923
Loss from operations	(12,339)	(16,464)	(22,058)	(33,698)
Equity in loss of affiliates	(3,960)	(4,194)	(9,726)	(8,158)
Investment income	1,892	1,106	4,036	3,083
Interest expense	(4,164)	(3,491)	(8,795)	(7,117)
Loss on prepayment of debt	(2,294)	—	(2,294)	—
Net loss	(20,865)	(23,043)	(38,837)	(45,890)
Accretion of dividends on preferred stock	(335)	(323)	(670)	(642)
Net loss applicable to common stock	$ (21,200)	$ (23,366)	$ (39,507)	$ (46,532)
Basic and diluted net loss per share	$ (0.39)	$ (0.58)	$ (0.73)	$ (1.15)
Shares used in computing basic and diluted net loss per share	54,117	40,492	54,022	40,322

See accompany notes.

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

	Six months ended June 30,	
	2002	2001
Net cash used in operating activities	$ (70,777)	$ (24,222)
Investing activities:		
Short-term investments	(31,372)	(5,472)
Property and equipment	(12,450)	(3,006)
Other assets	(2,667)	(17,683)
Investment in affiliates	(3,690)	(3,333)
Net cash used in investing activities	(50,179)	(29,494)
Financing activities:		
Net proceeds from issuance of equity securities	6,475	24,379
Proceeds from long-term borrowings	18,513	4,043
Net proceeds from issuance of convertible debt	120,935	—
Principal payments on debt and capital lease obligations	(1,901)	(1,585)
Principal payment on prepayment of debt	(40,060)	—
Net cash provided from financing activities	103,962	26,837
Net decrease in cash and cash equivalents	(16,994)	(26,879)
Cash and cash equivalents at beginning of period	127,011	39,615
Cash and cash equivalents at end of period	$ 110,017	$ 12,736
Supplemental disclosures of cash flow information:		
Interest paid	$ 34,003	$ 1,524
Supplemental disclosures of non-cash financing activities:		
Additions to debt for licensing costs	—	13,500

See accompanying notes.

ISIS PHARMACEUTICALS, INC.
NOTES TO CONDENSED FINANCIAL STATEMENTS
June 30, 2002
(Unaudited)

1. Basis of Presentation

The unaudited interim financial statements for the six month periods ended June 30, 2002 and 2001 have been prepared on the same basis as the Company's audited financial statements for the year ended December 31, 2001. The financial statements include all adjustments (consisting only of normal recurring adjustments) which the Company considers necessary for a fair presentation of the financial position at such dates and the operating results and cash flows for those periods. Results for the interim periods are not necessarily indicative of the results for the entire year. For more complete financial information, these financial statements, and notes thereto, should be read in conjunction with the audited financial statements for the year ended December 31, 2001 included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission.

Revenue Recognition

Revenue is generally recognized when all contractual obligations have been satisfied and collection of the resulting receivable is reasonably assured.

Research and development revenue under collaborative agreements.

Research and development revenue under collaborative agreements is recognized as the related expenses are incurred, up to contractual limits. Payments received under these agreements related to future performance are deferred and recorded as revenue earned over their specified future performance period. Revenue related to nonrefundable, up-front fees is recognized over the period of the contractual arrangements as performance obligations related to the services to be provided have been satisfied. Revenue related to milestones is recognized upon completion of the milestone's performance requirement. Isis recognized revenue from federal research grants during the period in which the related expenditures are incurred. Revenue from product sales is recognized as the products are shipped.

As part of the Company's alliance with Eli Lilly and Company, Lilly provided a $100 million interest-free loan to fund the research collaboration. As of June 2002, Isis had drawn down $32.5 million on the $100 million loan. Isis discounted the $32.5 million that had been drawn on the loan as of June 30, 2002, to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time Isis entered into the loan. Isis is accreting the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan, represents value given to Isis by Lilly to help fund the research collaboration, and Isis is accounting for the difference as deferred revenue related to the collaboration, which is recognized as revenue over the period of performance.

Research and development revenue from affiliates

Research and development revenue from affiliates is recognized as the related expenses are incurred, up to contractual limits. Revenue related to milestones is recognized upon completion of the milestone's performance requirement, unless consideration for achievement of the milestone is in cash in exchange for the Company's common stock.

Licensing and royalty revenue

Licensing and royalty revenue for which no services are required to be performed in the future is recognized immediately, if collectibility is reasonably assured.

Use of Estimates

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

Accounting Pronouncements

In April 2002 the Financial Accounting Standards Board (FASB), issued Statement of Financial Accounting Standards (SFAS) No. 145,"Rescission of FASB Statements No. 4, 44, and 64, Amendment of FASB Statement No. 13, and Technical Corrections." FASB No. 4 required all gains or losses from extinguishment of debt to be classified as extraordinary items net of income taxes. SFAS No. 145 requires that gains and losses from extinguishment of debt be evaluated under the provisions of Accounting Principles Board Opinion No. 30, and be classified as ordinary items unless they meet the specific criteria for treatment as an extraordinary item. The Company adopted the provisions of SFAS 145 effective January 1, 2002, and applied them to its prepayment in May 2002 of the Company's 14% Senior Subordinated Notes. The Company does not anticipate that the adoption of this statement will have a material effect on its financial position or results of operations.

2. Strategic Alliances

Affiliates

In April 1999, Orasense Ltd. (Orasense) was formed to develop technology for the oral formulation of oligonucleotide drugs. In January 2000, a second joint venture, HepaSense Ltd. (HepaSense), was formed to treat patients chronically infected with the Hepatitis C virus. Both affiliates are Bermuda limited companies. Each entity's outstanding common stock is owned 80.1% by Isis and 19.9% by Elan. The original research agreement and funding period for Orasense and HepaSense ended in April 2002 and July 2002, respectively. Isis and Elan are in the process of negotiating the next steps for both joint ventures. The collaborations are continuing through this negotiation process.

Elan and its subsidiaries have retained significant minority investor rights that are considered "participating rights' as defined in EITF 96-16 in each entity. Therefore, Isis does not consolidate the financial statements of Orasense or HepaSense, but instead accounts for the investments in each under the equity method of accounting. For the quarter and six month periods ended June 30, 2002, Isis recognized $2.1 million and $5.1 million, respectively, in revenue for research and development activities performed for these joint ventures. For the three and six month periods ended June 30, 2001, Isis reported $2.4 million and $4.1 million in revenue, respectively. These amounts are included as research and development revenue from affiliates for the respective periods.

In April 2002, Isis achieved a development milestone in its HepaSense Ltd. joint venture with Elan triggering a $3.75 million equity purchase by Elan of Isis common stock at a price of $29.74. Elan also received a warrant to purchase 6,304 shares of Isis common stock at an exercise price of $59.48 per share. The result of this transaction increased the Company's cash balance and was not recorded as revenue.

The results of operations of Orasense for the quarter and six month periods ended June 30, 2002 and 2001 are as follows (in thousands):

	Three months ended June 30,		Six months ended June 30,	
	2002	2001	2002	2001
Revenue	$ —	$ —	$ —	$ —
Research and development expense	1,080	3,173	4,311	5,633
Net loss	$ (1,080)	$ (3,173)	$ (4,311)	$ (5,633)

The results of operations of HepaSense for the quarter and six month periods ended June 30, 2002 and 2001 are as follows (in thousands):

	Three months ended	Six months ended

	June 30,		June 30,	
	2002	2001	2002	2001
Revenue	$ —	$ —	$ —	$ —
Research and development expense	3,864	2,062	7,833	4,216
Net loss	$ (3,864)	$ (2,062)	$ (7,833)	$ (4,216)

U.S. Army Medical Research Institute & Infectious Diseases

In March 2002, Ibis Therapeutics, a division of Isis, transitioned its government-sponsored research program to discover novel antibacterial drugs for biological warfare defense to the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID. As a result of this transition, Ibis received a new three-year contract from USAMRIID to advance Ibis' work in developing therapeutic countermeasures to biological warfare. We expect to receive funding of up to $2.4 million under this contract. This contract builds on Ibis's earlier research programs with the Defense Advance Research Projects Agency, or DARPA. Transition from DARPA to other government agencies for later-stage program development is a direct result of agency selection and demonstration of a successful initiative.

Merck and Co., Inc.

In April 2002, Isis extended for a second time its collaboration with Merck to discover drug candidates to treat patients with HCV. The objective of the one-year extension is to continue Isis' discovery efforts to identify additional novel compounds for Merck to potentially develop as new treatments for HCV. As part of the extension, Merck paid Isis a research milestone established in the initial agreement, and has agreed to pay Isis research support for an additional year and clinical development milestone payments for compounds that arise from the collaboration and royalties from product sales. Isis began the original three-year drug discovery collaboration with Merck in June 1998 and announced the first one-year extension in May 2001.

Eli Lilly and Company

In June 2002, Isis expanded the Company's antisense drug discovery collaboration with Lilly beyond the original areas of inflammatory and metabolic diseases to include the discovery of antisense drugs to inhibit specific gene targets associated with cancer. The expanded collaboration will focus initially on several antisense preclinical compounds, including ISIS 23722, directed at cellular regulators

of cancer cell death, or apoptosis. Lilly paid Isis an up-front fee, which the Company is recognizing as revenue over the two-year term of the expansion.

3. Comprehensive Loss

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

	Statements of Comprehensive Loss			
	Three months ended June 30,		Six months ended June 30,	
	2002	2001	2002	2001
Comprehensive loss:				
Change in unrealized gains (losses)	$ (1,445)	$ (30)	$ (1,260)	$ 443
Net loss applicable to common stock	(21,200)	(23,366)	(39,507)	(46,532)
Comprehensive loss	$ (22,645)	$ (23,396)	$ (40,767)	$ (46,089)

4. Debt Issuance and Debt Prepayment

In May 2002, Isis issued in a private placement $125 million of $5^1/2\%$ convertible subordinated notes due May 2009. The Company received approximately $121 million of proceeds net of offering costs.

In May 2002, Isis prepaid its 14% Senior Subordinated Notes totaling approximately $74 million with proceeds the Company received from the above mentioned debt offering. The transaction resulted in a payment of $40.1 million in principal, $32.6 million in accrued interest, and a $2.3 million loss on prepayment of debt which consisted of unamortized issuance costs, unamortized warrants and prepaid interest.

5. Subsequent Events

On July 3, 2002 the Company prepaid $19.7 million of 12% convertible debt held by Elan with $14.7 million in cash. This prepayment resulted in a gain of approximately $5 million, which will be recorded in the third quarter of 2002 as a gain from prepayment of debt.

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

In addition to historical information contained in this Report, this Report contains forward-looking statements regarding our business and the therapeutic and commercial potential of our technologies and products in development. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those risks and uncertainties inherent in the process of discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, in the process of conducting gene functionalization and target validation services, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this Form 10-Q. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in our Annual Report on Form 10-K for the year ended December 31, 2001, 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 17 of this Report. As a result, you are cautioned not to rely on these forward-looking statements.

Since our inception in 1989, we have pioneered the science of antisense for the development of a new class of drugs. We can design antisense drugs to treat a wide variety of diseases. Due to their gene selectivity, antisense drugs have the potential to be highly effective and less toxic than traditional drugs. We have made significant progress in understanding the capabilities of antisense drugs in treating disease. We have developed new chemistries and novel formulations to enhance the potency and utility of antisense drugs, and we have successfully turned our expertise into a broad pipeline of 13 antisense products currently in all phases of clinical development. Our drugs in development treat a variety of health conditions, including cancer and inflammatory, viral, metabolic and dermatological diseases, and are being studied in intravenous, subcutaneous, topical cream, enema and oral formulations. We achieved marketing clearance for the world's first antisense drug Vitravene (fomivirsen) in 1998.

Established in 2000, GeneTrove is our functional genomics division, which commercializes the first step of our antisense drug discovery program. GeneTrove capitalizes on the specificity of antisense, using it as a tool to identify what a gene does, which is called gene functionalization, and whether a specific gene is a good target for drug discovery, which is called target validation. GeneTrove provides valuable functional genomics services to the pharmaceutical and biotechnology industry, potentially enhancing and expediting drug discovery and development decisions, and generating near-term revenue for us in the process. We have collaborations with nine major pharmaceutical partners for these services, including Abbott Laboratories, Inc., Aventis (formerly Rhone-Poulenc Rorer), Amgen Inc., Celera Genomics Group, Chiron Corporation, Eli Lilly and Company, Johnson & Johnson Pharmaceutical Research & Development, LLC, Merck & Co., Inc. and Pharmacia Corporation. We expect these collaborations to fund the functionalization of approximately 1,400 new genes over the next two to three years. We have supplemented our GeneTrove services business with the introduction in August 2001 of a subscription database product. This database is expected to contain proprietary information about the function of thousands of genes, which we believe pharmaceutical companies will find valuable in designing and prioritizing their drug discovery programs. In addition to GeneTrove's functional genomics services and its database product, partners can license access to our functional genomics patent portfolio.

Our Ibis Therapeutics division is taking advantage of the investment we have made in RNA-based drug discovery. The division is using its proprietary technology to create small molecule drugs that bind to structured regions of RNA—areas that are not available to antisense drug discovery. RNA is an optimal target as it is universal, simple in structure and predictable. Historically, the division has focused primarily on the research and development of anti-bacterials, anti-virals and anti-fungals, Ibis has since expanded its program to include a diagnostic application of its technology. Since its inception, Ibis has received significant financial support from various federal government agencies to use its

technology for the development of RNA-based countermeasures to biological warfare. In October 2001, Ibis received a two-year contract with the Defense Advanced Research Projects Agency, or DARPA, to develop a sensor to detect infectious agents used in biological warfare attacks. Additionally, in March 2002, Ibis transitioned its government-sponsored research program to discover novel antibacterial drugs for biological warfare defense to the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID. Ibis received a new three-year contract from USAMRIID to advance Ibis' work in developing therapeutic countermeasures to biological warfare and expects to receive funding of up to $2.4 million under this contract.

Critical Accounting Policies

We prepare our financial statements in conformity with accounting principles generally accepted in the United States of America. As such, we are required to make certain estimates, judgments and assumptions that we believe are reasonable, based upon the information available to us. These estimates and assumptions affect the reported balances and amounts within our financial statements and supporting notes thereto. The significant accounting policies, which we believe are the most critical to aid in fully understanding and evaluating our reported financial results, include the following:

Revenue Recognition

We generally recognize revenue when all contractual obligations have been satisfied and we are reasonably assured of collecting the resulting receivable. We often enter into collaborations where we receive nonrefundable up-front payments for prior or future expenditures. In compliance with current accounting rules, we recognize revenue related to up-front payments over the period of the contractual arrangements as we satisfy our performance obligations. Occasionally, we are required to estimate the period of a contractual arrangement or our performance obligation when the information is not clearly defined in the agreements we enter into. Should different estimates prevail, revenue recognized could be materially different. Agreements where we have made estimates of our continuing obligations include our collaborations with Lilly, Agouron Pharmaceuticals, Inc., a Pfizer Company, Amgen, Antisense Therapeutics Limited, Chiron and Merck. The collaboration with Agouron concluded in June 2002.

As part of our Lilly alliance, Lilly provided a $100 million interest-free-loan to fund the research collaboration. As of June 30, 2002 we had drawn down $32.5 million on the $100 million loan. We discounted the $32.5 million that had been drawn on the loan as of June 30, 2002 to its net present value by imputing interest on the amount at 20%, which represented market conditions in place at the time we entered into the loan. We are accreting the loan up to its face value over its term by recording interest expense. The difference between the cash received and the present value of the loan, represents value given to us by Lilly to help fund the research collaboration, and is accounted for as deferred revenue related to the collaboration, and is recognized as revenue over the period of performance.

Additionally, licensing and royalty agreements we enter into for which we have no future performance obligations and are reasonably assured of collecting the resulting receivable are recognized as revenue immediately. Licensing and royalty agreements where we have no future obligations include Eyetech Pharmaceuticals in 2001.

Valuation of Intellectual Property

We evaluate our licenses and patent assets for impairment on a quarterly basis, and whenever indicators of impairment exist. During this process, we review our portfolio of pending domestic and international patent applications, domestic and international issued patents, and licenses we have acquired from other parties. To determine if any impairment is present we consider challenges or

potential challenges to our existing patents, the likelihood of applications being issued, the scope of our issued patents and our experience. In the event that we determine an impairment exists where we had previously determined that one did not exist, it may result in a material adjustment to our financial statements.

Valuation of Short-Term Investments

We invest our excess cash in U.S. Government securities and debt instruments of financial institutions and corporations with strong credit ratings. We have established guidelines relative to diversification and maturities that maintain safety and liquidity. These guidelines are periodically reviewed and modified to take advantage of trends and interest rates. In determining if and when a decline in market value below amortized cost is other-than-temporary, we, together with our external portfolio managers, evaluate the market conditions, offering prices, trends of earnings, price multiples, and other key measures for our investments in debt instruments. When we deem such a decline in value is other than temporary, we recognize an impairment loss in the period operating results to the extent of the decline. To date, we have not had any material losses related to our cash or short-term investments.

Results of Operations

Revenue

Our total revenue for the quarter and six months ended June 30, 2002, was $20.1 million and $38.0 million, respectively, compared to $7.6 million and $12.2 million for the same periods in 2001. The $25.8 million increase in revenue for the six months ended June 30, 2002, was primarily due to an increase in research and development revenue under collaborative agreements which was a result of our success in attracting new collaboration partners and signing new technology licenses. The most significant contributor to the increase in revenue was our strategic alliance with Lilly. As part of the Lilly alliance, we licensed our Phase III investigational drug, Affinitac™ (formerly known as LY900003, ISIS 3521).

Under the category of research and development revenue under collaborative agreements, for the quarter and six months ended June 30, 2002, we reported $17.9 million and $32.6 million, compared to $5.1 million and $7.9 million for the same periods in 2001. The increase of $24.7 million for the six months ended June 30, 2002 is a result of our entering into a variety of new collaboration agreements. Contributing to a majority of the increase was revenue associated with our strategic alliance with Lilly, which we entered into in August 2001. The revenue from the Lilly alliance included revenue from the reimbursement of development costs and the license of Affinitac and revenue from the $32.5 million draw down of the $100 million interest-free loan to fund the research collaboration. Also contributing to the increase was revenue associated with our GeneTrove division's partnerships with Amgen, Celera, Chiron, Merck and Pharmacia. Additionally, in October 2001, our Ibis division initiated a new biological warfare defense research program with DARPA, which also contributed to the quarter-to-quarter increase in revenue. In March 2002, Ibis entered into a three-year contract valued at up to $2.4 million from the U.S. Army Medical Research Institute of Infectious Diseases, or USAMRIID which also contributed to the revenue increase in the quarter.

Research and development revenue from affiliates consisted of revenue associated with our two joint ventures with Elan, Orasense and HepaSense. For the quarter and six months ended June 30, 2002, we recognized $2.1 million and $5.1 million, respectively, as revenue from affiliates. During the same periods in 2001, we recognized $2.4 million and $4.1 million as revenue from affiliates. The increase of $1.0 million for the six months ended June 30, 2002 in revenue from affiliates was a result of increased development activities performed for each joint venture in 2002 compared to 2001. The original research agreement and funding period for Orasense and HepaSense ended in April 2002 and

July 2002, respectively. We and Elan are in the process of negotiating the next steps for both joint ventures. The collaborations are continuing through this negotiation process.

Our revenue from licensing activities and royalties was $296,000 for the six months ended June 30, 2002, compared with $174,000 for the same period in 2001.

Operating Expenses

Total operating expenses for the quarter and six months ended June 30, 2002 totaled $32.4 million and $60.1 million, respectively, compared to $24.1 million and $45.9 million for the same periods of 2001. The increase for the quarter and six months ended June 30, 2002 was the result of increased research and development expenses in 2002 over 2001, partially offset by a decrease in general and administrative expenses, and a reversal of compensation expense related to variable stock options due to the decrease in market value of our stock. Partially offsetting the increase in research and development expenses, and contributing to the decrease in general and administration expenses, was the effect of capitalizing approximately $2.0 million and $3.9 million for the quarter and six months ended June 30, 2002, respectively, in costs related to the manufacturing of our drugs. Historically, we had expensed drug manufacturing costs as they were incurred. In 2002, in response to the advancement of our pipeline into later stages of clinical development and as a result of the increasing number of clinical supply agreements where we sell drug that we manufacture to partners, we began capitalizing the related manufacturing costs for our drugs. We will expense manufacturing costs when we ship our drugs to partners and as we use our drugs in our own clinical trials. This may result in period to period differences in operating expenses related to the volume of drug production and the timing of drug shipments.

Our research and development expenses consist of costs for antisense drug discovery, including costs associated with our GeneTrove division, antisense drug development, our Ibis Therapeutics' division and R&D Support costs. For the quarter and six months ended June 30, 2002, we reported total research and development expenditures of $31.5 million and $58.5 million, respectively, compared to $19.9 million and $39.1 million reported in 2001, respectively. The $19.4 million increase for the first six months in 2002 over 2001 was primarily due to added activities on behalf of our partners, particularly Lilly. In addition, we continued to advance the clinical development of the 13 products in our pipeline. We continued progress of our Phase III clinical trial for Affinitac for the treatment of non-small cell lung cancer which was initiated in October 2000. Additionally, in June 2002, we initiated a European Phase III clinical trial for ISIS

2302, which is the second Phase III study we are conducting for ISIS 2302 in Crohn's disease. We are continuing to advance our Phase III trial for Isis 2302, inititated in November 2001. This increase was partially offset by the effect of capitalizing costs associated with the manufacture of our drugs.

Antisense drug discovery costs for the quarter and six month periods ended June 30, 2002 totaled $10.7 million and $19.5 million, respectively, compared to $4.8 million and $9.1 million for the same periods of 2001. The increase was principally a result of increased gene functionalization and target validation activities including those to support our GeneTrove partnerships. Also contributing to the increase were costs associated with our continued database development and costs associated with our Lilly research collaboration.

Antisense drug development expenditures for the quarter and six month periods ended June 30, 2002 totaled $13.0 million and $24.5 million, respectively, compared to $10.0 million and $19.3 million for the same periods of 2001. The increase of $5.2 million for the six months ended June 30, 2002, is primarily a result of additional expenses related to the expansion and advancement of our pipeline. At June 30, 2002 we had 13 products in development including two products, Affinitac and ISIS 2302, in Phase III clinical trials and six products in Phase II clinical trials compared to six in Phase II and III

combined for the same period in 2001. Offsetting the increase in development expenses was the impact of capitalizing costs related to the manufacturing of our drugs as discussed above.

Expenditures related to Affinitac for the three and six months ended June 30, 2002 were $4.1 million and $6.5 million, compared to $3.5 million and $5.7 million for the same periods of 2001. The increase of $834,000 for the six months ended in June 30, 2002 compared to the same period of 2001 was primarily a result of costs related to our Phase III trial. These costs were partially offset by increase production of Affinitac for clinical trials during the quarter, resulting in the capitalization of drug manufacturing costs during the quarter. A significant portion of this drug is expected to be shipped during the third quarter of 2002. If we and Lilly determine that the data from Isis' on-going Phase III trial are sufficiently positive to support a single study NDA, Lilly and we plan to file the NDA in 2003. If we and Lilly determine that two Phase III studies reflecting positive data are required, Lilly and we plan to file the NDA in 2004 with data from both Isis' Phase III trial and Lilly's Phase III trial. If we file an NDA application, our expenditures related to Affinitac will increase.

Our second drug in Phase III clinical trials, ISIS 2302 for Crohn's disease, had development expenditures totaling $1.8 million and $3.2 million for the three and six months ended June 30, 2002, respectively, compared to $1.3 million and $2.4 million for the same periods of 2001. The increase of $840,000 for the six months ended June 30, 2002, is a result of our initiation of a Phase III trial in November 2001, which resulted in additional expenses for the first half 2002 over the same period of 2001. Additionally, costs associated with our Phase III European Crohn's trial initiated in June 2002 contributed to the increase in 2002 over 2001.

Ibis expenditures for the three and six months ended June 30, 2002 totaled $2.2 million and $4.2 million, compared to $1.7 million and $3.5 million for the same periods in 2001. The increase of $682,000 was primarily a result of expenses related to Ibis' performance obligations under its multi-year government contracts with DARPA, awarded in the fourth quarter 2001, and with USAMRIID awarded in March 2002.

R&D Support costs for the quarter and six month periods ended June 30, 2002, totaled $5.6 million and $10.3 million, respectively, compared to $3.4 million and $7.2 million for 2001. The increase is a direct result of increases in our research and development efforts. While we work to control R&D Support costs, these costs will increase as direct research and development costs increase. We expect R&D Support costs will continue to increase in 2002 as we hire scientific personnel to support our Lilly collaboration, our government contracts, our GeneTrove collaborations and our expanding pipeline.

General and administration expenses for the three and six months ended June 30, 2002 totaled $2.4 million and $4.7 million, respectively, compared to $2.8 million and $5.6 million for the same periods of 2001. The decrease in expense was primarily a result of capitalizing costs directly related to the manufacturing of our drugs as previously discussed.

Compensation expense related to stock options for the six months ended June 30, 2002 included a reversal of $3.1 million in previously recorded non-cash compensation expense related to stock options accounted for as variable stock options. Variable stock options can result in significant increases and decreases in compensation expense as a result of the variability in our stock price. The majority of these options expire at the end of 2002.

Equity in Loss of Affiliates

Equity in loss of affiliates for the quarter and six month periods ended June 30, 2002 was $4.0 million and $9.7 million, respectively, compared to $4.2 million and $8.2 million for the same periods ended June 30, 2001. We use the equity method of accounting for our investments in Orasense and HepaSense. As a result, we recognized our portion, 80.1%, of the total loss reported by Orasense

and HepaSense under equity in loss of affiliates. The increase of $1.5 million for the six months ended June 30, 2002 compared to the same period of 2001 is a result of increased development activities performed by Orasense and HepaSense. The original research agreement and funding period for Orasense and HepaSense ended in April 2002 and July 2002, respectively. We and Elan are in the process of negotiating the next steps for both joint ventures. The collaborations are continuing through this negotiation process.

Investment Income

For the quarter and six month periods ended June 30, 2002, investment income was $1.9 million and $4.0 million, respectively, compared to $1.1 million and $3.1 million for the same periods of 2001. Although our average cash and short-term investment balance was significantly higher during 2002 compared to 2001, our investment income was directly affected by the decline in interest rates as a result of current market conditions. Our investment policy allows for investments in premium grade corporate bonds and government backed securities. The rates of return on these types of investments during 2002 were less than those available in 2001.

Interest Expense

Interest expense increased to $4.2 million and $8.8 million for the quarter and six month periods ended June 30, 2002, compared with $3.5 million and $7.1 million for the same periods in 2001. Interest expense increased by $1.7 million during the six months ended June 30, 2002 compared to the same period of 2001. This increase was primarily a result of increased interest accrued on our 14% Senior Subordinated Notes through May 1, 2002, when these notes were repaid, our borrowings under the Elan lines of credit for our Orasense and HepaSense joint ventures and the May 1, 2002 issuance of $125 million of 5 1/2% convertible subordinated notes. Also contributing to the increase during 2002 were the effects of the outstanding cumulative borrowing of $32.5 million from our $100 million loan made available to us by Lilly. The increase was partially offset by the $74 million repayment on May 1, 2002 of our 14% Senior Subordinated Notes. The prepayment of our 14% Senior Subordinated Notes resulted in a payment of $40.1 million in principal, $32.6 million in accrued interest, and a $2.3 million loss on prepayment of debt which consisted of unamortized issuance costs, unamortized warrants and prepaid interest. As a result of the May 2002 repayment of the 14% Senior Subordinated Notes, and the July 2002 repayment of our borrowing under the Elan lines of credit, we expect our interest expense to decrease.

Interest and principal payments were deferred on our 14% Senior Subordinated Notes through May 1, 2002, when these notes were repaid, and on our borrowings of $919,000 and $2.8 million under the Elan lines of credit for our Orasense and HepaSense joint ventures, respectively, during the first half of 2002. For the six months ended June 30, 2002, $6.2 million of the $8.8 million in interest was primarily accrued under various long-term debt agreements, and did not require cash payments. In July 2002, we prepaid $19.7 million of our Elan debt related to Orasense and HepaSense.

Loss on Prepayment of Debt

For the quarter and six month periods ended June 30, 2002, we reported a $2.3 million loss on the prepayment of approximately $74 million of our 14% Senior Subordinated Notes, which represented amounts related to unamortized issuance costs, unamortized warrants and prepaid interest. Additionally, on July 3, 2002 we prepaid $19.7 million of 12% convertible debt held by Elan with $14.7 million in cash. This prepayment resulted in a gain of approximately $5 million, which will be recorded in the third quarter of 2002 as a gain from prepayment of debt.

Net Loss Applicable to Common Stock

For the three and six months ended June 30, 2002, we reported a net loss of $20.9 million and $38.8 million, respectively, compared to $23.0 million and $45.9 million for the corresponding periods of 2001. Our net loss applicable to common stock was $21.2 million and $39.5 million for the three and six months ended June 30, 2002, respectively, and $23.4 million and $46.5 million for the same periods in 2001. The decrease of $7.0 million for the six months ended June 30, 2002 compared to the same period in 2001, was primarily a result of a decrease in loss from operations. The decrease was partially offset by the $2.3 million loss reported for the prepayment of our 14% Senior Subordinated Notes.

Liquidity and Capital Resources

We have financed our operations with revenue from contract research and development, revenue from the sale or licensing of our intellectual property, the sale of our equity securities, and the issuance of long-term debt. From our inception through June 30, 2002, we have earned approximately $308.3 million in revenue from contract research and development and the sale and licensing of our intellectual property. From our inception through June 30, 2002, we have raised net proceeds of approximately $585.0 million from the sale of equity securities. We have borrowed approximately $252.7 million net of debt issuance costs, under long-term debt arrangements to finance a portion of our operations.

As of June 30, 2002, we had cash, cash equivalents and short-term investments totaling $325.1 million and working capital of $301.2 million. In comparison, we had cash, cash equivalents and short-term investments of $312.0 million and working capital of $280.6 million as of December 31, 2001. The increase in our cash, cash equivalents and short-term investments, and working capital was due primarily to our issuance of $125 million of 5 1/2% convertible subordinated notes and partially offset by the prepayment of approximately $74 million in debt and cash used for operations.

As of June 30, 2002, our long-term obligations totaled $191.7 million, versus $125.7 million at December 31, 2001. In May 2002, we increased our long-term obligations by completing a convertible debt offering of $125 million of 5 1/2% convertible subordinated notes due May 2009, which raised approximately $121 million net of issuance costs. We used $74 million of the proceeds from this debt offering to prepay debt which was outstanding as of May 1, 2002. The prepayment of debt resulted in a payment of $40.1 million in principal, $32.6 million in accrued interest, and a $2.3 million loss on prepayment of debt which consisted of unamortized issuance costs, unamortized warrants and prepaid interest. The $32.6 million in interest expense related to the prepayment of our 14% Senior Subordinated Notes is included in our statement of cash flows for the six months ended June 30, 2002 in the line item titled net cash used in operating activities. The $40.1 million of principal related to this debt prepayment is included under financing activities in the line item titled principal payment of prepayment of debt. On July 3, 2002 we prepaid $19.7 million of 12% convertible debt held by Elan with $14.7 million in cash. This prepayment resulted in a gain of approximately $5 million, which will be recorded in the third quarter of 2002 as a gain from prepayment of debt. We expect that capital lease obligations will increase over time to fund capital equipment acquisitions required for our growing business. We will continue to use lease financing as long as the terms remain commercially attractive. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments at June 30, 2002 combined with investment income and committed contractual cash payments from our partners will be sufficient to meet our anticipated requirements for at least the next 36 months.

The following table summarizes our contractual obligations as of June 30, 2002. The table provides a breakdown of when obligations become due.

	Payments Due by Period (in 000s)				
Contractual Obligations	**Total**	**Less than 1 year**	**1-3 years**	**4-5 years**	**After 5 years**
Debt	$ 194,796	$ 6,933	$ 41,738	$ 25,093	$ 121,032
Capital Lease Obligations	$ 6,602	$ 2,804	$ 3,798	$ —	$ —
Operating Leases	$ 17,333	$ 2,355	$ 4,671	$ 2,099	$ 8,208

Prospective Information

On July 3, 2002 we prepaid $19.7 million of 12% convertible debt held by Elan with $14.7 million in cash. This prepayment resulted in a gain of approximately $5 million, which will be recorded in the third quarter of 2002 as a gain from prepayment of debt. The effects of the prepayment will result in a

decrease of $19.7 million in our contractual obligations for 2005 and 2006 as outlined in the above table.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information in this Report you should carefully consider the risks described below before purchasing our securities. If any of the following risks actually occur, our business could be materially harmed, and our financial condition and results of operations could be materially and adversely affected. As a result, the trading price of our securities could decline, and you might lose all or part of your investment.

RISKS RELATED TO OUR BUSINESS

If we or our partners fail to obtain regulatory approval for our products, we will not be able to sell them.

We and our partners must conduct time-consuming, extensive and costly clinical trials to show the safety and efficacy of each of our drug candidates, before a drug candidate can be approved for sale. We must conduct these trials in compliance with U.S. Food and Drug Administration regulations and with comparable regulations in other countries. If the FDA or another regulatory agency believes that we or our partners have not sufficiently demonstrated the safety or efficacy of our drug candidates, it will not approve them or will require additional studies, which can be time consuming and expensive and which will delay commercialization of a drug candidate. We and our partners may not be able to obtain necessary regulatory approvals on a timely basis, if at all, for any of our drug candidates. Failure to receive these approvals or delays in such receipt could prevent or delay commercial introduction of a product and, as a result, could negatively impact our ability to generate revenue from product sales. In addition, following approval of a drug candidate, we and our partners must comply with comprehensive government regulations regarding how we manufacture, market and distribute products. If we fail to comply with these regulations, regulators could force us to withdraw a drug candidate from the market or impose other penalties or requirements that could have a similar negative impact.

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

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

Drug discovery and development has inherent risks, including the risk that molecular targets prove not to be important in a particular disease, the risk that compounds that demonstrate attractive activity in preclinical studies do not demonstrate similar activity in human beings, and the risk that a compound is not safe or effective for use in humans. Antisense technology in particular is relatively new and unproven. Most of our resources are being applied to create safe and effective drugs for human use. Any of the risks described above could prevent us from meeting this goal. In the past, we have invested in clinical studies of drug candidates, including some that remain in our pipeline, that have not resulted in proof of efficacy against targeted indications.

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

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

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

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

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

If any of our collaborative partners fail to fund our collaborative programs or develop or sell any of our products under development, or if we are unable to obtain additional partners, progress on our drug development programs could be delayed or stop.

We have entered into collaborative arrangements with third parties to develop certain product candidates. We enter into these collaborations in order to:

- fund our research and development activities;
- access manufacturing by third parties;
-

seek and obtain regulatory approvals; and

- successfully commercialize existing and future product candidates.

If any of our partners fails to develop or sell any drug in which we have retained a financial interest, our business may be negatively affected. These collaborations may not continue or result in commercialized drugs. Our collaborators can terminate their relationships with us under certain circumstances, some of which are outside of our control. Our most advanced drug candidate, Affinitac, is being developed collaboratively with Lilly, with the development funded by Lilly. Additional drug candidates in our development pipeline are being developed and/or funded by corporate partners, including Antisense Therapeutics, Limited, Elan, Merck and OncoGenex Technologies Inc. Failure by any of these pharmaceutical company partners to continue to fund and/or develop these drug candidates would have a material adverse effect on our business.

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

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

If our GeneTrove business is unable to market its products and services as planned, we could lose our investment in this technology.

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

In addition, if customers do not subscribe to the database at the level we have planned, our GeneTrove business could fail to make the planned contribution to our financial performance.

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

Because drug discovery and development and the development of database products and research services require substantial lead time and money prior to commercialization, our expenses have exceeded our revenues since we were founded in January 1989. As of June 30, 2002, our accumulated losses were approximately $426 million. Most of the losses resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. Most of our revenue has come from collaborative arrangements, with additional revenue from interest income and research grants and the sale or licensing of patents. Our current product revenues are derived solely from sales of Vitravene. This product has limited sales potential. We expect to incur additional operating losses over the next several years, and these losses may increase if we cannot increase or sustain revenue. We may not successfully develop any additional products or services, or achieve or sustain future profitability.

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

Most of our product candidates are still undergoing clinical trials or are in the early stages of research and development. All of our products under development will require significant additional research, development, preclinical and/or clinical testing, regulatory approval and a commitment of significant additional resources prior to their commercialization. Based on our current operating plan, we believe that our available cash, cash equivalents and short-term investments at June 30, 2002, combined with investment income and committed contractual cash payments will be sufficient to meet our anticipated requirements for at least the next 36 months. If we fail to meet our goals regarding commercialization of our drug products, gene function database product and research services and licensing of our proprietary technologies, we may need additional funding in the future. Our future capital requirements will depend on many factors, such as the following:

- the profile and launch timing of our drugs;
- continued scientific progress in our research, drug discovery and development programs;
- the size of these programs and progress with preclinical and clinical trials;
- the time and costs involved in obtaining regulatory approvals;
- competing technological and market developments, including the introduction by others of new therapies that address our markets;
- success in the marketing of our gene function database and research service products; and
- changes in existing collaborative relationships and our ability to establish and maintain additional collaborative arrangements.

If we need additional funds, we may need to raise them through public or private financing. Additional financing may not be available at all or on acceptable terms. If additional funds are raised

by issuing equity securities, the shares of existing stockholders will be diluted and their price, as well as the price of our other securities, may decline. If adequate funds are not available, we may be required to cut back on one or more of our research, drug discovery or development programs or obtain funds through arrangements with collaborative partners or others. These arrangements may require us to give up rights to certain of our technologies, product candidates or products.

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

If we successfully commercialize any of our drug candidates, we may be required to establish large-scale commercial manufacturing capabilities. In addition, as our drug development pipeline increases and matures, we will have a greater need for clinical trial and commercial manufacturing capacity. Pharmaceutical products of the chemical class represented by our drug candidates, called oligonucleotides, have never been manufactured on a large scale, and to our knowledge there is no commercial scale oligonucleotide manufacturer in business today. We have a limited number of suppliers for certain capital equipment and raw materials that we use to manufacture our drugs, and some of these suppliers will need to increase their scale of production to meet our projected needs for commercial manufacturing. Further, we must continue to improve our manufacturing processes to allow us to reduce our product costs. We may not be able to manufacture at a cost or in quantities necessary to make commercially successful products.

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

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

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

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

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

If we are unable to protect our patents or our proprietary rights, others may be able to compete more directly against us.

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

Intellectual property litigation could be expensive and prevent us from pursuing our programs.

It is possible that in the future we may have to defend our intellectual property rights. In the event of an intellectual property dispute, we may be forced to litigate to defend our rights or assert them against others. Disputes could involve litigation or proceedings declared by the U.S. Patent and Trademark Office or the International Trade Commission. Intellectual property litigation can be extremely expensive, and this expense, as well as the consequences should we not prevail, could seriously harm our business.

On July 9, 2001, we initiated litigation against Sequitur, Inc. alleging patent infringement. On December 12, 2001, we initiated a second action against Sequitur, Inc. alleging patent infringement. On May 2, 2002 we initiated a third action against Sequitur, Inc. alleging patent infringement. If we do not prevail in the defense of these patents, it could impact our ability to realize future licensing revenues.

If a third party claims that our products or technology infringe their patents or other intellectual property rights, we might be forced to discontinue an important product or product line, alter our products and processes, pay license fees or cease certain activities. We may not be able to obtain a license to such intellectual property on favorable terms, if at all. There are many patents issued or applied for in the biotechnology industry, and we may not be aware of patents or applications held by others that relate to our business. This is especially true since patent applications in the United States are filed confidentially. Moreover, the validity and breadth of biotechnology patents involve complex legal and factual questions for which important legal issues remain unresolved.

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

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

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

We are dependent on the principal members of our management and scientific staff. We do not have employment agreements with any of our management. The loss of our management and key scientific employees might slow the achievement of important research and development goals. It is also critical to our

success that we recruit and retain qualified scientific personnel to perform research and development work. We may not be able to attract and retain skilled and experienced scientific personnel on acceptable terms because of intense competition for experienced scientists among many pharmaceutical and health care companies, universities and non-profit research institutions. Our collaboration with Lilly requires us to add a significant number of skilled scientific personnel. Our inability to add these employees may impact the success of our Lilly collaboration.

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

The market price of our common stock, like that of the securities of many other biopharmaceutical companies, has been and is likely to continue to be highly volatile. These fluctuations in our common stock price may significantly affect the trading price of the convertible notes. During the 12 months preceding June 30, 2002, the market price of our common stock has ranged from $6.76 to $27.15 per share. The market price of our securities can be affected by many factors, including, for example, fluctuations in our operating results, announcements of collaborations, clinical trial results, technological innovations or new drug products being developed by us or our competitors, governmental regulation, regulatory approval, developments in patent or other proprietary rights, public concern regarding the safety of our drugs and general market conditions.

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

Our certificate of incorporation provides for classified terms for the members of our board of directors. Our certificate also includes a provision that requires at least $66^{2}/_{3}$% of our voting stockholders to approve a merger or certain other business transactions with, or proposed by, any holder of 15% or more of our voting stock, except in cases where certain directors approve the transaction or certain minimum price criteria and other procedural requirements are met.

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

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

We have granted registration rights in connection with the issuance of our securities to Elan International Services, Ltd., Eli Lilly and Company, Hybridon, Inc. and Reliance Insurance Company. In the aggregate, these registration rights cover approximately 4,166,667 shares of our common stock which are currently outstanding, an additional $4.5 million of our common stock we are obligated to issue to Hybridon and additional shares of our common stock which may become outstanding upon the conversion of outstanding convertible securities. If these registration rights are exercised by the holders, it will bring additional shares of our common stock into the market, which may have an adverse effect on the price of our securities.

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

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

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

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.

PART II—OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

On July 9, 2001, we filed suit against Sequitur, Inc. in the United States District Court for the Southern District of California. The suit alleges infringement of United States Patent No. 6,001,653 entitled "Human Type 2 RNase H", which was issued to Isis on December 14, 1999. In response to this suit, Sequitur has filed certain counterclaims. We believe that we have meritorious defenses to all of these counterclaims. On December 12, 2001, we filed a second suit against Sequitur, Inc. in the U.S. District Court for the Southern District of California. The suit alleges infringement of U.S. Patent No. 6,326,199 entitled "Gapped 2' Modified Oligonucleotide", which was issued to us on December 4, 2001. Sequitur has answered but not filed any counterclaims. On June 12, 2002 the first and second suits were consolidated for all purposes including through trial. On May 2, 2002, we filed a third suit against Sequitur, Inc. in the United States District Court for the Southern District of California. The suit alleges infringement of (i) United States patent No. 5,959,097 entitled "Antisense Modulation of MEK2 Expression," which was issued to Isis on September 28, 1999, (ii) United States patent No. 5,958,733 entitled "Antisense Modulation of Akt-1 Expression," which was issued to Isis on September 28, 1999, (iii) United States patent No. 6,043,090 entitled "Antisense Inhibition of Human Akt-2 Expression," which was issued to Isis on September 28, 2000, and (iv) United States patent No. 6,096,543 entitled "Antisense Inhibition of Human MEK1 Expression," which was issued to Isis on August 1, 2000. Sequitur has answered but not filed any counterclaims.

ITEM 2. CHANGES IN SECURITIES

On May 1, 2002, we issued and sold $125 million of 5 1 /2% convertible subordinated notes due 2009 in a private placement in reliance on an exemption from registration under Section 4(2) of the Securities Act. The initial purchasers of the notes in that offering were UBS Warburg LLC, Robertson Stephens, Inc., Needham & Company, Inc. and Roth Capital Partners, LLC. These initial purchasers purchased the convertible notes at an aggregate purchase price equal to 97% of the aggregate principal amount of the convertible notes. The initial purchasers then resold the notes in offerings in reliance on an exemption from registration under Rule 144A and Regulation S of the Securities Act. The notes are convertible into 60.1504 shares of our common stock, par value $0.001 per share, per $1,000 principal amount of notes and subject to adjustment in certain circumstances. This results in an initial conversion price of $16.625 per share.

ITEM 3. DEFAULT UPON SENIOR SECURITIES

Not applicable.

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

On May 31, 2002, the Company's Annual Meeting of Stockholders was held in Carlsbad, California for the following purposes:

(1) To elect two (2) directors to serve as Class I directors of the Company. For Director number one, Joseph H. Wender, the number of votes for and against was 45,720,639 and 256,333 respectively. For Director number two, B. Lynne Parshall, the number of votes for and against was 45,719,639 and 257,333, respectively.

(2) To approve the 2002 Non-Employee Directors' Stock Option Plan which was adopted by the Board of Directors on September 11, 2001, subject to stockholder approval. The plan amends, restates and reiterates the Company's 1992 Non-Employee Directors' Stock Option Plan previously approved by the stockholders. The number of votes for, against and abstaining was 35,441,839, 10,382,149 and 152,984, respectively.

(3) To ratify the appointment of Ernst & Young LLP as the Company's independent auditors for the fiscal year ending 2002. The number of votes for, against and abstaining was 45,221,206, 703,846 and 51,920, respectively.

ITEM 5. OTHER INFORMATION

Not applicable.

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a. Exhibits

Exhibit Number		Description of Document
10.1	—	Amendment No. 1 to Securities Purchase Agreement dated January 14, 2000 between the Registrant and Elan International Services, Ltd. (with certain confidential information deleted).
10.2	—	Amended and Restated Collaboration Agreement dated June 17, 2002 between the Registrant and Eli Lilly and Company (with certain confidential information deleted).
10.3	—	Amendment No. 2 to Agreement between the Registrant and Merck & Co., dated April 19, 2002 (with certain confidential information deleted).
99.1	—	Certification

b. Reports on Form 8-K

On April 23, 2002, the Registrant filed a report on Form 8-K for the announcement of its intention to offer $125 million of convertible subordinated notes due 2009 in a private placement and the related press release dated April 23, 2002.

On April 24, 2002, the Registrant filed a report on Form 8-K to report first quarter highlights and financial results for the quarter ended March 31, 2002.

On April 24, 2002, the Registrant filed a report on Form 8-K for the announcement of its intention to retire its 14% Senior Subordinated Notes and the related press release dated April 24, 2002. The total amount of this debt, including principal plus interest, was approximately $74 million.

Isis Pharmaceuticals, Inc.
(Registrant)

SIGNATURES

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

Signatures	Title	Date
/s/ STANLEY T. CROOKE, M.D., PH.D. Stanley T. Crooke, M.D., Ph.D.	Chairman of the Board, President, and Chief Executive Officer (Principal executive officer)	August 14, 2002
/s/ B. LYNNE PARSHALL B. Lynne Parshall, Esq.	Director, Executive Vice President, Chief Financial Officer and Secretary (Principal financial and accounting officer)	August 14, 2002

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Exhibit 10.1

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

AMENDMENT NO. 1 TO
SECURITIES PURCHASE AGREEMENT

This Amendment No. 1 to Securities Purchase Agreement (the "Amendment"), is effective as of April 25, 2002 ("Effective Date") between Isis Pharmaceuticals, Inc., a Delaware corporation ("Isis"), and Elan International Services, Ltd., a Bermuda exempted limited liability company ("EIS") and a wholly-owned subsidiary of Elan Corporation, plc, an Irish public limited company.

A. WHEREAS, Isis and EIS entered into that certain Securities Purchase Agreement dated January 14, 2000 (the "Original Agreement"); and

B. WHEREAS, Isis and EIS wish to amend the Original Agreement to decrease the Second Common Stock Purchase Price and to provide for a Third Subsequent Purchase Date, as more fully described below.

NOW THEREFORE, in consideration of the mutual promises contained in this Amendment, Isis and EIS agree to amend the Original Agreement as follows:

All capitalized terms not otherwise defined herein, will have the meanings ascribed to them in the Original Agreement.

ARTICLE 1. AMENDMENTS

1.1 *Recital A.* Recital A of the Original Agreement is hereby amended such that the language "Section 1(b)(ii) and (iii)" appearing in clauses (ii) and (iii) of Recital A is replaced by the following language "Sections 1(b)(ii), 1(b)(iii) and 1(b)(iv)." All other provisions of Recital A will remain unchanged and will continue in full force and effect.

1.2 *Amendment and Restatement of Section 1(b)(iii).* Section 1(b)(iii) of the Original Agreement is hereby amended, restated and replaced in its entirety by the following language:

"(iii) On any day within 5 trading days after the Completion Date (the "Second Subsequent Purchase Date"), the Company shall issue and sell to EIS, and EIS shall purchase from the Company, for an aggregate purchase price of US$3,750,000 (the "Second Common Stock Purchase Price"), (A) 126,092 shares of Common Stock and (B) a Warrant to purchase 6,304 shares of Common Stock, pursuant to a warrant certificate in the form attached hereto as Exhibit G. "*Completion Date*" will mean April 22, 2002. The purchase by EIS of the securities to be issued on the Second Subsequent Purchase Date is conditioned upon EIS obtaining requisite approval, if any, pursuant to the Mergers Act."

1.3 *Addition of Section 1(b)(iv).* The Original Agreement is hereby amended to include the following language as Section 1(b)(iv) thereto:

"(iv) On any day within 5 trading days after the receipt by EIS from the Company of notification of the occurrence of the Additional Completion Date (the "Third Subsequent Purchase Date"), the Company shall issue and sell to EIS, and EIS shall purchase from the Company, for an aggregate purchase price of [***] (the "Third Common Stock Purchase Price"), (A) the number of shares of Common Stock determined by dividing the Third Common Stock Purchase Price by [***] of the average closing price of the Common Stock for the [***] trading days ending two days prior to the Additional Completion Date and (B) a Warrant to purchase a number of shares of Common Stock equal to [***] of the aggregate

number of shares of Common Stock to be purchased by EIS pursuant to clause (iv)(A) above, pursuant to a warrant certificate in the form attached hereto as Exhibit G (except that the warrant will reference the Third Subsequent Purchase Date). "*Additional Completion Date*" will mean either (a) the date upon which the clinical trial ISIS 14803-CS2 is completed with results sufficient to demonstrate [***]. The purchase by EIS of the securities to be issued on the Third Subsequent Purchase Date is conditioned upon EIS obtaining requisite approval, if any, pursuant to the Mergers Act."

1.4 *Addition of Section 1(d)(iv).* The Original Agreement is hereby amended to include the following language as Section 1(d)(iv) thereto:

"(iv) On the Third Subsequent Purchase Date, EIS shall pay the Third Common Stock Purchase Price by wire transfer to an account designated by the Company and the parties hereto shall execute and deliver to each other, as applicable: (A) a certificate or certificates for the Common Stock to be purchased on the Third Subsequent Purchase Date, as determined pursuant to Section 1(b)(iv) hereof; (B) the Warrant to be issued pursuant to Section 1(b)(iv) hereof; (C) a secretary certificate of the Company, in substantially the form of Exhibit H; and (D) any other documents or instruments reasonably requested by a party hereto."

1.5 *Amendment and Restatement of Section 17.* Section 17 of the Original Agreement is hereby amended, restated and replaced in its entirety by the following language:

"*Assignments and Transfers.* This Agreement and all of the provisions hereof shall be binding upon and inure to the benefit of the parties hereto and their respective successors and permitted assigns. This Agreement, the shares of Series B Preferred Stock and the shares of Common Stock being purchased hereunder by EIS, the Note, the Warrants, and the shares of Common Stock underlying the Series B Preferred Stock, the Note and the Warrants may be transferred by EIS to its affiliates and subsidiaries, as well as any special purpose financing or similar vehicle established by EIS or its affiliates, provided, however, that EIS shall remain liable for its obligations hereunder after any such assignment. Other than as set forth above, no party shall transfer or assign this Agreement, the shares of Series B Preferred Stock and Common Shares being purchased hereunder by

EIS, the Note, the Warrants, and the shares of Common Stock underlying the Series B Preferred Stock, the Note and the Warrants, or any interest therein, without the prior written consent of the other party; provided, however, that (a) no consent shall be required in connection with any such transfer or assignment by a party pursuant to a sale of all or substantially all of the business of such party whether by merger, sale of stock, sale of assets or otherwise and (b) the restriction on the transfer of the Common Shares being purchased hereunder by EIS and the shares of Common Stock underlying the Series B Preferred Stock, the Note and the Warrants will not apply to (i) Securities registered under the Securities Act, (ii) Securities sold pursuant to 144 under the Securities Act, and (iii) Securities sold in private transaction to an entity that is primarily engaged in the business of investing in publicly-traded securities."

1.6 The parties agree that the Common Stock purchased on the Third Subsequent Purchase Date and the Common Stock issuable upon the exercise of the Warrant purchased on the Third Subsequent Purchase Date are included in the definition of Registrable Securities under that certain Registration Rights Agreement between Isis and EIS dated January 14, 2000.

ARTICLE 2. GENERAL PROVISIONS

2.1 *Original Agreement.* Except as specifically provided in this Amendment, all other terms and conditions of the Original Agreement will remain in full force and effect.

2.2 *Entire Agreement.* This Amendment, the Original Agreement and the other Transaction Documents contain the entire understanding of the parties with respect to the subject matter hereof and thereof and supersede all prior agreements and understandings among the parties with respect thereto.

2.3 *Other General Provisions.* Section 8 and Sections 10 through 18 of the Original Agreement, will apply to this Amendment.

IN WITNESS WHEREOF, the parties hereto have executed this Amendment as of the date first written above:

ISIS PHARMACEUTICALS, INC.	ELAN INTERNATIONAL SERVICES, LTD
Name	Name
/s/ B. LYNNE PARSHALL	/s/ DEBRA MOORE BURYS
Signature	Signature
Title	Title

QuickLinks

Exhibit 10.2

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

AMENDED AND RESTATED COLLABORATION AGREEMENT

BETWEEN

ELI LILLY AND COMPANY

AND

ISIS PHARMACEUTICALS, INC.

June 17, 2002

AMENDED AND RESTATED COLLABORATION AGREEMENT

THIS AMENDED AND RESTATED COLLABORATION AGREEMENT (the ***"Agreement"***) is entered into and effective as of June 17, 2002 (the ***"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 wish to establish a collaborative relationship 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 entered into a collaboration agreement (the "Original Agreement") effective as of the Effective Date, and both parties now are desirous of amending and restating the terms of the Original Agreement.

AGREEMENT

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

ARTICLE 1

DEFINITIONS

1.1 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.

ARTICLE 2

COLLABORATION OVERVIEW AND GOVERNANCE

2.1 The Collaboration. Lilly and Isis hereby agree to undertake the Collaboration during the Collaboration Term under the terms and conditions set forth in this Agreement. The Collaboration shall consist of the Reagent Provision Program, the Target Validation Program and the Antisense Drug Discovery Program.

2.2 Reagent Provision Program. Under the Reagent Provision Program Isis will identify ASO Compounds using Antisense Technology that are directed to Targets identified by Lilly and provide such ASO Compounds to Lilly for use in Lilly's research efforts outside of the Collaboration. The Joint Research Committee will manage the Reagent Provision Program as set forth below. The activities to be undertaken by the Parties in the course of Reagent Provision Program are set forth in detail in the Collaborative Research Plan, which is attached hereto as ***Schedule 2.2*** and is incorporated by reference as part of the Agreement.

2.3 Drug Discovery Target Validation Program. The goal of the drug discovery Target Validation Program is to provide information regarding gene functionalization and validation for drug discovery with respect to Targets related to the Collaboration Therapeutic Areas. An additional purpose of the Target Validation Program is to validate and prioritize Targets related to the Collaboration Therapeutic Areas for potential inclusion in the Antisense Drug Discovery

Program. The Joint Research Committee will manage the Target Validation Program as set forth below. The activities to be undertaken by the Parties in the course of Target Validation Program are set forth in detail in the Collaborative Research Plan.

2.4 Antisense Drug Discovery Program. The goal of the Antisense Drug Discovery Program is to develop Drug Discovery ASO Compounds directed against Targets related to the Collaboration Therapeutic Areas and to qualify such Drug Discovery ASO Compounds as Development Candidates for development by Lilly or by Isis as pharmaceutical products. The Joint Research Committee will manage the Antisense Drug Discovery Program as set forth below. The activities to be undertaken by the Parties in the course of the Antisense Drug Discovery Program are set forth in detail in the Collaborative Research Plan.

2.5 Governance—Executive Committee. The strategic direction and overall management of the Collaboration shall be the responsibility of the Executive Committee. The Executive Committee shall consist of three (3) members from each Party. The initial members of the Executive Committee are 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. Not later than thirty (30) days after the Effective Date the Executive Committee shall hold an organizational meeting to establish the operational requirements for the Executive Committee. 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 Collaboration Term and for one (1) year thereafter the Executive Committee shall meet at least every six (6) months to review the research carried out under the Collaboration and to consider modifications to the strategy and goals of the Reagent Provision Program, 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 periodically review the Collaborative Research Plan from a strategic perspective, including consideration of expanding or contracting the Collaboration Therapeutic Areas;

(b) to review changes to the Collaborative Research Plan made by the Joint Research Committee or an Operating Committee as permitted by Sections 2.6.2 and 2.7.2, respectively, and to resolve any matters related thereto that are appealed to the Executive Committee by the Joint Research Committee or an Operating Committee;

(c) to periodically 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;

(d) to attempt to resolve any disagreements between the Parties with respect to the research conducted under the Collaboration, including those disagreements referred to it by the Joint Research Committee, the IP Committee or any Operating Committee;

(e) to approve changes to the allocation of Collaboration Funds set forth in the Collaborative Research Plan between the Target Validation Program and Antisense Drug Discovery Program, on the one hand, and the Reagent Provision Program, on the other hand;

(f) to approve changes to the assignment of Collaboration Funds and Collaboration FTEs between the Collaboration Therapeutic Areas as set forth in the Collaborative Research Plan;

(g) to propose to Lilly changes in the amount and/or timing of funding under the Loan Agreement as provided for in Sections 9.1.5 and 9.1.6, in the unexpected event that such is necessary;

(h) to provide guidance to the Joint Research Committee as to the data package required by Lilly in considering a Development Candidate for further development and commercialization efforts; and

(i) to establish and oversee an intellectual property committee that will operate in accordance with Section 2.7.2.

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, including matters referred to it for decision by the Joint Research Committee, then the matter shall be referred to [***]

2.6 Governance—Joint Research Committee. Promptly after the Effective Date a Joint Research Committee shall be established. The Joint Research Committee shall have the day-to-day management responsibilities for the Target Validation Program and the Antisense Drug Discovery Program in the Collaboration Therapeutic Areas. The Joint Research Committee shall consist of three (3) members from each Party, as appointed by each such Party. The Joint Research Committee shall be subordinate to the Executive Committee, which shall have the right upon timely appeal to review, accept, reject or modify all actions of the Joint Research Committee. The initial members of the Joint Research Committee are listed on ***Schedule 2.6***. Each Party will designate a member of the Joint Research Committee who will be the primary contact for that Party on the Joint Research Committee. Not later than thirty (30) days after Effective Date

the Joint Research Committee shall meet to hold an organizational meeting to establish the operational requirements for the Joint Research Committee. The Lilly representatives that are the designated primary contacts on the Joint Research Committee

shall be responsible for scheduling the first meeting for that purpose. Either Party can change its representatives on the Joint Research Committee by written notice to the other Party. If Lilly extends the Oncology Term pursuant to Section 13.1.2(a), the Joint Research Committee shall be expanded to consist of a total of four (4) members from each Party, as appointed by each such Party, unless the parties agree otherwise.

2.6.1 Joint Research Committee Meetings. The Joint Research Committee shall meet at least quarterly to review the research carried out under the Collaboration and, if necessary, to consider modifications to the Collaborative Research Plan. 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 Joint Research Committee shall agree. Each Party shall bear its own costs associated with holding and attending such meetings. If mutually agreed by the Parties, such meeting may be held by videoconference or teleconference. An agenda shall be agreed upon by the members of the Joint Research Committee and be distributed to the Parties no less than one (1) week before any quarterly meeting. If a representative of a Party on the Joint Research Committee is unable to attend a meeting of the Joint Research 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 Joint Research Committee. Minutes of all Joint Research Committee meetings shall be kept by the hosting Party and sent to all members on the Joint Research Committee for review and approval within seven (7) days after each meeting. Minutes shall be deemed approved unless any member of the Joint Research Committee objects to the accuracy of such minutes by providing written notice to the other members of the Joint Research 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. Any changes made by the Joint Research Committee to the Critical Success Factors shall be included in the minutes. A current and complete version of the Critical Success Factors shall be provided in the minutes of the Joint Research Committee meeting.

2.6.2 Joint Research Committee Responsibilities. The Joint Research Committee shall oversee implementation and execution of the Collaborative Research Plan. The Joint Research Committee shall be responsible for planning, managing, directing and overseeing specific activities under its areas of responsibility, including but not limited to the following, any of which may be delegated to an Operating Committee, as the Joint Research Committee deems appropriate consistent with the goals of the Collaboration:

(a) reviewing the Collaborative Research Plan from a scientific and operational perspective;

(b) making 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, so long as such changes do not cause the Collaboration to exceed the budget established for the Target Validation Program and the Antisense Drug Discovery Program in the Collaborative Research Plan, as such budget may be amended by the Executive Committee;

(c) proposing other changes to the Collaborative Research Plan to the Executive Committee as it deems necessary to accomplish the purpose of the Collaboration;

(d) prioritizing and monitoring progress of antisense lead identification for the Reagent Provision Program, Target Validation Program and Drug Discovery Program; *provided, however,* that if there is a disagreement concerning the prioritization of a Reagent Target or a

Validation Target, such disagreement shall be appealed to the Executive Committee, and, in the event the Executive Committee is unable to resolve such disagreement, such prioritization shall be decided by Lilly;

(e) reviewing the progress and results of the Collaboration to ensure, to the extent reasonably practical, that the Parties are meeting their commitments for both human and financial support and are each fulfilling all of their respective contractual obligations;

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

(g) referring disputes or appealing decisions to the Executive Committee as necessary;

(h) approving changes to the allocation of Collaboration Funds set forth in the Collaborative Research Plan (i) within the Reagent Provision Program, (ii) between the Target Validation Program and the Antisense Drug Discovery Program and (iii) among the Collaboration Therapeutic Areas, so long as such changes do not cause the Collaboration to exceed the budget established for the Target Validation Program and the Antisense Drug Discovery Program in the Collaborative Research Plan, as such budget may be amended by the Executive Committee;

(i) reallocating Collaboration FTEs within each Collaboration Therapeutic Area;

(j) reviewing and approving the use of any Third Party in the Collaboration, including review and approval of any related Third Party contract;

(k) reviewing and monitoring 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) determining assignment of Collaboration Funds and Collaboration FTEs assigned to each Collaboration Therapeutic Area;

(m) adopting and modifying 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 Joint Research Committee minutes;

(n) determining whether a Validation Target is an Accepted Validation Target or Rejected Validation Target;

(o) designating Drug Discovery Targets;

(p) making a determination of whether a Drug Discovery ASO Compound meets the criteria for designation as a Development Candidate and making such designations; and

(q) coordinating with the IP Committee to optimize the value of the intellectual property arising from the Collaboration.

2.6.3 Joint Research Committee Decisions. Decisions of the Joint Research Committee shall be made by unanimous vote with each member having one (1) vote. All issues voted on by the Joint Research Committee shall be appealable to the Executive Committee. No vote of the Joint Research Committee may be taken unless all of the members of such Joint Research Committee vote. Any Party desiring to appeal an issue to the Executive Committee shall make its appeal in writing to all Executive Committee members within ten (10) days of receipt of the minutes for the meeting at which the issue was voted on. Action pursuant to any decision appealed to the Executive Committee shall be suspended pending a determination by the Executive Committee to accept, reject or modify the decision of the Joint Research Committee. If it is not feasible to suspend the action without causing potential damage to the Collaboration, the

Executive Committee shall be requested to provide immediate review. Any Party may at any time request reconsideration of any issue by the Joint Research Committee or Executive Committee if such Party in good faith believes that substantial changes in circumstances have occurred which necessitates such reconsideration.

2.6.4 Joint Research Committee Semiannual Status Reports. During the Collaboration Term and upon expiration thereof the Joint Research Committee shall provide the Executive Committee with a semiannual status report (which may be in the form of a presentation) that generally summarizes the research and development efforts conducted by each Party under the Collaboration during the two (2) previous Calendar Quarters. Such reports shall be submitted or presented to the Executive Committee to coincide with the semiannual meeting of Executive Committee. 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 Joint Research Committee shall establish annual goals and objectives for each year of the Collaboration to be provided to and approved by the Executive Committee.

2.7 Governance—Operating Committees. The Executive Committee and the Joint Research Committee may appoint one or more other working teams (***"Operating Committees"***) to perform such functions as the Executive Committee or Joint Research Committee, respectively, may determine. All Operating Committees shall have at least one (1) representative of each Party. Operating Committees shall have such decision-making authority as may be delegated to them by the Executive Committee or Joint Research Committee (in either case, the ***"Delegating Committee"***). All issues voted on by an Operating Committee shall be appealable to the Delegating Committee. No vote of an Operating Committee may be taken unless all of the members of such Operating Committee vote. Any Party desiring to appeal an issue to the Delegating Committee shall make its appeal in writing to all Delegating Committee members within ten (10) days of receipt of the minutes for the meeting at which the issue was voted on. Action pursuant to any decision appealed to the Delegating Committee shall be suspended pending a determination by the Delegating Committee to accept, reject or modify the decision of such Operating Committee. If it is not feasible to suspend the action without causing potential damage to the Collaboration, the Delegating Committee shall be requested to provide immediate review. Any Party may at any time request reconsideration of any issue by the Delegating Committee if such Party in good faith believes that substantial changes in circumstances have occurred which necessitates such reconsideration. Each Operating Committee shall meet as agreed by its members or directed by the Joint Research Committee. Each Party shall bear its own costs associated with holding and attending such meetings. If mutually agreed by the Parties, such meeting may be held by videoconference or teleconference. If the representative of a Party is unable to attend a meeting, such Party may designate an alternate to attend such meeting and vote on behalf of such missing representative. Minutes of all Operating Committee meetings shall be kept by the hosting Party and sent to the other Party for review and approval within seven (7) days after each meeting. Minutes shall be deemed approved unless a Party objects to the accuracy of such minutes by providing written notice to the other Party 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. Any changes made by an Operating Committee to the Critical Success Factors shall be included in such minutes

2.7.1 Operating Committees. Without limiting the generality of the foregoing, the Joint Research Committee shall establish the following four (4) Operating Committees, with such number of representatives of each Party and such decision-making authority as the Joint Research Committee shall determine:

(i) the Reagent Provision Operating Committee, which shall be responsible for matters relating to the Reagent Provision Program, including, without limitation, managing the

submission and acceptance of Reagent Targets and the timeframe for delivery of Reagent ASO Compounds and providing each Party with a written quarterly report that lists the Reagent Targets for which Isis has provided Lilly with Reagent ASO Compounds during the preceding Calendar Quarter and such Reagent ASO Compounds, the Reagent Targets for which Isis is scheduled to provide Lilly with Reagent ASO Compounds during the ensuing Calendar Quarter, and the anticipated timing of delivery of such Reagent ASO Compounds;

(ii) the Inflammation/Bone Operating Committee, which shall be responsible for matters relating to the activities of the Collaboration in the Collaboration Therapeutic Areas of inflammation and bone;

(iii) the Metabolic Disease Operating Committee, which shall be responsible for matters relating to the activities of the Collaboration in the Collaboration Therapeutic Area of metabolic disease; and

(iv) the Oncology Operating Committee, which shall be responsible for matters relating to the activities of the Collaboration in the Collaboration Therapeutic Area of oncology, and which shall be established promptly after the Restatement Date and exist and operate during the Oncology Term and any extensions thereof.

For avoidance of doubt, it is intended that the Executive Committee and Joint Research Committee will delegate decision-making authority for day-to-day management of the Collaboration to the Operating Committees described in Section 2.7.1. The Joint Research Committee will manage issues that effect more than one Operating Committee or Collaboration Therapeutic Area. While the Joint Research Committee retains the ability to review the decisions of the Operating Committees, it is intended that the Operating Committees shall be given sufficient latitude to make decisions without the need to first consult the Joint Research Committee.

2.7.2 IP Committee. The Executive Committee shall establish a committee that is responsible for intellectual property issues arising in the course of the Collaboration and thereafter (the ***"IP Committee"***). The IP Committee shall be subordinate to the Executive Committee and shall work closely with the Joint Research Committee to implement the activities of the Parties as contemplated by Article 12 and as otherwise agreed by the Parties.

2.8 Dissolution of the Committees. Except as the Parties may otherwise agree in writing, once the Collaboration Term has expired or is terminated, the Joint Research Committee shall dissolve. The Executive Committee shall cease having regular meetings twelve (12) months after expiration or termination of the Collaboration Term but shall meet on an *ad hoc* basis for so long thereafter as is necessary to oversee the activities of the IP Committee. The IP Committee shall continue for so long as there are Patent Rights that are licensed by a Party to the other Party under this Agreement.

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 initial Alliance Managers are listed on ***Schedule 2.9***. The Alliance Managers' responsibilities shall include maintenance of a current list of Reagent Targets, Validation Targets (including Rejected Validation Targets and Accepted Validation Targets), Drug Discovery Targets and Reserved Targets, coordinating meetings of the Joint Research Committee and 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 herein and in the Collaborative Research Plan. Isis and Lilly each acknowledge that there will be a reasonable initial hiring ramp-up period before the number of Collaboration FTEs dedicated to the Collaboration reaches the level specified in the Collaborative Research Plan. Isis shall use its best efforts to ramp-up to the number of Isis Collaboration FTEs specified in the Collaborative Research Plan as soon as possible after the Effective Date. Lilly shall use its best efforts to ramp-up to the number of Lilly Collaboration FTEs specified in the Collaborative Research Plan as soon as possible after the Effective Date. By 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. Upon the approval of the Joint Research Committee, each Party may place one or more employees at the other Party's facilities in order to participate in the conduct of the Collaboration. Such employee(s) shall be fully committed to the Collaboration as Collaboration FTEs. Each Party shall bear the travel, lodging and meal expenses of any of its Collaboration FTEs who visit the other Party's facilities as described in the preceding sentence and shall not be reimbursed by the other Party or out of the Collaboration Funds for any such expenses. Effective on the Restatement Date and until the expiration of the Oncology Term, the therapeutic area of oncology shall be included within the Collaboration Therapeutic Areas for purposes of the Antisense Drug Discovery Program only, and Isis and Lilly will conduct the research activities set forth in that portion of the Collaborative Research Plan related to oncology (the "***Oncology Research Plan***") as a part of the Collaboration; *provided*, *however*, upon agreement of the Parties (such agreement being noted in the Collaborative Research Plan) the therapeutic area of oncology may be included within the Collaboration Therapeutic Areas for the purposes of the drug discovery Target Validation Program as well as the Antisense Drug Discovery Program. Promptly after the Restatement Date, Isis shall use its best efforts to ramp-up to the number of additional Isis Collaboration FTEs as specified in the Oncology Research Plan to carry out the objectives set forth therein as soon as possible after the Restatement Date. Lilly shall apply an appropriate number of FTEs to achieve the objectives set out for Lilly in the Oncology Research Plan. FTEs applied by Lilly to carry out the work set forth in the Oncology Research Plan shall not be considered to be Lilly Collaboration FTEs and such FTEs shall not be reimbursed with Collaboration Funds. If during the Oncology Term or any extensions thereof Isis believes that Lilly is applying an insufficient number of FTEs to accomplish the objectives of the Oncology Research Plan Isis may petition the Executive Committee to review the Lilly effort and to require Lilly to apply additional FTEs if necessary. Lilly shall track the FTEs applied by Lilly to carry out the work as set forth in the Oncology Research Plan and report such FTE effort to Isis on a quarterly basis as a part of the reporting requirement under Section 9.1.1.

3.2 Subcontracting. Except to the extent approved by the Joint Research 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 IP Committee 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 Joint Research 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. In addition to a Party's employees located at the other Party's facilities pursuant to Section 3.1, 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 Reagent ASO Compounds, 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 Description and Term. The Reagent Provision Program shall commence on the Effective Date and be conducted by Isis during the Reagent Provision Term in accordance with the Collaborative Research Plan. The Reagent Provision Term shall become effective on the Effective Date and shall continue in effect for four (4) years, unless Lilly exercises it option to extend the Reagent Provision Term, as provided in Section 13.1, the Parties otherwise mutually agree to extend or terminate the Reagent Provision Program, or the Collaboration is terminated in accordance with Article 13. The Parties estimate that approximately six hundred and seventy-five (675) Targets from any therapeutic

area of interest to Lilly will be analyzed in the course of the Reagent Provision Program. Such Targets shall be selected by Lilly and designated as Reagent Targets.

4.2 Reagent Targets. For each Reagent Target, Isis will use reasonable efforts to promptly provide to Lilly Reagent ASO Compounds for each Reagent Target in accordance with the Collaborative Research Plan. Each Reagent ASO Compound shall be delivered to Lilly in accordance with the specifications set forth in the Collaborative Research Plan. Isis will also promptly provide to Lilly Reagent Target gene reduction data generated by Isis on the inhibition of the Reagent Target by each Reagent ASO Compound delivered to Lilly. Isis shall also provide to Lilly ongoing consultation as reasonably requested by Lilly on the utilization of each Reagent ASO Compound in Lilly's research efforts during the Collaboration Term. Lilly will use best efforts to request, and Isis will use best efforts to provide to Lilly, Reagent ASO Compounds at the flow rate that is specified in the Collaborative Research Plan; *provided*, *however*, that if Lilly requests Reagent ASO Compounds at a flow rate that is greater than that specified in the Collaborative Research Plan, Isis will use reasonable efforts to provide the Reagent ASO Compounds to Lilly at such greater flow rate.

4.3 Isis Use of Reagent Targets and Reagent ASO Compounds. Except as provided otherwise in this Agreement, [***]

4.4 Isis GeneTrove Database. It is the intention of the Parties that the designation of Targets to be included in the Reagent Provision Program, the Target Validation Program or the Antisense Drug Discovery Program shall not influence the analysis or prioritization of Targets by Isis outside the course of the Collaboration. To this end, Isis shall not utilize Lilly Confidential Information outside the Collaboration for the purpose of prioritizing the Targets to be analyzed for inclusion in the GeneTrove Database or for any other purpose except as expressly permitted by this Agreement. [***]

[***]

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

4.6 Lilly Confidential Information. All information provided to Isis by Lilly with respect to a Reagent 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 Reagent 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.

4.7 Use and Disclosure. Use of Reagent ASO Compounds and Reagent Targets by a Party 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, including through use of Reagent ASO Compounds, Reagent Non-ASO Compounds, or Reagent 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.

ARTICLE 5

THE DRUG DISCOVERY TARGET VALIDATION PROGRAM

5.1 Description and Term. The drug discovery Target Validation Program shall commence on the Effective Date and be conducted by Lilly and Isis during the Target Validation Program Term in accordance with the Collaborative Research Plan. The Target Validation Program Term shall become effective on the Effective Date and shall continue in effect for four (4) years, unless Lilly exercises it

option to extend the Target Validation Program Term, as provided in Section 13.1, the Parties otherwise mutually agree to extend or terminate the Target Validation Program, or the Collaboration is terminated in accordance with Article 13. The Collaborative Research Plan includes the Critical Success Factors for the Target Validation Program including the Critical Success Factors for Validation Targets. By execution of this Agreement, the initial Collaborative Research Plan, including the Critical Success Factors, are approved by each Party. The Joint Research Committee is responsible for implementing the Collaborative Research Plan and any modifications or amendments thereto consistent with the terms of this Agreement.

5.2 Target Designation. The Parties estimate that approximately three hundred and twenty five (325) Targets will be analyzed in the course of the drug discovery Target Validation Program. Such Targets shall be selected by Lilly 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 fifteen (15) 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 set forth in the Collaborative Research Plan. All results generated in the course of Target Validation Program shall be promptly provided to a member of the Joint Research Committee for the other Party by means of a written report generated by the Parties and by placing such results in the shared database described in the Collaborative Research Plan. Following consultation with Isis, Lilly shall decide whether to conduct Validation Tier 1 studies and/or Validation Tier 2 studies (as such terms are defined in the Collaborative Research Plan) with respect to each Validation Target. [***]

5.4 Joint Research Committee Review. At the next Joint Research Committee meeting following the completion of the evaluation of a Validation Target under the Target Validation Program, the Joint Research 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 set out in the Collaborative Research Plan. If the Joint Research Committee determines that a Validation Target meets the Critical Success Factors, such Validation Target shall be deemed an ***"Accepted Validation Target."*** If the Joint Research 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 [***]

5.6 Rejected Validation Targets [***]

5.6.1 [***]

5.6.2 [***]

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

5.8 Exclusive Targets. During the Reagent Provision Term or the Target Validation Program Term, as applicable, Lilly may elect to designate any Reagent Target or 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.

ARTICLE 6

THE ANTISENSE DRUG DISCOVERY PROGRAM

6.1 Description and Term. The Antisense Drug Discovery Program shall be conducted by Isis and Lilly during the Antisense Drug Discovery Term in accordance with the Collaborative Research Plan, except that the Antisense Drug Discovery Program in the Collaboration Therapeutic Area of oncology shall be conducted solely during the Oncology Term, as more fully described in Section 13.1.2. The Antisense Drug Discovery Term shall become effective on the Effective Date and shall continue in effect for four (4) years, unless Lilly exercises it 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. The Oncology Term shall commence on the Restatement Date and shall continue in effect for two (2) years thereafter, unless extended or 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 Joint Research 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 Joint Research Committee shall designate the Drug Discovery Targets to be analyzed under the Antisense Drug Discovery Program in one or more Collaboration Therapeutic Areas. [***] Targets designated as Drug Discovery Targets may include any Target that is suspected of playing a role in a Collaboration Therapeutic Area, including Reserved Targets, Reagent Targets, Accepted Validation Targets, Exclusive Targets, Rejected Validation Targets, and other Targets that the Joint Research Committee determines to be of interest based on the scientific merits of applying Antisense Technology to modulate such Target; [***] The initial Drug Discovery Targets provided by Isis for each Collaboration Therapeutic Area and the stage of development of such Targets as of the Effective Date (*i.e.*, whether such Target is a Stage 1, Stage 2 or Stage 3 Drug Discovery Target) are identified in the Collaborative Research Plan.

6.2.2 Disagreements Regarding Drug Discovery Target Designation. If the Joint Research Committee cannot agree on whether to designate a Target a Drug Discovery Target, the matter shall be referred to the Executive Committee for a decision. 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 Joint Research Committee of a Target as a Drug Discovery Target, the Joint Research 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 (or, with respect to any Drug Discovery ASO Compound corresponding to a Drug Discovery Target in the Collaboration Therapeutic Area of oncology, during the Oncology 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 Joint Research Committee that such Drug Discovery ASO Compound be designated a Development Candidate and, at the next meeting of the Joint Research Committee, the Joint Research Committee shall vote on such matter. Either Party may appeal the outcome of such vote to the Executive Committee, in which event the Executive Committee shall meet as promptly as practicable thereafter to resolve the matter. If the Joint Research Committee (in the absence of an appeal to the Executive Committee) or 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 (or, with respect to any Drug Discovery ASO Compound corresponding to a Drug Discovery Target in the Collaboration Therapeutic Area of oncology, after the Oncology

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 Joint Research Committee during the Antisense Drug Discovery Term or Oncology Term, as applicable. 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 (or, in the case of Drug Discovery Targets in the Collaboration Therapeutic Area of oncology, within ten (10) days following expiration or termination of the Oncology Term) and again on the first (1st) 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 six (6) months following such expiration or termination of the Antisense Drug Discovery Term or Oncology Term, as applicable, until the [***] anniversary of the expiration or termination (subject to Article 13) of the Antisense Drug Discovery Term or Oncology Term, as applicable, 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 or Oncology Term, as applicable (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.

6.6 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 Joint Research Committee may designate a Drug Discovery Target as an ***"Abandoned Drug Discovery Target"*** if such Joint Research Committee concludes that such Drug Discovery Target should no longer be the subject of an Active Program as part of the Collaboration. Such vote shall be appealable to the Executive Committee. [***]

6.8 Reserved Targets. During the 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 Antisense Drug Discovery Term, the total number of both (i) Drug Discovery Targets that are the subject of an Active Program and (ii) Reserved Targets, shall [***]; *provided, however,* that if Lilly does not extend the Oncology Term pursuant to Section 13.1.2(a), then from expiration or termination of the Oncology Term through the remainder of the Antisense Drug Discovery Term, then the total number of both Drug Discovery Targets that are the subject of an Active Program and Reserved Targets shall not exceed [***]; and *provided, further,* that if Lilly extends the Oncology Term pursuant to Section 13.1.2(a), then the total number of both Drug Discovery Targets that are the subject of an Active Program and Reserved Targets shall not exceed the sum of: [***] The Joint Research Committee shall decrease the total number of Drug Discovery Targets that are the subject of an Active Program and Reserved Targets to [***] by the expiration of the Antisense Drug Discovery Term or any

extensions thereof if the Oncology Term is not extended pursuant to Section 13.1.2(a) or [***] if the Oncology Term is extended pursuant to Section 13.1.2(a). For purposes of clarification, upon exercise by Lilly of its option under Section 8.2.3 with respect to a Drug Discovery Target, such Drug Discovery Target shall no longer be counted toward the maximum number of Drug Discovery Targets and Reserved Targets permitted by this Section 6.9. Effective as of the [***] anniversary of the expiration of the Antisense Drug Discovery Term, no Target shall be deemed a Reserved Target for purposes of this Agreement.

ARTICLE 7

DEVELOPMENT, COMMERCIALIZATION, MANUFACTURING AND SUPPLY

7.1 Research Supply. Isis shall supply Reagent ASO Compounds, 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 Reagent ASO Compound, 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 Reagent ASO Compounds, Validation ASO Compound and/or Drug Discovery ASO Compound in accordance with the specifications set out in the Collaborative Research Plan.[***] after receipt of such Reagent ASO Compound, 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 Reagent ASO Compound, Validation ASO Compound or Drug Discovery ASO Compound requested by and delivered to Lilly in any one order. For any quantities of Reagent ASO Compound, Validation ASO Compound or Drug Discovery ASO Compound requested by and delivered to Lilly [***] 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 Reagent ASO Compound, 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 Reagent ASO Compound, 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 Reagent ASO Compound, Validation ASO Compound or Drug Discovery ASO Compound. Isis will also provide any information and documentation on such Reagent ASO Compound, Validation ASO Compound or Drug Discovery ASO Compound that is required by regulatory authorities. Isis will supply any such Reagent ASO Compound, 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 Reagent ASO Compound, Validation ASO Compound or Drug Discovery ASO Compound to Lilly or if Lilly determines to obtain supply of any such Reagent ASO Compound, 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.

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.

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 during the Target Validation Program Term and [***] year thereafter, 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 [***] 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.

(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 CSAG Approval 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 six (6) month period Lilly shall have no obligation to provide such summary reports to Isis.

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 if Lilly does not extend the Oncology Term in accordance with Section 13.1.2(a), Lilly's option under this Section 8.2.3 shall be exercisable only (A) for a period of [***] after the expiration of the Oncology Term with respect to any Drug Discovery Target in the Collaboration Therapeutic Area of oncology that was a Stage I Drug Discovery Target at the time it became a Drug Discovery Target hereunder, and (B) during the Oncology Term with respect to any Drug Discovery Target in the Collaboration Therapeutic Area of oncology that was a Stage II or Stage III Drug Discovery Target at the time it became a Drug Discovery Target hereunder; *further 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 CSAG Approval 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.

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.

8.4 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 [***] 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 [***] 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 two (2) 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.

8.7 Isis GeneTrove Database Subscription. Until November 1, 2001, Lilly shall have the right to become [***] for the GeneTrove Database for a period of [***] [***] During such [***] month period, Lilly shall have the option of becoming a subscriber to the Genetrove Database [***] and otherwise upon the terms and conditions set forth in ***Schedule 8.7*** hereto and thereafter, during the Collaboration Term, Lilly shall have the option of becoming a subscriber to the GeneTrove Database [***] preceding Lilly's exercise of such option for a comparable subscription.

8.8 Technology Transfer. Upon expiration or termination (other than for breach by Lilly) of the Collaboration Term, Lilly shall have the option to obtain a non-exclusive license, including the right to sublicense solely in connection with the grant of a license to develop, make, use, import, offer for sale and sell Lilly Products, to use the Isis Technology described in ***Schedule 8.8*** hereto on the terms set forth in such ***Schedule 8.8.***

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 Reagent Target, Validation Target or Drug Discovery Target is subject to restrictions on Isis' use of such Target outside the Collaboration pursuant to Section 4.3, 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 or 8.3, Isis shall not [***] The Parties acknowledge that, as of the Restatement Date, neither Party has committed to [***] However, upon mutual written agreement of the Parties during the Collaboration Term, the Reagent Provision Program, Target Validation Program and/or Antisense Drug Discovery Program, as applicable, may be expanded to include activities directed to [***].

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.

9.1.1 Collaboration FTEs. Collaboration FTEs shall be billed against the Collaboration Funds at the FTE Rate. Each Party 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 Collaboration Term, each Party shall submit to the other Party within [***] days following each Calendar Quarter a written statement accompanied by a certificate signed by the Vice President of Finance or Director of Finance on behalf of Isis, or in the case of Lilly, the Director of Finance for Lilly Research Laboratories (or successor positions), setting forth (i) the number of Collaboration FTEs dedicated to work on the Collaboration for the previous Calendar Quarter, (ii) the dollar amount of Collaboration Funds expended during the Calendar Quarter for which the report is made and the subject matter of such expenditures; and (iii) a description of the activities conducted. Isis will also include in such report to Lilly the beginning balance of Collaboration Funds for such Calendar Quarter. Within [***] days of receipt of Lilly's report for any Calendar Quarter, Isis shall submit to Lilly an additional written statement, accompanied by a certificate signed by the Vice President of Finance or Director of Finance of Isis, setting forth the amount of Collaboration Funds expended in the preceding Calendar Quarter, the ending balance of Collaboration Funds at the end of such Calendar Quarter and the total amount of monies to be reimbursed to Lilly by Isis from Collaboration Funds for expenses incurred by Lilly under the Collaboration. Isis shall reimburse Lilly concurrently with the delivery

of the report under the preceding sentence. Such reimbursement shall be made by wire transfer to an account designated by Lilly.

9.1.2 Reagents. Isis shall charge the Collaboration Funds for Reagent ASO Compounds provided to Lilly by Isis under the Reagent Provision Program at the Isis HTS Standard Cost or Isis RTS Standard Cost, as applicable, in accordance with the provisions of Section 9.1.1.

9.1.3 Protected Targets. For each Target that Lilly designates as a Protected Target pursuant to Section 4.4 (ii), Lilly shall pay to Isis an premium amount that [***] of the amount that is charged by Isis against the Collaboration Funds under Section 9.1.2 with respect to ASO Compounds to such Protected Target. Such premium amount shall be paid by Lilly within thirty (30) days after (i) Lilly or the Collaboration receives such ASO Compound to such Protected Target and (ii) Isis notifies Lilly that the Collaboration Funds have been charged for delivery of such ASO Compounds, such notice also specifying the amount charged against the Collaboration Funds for such ASO Compounds. For avoidance of doubt, the premium amount paid by Lilly pursuant to Section 9.1.3 shall not be charged against the Collaboration Funds.

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 one (1) time per year.

9.1.5 Increase in Loan Commitment. Lilly and Isis have agreed on the Lilly Loan commitment and the Loan Disbursement schedule set forth in the Loan Agreement based on the mutual understanding of Lilly and Isis that that Loan commitment and Loan Disbursement schedule will provide Collaboration Funds on a timely basis to allow completion of the Collaboration activities during the initial term of the Collaboration as set forth in this Agreement. If, pursuant to Subsection 2.5.2(g), the Executive Committee recommends to Lilly that an increase in Collaboration Funds is desirable to cover Collaboration efforts during the initial four (4) year term of the Collaboration as a result of expanding the therapeutic area focus of the Collaboration, Lilly may at its sole option either increase the Loan commitment under the Loan Agreement or pay cash to provide sufficient Collaboration Funds to cover such expanded area of focus, and Lilly and Isis agree to execute such amendments to the Loan Agreement as are necessary to cover the increased Loan commitment and adjustments in the Loan Disbursement schedule. The Parties acknowledge that as a result of expanding the therapeutic area focus of the Collaboration to include oncology there may need to be an increase in the total amount of the Collaboration Funds. Before the commencement of the fourth (4^{th}) year of the Collaboration, the Executive Committee shall determine whether there are sufficient Collaboration Funds to fulfill the objectives and funding amount of the Collaborative Research Plan, as approved by the Executive Committee, through the end of the fourth (4^{th}) year of the Collaboration. If there are insufficient Collaboration Funds to meet the objectives and funding amount of the Collaborative Research Plan as approved by the Executive Committee, then Isis shall have the right to cause Lilly to increase the Collaboration Funds to the total funding amount as specified in such approved Collaborative Research Plan; *provided, however,* the amount that the Collaboration Funds may be increased above the original Loan amount as provided in the Loan Agreement shall not exceed the total amount of the sum of (i) the Collaboration Funds actually spent on the oncology

Collaboration Therapeutic Area before the commencement of the fourth (4^{th}) year of the Collaboration plus (ii) the Collaboration Funds allocated to the oncology Collaboration Therapeutic Area in the Collaborative Research Plan approved by the Executive Committee for the fourth (4^{th}) year of the Collaboration, *and further provided,* that Lilly may at its sole option either increase the Loan commitment under the Loan Agreement or pay cash to provide sufficient Collaboration Funds to cover such additional Collaboration Funds.

9.1.6 Modifications to Loan Disbursement Schedule. While not expected, if for any reason there is a substantial acceleration or delay in the conduct of Collaboration activity from the Collaborative Research Plan used in determining the Loan Disbursement schedule set forth in the Loan Agreement, the Executive Committee shall recommend modifications to Lilly in the Loan Disbursement schedule as appropriate to reflect the resulting acceleration or delay in the need to provide Collaboration Funds, and, if such recommended modifications are acceptable to Lilly, then Lilly and Isis agree to execute such amendments to the Loan Agreement as are appropriate to reflect the changes recommended by the Executive Committee to the Loan Disbursement schedule.

9.1.7 Action by Executive Committee. If either Party believes that activity by the Executive Committee pursuant to Section 9.1.5 or 9.1.6 is appropriate, it shall so notify the other Party in writing, and the Parties will cooperate in calling an Executive Committee meeting to consider such matters at the earliest feasible time thereafter.

9.1.8 Payment of Royalty Reduction Fee. Lilly shall pay to Isis One Million and [***] 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 [***] or another Drug Discovery Target if [***] becomes an Abandoned Drug Discovery Target, as more fully described in Section 9.4.2.

9.2 Technology Access Fee. If Lilly is conducting any research, development or commercialization activities relating to any Lilly Product as of the fourth (4^{th}) 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 thirty (30) days after the fourth (4^{th}) 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.

Capitalized terms used in this Section 9.2 that are not defined in this Agreement shall have the meanings set forth in the Loan Agreement.

9.2.2 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 one percent [***] 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 [***]

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* [***]

9.4 Pass Through Royalties. [***]

9.4.1 [***]

9.4.2 [***]

9.4.3 [***]

9.4.4 [***]

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 Elan, 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 [***] 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 [***] days 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 [***].

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 9.1, 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 a Collaboration Therapeutic Area 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 not 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 completion of the Collaboration, 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, through their interactions on the Executive Committee and the IP Committee, 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. With respect to inventions arising in the course of the Collaboration, and when appropriate, the Parties shall file patent applications containing ASO Compound composition of matter claims and claims directed to the use of such ASO Compound (each, an ***"ASO Composition of Matter Patent Right"***) 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 ASO Composition of Matter Patent Right solely owned by Isis unless such ASO Composition of Matter Patent Right is exclusively licensed to Lilly under Article 8 in which case the terms of Section 12.6 shall apply; *provided, however,* that the Parties shall reimburse [***] of Isis' external costs of filing, prosecuting, maintaining and extending ASO Composition of Matter Patent Rights claiming Drug Discovery ASO Compounds and/or the use of Drug Discovery ASO Compounds directed to a Drug Discovery Target until such time as either such Target ceases to be a Drug Discovery Target for purposes of this Agreement, Lilly exclusively licenses such ASO Composition of Matter Patent Right, or Lilly elects to discontinue such reimbursement pursuant to Section 12.6. 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 Lilly Collaboration Patent Rights. The

Executive Committee shall designated 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. Each Party shall provide the IP Committee 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 IP Committee. 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 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.

12.4 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 Controlled by such Party Covering a Product being developed or commercialized by the other Party hereunder or of any Collaboration Patent Right, 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. 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, 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; *provided, however,* Lilly shall be responsible [***] of Isis' external costs of filing, prosecuting, maintaining and extending such Isis Collaboration Patent Rights incurred on and after such time as any Isis Collaboration Patent Right is exclusively licensed to Lilly under Article 8. 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 [***] 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 the 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 one (1) 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 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 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 owner of the Collaboration Know-How or 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 Patent Right or 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.

ARTICLE 13

TERM AND TERMINATION

13.1 Term of Collaboration.

13.1.1 The Collaboration Term. The Collaboration Term shall become effective on the Effective Date and shall continue in effect for four (4) years unless terminated in accordance with this Article 13. Prior to the close of the Collaboration Term, Lilly shall have the option to extend each or all of the Reagent Provision Program Term, Target Validation Program Term, and/or the 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 Reagent Provision Program Term, Target Validation Program Term, and/or

the 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 Reagent Provision Program Term, Target Validation Program Term, and/or the Drug Discovery Program Term. If the Reagent Provision Program Term, Target Validation Program Term, and/or the 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) such funding amount shall be the same as provided in this Agreement for the Reagent Provision Program, Target Validation Program, and/or the Drug Discovery Program, as applicable, such funding amount adjusted for the reduction in the duration of the extension period as compared to the original Collaboration Term.

13.1.2 Oncology Collaboration Therapeutic Area. The Oncology Term shall commence on the Restatement Date and shall continue in effect for two (2) years thereafter unless terminated in accordance with this Article 13.

(a) Extension. Lilly may, in its sole discretion, extend the Oncology Term to the end of the initial four (4) year Collaboration Term by providing written notice to Isis at least six (6) months before the expiration of the Oncology Term. If Lilly extends the Oncology Term the Parties shall promptly discuss and agree to an amended Oncology Research Plan that shall be focused on the discovery and development of ASO Compounds in the area of oncology. Such amended Oncology Research Plan shall be deemed a part of the Collaborative Research Plan and shall provide for (i) a mutually agreed upon number of Isis Collaboration FTEs to work on the objectives of the amended Oncology Research Plan, but in no event less than [***] such Isis Collaboration FTEs and (ii) an amended number of Reserved Targets and Drug Discovery Targets as provided in Section 6.9.

(b) Termination. If (i) the Drug Discovery Target Survivin is designated an Abandoned Drug Discovery Target during the first eighteen (18) months of the Oncology Term or (ii) Lilly elects to discontinue Phase III Clinical Trials on Isis 3521, Lilly shall have the option of terminating the Oncology Term effective upon six (6) months' advance written notice to Isis. If Lilly exercises its option to terminate under this Section 13.1.2(b) oncology shall cease to be a Collaboration Therapeutic Area as of the effective date of such termination. Upon the effective date

of such termination, the Joint Research Committee shall reassign the Isis Collaboration FTEs assigned to the Collaboration Therapeutic Area of oncology to the remaining Collaboration Therapeutic Areas for the remainder of the Oncology Term.

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 prior to the fourth (4^{th}) anniversary after the Effective Date 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 all of the Reagent Provision Program, 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 Reagent Provision Program, 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 all of the Reagent Provision Program, 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; and

(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.

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 and 8.3 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 [***] 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;

(h) 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;

(i) 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;

(j) the Technology Transfer described in Section 8.8 shall (i) occur immediately upon termination under this Section by Lilly, (ii) be at no cost to Lilly and (iii) Lilly shall have the right to practice such technology so transferred for research, development and commercialization purposes; and

(k) 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, 8.2, 8.4 and 8.5 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 Joint Research Committee shall establish a procedure for publication review and approval and each Party shall first submit to the Joint Research 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 Joint Research 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 Joint Research 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 Joint Research 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 Joint Research 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 Joint Research Committee fails to approve of such Party's proposed publication, then such proposed publication shall be regarded as denied by the Joint Research Committee and shall not be published.

ARTICLE 15

15.1 HSR Act Compliance. Notwithstanding anything to the contrary in this Agreement, the Effective Date of this Agreement and commencement of the Collaboration shall not occur until such time as (1) the Parties shall have complied with all applicable requirements of the Hart Scott Rodino Antitrust Improvements Act of 1976, as amended the ***"HSR Act"***); (2) the waiting period under the HSR Act shall have expired or earlier been terminated; (3) no judicial or administrative proceeding opposing consummation of all or any part of this Agreement shall be pending; (4) no injunction (whether temporary, preliminary or permanent) prohibiting consummation of the transactions contemplated by this Agreement or any material portion hereof shall be in effect; and (5) no requirements or conditions shall have been imposed in connection therewith which are not reasonably satisfactory to the Parties (collectively, the ***"HSR Conditions"***).

15.2 Cooperation on Filing. Both Lilly and Isis shall file, as soon as reasonably practicable after the Effective Date of this Agreement, with the Federal Trade Commission (***"FTC"***) and the Antitrust Division of the United States Department of Justice (***"DOJ"***) the notification and report form (***"Report"***) required of each of them in the reasonable opinion of either or both Parties under the HSR Act with respect to the transactions described in this Agreement and any other agreements between the Parties contemplated hereby (collectively, the ***"Transactions"***). Each Party shall cooperate with the other to the extent necessary to assist the other Party in the preparation of its Report and to proceed to obtain necessary approvals under the HSR Act to complete the Transactions including, but not limited to, the expiration or earlier termination of any and all applicable waiting periods required by the HSR Act (***"Required Approval"***). Each Party will use reasonable efforts to obtain the Required Approval. Each Party shall use reasonable good faith efforts to assist the other Party in eliminating any concern on the part of any court of governmental authority regarding the legality of the Transactions. Such assistance shall include, if required by federal or state antitrust authorities, such Party's taking all reasonable steps to secure Required Approval. The other Party shall cooperate in good faith, at its own cost, with any government investigation regarding the legality of the Transactions and promptly produce documents, witnesses, and information demanded by the FTC or DOJ, whether by informal request or by formal HSR Act Second Request or other legal process; *provided, however,* that neither Party shall be obligated to proceed to seek Required Approval if it has received a second request for documents that it determines is unreasonably burdensome or costly with which to comply; and *provided, further,* that neither Party shall be obligated to proceed with litigation if the transaction is challenged by the FTC or the DOJ. If either Party determines that it does not wish to proceed with the Report process, either because of a burdensome second request or litigation, the Parties will discuss in good faith whether there are any modifications to the Agreement or any other agreement between the Parties contemplated hereby that will avoid antitrust issues and facilitate obtaining the Required Approval. Neither Party shall be obligated in any way to engage in further negotiations of the terms of this Agreement or any other agreement between the Parties contemplated hereby, even if modifications are identified that will facilitate obtaining Required Approval. If an unreasonably burdensome request is received or litigation is commenced, either Party may terminate this Agreement.

ARTICLE 16

MISCELLANEOUS

16.1 Key Personnel. During the Collaboration Term, Isis shall inform Lilly [***] leave the employ of Isis. In 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,

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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(a) 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 Deputy 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 Loan Agreement, Registration Rights Agreement and the Securities Purchase Agreement, constitutes 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 or Joint Research 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 or Joint Research 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/ AUGUST M. WATANABE	By: /s/ B. LYNNE PARSHALL
August M. Watanabe Executive Vice President Science and Technology	B. Lynne Parshall Executive Vice President and Chief Financial Officer

[SIGNATURE PAGE TO COLLABORATION AGREEMENT]

List of Schedules

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.

[***]

"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.

"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.

"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.

"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 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, collectively, the Reagent Provision Program, the Target Validation Program and the Antisense Drug Discovery Program.

"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" shall mean the Isis Collaboration Patent Rights, the Lilly Collaboration Patent Rights and the Joint Collaboration Patent Rights.

"Collaboration Term" means the term of the collaborative research efforts carried out pursuant to this Agreement and any extension thereof.

"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" shall mean, 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

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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.

"CSAG Approval" means [***]

"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 Joint Research 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 Joint Research 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.

"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 [***] (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 Joint Research 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.

"FTE Rate" [***]

"GeneTrove Database" means Isis' proprietary GeneTrove Human Gene Function Database consisting, without limitation, of data from the study of the effect of gene-specific inhibition of up to 10,000 human genes in a set of human cell-based pharmacology assays utilizing Isis' proprietary antisense technology, and software appropriate for storing, viewing and performing queries on the incorporated data.

"GeneTrove Database Queue" means those human genes which have been identified and prioritized in Isis' HTS and RTS queue to begin the work required to identify a lead antisense oligonucleotide. The GeneTrove Database Queue will contain the number of genes which can reasonably be screened within three to six months using Isis' combined RTS and HTS resources.

"HTS Standard Cost" [***]

[***]

"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.

"IP Committee" has the meaning provided in Section 2.7.2.

"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 the Effective Date or 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 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 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. The existing Isis Internal Programs in the Collaboration Therapeutic Areas as of the date of this Agreement are listed in ***Schedule A***.

"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 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 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.

"Joint Research Committee" means the committee established pursuant to Section 2.6.

"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.

"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.

[***]

"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, as more fully described in Section 13.1.2.

"Operating Committees" has the meaning provided in Section 2.7.

"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" [***]

"Project Sanction Approval" means [***]

"Proposed Validation Target" has the meaning set forth in Section 5.2.

"Protected Target" has the meaning set forth in Section 4.4.

"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 this Agreement, as described in Section 2.2, Article 4 and the Collaborative Research Plan.

*"**Reagent Provision Term**"* means the term of the Reagent Provision Program carried out pursuant to this Agreement and any extension thereof.

*"**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 date set forth in the first paragraph of this 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.

*"**RTS Standard Cost**"* for any Reagent ASO Compound for any year of the Collaboration Term means [***]

*"**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.

*"**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

INITIAL MEMBERS OF THE EXECUTIVE COMMITTEE

Lilly	Isis
[***]	[***]
[***]	[***]
[***]	[***]

SCHEDULE 2.6

INITIAL MEMBERS OF THE JOINT RESEARCH COMMITTEE

Lilly	Isis
[***]	[***]
[***]	[***]
[***]	[***]

SCHEDULE 2.9

INITIAL ALLIANCE MANAGERS

Lilly	Isis
[***]	[***]

SCHEDULE 8.7

GENETROVE DATABASE SUBSCRIPTION TERMS

[***]

SCHEDULE 8.8

TECHNOLOGY TRANSFER TERMS

[***]

SCHEDULE 9.4.3

MILESTONES AND ROYALTIES UNDER SECTION 9.4.3 AND 9.4.4

MILESTONE PAYMENTS[

[***]

[***]

[***]

SCHEDULE A

EXISTING ISIS INTERNAL PROGRAMS

[***]

[***]

ADDITIONAL EXISTING ISIS INTERNAL PROGRAMS IN THE AREA OF ONCOLOGY AS OF THE RESTATEMENT DATE

TO BE CONFIRMED

[***]

SCHEDULE B
ISIS MANUFACTURING PATENT RIGHTS

[***]

SCHEDULE C

ISIS CORE TECHNOLOGY PATENT RIGHTS

[***]

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SECOND AMENDMENT TO
RESEARCH COLLABORATION AND LICENSE AGREEMENT

This second amendment ("Amendment") to the Research Collaboration And License Agreement is made and effective this 19th day of April, 2002 between Merck & Co., Inc., a corporation organized and existing under the laws of New Jersey ("Merck") and Isis Pharmaceuticals, Inc., a corporation organized and existing under the laws of Delaware ("Isis") together referred to as the "Parties".

WITNESSETH:

WHEREAS, Merck and Isis have entered into a Research Collaboration And License Agreement effective as of June 1, 1998 and agreed to extend the Research Program Term in a First Amendment dated February 28, 2001(collectively "License Agreement"). Capitalized terms not otherwise defined in this Amendment shall have the meanings ascribed to them in the License Agreement.

WHEREAS, the Extended Research Program Term is to expire on June 1, 2002; and

WHEREAS, the PARTIES desire to further extend the Extended Research Program Term;

NOW, THEREFORE, in consideration of the foregoing premises and the mutual covenants herein contained, the Parties hereby agree as follows:

1. Isis and Merck shall extend their engagement in the Extended Research Program upon the terms and conditions set forth in this Amendment. The activities to be undertaken in the course of the Extended Research Program are set forth in Article II and in Attachment 2.1 of the License Agreement as modified by this Amendment.

2. The Extended Research Program Term shall be one year, from June 1, 2002 to May 31, 2003.

3. In consideration for Isis's performance of its obligations under the Research Program as amended, Merck shall pay Isis: (a) an amount equal to [***] The first such installment shall be due no later than June 30, 2002. The remaining installments shall be due at the end of each succeeding calendar quarter.

4. During the Extended Research Program Term, Isis shall dedicate the efforts of [***] FTEs.

5. Within thirty (30) days of the execution of this Amendment, Merck shall make a payment to Isis of [***]dollars in full satisfaction of the obligation set forth in by Section 5.3.7 of the Agreement.

6. Replace Section 5.3.2 in its entirety with new 5.3.2:

   5.3.2.(new) The Milestones set forth in Section 5.3.1 shall be paid for the first HCV Human Product. In the event a second HCV Human Product is being developed in addition to the first HCV Human Product, a Milestone of [***]upon approval by Merck's Research Management Committee (or its successors) in its sole discretion, of a [***]and the Milestones in Sections 5.3.1(d) and (e) will be paid for the second HCV Human Product. No additional Milestone payments will be made on any other HCV Human Products.

7. Should Merck determine at any time during the Extended Research Program Term that productivity of the Isis personnel is not reasonably expected to adequately satisfy the objectives of the Research Program, then Merck may terminate the extended Research Program on ninety (90) days written notice. Such termination of the extended Research Program shall not terminate the License Agreement.

8. From and after the date first written above, all references in the License Agreement to "this Agreement" or "this License Agreement", "hereunder", "hereof", "herein" or words of similar import, shall be reference to the License Agreement, as amended by this Second Amendment.

Except as expressly amended by this Second Amendment, the License Agreement remains in full force and effect and unchanged.

9. The Amendment may be executed in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

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

MERCK & CO., INC.		ISIS PHARMACEUTICALS, INC.	
BY:	/s/ PETER S. KIM	BY:	/s/ B. LYNNE PARSHALL
Name Title:		Name: Title:	B. Lynne Parshall Executive Vice President

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SECOND AMENDMENT TO RESEARCH COLLABORATION AND LICENSE AGREEMENT

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Exhibit 99.1

CERTIFICATION

Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, Stanley T. Crooke, the Chief Executive Officer of Isis Pharmaceuticals, Inc., (the "Company"), and B. Lynne Parshall, the Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Quarterly Report on Form 10-Q for the period ended June 30, 2002, to which this Certification is attached as Exhibit 99.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Periodic Report and the results of operations of the Company for the period covered by the Periodic Report.

Dated: August 14, 2002

/s/ STANLEY T. CROOKE	/s/ B. LYNNE PARSHALL
Stanley T. Crooke, M.D., Ph.D. Chief Executive Officer	B. Lynne Parshall, Esq. Chief Financial Officer

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CERTIFICATION