SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D. C. 20549

FORM 8-K

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

Date of report (Date of earliest event reported): AUGUST 29, 2001

ISIS PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in Charter)

DELAWARE
(State or Other Jurisdiction of Incorporation)

000-19125	330336973
(Commission File No.)	(IRS Employer Identification No.)

2292 FARADAY AVENUE
CARLSBAD, CA 92008
(Address of Principal Executive Offices and Zip Code)

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

ITEM 2. ACQUISITION OR DISPOSITION OF ASSETS.

Under the terms of a Securities Purchase Agreement between Isis Pharmaceuticals, Inc. and Eli Lilly and Company, on August 29, 2001, Lilly purchased 4,166,667 shares, or approximately nine percent (9%), of Isis' Common Stock at an aggregate purchase price of $75 million, or $18 per share. In addition, Lilly has committed to loan Isis $100 million to fund a research collaboration pursuant to a Collaboration Agreement between Isis and Lilly which provides for Isis and Lilly to collaborate over a four-year period for the discovery of antisense drugs for metabolic and inflammatory diseases. In connection with the research collaboration, the companies will use the Isis GeneTrove antisense technology to determine the functional role of human genes in disease and to identify genes as potential drug targets for the antisense drug discovery collaboration. The loan is repayable in cash or, at Isis' option, convertible into Isis Common Stock at a conversion price of $40 per share at the end of the research collaboration's term.

Isis and Lilly also entered into a Development and License Agreement (the "License Agreement"), pursuant to which Lilly has licensed ISIS 3521, an antisense compound in early Phase III clinical trials for the treatment of non-small cell lung cancer. Under the License Agreement Lilly has obtained exclusive worldwide commercialization rights to ISIS 3521. For the license of ISIS 3521, Lilly has agreed to pay Isis $25 million in upfront fee. In addition, Lilly will reimburse Isis for the remaining Phase III development and registration costs. Isis may receive up to $50 million in milestone payments upon successful submissions and approvals of ISIS 3521 for the treatment of non-small cell lung cancer and royalties on product sales, as well as additional milestones and royalties for other indications. Isis may also receive licensing fees, milestones, royalties and other contingent payments based on the success of the gene functionalization and antisense drug discovery programs.

The terms of the license, research and investment arrangements were

determined in negotiations between Isis and Lilly and their respective representatives and were subject to approval of the United States Federal Antitrust Agencies.

ITEM 7. EXHIBITS.

2.1	Securities Purchase Agreement, dated August 17, 2001, between Isis Pharmaceuticals, Inc. and Eli Lilly and Company.
2.2	Loan Agreement, dated August 17, 2001, between Isis Pharmaceuticals, Inc. and Eli Lilly and Company.
2.3	Registration Rights and Standstill Agreement, dated August 17, 2001, between Isis Pharmaceuticals, Inc. and Eli Lilly and Company.
2.4	Collaboration Agreement, dated August 17, 2001, between Isis Pharmaceuticals, Inc. and Eli Lilly and Company. (Certain confidential information deleted)
2.5	Development and License Agreement, dated August 14, 2001, between Isis Pharmaceuticals, Inc. and Eli Lilly and Company. (Certain confidential information deleted)
2.6	Isis 3521 Clinical Supply Agreement, dated August 29, 2001, between Isis Pharmaceuticals, Inc. and Eli Lilly and Company, which is Exhibit B to the Development and License Agreement dated August 14, 2001 (i.e., Exhibit 2.5). (Certain confidential information deleted)
99.1	Press Release dated August 22, 2001.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ISIS PHARMACEUTICALS, INC.

Dated: August 29, 2001

By:/s/ B. LYNNE PARSHALL

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

INDEX TO EXHIBITS

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Exhibit 2.1

ISIS PHARMACEUTICALS, INC.

SECURITIES PURCHASE AGREEMENT

Dated as of August 17, 2001

SECURITIES PURCHASE AGREEMENT

This SECURITIES PURCHASE AGREEMENT, dated as of August 17, 2001 (this "Agreement"), is by and between Isis Pharmaceuticals, Inc., a Delaware corporation (the "Company"), and Eli Lilly and Company, an Indiana corporation (the "Purchaser").

WHEREAS, the Company and the Purchaser wish to enter into a collaboration arrangement pursuant to which they will conduct certain research and development programs relating to antisense oligonucleotides;

WHEREAS, to further these joint collaboration efforts, the Company wishes to issue and sell to the Purchaser an aggregate of four million one hundred sixty-six thousand six hundred sixty-seven (4,166,667) shares (the "Shares") of the Company's Common Stock, par value $.001 per share of the Company ("Common Stock");

WHEREAS, the Purchaser wishes to purchase the Shares on the terms and subject to the conditions set forth in this Agreement; and

WHEREAS, in conjunction with the purchase and sale of the Shares pursuant to this Agreement, the Company and the Purchaser are entering into a Loan Agreement (the "Loan Agreement"), pursuant to which the Company shall issue a promissory note (the "Note") in favor of the Purchaser, a Collaboration Agreement (the "Collaboration Agreement"), and a Registration Rights and Standstill Agreement (the "Registration Rights Agreement"), each as of the date hereof;

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

ARTICLE I
PURCHASE OF SHARES

SECTION 1.01. PURCHASE AND SALE OF SHARES. Subject to the terms and conditions hereof and on the basis of the representations and warranties set forth herein, the Company agrees to issue and sell to the Purchaser, and the Purchaser agrees to purchase the Shares from the Company, at the Closing (as defined below), at a per share price equal to $18.00 for an aggregate purchase price of Seventy-Five Million and Six Dollars ($75,000,006).

SECTION 1.02. CLOSING. The closing of the purchase and sale of the Shares (the "Closing") shall take place at the offices of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, at 10:00 a.m., Indianapolis time, on the third business day following the termination or expiration of the required waiting period under the HSR Act (as defined below), or at such other location, date and time as may be agreed upon by the Purchaser and the Company (such date and time being referred to herein as the "Closing Date"). At the Closing, the Company shall issue and deliver to the Purchaser a stock certificate, registered in the name of the Purchaser, representing the Shares, against payment of the purchase price therefor by wire transfer.

ARTICLE II
REPRESENTATIONS AND WARRANTIES
OF THE COMPANY

The Company represents and warrants to the Purchaser that, except as set forth in the Disclosure Schedule attached hereto (the "Disclosure Schedule"):

SECTION 2.01. ORGANIZATION. The Company is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware. The Company has all requisite corporate power and authority and all requisite licenses, permits and approvals of Governmental Entities (as defined below) to carry on the businesses as they are now being conducted and to own and use the properties owned and used by it except where the failure to obtain such licenses, permits and approvals would not have a Company Material Adverse Effect. The Company is not in default under or in violation of any provision of its Certificate of Incorporation or Bylaws. The Company is duly qualified to do business and is in good standing as a foreign corporation in each other jurisdiction in which the ownership, operation or leasing of its properties or assets or the nature of its business requires such qualification, except where the failure so to qualify would not have a Company Material Adverse Effect (as defined below). Each of the Company's subsidiaries is a corporation duly organized, validly existing and in good standing under the laws of the jurisdiction of its incorporation. Each such subsidiary has all requisite corporate power and authority, and all requisite licenses, permits and approvals of Governmental Entities, to carry on the business as it is now being conducted and to own and use the properties owned and used by it except where the failure to obtain such licenses, permits and approvals would not have a Company Material Adverse Effect. No such subsidiary is in default under or in violation of any provision of its certificate or articles of incorporation or Bylaws. Each such subsidiary is duly qualified to do business and is in good standing as a foreign corporation in each other jurisdiction in which the ownership, operation or leasing of its properties or assets or the nature of its business requires such qualification, except where the failure so to qualify would not have a Company Material Adverse Effect.

SECTION 2.02 CAPITALIZATION. The Company has reserved a sufficient number of shares of Common Stock: (i) for issuance of the Shares to the Purchaser at the Closing, and (ii) for issuance upon conversion of the Note. The Shares, when issued against payment therefor in accordance with this Agreement, will be duly and validly issued, fully paid and nonassessable, will not be issued in violation of any preemptive or similar rights. The shares of Common Stock underlying the Note, when issued upon conversion thereof, will be duly and validly issued, fully paid and nonassessable, and will not be issued in violation of any preemptive or similar rights. Section 2.02 of the Disclosure Schedule sets forth the capitalization table of the Company's capital stock on a fully diluted basis as of June 30, 2001, subject to the assumptions and projections set forth therein with regard to which the Company makes no representation as to their reasonableness or appropriateness.

SECTION 2.03. REGISTRATION RIGHTS. Except as provided herein, pursuant to the Registration Rights Agreements with Elan International Services, Ltd., and granted in connection with the Purchase Agreement dated October 24, 1997 for 14% Subordinated Discount Notes due November 1, 2007 and Warrants to Purchase Common Stock between the Company and the Purchaser listed on Schedule I thereto, the Company is not under any contractual obligation to register any of its presently outstanding securities or any of its securities which may hereafter be issued.

SECTION 2.04. AUTHORIZATION OF TRANSACTION. The Company has all requisite power and authority to execute and deliver this Agreement and to perform its obligations hereunder. The execution and delivery by the Company of this Agreement and the Loan Agreement, the Note, the Collaboration Agreement and the Registration Rights Agreement (each, a "Company Ancillary Document"), the performance by the Company of its obligations hereunder and thereunder, and the consummation of the transactions contemplated hereunder and thereunder, have been duly authorized by all requisite corporate action of the Company and will not violate the Certificate of Incorporation or Bylaws of the Company or any provision of any agreement or other instrument filed as an exhibit to the Company Reports except where such violation would not materially impede the Company's ability to perform its obligations under this Agreement.

SECTION 2.05. VALIDITY. This Agreement has been duly executed and delivered by the Company and constitutes the legal, valid and binding obligation of the Company, enforceable against the Company in accordance with its terms except (a) that enforcement may be limited by (i) applicable bankruptcy, insolvency, reorganization, arrangement, moratorium or other similar laws affecting creditors' rights, and (ii) general equity principles and limitations on the availability of equitable relief, including specific performance, and (b) that any rights to indemnity or contribution hereunder or thereunder may be limited by state and federal securities laws and by public policy considerations.. Each Company Ancillary Document to which the Company is a party, when executed and delivered in accordance with this Agreement, will constitute the legal, valid and binding obligation of the Company, enforceable against the Company in accordance with its terms except (a) that enforcement may be limited by (i) applicable bankruptcy, insolvency, reorganization, arrangement, moratorium or other similar laws affecting creditors' rights, and

(ii) general equity principles and limitations on the availability of equitable relief, including specific performance, and (b) that any rights to indemnity or contribution hereunder or thereunder may be limited by state and federal securities laws and by public policy considerations.

SECTION 2.06. NONCONTRAVENTION. Subject to compliance with the applicable requirements of the Securities Act of 1933, as amended (the "Securities Act"), and any applicable state securities laws and the Securities Exchange Act of 1934, as amended (the "Exchange Act"), neither the execution and delivery of this Agreement or the Company Ancillary Documents by the Company nor the consummation by the Company of the transactions contemplated hereby, will (a) require on the part of the Company any filing with, or permit, authorization, consent or approval of, any court, arbitrational tribunal, administrative agency or commission or other governmental authority or regulatory agency (a "Governmental Entity"), except for (i) any filing, permit, authorization, consent or approval which if not obtained or made would not have a material adverse effect on the assets, business, financial condition, results of operations or future prospects (other than prospects relating to the economy

in general or the pharmaceutical or biotechnology industries in general) of the Company (a "Company Material Adverse Effect") or on the ability of the Company and Purchaser to consummate the transactions contemplated by this Agreement, (ii) such filings, if any, as may be required under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the rules and regulations promulgated thereunder (the "HSR Act"), or (iii) any such filing, or permit, authorization, consent or approval which may be properly obtained following the Closing, (b) conflict with, result in breach of, constitute (with or without due notice or lapse of time or both) a default under, result in the acceleration of, create in any party any right to accelerate, terminate, modify or cancel, or require any notice, consent or waiver under, any contract, lease, sublease, license, sublicense, franchise, permit, indenture, agreement or mortgage for borrowed money, instrument of indebtedness, Security Interest (as defined below) or other arrangement to which the Company is a party or by which it is bound or to which any of its assets is subject, other than any conflict, breach, default, acceleration, termination, modification or cancellation which individually or in the aggregate would not have a Company Material Adverse Effect or have a material adverse effect on the ability of the parties to consummate the transactions contemplated by this Agreement, or (c) violate any order, writ, injunction, decree, statute, rule or regulation applicable to the Company or any of its properties or assets which individually or in the aggregate would have a Company Material Adverse Effect or have a material adverse effect on the ability of the parties to consummate the transactions contemplated by this Agreement.

For purposes of this Agreement, "Security Interest" means any mortgage, pledge, security interest, encumbrance, charge or other lien (whether arising by contract or operation of law), other than (a) mechanic's, materialmen's and similar liens, (b) liens arising under worker's compensation, unemployment insurance, social security, retirement, and similar legislation, and (c) liens on goods in transit incurred pursuant to documentary letters of credit, in each case arising in the ordinary course of business consistent with past practice and custom.

SECTION 2.07. REPORTS AND FINANCIAL STATEMENTS.

(a) The Company has timely filed with the Securities and Exchange Commission (the "SEC") all reports required to be filed by the Company under Section 13 of the Exchange Act with the SEC (such reports are collectively referred to herein as the "Company Reports"). As of their respective dates, the Company Reports did not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading. The audited financial statements and unaudited interim financial statements of the Company included in the Company Reports (i) comply as to form in all material respects with applicable accounting requirements and the published rules and regulations under the Exchange Act as promulgated by the SEC with respect thereto, (ii) have been prepared in accordance with United States generally accepted accounting principles ("GAAP") applied on a consistent basis throughout the periods covered thereby (except as may be indicated therein or in the notes thereto, and in the case of quarterly financial statements, as permitted by Form 10-Q under the Exchange Act and subject to normal year end audit adjustments), (iii) fairly present the consolidated financial condition, results of operations and cash flows of the Company as of the respective dates thereof and for the periods referred to therein, and (iv) are consistent with the books and records of the Company.

(b) As to each contract that is material to the

Company's business and which has been filed by the Company as an exhibit to any of the Company Reports, neither the Company nor, to the knowledge of the Company, any other party thereto is in breach or default thereunder, other than breaches or defaults which do not, either individually or in the aggregate, have a Company Material Adverse Effect.

SECTION 2.08 ENVIRONMENTAL AND SAFETY LAWS. To the best of its knowledge, the Company is not in violation of any applicable statute, law or regulation relating to the environment or occupational health and safety other than violations which would not result in a Company Material Adverse Effect, and to the best of its knowledge, no material expenditures are or will be required in order to comply with any such existing statute, law or regulation.

SECTION 2.09 ABSENCE OF MATERIAL ADVERSE CHANGES. As of the date of this Agreement, since June 30, 2001, except as contemplated by this Agreement and the Company Ancillary Documents, the Company has not (a) made, paid or declared any dividend or distribution to any equity holder (in such capacity), (b) varied its business plan or practices, in any material respect, from past practices, (c) entered into any financing, joint venture, license or similar arrangement that would limit or restrict its ability to perform its obligations hereunder and under each of the other Company Ancillary Documents to which it is a party, (d) suffered or permitted to be incurred any liability or obligation or any lien or encumbrance against any of its properties or assets that would limit or restrict its ability to perform its obligations hereunder and under each of the other Company Ancillary Documents to which it is a party, or (e) no other event shall have occurred which can be reasonably expected to result in any Company Material Adverse Effect.

SECTION 2.10 ABSENCE OF UNDISCLOSED LIABILITIES. The Company has no material obligations or liabilities of any nature (matured or unmatured, fixed or contingent) other than (a) those set forth or adequately provided for in the Company Reports, (b) those incurred in the ordinary course of business and not required to be set forth in the balance sheet included in its most recent Company Report under GAAP, (c) those incurred in the ordinary course of business since the date of the Company's balance sheet included in its most recent Company Report and not reasonably likely to have a Company Material Adverse Effect, and (d) those incurred in connection with the execution of this Agreement.

SECTION 2.11 BROKERS' FEES. Other than payments to be made to SG Cowan, the Company has no liability or obligation to pay any fees or commissions to any broker, finder or agent with respect to the transactions contemplated by this Agreement.

SECTION 2.12 RESTRICTIONS ON THE SHARES. The Shares are not subject to any restriction on transfer imposed by the Company, except restrictions on resale of the Shares imposed pursuant to the Securities Act or applicable state securities laws and restrictions pursuant to this Agreement.

SECTION 2.13. LITIGATION. The Company is not a party to or, to the actual knowledge of the Company's Chairman of the Board, Chief Executive Officer, Chief Financial Officer or General Counsel, threatened to be made a party to (a) any unsatisfied judgment, order, decree, stipulation or injunction or (b) any claim, complaint, action, suit, proceeding, hearing or

investigation of or before any Governmental Entity or before any arbitrator that, in the case of either (a) or (b), reasonably could be expected to have a Company Material Adverse Effect or a material adverse effect on the ability of the parties to consummate the transactions contemplated by this Agreement.

ARTICLE III
REPRESENTATIONS AND WARRANTIES OF THE PURCHASER

The Purchaser hereby represents and warrants to the Company that:

SECTION 3.01. AUTHORIZATION OF AGREEMENTS, ETC. Purchaser has all requisite corporate power and authority to execute and deliver this Agreement and to perform its obligations hereunder. The execution and delivery by the Purchaser of this Agreement and the Loan Agreement, the Collaboration Agreement, and the Registration Rights Agreement (each, a "Purchaser Ancillary Document") to be delivered by the Purchaser, the performance by the Purchaser of its obligations hereunder and thereunder, and the consummation of the transactions contemplated hereunder and thereunder, have been duly authorized by all requisite corporate action of the Purchaser and will not violate the Articles of Incorporation or By-Laws of the Purchaser or any provision of any agreement or other instrument to which the Purchaser is bound.

SECTION 3.02. VALIDITY. This Agreement has been duly executed and delivered by the Purchaser and constitutes the legal, valid and binding obligation of the Purchaser, enforceable against the Purchaser in accordance with its terms except (a) that enforcement may be limited by (i) applicable bankruptcy, insolvency, reorganization, arrangement, moratorium or other similar laws affecting creditors' rights, and (ii) general equity principles and limitations on the availability of equitable relief, including specific performance, and (b) that any rights to indemnity or contribution hereunder or thereunder may be limited by state and federal securities laws and by public policy considerations.. Each Purchaser Ancillary Document to which the Purchaser is a party, when executed and delivered in accordance with this Agreement, will constitute the legal, valid and binding obligation of the Purchaser, enforceable against the Purchaser in accordance with its terms except (a) that enforcement may be limited by (i) applicable bankruptcy, insolvency, reorganization, arrangement, moratorium or other similar laws affecting creditors' rights, and (ii) general equity principles and limitations on the availability of equitable relief, including specific performance, and (b) that any rights to indemnity or contribution hereunder or thereunder may be limited by state and federal securities laws and by public policy considerations..

SECTION 3.03. INVESTMENT REPRESENTATIONS. The Purchaser (a) is an "accredited investor" within the meaning of Rule 501 promulgated under the Securities Act and was not organized for the specific purpose of acquiring the Shares or the Note issued pursuant to the Loan Agreement; (b) is domiciled in the State of Indiana; (c) is acquiring the Shares and the Note issued pursuant to the Loan Agreement for its own account for the purpose of investment and not with a view to or for sale in connection with any distribution thereof; and (d) understands that (i) the Shares and the Note issued pursuant to the Loan Agreement have not been registered under the Securities Act by reason of their issuance in a transaction exempt from the registration requirements of the Securities Act pursuant to Section 4(2) thereof or Regulation D promulgated

under the Securities Act, (ii) the Shares and the Note issued pursuant to the Loan Agreement must be held indefinitely unless a subsequent disposition thereof is registered under the Securities Act or is exempt from such registration and understands and is capable of bearing the economic risk of such an investment in the Shares and the Note issued pursuant to the Loan Agreement, (iii) the Shares and the Note issued pursuant to the Loan Agreement will bear a legend to such effect (as set forth below) and (iv) the Company will make a notation on its transfer books to such effect.

The Shares shall bear substantially the following legend:

> "The shares represented by this certificate have not been registered under the Securities Act of 1933, as amended, or applicable state securities laws. The shares have been acquired for investment and may not be sold, transferred or otherwise disposed of except in compliance with such act and laws."

SECTION 3.04. BROKERS' FEES. Other than payments to be made to Merrill Lynch & Co., the Purchaser has no liability or obligation to pay any fees or commissions to any broker, finder or agent with respect to the transactions contemplated by this Agreement.

SECTION 3.05. NONCONTRAVENTION. Subject to compliance with the applicable requirements of the Securities Act, and any applicable state securities laws and the Exchange Act, neither the execution and delivery of this Agreement or the Purchaser Ancillary Documents by the Purchaser nor the consummation by the Purchaser of the transactions contemplated hereby, will (a) require on the part of the Purchaser any filing with, or permit, authorization, consent or approval of, any Governmental Entity, except for (i) any filing, permit, authorization, consent or approval which if not obtained or made would not have a material adverse effect on the assets, business, financial condition, results of operations or future prospects (other than prospects relating to the economy in general or the pharmaceutical or biotechnology industries in general) of the Purchaser (a "Purchaser Material Adverse Effect") or on the ability of the Company and Purchaser to consummate the transactions contemplated by this Agreement, (ii) such filings, if any, as may be required under the HSR Act, or (iii) any such filing, or permit, authorization, consent or approval which may be properly obtained following the Closing, (b) conflict with, result in breach of, constitute (with or without due notice or lapse of time or both) a default under, result in the acceleration of, create in any party any right to accelerate, terminate, modify or cancel, or require any notice, consent or waiver under, any contract, lease, sublease, license, sublicense, franchise, permit, indenture, agreement or mortgage for borrowed money, instrument of indebtedness, Security Interest or other arrangement to which the Purchaser is a party or by which it is bound or to which any of its assets is subject, other

than any conflict, breach, default, acceleration, termination, modification or cancellation which individually or in the aggregate would not have a Purchaser Material Adverse Effect or have a material adverse effect on the ability of the parties to consummate the transactions contemplated by this Agreement, or (c) violate any order, writ, injunction, decree, statute, rule or regulation applicable to the Purchaser or any of its properties or assets which individually or in the aggregate would have a Purchaser Material Adverse Effect or have a material adverse effect on the ability of the parties to consummate the transactions contemplated by this Agreement.

ARTICLE IV
CONDITIONS

SECTION 4.01. CONDITIONS TO PURCHASER'S OBLIGATIONS. The obligation of the Purchaser to purchase and pay for the Shares is subject to the satisfaction, on or before the Closing Date, of each of the following conditions, each of which may be waived at the option of the Purchaser:

(a) REPRESENTATIONS AND WARRANTIES TO BE TRUE AND CORRECT. The representations and warranties contained in Article II and any Company Ancillary Document shall be true, complete and correct on and as of the Closing Date with the same effect as though such representations and warranties had been made on and as of such date, except to the extent such representations and warranties expressly relate to an earlier date, in which case, they shall be true, complete and correct as of such date.

(b) PERFORMANCE. The Company shall have performed all obligations and agreements and complied with all covenants to be performed or complied with by them on or before the Closing Date pursuant to this Agreement and any Company Ancillary Document.

(c) CLOSING CERTIFICATES. The Purchaser shall have received a certificate from an officer of the Company, dated the Closing Date, in form and substance reasonably satisfactory to the Purchaser and its counsel, certifying that (i) the conditions set forth in Section 4.01(a) and Section 4.01(b) have been satisfied and (ii) resolutions approving this Agreement and each Company Ancillary Document and the transactions contemplated hereby and thereby have been duly adopted by the Board of Directors of the Company.

(d) PROCEEDINGS SATISFACTORY. All actions, proceedings, instruments and documents required to carry out the transactions contemplated by this Agreement or incidental hereto, and all other related legal matters, shall be reasonably satisfactory to counsel to the Purchaser, and such counsel shall have been furnished with such other instruments and documents as they shall have reasonably requested.

(e) OPINION OF COMPANY'S GENERAL COUNSEL. The Purchaser shall have received from the Company's General Counsel, an opinion dated the Closing Date, with respect to the matters set forth on EXHIBIT A.

(f) REVIEW OF BUSINESS AND LEGAL MATTERS. The Purchaser and its accountants and counsel shall have completed a review of business, accounting and legal matters with respect to the Company prior to the execution hereof, and nothing shall have come to the attention of the Purchaser or its counsel or accountants prior to the execution hereof that causes the Purchaser to reasonably conclude that (i) the Company Reports do not present fairly the financial position and results of operations of the Company as of their respective dates, or (ii) there

is any material breach or inaccuracy in the representations and warranties of the Company set forth in this Agreement or any Company Ancillary Document.

(g) NO MATERIAL ADVERSE CHANGE. Since the date hereof, there shall not have occurred and be continuing, and no event shall have occurred which (in the reasonable judgment of the Purchaser) can be reasonably expected to result in any Company Material Adverse Effect.

(h) REGISTRATION RIGHTS AGREEMENT. The Company shall have executed and delivered the Registration Rights Agreement.

(i) COLLABORATION AGREEMENT. The Company shall have executed and delivered the Collaboration Agreement and all conditions to commencement of the collaboration to be performed by the Company thereunder prior to its effectiveness shall have been satisfied.

(j) LOAN AGREEMENT AND NOTE. The Company shall have executed and delivered the Loan Agreement and the Note.

(k) OTHER APPROVALS. If applicable, the waiting period under the HSR Act shall have expired or been terminated. All other consents, authorizations and approvals, waivers or exemptions, and filings and registrations, required to be obtained from or made with any person in connection with the execution, delivery and performance by the Company of this Agreement and the Company Ancillary Documents and the consummation by the Company of the transactions contemplated hereby and thereby shall have been obtained or made, and all required filings shall have become effective except for such filings which may be properly made following the Closing.

(l) NO LITIGATION. No injunction shall be outstanding, which would prevent consummation of the transactions contemplated by this Agreement or the Company Ancillary Documents. No action, suit or proceeding shall be pending or threatened in writing by any government agency or instrumentality or other person, with respect to which the Purchaser shall have reasonably concluded that the plaintiff has a reasonable probability of prevailing, and wherein an unfavorable judgment, order, decree, stipulation or injunction would (i) cause the transactions contemplated by this Agreement or the Company Ancillary Documents to be rescinded following consummation, (ii) materially and adversely affect the right of the Company to own, operate or control its business in the manner contemplated by the Company Ancillary Documents, or (iii) cause the Purchaser or the Company to be subject to any material award of damages or governmental sanction.

SECTION 4.02. CONDITIONS TO OBLIGATIONS OF THE COMPANY. The obligations of the Company to consummate the transactions contemplated hereby are subject to the satisfaction, on or before the Closing Date, of each of the following conditions, each of which may be waived at the option of the Company:

(a) REPRESENTATIONS AND WARRANTIES TO BE TRUE AND CORRECT. The representations and warranties contained in Article III and any Purchaser Ancillary Document shall be true, complete and correct on and as of the Closing Date with the same effect as though such representations and warranties had been made on and as of such date.

(b) PERFORMANCE. The Purchaser shall have performed all obligations and agreements and complied with all covenants to be performed or complied with by it on or before the Closing Date pursuant to this Agreement or any Purchaser Ancillary Document.

(c) CLOSING CERTIFICATES. The Company shall have received a certificate from an officer of the Purchaser, dated the Closing Date, in form and substance reasonably satisfactory to the Company and its counsel, certifying that (i) the conditions set forth in Section 4.02(a) and Section 4.02(b) have been satisfied and (ii) resolutions approving this Agreement and each Purchaser Ancillary Document and the transactions contemplated hereby and thereby have been duly adopted by the Board of Directors of the Purchaser.

(d) PROCEEDINGS SATISFACTORY. All actions, proceedings, instruments and documents required to carry out the transactions contemplated by this Agreement or incidental hereto, and all other related legal matters, shall be reasonably satisfactory to counsel to the Company, and such counsel shall have been furnished with such other instruments and documents as they shall have reasonably requested.

(e) REGISTRATION RIGHTS AGREEMENT. The Purchaser shall have executed and delivered the Registration Rights Agreement.

(f) COLLABORATION AGREEMENT. The Purchaser shall have executed and delivered the Collaboration Agreement and all conditions to commencement of the collaboration to be performed by the Purchaser thereunder prior to its effectiveness shall have been satisfied.

(g) LOAN AGREEMENT. The Purchaser shall have executed and delivered the Loan Agreement and made the first Disbursement under the Loan Agreement.

(h) OTHER APPROVALS. If applicable, the waiting period under the HSR Act shall have expired or been terminated. All other consents, authorizations and approvals, waivers or exemptions, and filings and registrations, required to be obtained from or made with any person in connection with the execution, delivery and performance by the Purchaser of this Agreement and the Purchaser Ancillary Documents and the consummation by the Purchaser of the transactions contemplated hereby and thereby shall have been obtained or made, and all required filings shall have become effective except for such filings which may be properly made following the Closing.

(i) NO LITIGATION. No injunction shall be outstanding, which would prevent consummation of the transactions contemplated by this Agreement or the Purchaser Ancillary Documents. No action, suit or proceeding shall be pending or threatened in writing by any government agency or instrumentality or other person, with respect to which the Company shall have reasonably concluded that the plaintiff has a reasonable probability of prevailing, and wherein an unfavorable judgment, order, decree, stipulation or injunction would (i) cause the transactions contemplated by this Agreement or the Purchaser Ancillary Documents to be rescinded following consummation or (ii) cause the Company or the Purchaser to be subject to any material award of damages or governmental sanction.

ARTICLE V
TERMINATION

SECTION 5.01. TERMINATION. This Agreement may be terminated and the transactions contemplated hereby may be abandoned at any time prior to the Closing:

(a) by mutual written consent of the Purchaser and the Company;

(b) by the Purchaser, if (i) there has been a material breach by the Company of any representation, warranty, covenant or agreement set forth in this Agreement or any Company Ancillary Document that has not been corrected by the Company within ten (10) days of receiving notice of such breach from Purchaser or (ii) the Closing shall not have occurred on or prior to December 31, 2001, by reason of the failure of any condition precedent set forth in Section 4.01, unless such failure results primarily from the breach by the Purchaser of any of its representations, warranties, covenants or agreements set forth in this Agreement or any Purchaser Ancillary Document; or

(c) by the Company, if (i) there has been a material breach by the Purchaser of any representation, warranty, covenant or agreement set forth in this Agreement or any Purchaser Ancillary Document that has not been corrected by Purchaser within ten (10) days of receiving notice of such breach from the Company or (ii) the Closing shall not have occurred on or prior to December 31, 2001, by reason of the failure of any condition precedent set forth in Section 4.02, unless such failure results primarily from the breach by the Company of any of its representations, warranties, covenants or agreements set forth in this Agreement or any Company Ancillary Document.

SECTION 5.02. PROCEDURE UPON TERMINATION. If this Agreement is terminated pursuant to Section 5.01, the party terminating this Agreement shall promptly deliver written notice thereof to the other party hereto, and, upon such notice, this Agreement shall terminate and the transactions contemplated hereby shall be abandoned without further action on the part of either of the parties hereto, but such termination shall not relieve either party of responsibility for damages arising out of any breach by such party.

ARTICLE VI

CONFIDENTIALITY; NON-DISCLOSURE; COOPERATION

SECTION 6.01. CONFIDENTIALITY; NON-DISCLOSURE. The parties hereto agree that the provisions of the Collaboration Agreement relating to confidentiality and non-disclosure are incorporated herein by reference.

SECTION 6.02. COOPERATION UPON SALE OF SECURITIES. In the event that the Purchaser or any affiliate transferee of Purchaser proposes to sell, transfer or otherwise dispose of any securities of the Company prior to the termination of the Collaboration Agreement, the Purchaser or such affiliate transferee, as appropriate, shall notify the Company in writing at least fifteen (15) days prior to such proposed sale, transfer or other disposition thereof and further agrees to cooperate and coordinate with the Company in the development by the Purchaser or such affiliate transferee, as appropriate, and the Company of a standby statement to be used in responding to any inquiries from third parties (or if deemed appropriate by the Company or the Purchaser or such affiliate transferee, as appropriate, a press release of that party) that would, as appropriate, indicate the continuing strong support by the Purchaser or such affiliate transferee, as appropriate, of the collaboration activities, and the Company, notwithstanding the decision of the Purchaser or such affiliate transferee, as appropriate, to dispose of some of its holdings of the Company's securities. Subject to the required notice above, the Company and the Purchaser or affiliate transferee shall provide each other with comments on any such proposed standby statement or press release in such manner as is necessary to not cause a delay in the Purchaser's or such affiliate transferee's, as appropriate, proposed sale, transfer or other disposition of such securities. Purchaser shall cause any affiliate transferee to agree to be bound by this Section 6.02.

ARTICLE VII
MISCELLANEOUS

SECTION 7.01. PARTIES IN INTEREST. All representations, covenants and agreements contained in this Agreement by or on behalf of the parties hereto shall bind and inure to the benefit of the respective successors and assigns of the parties hereto whether so expressed or not. Without limiting the generality of the foregoing, all representations, covenants and agreements benefiting the Purchaser shall inure to the benefit of any and all subsequent holders from time to time of the Shares.

SECTION 7.02. SURVIVAL OF AGREEMENTS. All covenants, agreements, representations and warranties of the parties made in Articles 2 and 3 of this Agreement, any Company Ancillary Document, or any Purchaser Ancillary Document shall survive the execution and delivery of this Agreement, any investigation at any time made by the Purchaser or on its behalf, and the issuance, sale and delivery of the Shares.

SECTION 7.03. NOTICES. All notices and other communications that are required or permitted to be given under this Agreement shall be in writing and shall be delivered

personally, mailed by certified or registered mail, return receipt requested, sent by reputable overnight courier or sent by confirmed telecopier, addressed as follows:

(a) if to the Company, at 2292 Faraday Avenue, Carlsbad, California 92008, Attention: Chief Financial Officer, telephone: 760-679-5500; fax: 760-679-5592 with a copy (which shall not constitute notice to the Company) to Cooley Godward LLP, 4365 Executive Drive, Suite 1100, San Diego, CA 92121, Attn: Julie M. Robinson, telephone 858-550-6000; fax 858-453-3555; and

(b) if to the Purchaser, at Lilly Corporate Center, Indianapolis, Indiana 46285, Attention: Rebecca O. Kendall, Esq., Senior Vice President and General Counsel, telephone: 317-276-2703; fax: 317-433-3000, with a copy (which shall not constitute notice to the Purchaser) to Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, Attention: Richard D. DiMarchi, Group Vice President, Lilly Research Laboratories, telephone: 317-276-5624; fax 317-277-7979.

or to such other address and/or such other addressee as any of the above shall have specified by notice hereunder. Each notice or other communication that shall be delivered personally, mailed, sent by overnight courier or telecopied in the manner described above shall be deemed sufficiently given, served, sent, received or delivered for all purposes at such time as it is delivered to the addressee (with the return receipt, the delivery receipt or the affidavit of messenger being deemed conclusive, but not exclusive, evidence of such delivery) or at such time as delivery is refused by the addressee upon presentation.

SECTION 7.04. ASSIGNMENT. Neither the Company nor the Purchaser may assign any of its rights or obligations hereunder without the express written consent of the other party. The Purchaser shall not transfer, sell or otherwise dispose of any of the Shares or other securities of the

Company issued pursuant to the Loan Agreement or otherwise, without the prior written permission of the Company until the earlier of (i) the termination of the Collaboration Agreement and (ii) the fourth anniversary of the Closing; provided, however, that subject to Section 6.02, following the first anniversary of the Closing, Purchaser may sell, transfer or otherwise dispose of the Shares or other securities of the Company issued pursuant to the Loan Agreement or otherwise (i) pursuant to Rule 144 of the Securities Act or (ii) to one or more persons in private placements exempt from registration under the Securities Act, pursuant to Section 4(1) thereof or otherwise, if such person or persons satisfy all investor suitability requirements and other restrictions on transfer under applicable federal and state securities laws and regulations, except that the Purchaser shall not resell Common Stock to any person or group as such terms are defined in Section 13 of the Exchange Act and regulations thereunder that would result in such person or group beneficially owning more than three percent (3%) of the then outstanding shares of Common Stock of the Company; and provided further, that Purchaser may sell, transfer or otherwise dispose of Registrable Securities in a registered transaction pursuant to and as provided by the Registration Rights Agreement; provided further that Purchaser shall cause any affiliate transferee to agree to be bound by this Section 7.04.

SECTION 7.05. REMEDIES. If any party to this Agreement obtains a judgment against any party hereto by reason of any breach of this Agreement or the failure of such other

party to comply with the provisions hereof, a reasonable attorneys' fee as fixed by the court shall be included in such judgment. No remedy conferred upon any party to this Agreement is intended to be exclusive of any other remedy herein or by law provided or permitted, but each such remedy shall be cumulative or shall be in addition to every other remedy given hereunder or now or hereafter existing at law or in equity or by statute.

SECTION 7.06. WAIVER. None of the terms of this Agreement shall be deemed to have been waived by any party hereto, unless such waiver is in writing and signed by that party. No action taken pursuant to this Agreement, including any investigation by or on behalf of any party hereto, shall be deemed to constitute a waiver by the party taking such action of compliance with any representation, warranty, covenant or agreement contained herein. The waiver by any party hereto of a breach of any provision of this Agreement shall not operate or be construed as a waiver of any other provision of this Agreement or of any further breach of the provision so waived or of any other provision of this Agreement. No extension of time for the performance of any obligation or act hereunder shall be deemed an extension of time for the performance of any other obligation or act. The waiver by any party of any of the conditions precedent to its obligations under this Agreement shall not preclude it from seeking redress for breach of this Agreement.

SECTION 7.07. GOVERNING LAW. This Agreement shall be governed by and construed in accordance with the laws of the State of Delaware, without giving effect to its conflicts of law rules.

SECTION 7.08. ENTIRE AGREEMENT. This Agreement, including the Schedules and Exhibits hereto, the Company Ancillary Documents, and the Purchaser Ancillary Documents constitute the entire agreement of the parties with respect to the subject matter hereof. All Schedules and Exhibits hereto are hereby incorporated herein by reference.

SECTION 7.09. COUNTERPARTS. This Agreement may be executed in the original or by facsimile in any number of counterparts, each of which shall be effective only upon delivery and thereafter shall be deemed to be an original, and all of which shall be taken to be one and the same instrument with the same effect as if each of the parties hereto had signed the same signature page. Any signature page of this Agreement may be detached from any counterpart of this Agreement without impairing the legal effect of any signature thereon and may be attached to another counterpart of this Agreement identical in form hereto and having attached to it one or more additional signature pages.

SECTION 7.10. AMENDMENTS. This Agreement may not be amended, modified or changed in any respect without the written consent of the Company and the approval of the Purchaser.

SECTION 7.11. SEVERABILITY. Whenever possible, each provision of this Agreement shall be interpreted in such manner as to be effective and valid under applicable law, but if any provision of this Agreement shall be unenforceable or invalid under applicable law, such provision shall be ineffective only to the extent of such unenforceability or invalidity, and the remaining provisions of this Agreement shall continue to be binding and in full force and effect.

SECTION 7.12. FURTHER ASSURANCES. From and after the date hereof, each of the parties hereto agree to do or cause to be done such further acts and things and deliver or cause to be delivered to each other such additional assignments, agreements, powers and instruments, as each may reasonably require or deem advisable to carry into effect the purposes of this Agreement, the Purchaser Ancillary Documents, and the Company Ancillary Documents.

SECTION 7.13. HEADINGS. The section and other headings contained in this Agreement are for convenience only and shall not be deemed to limit, characterize or interpret any provision of this Agreement.

SECTION 7.14. CERTAIN DEFINED TERMS. As used in this Agreement, the following terms shall have the following meanings (such meanings to be equally applicable to both the singular and plural forms of the terms defined):

(a) "person" shall mean an individual, corporation, limited liability company, trust, partnership, joint venture, unincorporated organization, government agency or any agency or political subdivision thereof, or other entity; and

(b) "affiliate" shall mean, with respect to any person, a person who controls such person, who is controlled by such person or who is under common control with such person as such term is defined in Rule 12b-2 of the Exchange Act.

(c) "subsidiary" shall mean, as to the Company, any corporation of which more than 50% of the outstanding stock having ordinary voting power to elect a majority of the Board of Directors of such corporation (irrespective of whether or not at the time stock of any other class or classes of such corporation shall have or might have voting power by reason of the happening of any contingency) is at the time directly or indirectly owned by the Company, or by one or more of its subsidiaries, or by the Company and one or more of its subsidiaries.

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IN WITNESS WHEREOF, the Company and the Purchaser have executed this Securities Purchase Agreement as of the day and year first above written.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

Name: B. Lynne Parshall
Title: Executive Vice President and Chief Financial Officer

ELI LILLY AND COMPANY

By: /s/ Sidney Taurel

Printed: Sidney Taurel
Title: Chairman of the Board, Chief Executive Officer and President

EXHIBIT A

[OPINION OF ISIS GENERAL COUNSEL]

(a) The Company is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware and has full corporate power and authority to conduct its business as presently conducted, to enter into and perform the Agreement and the Company Ancillary Documents and to carry out the transactions contemplated by the Agreement and

the Company Ancillary Documents. The Company is qualified to do business in the State of California.

(b) The Shares have been duly authorized and are duly and validly issued, fully paid and non-assessable and free of statutory pre-emptive rights.

(c) The execution, delivery and performance by the Company of the Agreement and the Company Ancillary Documents have been duly authorized by all necessary corporate action and the Agreement and the Company Ancillary Documents have been duly executed and delivered by the Company. The Agreement and the Securities Purchase Agreement, Loan Agreement, Note and Registration Rights Agreement constitute the valid and binding obligations of the Company, enforceable in accordance with their terms except no opinion is rendered as to rights of indemnity under Section 8 of the Registration Rights Agreement and except as to enforcement of remedies to applicable bankruptcy, insolvency, reorganization, arrangement, moratorium or similar laws affecting generally the enforcement of creditors' rights and subject to a court's discretionary authority with respect to the granting of a decree ordering specific performance or other equitable principals and limitations on equitable relief. The execution and delivery of the Agreement and the Company Ancillary Documents and the offer, issue and sale of the Shares thereunder will not conflict with, or result in any breach of any of the terms, conditions, or provisions of, or constitute a default under, (i) the Certificate of Incorporation or Bylaws of the Company or (ii) any provision of California or federal law, statute rule or regulation or any provision of the Delaware General Corporation Law that would result in a material adverse effect on the Company.

(d) Except as obtained and in effect at the Closing, no consent, approval, order or authorization of, or registration, qualification, designation, declaration, or filing with, any governmental authority is required on the part of the Company in connection with the execution and delivery of the Agreement, or the offer, issue, sale and delivery of the Shares except for such state and federal securities filings which may be properly made following the Closing.

(e) Based on the representations of Purchaser in Article III of the Agreement, the offer, issuance and sale of the Shares pursuant to the Agreement are exempt from registration under the Securities Act.

Exhibit 2.2

LOAN AGREEMENT

THIS LOAN AGREEMENT (the "Agreement") is entered into as of the 17th day of August, 2001, (the "Execution Date"), by and between Eli Lilly and Company, an Indiana corporation ("Lilly"), and Isis Pharmaceuticals, Inc., a Delaware corporation ("Isis").

RECITALS

1. Lilly and Isis have contemporaneous with the execution of this Agreement entered into a Collaboration Agreement (the "Collaboration Agreement") pursuant to which Lilly and Isis will engage in certain research and development programs involving antisense oligonucleotides and related activities which will be funded by Isis.

2. In order to assure sufficient financial resources to perform its responsibilities under the Collaboration Agreement, Isis desires to obtain a loan from Lilly.

3. Lilly is willing to make a loan to Isis in accordance with the terms and conditions set forth herein.

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

ARTICLE I. DEFINITIONS

SECTION 1.01 DEFINED TERMS. As used in this Agreement, the following terms shall have the meanings specified below:

"AFFILIATE" means, when used with respect to a specified Person, another Person that directly or indirectly controls or is controlled by or is under common control with the Person specified.

"BUSINESS DAY" means any day other than a Saturday, Sunday, or day on which banking institutions in New York City are not required to be open.

"COMMITMENT" means the obligation of Lilly to make a Loan to Isis in the amount set forth in Section 2.01.

"COMMON STOCK" means the common stock, par value $.001 per share, of Isis.

"CONVERSION PRICE" has the meaning assigned to such term in Section 2.03.

"DEBT" means the total amount of the Loan referred to in Section 2.01 that remains outstanding at anytime.

"DEFAULT INTEREST" has the meaning assigned to such term in Section 2.07.

"DISBURSEMENT" has the meaning assigned to such term in Section 2.02.

"EFFECTIVE DATE" means the date on which the Collaboration Agreement transaction is closed. If for any reason whatsoever the Collaboration Agreement transaction is not closed, this Agreement shall be deemed void and of no force or effect.

"EVENT OF DEFAULT" has the meaning assigned to such term in Article VII.

"FINANCIAL OFFICER" of any corporation means the chairman, president, chief financial officer, or treasurer of such corporation.

"FUNDAMENTAL CHANGE" has the meaning assigned to it in Section 2.04.

"GOVERNMENTAL AUTHORITY" means any federal, state, local or foreign court or governmental agency, authority, instrumentality or regulatory

body.

"LOAN" means a loan of money from Lilly to Isis pursuant to this Agreement.

"PAYMENT DATE" shall mean the earliest of (i) the date of termination of the Collaboration Agreement other than pursuant to Section 13.4 thereof (termination for breach by Lilly); (ii) the date on which an Event of Default has occurred and not been cured within thirty (30) days of its occurrence; or (iii) the later of the date that is the fourth anniversary of the Closing Date or such longer period as may be necessary to reflect the extension, pursuant to Section 2.02(b) hereof and Sections 9.1.5 or 9.1.6 of the Collaboration Agreement of the final Disbursement hereunder, PROVIDED, HOWEVER, if any such date specified in (i), (ii) or (iii) herein is not a Business Day, the Payment Date shall be the first Business Day thereafter.

"PERSON" means any natural person, corporation, business trust, joint venture, association, company, limited liability company, partnership or government or any agency or political subdivision thereof.

"TRANSACTIONS" has the meaning assigned to such term in Section 3.02 in relation to Isis and in Section 4.02 in relation to Lilly.

SECTION 1.02. TERMS GENERALLY. The definitions in Section 1.01 shall apply equally to both the singular and plural forms of the terms defined. The words "include", "includes" and "including" shall be deemed to be followed by the phrase "without limitation".

ARTICLE II. LOAN COMMITMENT, DISBURSEMENTS AND REPAYMENT

SECTION 2.01. COMMITMENT.

Subject to the terms and conditions of this Agreement and relying on the representations and warranties set forth herein, Lilly agrees to make available to Isis a Loan in the aggregate principal amount of One Hundred Million Dollars ($100,000,000). Except as provided in Section 2.07, the Loan shall not bear interest. The Loan shall be evidenced by a promissory note as hereafter described, prepared in substantially the form attached to this Agreement as Exhibit "A" and dated as of the date of the first Loan Disbursement and payable to the order of Lilly on the Payment Date, either in cash or through conversion of the promissory note to Common Stock pursuant to Section 2.03.

SECTION 2.02. LOAN DISBURSEMENTS.

(a) Subject to the provisions of Subsection 2.02(b), the Loan shall be disbursed by Lilly to Isis in sixteen (16) increments (each a "Disbursement"), the first of which shall occur on the Closing Date (as defined in the Securities Purchase Agreement between Lilly and Isis of even date hereof (the "Securities Purchase Agreement")) of this Agreement, and the subsequent fifteen (15) of which shall occur on the dates and in the amounts set forth below:

DISBURSEMENT NUMBER	DISBURSEMENT DATE	AMOUNT
1	Closing Date	$10,000,000
2	9/28/01	$ 5,000,000
3	12/31/01	$ 5,000,000
4	03/29/02	$ 5,000,000
5	06/28/02	$ 7,500,000
6	09/30/02	$ 7,500,000
7	12/31/02	$ 7,500,000
8	03/31/03	$ 7,500,000
9	06/30/03	$ 6,250,000
10	09/30/03	$ 6,250,000

11 12/31/03
$ 6,250,000
12 03/31/04
$ 6,250,000
13 06/30/04
$ 5,000,000
14 09/30/04
$ 5,000,000
15 12/31/04
$ 5,000,000
16 03/31/05
$ 5,000,000

PROVIDED, HOWEVER, Lilly shall be under no obligation whatsoever to make any Disbursements after the earlier of the Payment Date or the date of termination of the Collaboration Agreement,

and the Commitment of Lilly to Isis under Section 2.01 shall be reduced by an amount equal to the aggregate amount of any such Disbursements not made prior to the Payment Date.

(b) Lilly may delay any Disbursement (i) in connection with and as specified by Section 2.5.2 of the Collaboration Agreement, which provides in certain cases for the Executive Committee to recommend to Lilly modification of the Disbursement schedule set forth in Section 2.02(a) in which event the Disbursement shall be made pursuant to such modified Disbursement schedule; and (ii) during any period of time that an Event of Default has occurred and has not been corrected by Isis, in which event any such delayed Disbursement shall be made by Lilly to Isis on the first Business Day following the date on which the reason for the delay ceases to exist.

(c) On or before the date of the first Disbursement pursuant to Subsection 2.02(a), Isis shall deliver to Lilly a promissory note covering the Debt and the Financial Officer's certificate called for under Article V.

(d) Lilly shall make each Disbursement to Isis by transferring the amount of such Disbursement by electronic funds transfer to such Isis bank account as is from time to time designated by Isis to Lilly in writing.

SECTION 2.03. REPAYMENT OF LOAN.

Isis shall pay to Lilly the entire unpaid amount of the Debt on the Payment Date in cash or through conversion of the promissory note into Common Stock of Isis pursuant to the following:

(a) Subject to the provisions of Section 2.04, if the Payment Date is not established as a result of termination of the Collaboration Agreement pursuant to Section 13.4 thereof (termination for breach by Isis) or as a result of an Event of Default, Isis shall have the right to require Lilly to convert the promissory note evidencing the entire outstanding Debt into that number of shares of Common Stock equal to the aggregate amount of the Debt divided by Forty Dollars per share, except that if Isis shall at any time subdivide (by any stock split, stock dividend or otherwise) its outstanding shares of Common Stock into a greater number of shares, the Forty Dollars ($40) per share price or that price as previously adjusted shall be proportionately reduced, and, conversely, in case the outstanding shares of Common Stock shall be combined into a smaller number of shares, that price per share in effect immediately prior to such combination shall be proportionately increased (the price per share of Common Stock as so calculated is defined as the "Conversion Price");

(b) Subject to the provisions of Section 2.04, if a determination of the Payment Date results from termination of the Collaboration Agreement pursuant to Section 13.4 thereof (termination for breach by Isis) or as a result of an Event of Default, Lilly shall have the right to convert the promissory note covering the entire outstanding Debt into that number of shares of Common Stock equal to the aggregate amount of the Debt divided by the Conversion Price; or

(c) If Isis does not elect the option set forth in Subsection 2.03(a) or Lilly does not elect the option set forth in Subsection 2.03(b), Isis shall pay the Debt to Lilly on the Payment Date by

transferring funds equal to the Debt by wire transfer to a Lilly bank account designated from time to time by Lilly.

The Party having an option to elect to convert the promissory note into Common Stock shall provide notice to the other Party no later than fifteen (15) days prior to the Payment Date of its election to so convert the Debt. If such election is made by a Party and legal counsel for Isis reasonably determines that Isis cannot legally issue the relevant shares of Common Stock to Lilly on the Payment Date, the Debt shall be paid to Lilly by Isis in cash on the Payment Date pursuant to the procedures set forth in Subsection 2.03(c).

SECTION 2.04. FUNDAMENTAL CHANGES. In case of any reclassification of the outstanding shares of Common Stock, or consolidation, merger or share exchange of Isis with another Person, or any other transaction or series of related transactions in which shares of Common Stock are changed into, converted into or exchanged for other securities or property in each case where Isis is not the surviving entity (each, a "Fundamental Change") the option to convert the promissory note to Common Stock as provided in Subsection 2.03(a) or Subsection 2.03(b), as relevant, shall terminate as of the date of the Fundamental Change, and the Debt shall be paid on the Payment Date solely in cash pursuant to the procedures set forth in Subsection 2.03(c).

SECTION 2.05. FRACTIONAL SHARES; PARTIAL CONVERSION. No fractional shares shall be issued upon conversion of the promissory note into shares of Common Stock. If any fractional share of Common Stock would, except for the provisions of this Section, be delivered upon such conversion, Isis, in lieu of delivering such fractional share shall pay to Lilly an amount in cash equal to the difference between the aggregate Conversion Price of the whole number of shares of Common Stock and the Debt outstanding. Except as provided in this Section 2.05, the option under Subsection 2.03(a) or Subsection 2.03(b) to convert the promissory note must be exercised, if at all, on the entire Debt outstanding on the Payment Date.

SECTION 2.06. OTHER MECHANICS. In the event of conversion of the promissory note to Common Stock, Isis shall deliver to Lilly on the Payment Date an opinion of counsel from Isis' General Counsel, dated as of the Payment Date, in substantially the same form and content as set forth on the attached Exhibit B.

SECTION 2.07. DEFAULT INTEREST. If Isis shall fail to make the payment on the Debt on the Payment Date, Isis shall on demand from time to time from Lilly pay interest on such defaulted amount ("Default Interest") up to (but not including) the date of actual payment (after as well as before judgement) at a rate per annum of Eighteen Percent (18%) or the maximum allowed by law if lower (computed on the basis of the actual number of days elapsed over a year of 365 days).

SECTION 2.08. PREPAYMENT.

(a) Isis shall have the right at any time, and from time to time, to prepay the Debt in cash prior to the Payment Date, in whole or in part, without penalty upon giving written notice to Lilly before noon Indianapolis time, at least one Business Day prior to prepayment. Prepayments shall be in a minimum amount of One Million Dollars ($1,000,000) or in integral multiples thereof.

(b) Each notice of prepayment shall specify the prepayment date and the amount of the Debt to be prepaid, shall be irrevocable and shall commit Isis to prepay such amount of the Debt as is stated therein on the date specified therein. All prepayments under this Section 2.08 shall be made by electronic funds transfer to Lilly's designated account.

ARTICLE III. ISIS' REPRESENTATIONS AND WARRANTIES

Section 3.01. ORGANIZATION AND POWERS. Isis represents and warrants to Lilly that Isis:

(a) is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware,

(b) has all requisite corporate power and authority to own its property and assets and to carry on its business as now conducted and as proposed to be conducted, and

(c) has the corporate power and authority to execute, deliver and perform its obligations under this Agreement and to borrow hereunder.

SECTION 3.02. AUTHORIZATION. Isis represents and warrants to Lilly that the execution, delivery and performance by Isis of this Agreement and the borrowing of the Loan and payment of the Debt and Default Interest (collectively, the "Transactions") (a) have been duly authorized by all requisite corporate action, and (b) will not (i) violate (A) any provision of any law, statute, rule or regulation or of the certificate of incorporation or other constitutive documents or bylaws of Isis; (B) any order of any Governmental Authority; or (C) any provision of any indenture, agreement or other instrument filed as an exhibit to the Company Reports (as defined in the Securities Purchase Agreement); (ii) be in conflict with, result in a breach of, or constitute (alone or with notice or lapse of time or both) a default under, any such indenture, agreement or other instrument; or (iii) result in the creation or imposition of any lien upon any property or assets of Isis except in each case where such violation, conflict or lien would not materially impede Isis' ability to fully perform its obligations under this Agreement.

SECTION 3.03. ENFORCEABILITY. Isis represents and warrants to Lilly that this Agreement constitutes a legal, valid and binding obligation of Isis, enforceable in accordance with its terms (subject, as to enforceability, to applicable bankruptcy, insolvency, reorganization, moratorium or other similar laws affecting creditors' rights generally and to general principles of equity, regardless of whether such enforceability is considered in a proceeding at law or in equity).

SECTION 3.04. GOVERNMENTAL APPROVALS. Isis represents and warrants to Lilly that no action, consent or approval of, registration or filing with, or other action by, any Governmental Authority is required in connection with the Transactions other than such filings (i) if any, as may be required under the HSR Act (as defined in the Securities Purchase Agreement) or (ii) which may be properly made upon or following conversion of the Note.

SECTION 3.05. LITIGATION. Isis represents and warrants to Lilly that there are no actions, proceedings or investigations filed or, to the actual knowledge of Isis' Chairman of the Board, Chief Executive Officer, Chief Financial Officer or General Counsel, threatened, against Isis in any court or before any Governmental Authority or arbitration board or tribunal which question the validity or legality of this Agreement, the Transactions or any action taken or to be taken by Isis pursuant to this Agreement and no order or judgment has been issued or entered restraining or enjoining Isis from the execution, delivery or performance of this Agreement.

SECTION 3.06. USE OF PROCEEDS. Isis represents and warrants to Lilly that all proceeds of the Loan shall be used solely for funding of the Collaboration.

SECTION 3.07. SOLVENCY. Isis represents and warrants to Lilly that it is not currently insolvent, i.e., unable to pay its debts and obligations as they become due for payment.

ARTICLE IV. LILLY REPRESENTATIONS AND WARRANTIES

Section 4.01. Organization and Powers. Lilly represents and warrants to Isis that Lilly:

(a) is a corporation duly organized, validly existing and in good standing under the laws of the State of Indiana, and

(b) has all requisite corporate power and authority to execute, deliver and perform its obligations under this Agreement.

SECTION 4.02. AUTHORIZATION. Lilly represents and warrants to Isis that the execution, delivery and performance by Lilly of this Agreement and the making of the Loan (collectively, the "Transactions") (a) have been duly authorized by all requisite corporate action, and (b) will not (i) violate (A) any provision of any law, statute, rule or regulation or of the certificate of incorporation or other constitutive documents or bylaws of Lilly; or (B) any order of any Governmental Authority; or (C) any provision of any indenture, agreement or other instrument filed as an exhibit to Lilly's reports required to be filed under Section 13 of the Exchange Act; (ii) be in conflict with, result in a breach of, or constitute (alone or with notice or lapse of time or both) a default under any such indenture, agreement or other instrument; or (iii) result in the creation or imposition of any lien under any property or assets of Lilly except in each case where such violation, conflict or lien would not materially impede Lilly's ability to fully perform its obligations under this Agreement.

SECTION 4.03. ENFORCEABILITY. Lilly represents and warrants to Isis that this Agreement constitutes a legal, valid and binding obligation of Lilly, enforceable in accordance with its terms (subject, as to enforceability, to applicable bankruptcy, insolvency, reorganization, moratorium or other similar laws affecting creditors' rights generally and to general principles of equity, regardless of whether such enforceability is considered in a proceeding at law or in equity).

SECTION 4.04. GOVERNMENTAL APPROVALS. Lilly represents and warrants to Isis that no action, consent or approval of, registration or filing with, or other action by, any Governmental

Authority is required in connection with the Transactions other than such filings (i) if any, as may be required under the HSR Act (as defined in the Securities Purchase Agreement) or (ii) which may be properly made upon or following conversion of the Note.

SECTION 4.05. LITIGATION. Lilly represents and warrants to Isis that there are no actions, proceedings or investigations filed or, to the actual knowledge of Lilly's Chairman of the Board, Chief Executive Officer, Chief Financial Officer or General Counsel, threatened, against Lilly in any court or before any Governmental Authority or arbitration board or tribunal which question the validity or legality of this Agreement, the Transactions or any action taken or to be taken by Lilly pursuant to this Agreement and no order or judgment has been issued or entered restraining or enjoining Lilly from the execution, delivery or performance of this Agreement.

ARTICLE V. CONDITIONS OF LENDING

SECTION 5.01. FIRST LOAN DISBURSEMENT. The obligations of Lilly to incur the Commitment set forth in Section 2.01, and to make the first Loan Disbursement pursuant to Section 2.02 of this Agreement are subject to the satisfaction of the conditions that on the date of such Loan Disbursement:

(a) The representations and warranties set forth in Article III shall be true and correct in all material respects with the same effect as though made on and as of that date, except to the extent such representations and warranties expressly relate to an earlier date,

(b) No Event of Default shall have occurred and be continuing, and

(c) Lilly shall have received a Financial Officer's Certificate of Isis confirming compliance with the conditions precedent set forth in paragraphs (a) and (b) above.

(d) If applicable, the waiting period under the HSR Act shall have expired or been terminated.

SECTION 5.02. SUBSEQUENT DISBURSEMENTS. The obligations of Lilly to make Loan Disbursements subsequent to the first Disbursement pursuant to Section 2.02 of this Agreement are subject to the satisfaction of the conditions that on the date of each subsequent Loan Disbursement:

(a) No Event of Default shall have occurred and be continuing,

(b) Lilly shall have received a Financial Officer's Certificate of Isis confirming compliance with the conditions precedent set forth in paragraph (a)above,

(c) In relation to the second Disbursement, Lilly shall have previously made the first Disbursement pursuant to Section 2.02 of this Agreement, and

(d) If applicable, the waiting period under the HSR Act shall have expired or been terminated.

ARTICLE VI. ISIS COVENANTS

Isis covenants and agrees with Lilly that so long as this Agreement shall remain in effect or the Debt shall be unpaid, unless Lilly shall otherwise consent in writing, it will not consolidate or merge with, or into, any other Person or liquidate, wind up or dissolve (or suffer any liquidation or dissolution) or sell, lease or otherwise transfer (in one transaction or a

series of transactions) all or substantially all of the assets, of Isis to any other Person, provided that Isis may merge with another Person if:

(a) Isis is the corporation surviving such merger, or if not, the surviving corporation succeeds to all the rights, duties and obligations of Isis under this Agreement, and

(b) Immediately after giving effect to such merger, no Event of Default as set forth in subsections (a) and (b) of Article VII shall have occurred and be continuing.

ARTICLE VII. EVENTS OF DEFAULT

An "Event of Default" includes any of the following:

(a) default shall be made in the payment of the Debt when and as the same shall become due and payable;

(b) Isis shall have breached any provision of the Collaboration Agreement that pursuant to Section 13.4 therein results in Lilly having terminated the Collaboration Agreement; or

(c) Isis shall have breached the Covenant set forth in Article VI above. Upon the occurrence of an Event of Default under this Subsection (c), Lilly shall have no remedies other than those specifically set forth for an Event of Default in this Agreement or in the Collaboration Agreement.

ARTICLE VIII. SUBORDINATION

The parties acknowledge and agree that the obligations evidenced by the Note and pursuant to this Agreement are hereby made expressly subordinate and subject in right of payment to the prior payment in full of all principal, interest and other charges relating to or arising under (a) the 14% Senior Subordinated Discount Notes due November 1, 2007, issued by Isis pursuant to that certain Purchase Agreement, dated October 24, 1997, between Isis and the Purchasers listed on Schedule I thereto (the "Senior Note Purchase Agreement"), and (b) all obligations of Isis for borrowed money or other similar obligations whether now existing or hereafter created or incurred, except for any such obligations arising in connection with a collaboration with a third party pharmaceutical or biotechnology company, which may be pari

passu with the obligations evidenced by the Note and pursuant to this Agreement. The parties hereto further expressly acknowledge and agree that the obligations of Isis evidenced by the promissory note and this Agreement rank pari passu with the obligations of Isis under those certain Convertible Promissory Notes issued by Isis to Elan International Services, Ltd. on April 20, 1999 and January 14, 2000. Notwithstanding the provisions of this Article VIII, Isis' failure to pay the Debt on the Payment Date shall constitute a material breach of this Agreement by Isis, and Lilly may pursue any legal remedy available to it in relation to such material breach.

ARTICLE IX. MISCELLANEOUS

SECTION 9.01. NOTICES. Except as otherwise expressly provided herein, notices and other communications provided for herein shall be in writing and shall be delivered by hand or overnight courier service or sent by telecopy, as follows:

(a) If to Isis

2292 Faraday Avenue
Carlsbad, CA 92008
Attention: Chief Financial Officer
Tel: 760-603-2460
Fax: 760-931-9639

with a copy to:

Cooley Godward LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121
Attn: Julie M. Robinson, Esq.
Tel: 858-550-6000
Fax: 858-453-3555

(b) If to Lilly:

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
Fax: 317-433-3000
telephone confirmation required at 317-276-2703
Attention: Rebecca O. Kendall, Esq., Senior Vice President and General Counsel

with a copy to:

Fax: 317-277-7979
telephone confirmation required at 317-276-6524
Attention: Richard D. DiMarchi, Ph.D., Group Vice President, Lilly Research Center

All notices and other communications given to any Party hereto in accordance with the provisions of this Agreement shall be deemed to have been given on the date of receipt if delivered by hand or overnight courier service or sent by telecopy to such Party as provided in this Section or in accordance with the latest unrevoked direction from such Party given in accordance with this Section.

SECTION 9.02. SURVIVAL OF AGREEMENT. All covenants, agreements, representations and warranties made by Isis herein and in the certificates or other instruments prepared or delivered in connection with or pursuant to this Agreement shall be considered to have been relied upon by Lilly and shall survive the making by Lilly of the Commitment set forth in Section 2.01 regardless of any investigation made by Lilly, and shall continue in full force and effect as long as the Debt or any other amount payable under this Agreement is outstanding and unpaid or the Commitment has not been terminated.

SECTION 9.03. SUCCESSORS AND ASSIGNS.

(a) Neither Party shall assign or delegate any of its rights and duties hereunder without the prior written consent of the other Party, and any attempt so to assign or delegate shall be void, except that Lilly may assign its rights and obligations hereunder, subject to the restrictions on transfer set forth in Section 7.04 of the Securities Purchase Agreement, in whole or in part, to an Affiliate without the approval or consent of Isis; provided that such Affiliate shall satisfy all investor suitability requirements and other restrictions on transfer under applicable state and federal securities laws and regulations and Lilly shall remain liable for all funding obligations hereunder;

(b) Subject to Subsection 8.03(a), whenever in this Agreement one of the Parties hereto or thereto is referred to, such reference shall be deemed to include the successors and assigns of such Party, and all covenants, promises and agreements by or on behalf of a Party that are contained in this Agreement shall bind and inure to the benefit of its successors and assigns.

SECTION 9.04. APPLICABLE LAW. All questions concerning the construction, validity and interpretation of this Agreement shall be construed in accordance with and governed by the laws of the State of New York without regard to principles of conflicts of laws.

SECTION 9.05. WAIVERS: AMENDMENT.

(a) No failure or delay of Lilly in exercising any power or right hereunder shall operate as a waiver thereof, nor shall any single or partial exercise of any such right or power, or any abandonment or discontinuance of steps to enforce such a right or power, preclude any other or further exercise thereof or the exercise of any other right or power. The rights and remedies of Lilly hereunder are cumulative and are not exclusive of any rights or remedies which it would otherwise have. No waiver of any provision of this Agreement or consent to any departure therefrom shall in any event be effective unless the same shall be permitted by Subsection (b) below, and then such waiver or consent shall be effective only in the specific instance and for the purpose for which given.

(b) Neither this Agreement nor any provision hereof may be waived,

amended or modified except pursuant to an agreement or agreements in writing entered into by Isis and Lilly.

SECTION 9.06. SEVERABILITY. In the event any one or more of the provisions contained in this Agreement should be held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein shall not in any way be affected or impaired thereby. The parties shall endeavor in good faith negotiations to replace the invalid, illegal or unenforceable provisions with valid provisions the economic, and legal, effect of which comes as close as possible to that of the invalid, illegal or unenforceable provisions.

SECTION 9.07. COUNTERPARTS. This Agreement may be executed in two or more counterparts, each of which shall constitute an original but all of which when taken together shall constitute but one contract.

SECTION 9.08. HEADINGS. Article and Section headings used herein are for convenience only, and do not constitute a part of this Agreement.

SECTION 9.09. RIGHT OF SETOFF. If a failure of Isis to pay the Debt on the Payment Date or to pay Default Interest shall have occurred and be continuing, Lilly is hereby authorized at any time and from time to time, to the fullest extent permitted by law, to set off and apply any and all monetary obligations at any time owing by Lilly to Isis now or hereafter existing against any outstanding Debt or Default Interest. Lilly agrees promptly to notify Isis after such setoff and application, but the failure to give such notice shall not affect the validity of such setoff and application. The rights of Lilly under this Section are in addition to other rights and remedies (including other rights of setoff) which it may have.

SECTION 9.10. CONFIDENTIALITY AND NONDISCLOSURE. The parties hereto agree that the provisions of the Collaboration Agreement relating to confidentiality and non-disclosure are incorporated herein by reference.

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IN WITNESS WHEREOF, the parties hereto have caused this Loan Agreement to be duly executed by their respective authorized officers as of the day and year first above written.

ELI LILLY AND COMPANY

By: /s/ Sidney Taurel

Printed: Sidney Taurel
Title: Chairman of the Board,
Chief Executive Officer and President

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

Name: B. Lynne Parshall
Title: Executive Vice President and
Chief Financial Officer

EXHIBIT A

THIS CONVERTIBLE SUBORDINATED PROMISSORY NOTE HAS NOT BEEN REGISTERED UNDER THE SECURITIES ACT OF 1933. NO SALE OR DISPOSITION MAY BE EFFECTED EXCEPT IN COMPLIANCE WITH RULE 144 UNDER SAID ACT OR AN EFFECTIVE REGISTRATION STATEMENT RELATED THERETO OR AN OPINION OF COUNSEL FOR THE HOLDER, SATISFACTORY TO THE COMPANY, THAT SUCH REGISTRATION IS NOT REQUIRED UNDER THE ACT OR RECEIPT OF A NO-ACTION LETTER FROM THE SECURITIES AND EXCHANGE COMMISSION.

CONVERTIBLE SUBORDINATED PROMISSORY NOTE

$100,000,000 August 29, 2001

FOR VALUE RECEIVED, ISIS PHARMACEUTICALS, INC., a Delaware corporation ("BORROWER"), hereby promises to pay to the order of ELI LILLY AND COMPANY, an Indiana corporation ("LENDER"), in lawful money of the United States of America and in immediately available funds, the principal sum of One Hundred Million Dollars ($100,000,000) (the "LOAN") together with accrued and unpaid interest thereon if applicable, each due and payable on the dates and in the manner set forth in the Loan Agreement (as defined below).

This Convertible Subordinated Promissory Note (this "NOTE") is the promissory note referred to in and is executed and delivered in connection with that certain Loan Agreement dated as of even date herewith and executed by Borrower in favor of Lender (as the same may from time to time be amended, modified or supplemented or restated, the "LOAN AGREEMENT"). All capitalized terms used herein and not otherwise defined herein shall have the respective meanings given to them in the Loan Agreement.

1. LOAN REQUESTS. At the time of any borrowing under this Note (or at the time of receipt of any payment of principal or conversion thereof into equity securities of the Borrower), Lender shall make or cause to be made, an appropriate notation on the Exhibit A attached hereto reflecting the amount of such borrowing (or the amount of such payment or conversion). The outstanding amount of this Note set forth on such Exhibit A shall be prima facie evidence of the principal amount thereof outstanding, but the failure to record, or any error in so recording, shall not limit or otherwise affect the obligations of Borrower to make payments of principal of or interest on this Note or to convert the same when due. Borrower and Lender acknowledge that the initial principal amount outstanding under this Note as of the date hereof shall be Ten Million Dollars ($10,000,000), as indicated on the attached Exhibit A.

2. CONVERTIBLE NOTE. This Note is convertible into the Common Stock of the Borrower under certain circumstances in accordance with the provisions of Section 2.03 of the Loan Agreement.

3. DEFAULT. Upon the occurrence of an Event of Default (as defined in the Loan Agreement) that has not been cured within 30 days of its occurrence, all unpaid principal, accrued interest and other amounts owing hereunder shall be or may become immediately due, payable and collectible by Lender pursuant to applicable law, all as provided in the Loan Agreement.

4. SUBORDINATION. The indebtedness evidenced by this Note is hereby expressly subordinated, to the extent, in the manner and to the indebtedness as set forth in Section 8.01 of the Loan Agreement.

5. WAIVER. Borrower waives presentment and demand for payment, notice of dishonor, protest and notice of protest of this Note, and shall pay all costs of collection when incurred, including, without limitation, reasonable attorneys' fees, costs and other expenses.

6. GOVERNING LAW. This Note shall be governed by, and construed and enforced in accordance with, the laws of the State of New York, excluding conflict of laws principles that would cause the application of laws of any other jurisdiction.

BORROWER ISIS PHARMACEUTICALS, INC.

By:/s/ B. LYNNE PARSHALL

Printed Name: B. LYNNE PARSHALL

Title: Executive Vice President and CFO

EXHIBIT A

PRINCIPAL BORROWINGS SCHEDULE

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DATE
BORROWING
REPAYMENT
PRINCIPAL
BALANCE -

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Closing
Date
$10,000,000
$0
$10,000,000
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EXHIBIT B

OPINION OF COUNSEL

(a) Isis is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware and has full corporate

power and authority to conduct its business as presently conducted.

(b) The Common Stock to be issued has been duly authorized and is duly and validly issued, fully paid and non-assessable and free of statutory pre-emptive rights.

(c) The issuance of the Common Stock pursuant to the conversion provisions in the Loan Agreement will not conflict with, or result in any breach of any of the terms, conditions, or provisions of, or constitute a default under, (i) the Certificate of Incorporation or Bylaws of Isis or (ii) any provision of California or federal law, statute, rule or regulation or any provision of the Delaware General Corporation Law.

(d) Except as obtained and in effect on the date of issuance of the Common Stock, no consent, approval, order or authorization of, or registration, qualification, designation, declaration, or filing with, any governmental authority is required on the part of Isis in connection with the issuance of the Common Stock pursuant to the conversion of the Loan Agreement.

ISIS PHARMACEUTICALS, INC.
REGISTRATION RIGHTS AND STANDSTILL AGREEMENT

THIS REGISTRATION RIGHTS AND STANDSTILL AGREEMENT (the "Agreement") is made as of August 17, 2001 by and between ISIS PHARMACEUTICALS, INC., a Delaware corporation (the "Company"), and ELI LILLY AND COMPANY, an Indiana corporation ("Lilly").

R E C I T A L S:

A. Pursuant to a Securities Purchase Agreement (the "PURCHASE AGREEMENT") and a Loan Agreement (the "LOAN AGREEMENT") each dated as of the date hereof, and each by and between the Company and Lilly, Lilly has acquired, or may acquire in the future, (i) certain shares of common stock, par value $.001 per share, of the Company (the "COMMON STOCK"), and (ii) a promissory note (the "Note"), which in certain circumstances may be converted into Common Stock.

B. The execution of the Purchase Agreement and the Loan Agreement has occurred on the date hereof, and it is a condition to the closing of the transactions contemplated thereby that the parties execute and deliver this Agreement.

C. The parties desire to set forth herein their agreement as to the terms and conditions set forth herein related to the granting of certain registration rights to the Holders (as defined below) relating to the Common Stock held by such Holders and the Common Stock underlying the Note.

A G R E E M E N T:

The parties hereto agree as follows:

1. CERTAIN DEFINITIONS. As used in this Agreement, the following terms shall have the following respective meanings:

"COMMISSION" shall mean the U.S. Securities and Exchange Commission.

"EXCHANGE ACT" shall mean the Securities Exchange Act of 1934, as amended, and the rules and regulations of the Commission thereunder, all as the same shall be in effect from time to time.

"HOLDERS" or "HOLDERS OF REGISTRABLE SECURITIES" shall mean Lilly and any other Person owning Registrable Securities to whom registration rights shall have been assigned in accordance with Section 10 below.

"PERSON" shall mean an individual, a corporation, a partnership, a company, an association, a joint stock company, a trust, a joint venture, an unincorporated organization and a governmental or quasi-governmental entity, or any department, agency or political subdivision thereof.

"REGISTRABLE SECURITIES" means (i) any shares of Common Stock purchased pursuant to the Purchase Agreement, (ii) any shares of Common Stock issued or issuable upon conversion of the Note and (iii) any Common Stock issued or issuable in respect of the securities referred to in clauses (i) and (ii) above upon any stock split, stock dividend, recapitalization or similar event; excluding in all cases, however, any such securities which are not held by a Holder.

The terms "REGISTER," "REGISTERED" and "REGISTRATION" refer to a registration effected by preparing and filing a registration statement in compliance with the Securities Act, and the declaration or order of the effectiveness of such registration statement.

"REGISTRATION EXPENSES" shall mean all expenses, other than Selling Expenses, incurred by the Company in complying with Sections 2 or 3 hereof, including without limitation, all registration, qualification and filing fees, exchange listing fees, printing expenses, escrow fees, underwriters' fees and expenses (excluding discounts and commissions), fees and disbursements of counsel for the Company, blue sky fees and expenses, the expense of any special audits incident to or required by any such registration and the fees and disbursements (not to exceed $20,000) of counsel for the Holders.

"SECURITIES ACT" shall mean the Securities Act of 1933, as amended, and the rules and regulations of the Commission thereunder, all as the same shall be in effect from time to time.

"SELLING EXPENSES" shall mean all underwriting discounts, selling commissions and stock transfer taxes applicable to the securities registered by the Holders and the costs of any accountants, attorneys or other experts retained by the Holders, except as expressly included in Registration Expenses.

2. DEMAND REGISTRATION.

(a) REQUESTS FOR REGISTRATION. Effective upon the second anniversary of the Closing (as defined in the Purchase Agreement), until expiration of such rights as set forth in Section 13 hereof, any Holder or Holders who collectively hold Registrable Securities representing at least 50% of the Registrable Securities then outstanding shall have the right at any time and from time to time, to request registration under the Securities Act of a minimum of 500,000 shares of Common Stock (as adjusted for any combinations, consolidations, splits, stock distributions, stock dividends or other recapitalizations with respect to such shares) on Form S-1, S-2 or S-3 (if available) or any similar registration statement (a "Demand Registration"), such form to be selected by the Company as appropriate. The request for the Demand Registration shall specify the approximate number of Registrable Securities requested to be registered. Within 20 days after receipt of any such request, the Company will give written notice of such requested registration to all other Holders of Registrable Securities. The Company shall include such other Holders' Registrable Securities in such offering if they have responded affirmatively within 20 days after the receipt of the Company's notice. The Holders in aggregate will be entitled to request only one Demand Registration hereunder, unless any Registrable Securities are issued upon conversion of the Note, in which case the Holders in aggregate will be entitled to request two Demand Registrations hereunder. A registration will not count as a Demand Registration until it has become effective and has been effective for 180 days (or until such lesser time as all Registrable Securities included therein shall have been sold thereunder), unless such Demand

Registration has not become effective due solely to the fault of the Holders requesting such registration, including a request by such Holders that such registration be withdrawn, unless the Holders have paid the Registration Expenses pursuant to the provisions of Section 4(b) hereof. The Company shall pay all Registration Expenses in connection therewith. The Holders whose Registrable Securities are included therein shall pay all Selling Expenses in connection therewith.

(b) PRIORITY ON DEMAND REGISTRATION. If, in connection with a Demand Registration, any managing underwriter (or, if such Demand Registration is not an underwritten offering, a nationally recognized independent underwriter selected by the Company and reasonably acceptable to the Holders of a majority of the Registrable Securities sought to be registered in such Demand Registration (and whose fees and expenses shall be borne solely by the Company)) advises the Company and the Holders of the Registrable Securities sought to be included in such Demand Registration ("Demanding Sellers") that, in its opinion, the inclusion of all the Registrable Securities and any other securities of the Company, in each case, sought to be registered in connection with such Demand Registration would adversely affect the marketability of the Registrable Securities sought to be sold pursuant thereto, then the Company shall include in the registration statement applicable to such Demand Registration only such securities as the Company and the Demanding Sellers are advised by such underwriter can be sold without such an effect (the "Maximum Demand Number"), as follows and in the following order of priority:

(i) first, the number of Registrable Securities sought to be registered by each Demanding Seller, PRO RATA in proportion to the number of Registrable Securities sought to be registered by all Demanding Sellers; and

(ii) second, if the number of Registrable Securities to be included under clause (i) next above is less than the Maximum Demand Number, the number of securities sought to be included by each other seller, PRO RATA in proportion to the number of securities sought to be sold by all such other sellers, which in the aggregate, when added to the number of securities to be included pursuant to clause (i) next above, equals the Maximum Demand Number.

Other than the securities issued by the Company to Reliance Insurance Company and to Elan International Services, Ltd. and their permitted transferees, no securities other than Registrable Securities hereunder shall be included in such Demand Registration without the prior written consent of Holders who collectively hold Registrable Securities representing at least 50% of the Registrable Securities then outstanding.

(c) RESTRICTIONS ON DEMAND REGISTRATION. The Company may

postpone the filing or the effectiveness of a registration statement for a Demand Registration one time in any 12 month period for up to 90 days if the Company determines in good faith that such Demand Registration would reasonably be expected to have a material adverse effect on any proposal or plan by the Company or would require disclosure of any information that the board of directors of the Company determines in good faith the disclosure of which would be detrimental to the Company; provided, however, that in such event, the Holders initially requesting such Demand

Registration will be entitled to withdraw such request and, if such request is withdrawn, such Demand Registration will not count as a Demand Registration hereunder.

(d) SELECTION OF UNDERWRITERS. The Holders will have the right to select the investment banker(s) and manager(s) to administer an offering pursuant to the Demand Registration, subject to the Company's prior written approval, which will not be unreasonably withheld or delayed.

(e) OTHER REGISTRATION RIGHTS. Except as provided in this Agreement, so long as any Holder owns any Registrable Securities, the Company will not grant to any Persons the right to request the Company to register any equity securities of the Company, or any securities convertible or exchangeable into or exercisable for such securities, which conflicts with the rights granted to the Holders hereunder, without the prior written consent of the Holders of at least 50% of the Registrable Securities.

3. PIGGYBACK REGISTRATIONS.

(a) RIGHT TO PIGGYBACK. Effective upon the second anniversary of the Closing (as defined in the Purchase Agreement), any time that the Company shall propose (whether in a primary offering or pursuant to the exercise of demand rights by others) to register Common Stock under the Securities Act (other than in a registration (i) on Form S-3 relating to sales of securities to participants in a Company dividend reinvestment plan, (ii) on Form S-4 or S-8 or any successor form or in connection with an acquisition or exchange offer or an offering of securities solely to the existing shareholders or employees of the Company, (iii) pursuant to a shelf registration statement filed pursuant to Section 3 of either of two Registration Rights Agreements by and between Elan International Services, Ltd., dated as of April 20, 1999 and as of January 14, 2001, (iv) pursuant to a shelf registration statement filed pursuant to Section 7.2 of the Master Agreement by and between Hybridon, Inc. and the Company, dated as of May 24, 2001 or (v) pursuant to a shelf registration statement filed to facilitate any equity line of credit financing), the Company shall give prompt written notice to all Holders of Registrable Securities of its intention to effect such a registration and, subject to Section 3(b) and the other terms of this Agreement, shall include in such registration all Registrable Securities that are permitted under applicable securities laws to be included in such registration and with respect to which the Company has received written requests for inclusion therein by the Holders within 20 days after the receipt of the Company's notice (each, a "PIGGYBACK REGISTRATION"; together with a Demand Registration, a "REGISTRATION").

(b) PRIORITY ON PIGGYBACK REGISTRATIONS. If a Piggyback Registration is an underwritten registration on behalf of the Company, and the managing underwriters advise the Company in writing that in their opinion the number of securities requested to be included in such registration exceeds the number that can be sold in such offering without adversely affecting the marketability of the offering, the Company shall include in such registration, only as may be permitted in the reasonable business judgment of the managing underwriters for such registration:

(i) first, up to that number of securities the Company proposes to sell;

(ii) second, up to that number of Registrable Securities requested to be included in such registration by the Holders and that number of securities requested to be included in such registration by any other Person entitled to registration rights with respect to such registration, PRO RATA among the Holders of such Registrable Securities and such other Persons, on the basis of the number of Registrable Securities and other securities of the Company requested to be included by each such Holder and such other Persons; and

(iii) third, up to that number of other securities requested to be included in such registration.

The Holders of any Registrable Securities included in such a registration shall execute an underwriting agreement and customary accompanying documents in form and substance satisfactory to the managing underwriters.

(c) RIGHT TO TERMINATE REGISTRATION. If, at any time after giving written notice of its intention to register any of its securities as set forth in Section 3(a) and prior to the effective date of the registration statement filed in connection with such registration, the Company shall determine for any reason not to register such securities, the Company may, at its election, give written notice of such determination to each Holder of Registrable Securities and thereupon be relieved of its obligation to register any Registrable Securities in connection with such registration (but not of its obligation to pay the Registration Expenses in connection therewith).

(d) SELECTION OF UNDERWRITERS. The Company shall have the right to select the investment banker(s) and manager(s) to administer an offering pursuant to a Piggyback Registration.

4. EXPENSES OF REGISTRATION; WITHDRAWAL RIGHTS.

(a) EXPENSES. Except as otherwise provided herein, all Registration Expenses incurred in connection with all registrations pursuant to Sections 2 and 3 shall be borne by the Company, and all Selling Expenses relating to securities registered on behalf of the Holders of Registrable Securities shall be borne by such Holders.

(b) WITHDRAWAL RIGHTS. Any Holder of Registrable Securities having notified or directed the Company to include any or all of its Registrable Securities in a registration statement under the Securities Act (whether pursuant to Section 2 or 3 hereof) shall have the right to withdraw any such notice or direction with respect to any or all of the Registrable Securities designated for registration thereby by giving written notice to such effect to the Company prior to the effective date of such registration statement. In the event of any such withdrawal, the Company shall not include such Registrable Securities in the applicable registration and such Registrable Securities shall continue to be Registrable Securities hereunder. No such withdrawal shall affect the obligations of the Company with respect to any Registrable Securities not so withdrawn; provided that in the case of a registration pursuant to Section 2 hereof, if such withdrawal shall reduce the number of Registrable Securities still sought to be included in such registration ("Included Securities") below the minimum number required

pursuant to Section 2(a) to be included therein, then the Company shall as promptly as practicable give each Holder of Included Securities notice to such effect, referring to this Agreement and summarizing this Section, and within ten business days following the effectiveness of such notice, either the Company or the Holders of a majority of the Included Securities may, by written notice to each Holder of Included Securities or the Company, respectively, elect that such registration statement not be filed or, if theretofore filed, be withdrawn. During such ten business day period, the Company shall not file such registration statement if not theretofore filed or, if such registration statement has been theretofore filed, the Company shall not seek, and shall use its best efforts to prevent, the effectiveness thereof. Any registration statement effected pursuant to Section 2 hereof and not filed or withdrawn in accordance with this Section 4(b) shall be counted as a Demand Registration for purposes of Section 2 hereof, unless the Holders of the Included Securities and the securities withdrawn from the registration statement pay the Registration Expenses.

5. HOLDBACK AGREEMENTS.

(a) The Company agrees, unless the underwriters managing the registered public offering otherwise agree, (i) not to effect any public sale or distribution of its equity securities, or any securities convertible into or exchangeable or exercisable for such securities, for its own account during the seven days prior to and during the 90-day period beginning on the effective date of any underwritten Demand Registration (except (A) as part of such underwritten registration, (B) pursuant to registration statements on Form S-4 or Form S-8 or any successor form, (C) pursuant to a registration statement then in effect or (D) as required under any existing contractual obligation of the Company), and (ii) to cause its officers and directors and to use reasonable efforts to cause each holder of at least 5% (on a fully-diluted basis) of its outstanding Common Stock, or any securities convertible into or exchangeable or exercisable for Common Stock, purchased from the Company at any time after the date of this Agreement (other than in a registered public offering) to agree not to effect any public sale or distribution (including sales pursuant to Rule 144) of any such securities during such periods (except as part of such underwritten registration, if otherwise permitted).

(b) Each Holder agrees, so long as such Holder holds at least 1% (on a fully diluted basis) of the outstanding Common Stock, if requested by the managing underwriter or underwriters in an underwritten offering of securities of the Company, not to effect any offer, sale, distribution or transfer, including a sale pursuant to Rule 144 (or any similar provision then effect) under the Securities Act (except as part of such underwritten registration), during the seven-day period prior to, and during the 180-day period (or such shorter period as may be agreed to in writing by the Company and the Holders of at least 50% of the Registrable Securities) following the effective date of such Registration Statement to the extent timely notified in writing by the managing underwriter or underwriters.

6. REGISTRATION PROCEDURES. Whenever the Company is under the obligation to register Registrable Securities hereunder, the Company will use all reasonable efforts to effect the Registration and the sale of such Registrable Securities, and pursuant thereto the Company will as expeditiously as possible:

(a) subject to Section 2(c) hereof, prepare and file with the Commission a registration statement on any form for which the Company qualifies with respect to such Registrable Securities and use all reasonable efforts to cause such registration statement to become effective (provided that before filing a registration statement or prospectus or any amendments or supplements thereto, the Company will (i) furnish to the counsel selected by the Holders copies of all such documents proposed to be filed, which documents will be subject to the prompt review of such counsel, and (ii) notify each Holder of Registrable Securities covered by such registration of any stop order issued or threatened in writing by the Commission);

(b) subject to Sections 2(c) and 6(e) hereof, prepare and file with the Commission such amendments and supplements to such registration statement and the prospectus used in connection therewith as may be necessary to keep such registration statement effective for, in the case of a Demand Registration, a period equal to the shorter of (i) six months and (ii) the time by which all securities covered by such registration statement have been sold, and comply with the provisions of the Securities Act with respect to the disposition of all securities covered by such registration statement during such period in accordance with the intended methods of disposition by the sellers thereof set forth in such registration statement;

(c) furnish to each seller of Registrable Securities such number of copies of such registration statement, each amendment and supplement thereto, the prospectus included in such registration statement (including each preliminary prospectus) and such other documents as such seller may reasonably request in order to facilitate the disposition of the Registrable Securities owned by such seller;

(d) use all reasonable efforts to register or qualify such Registrable Securities under the securities or blue sky laws of such jurisdictions as any seller reasonably requests and do any and all other acts and things which may be reasonably necessary or advisable to enable such seller to consummate the disposition in such jurisdictions of the Registrable Securities owned by such seller (provided that the Company will not be required to (i) qualify generally to do business in any jurisdiction where it would not otherwise be required to qualify but for this Section 6(d), or (ii) subject itself to taxation in any jurisdiction;

(e) notify each seller of such Registrable Securities, at any time when a prospectus relating thereto is required to be delivered under the Securities Act, of the occurrence of any event as a result of which the prospectus included in such registration statement contains an untrue statement of a material fact or omits any material fact necessary to make the statements therein in light of the circumstances under which they were made not misleading, and, at the request of any such seller, the Company will prepare a supplement or amendment to such prospectus so that, as thereafter delivered to the purchasers of such Registrable Securities, such prospectus will not contain an untrue statement of a material fact or omit to state any material fact necessary to make the statements therein in light of the circumstances under which they were made not misleading; provided, however, that the Company shall not be required to amend the registration statement or supplement the Prospectus for a period of up to six months if the board of directors of the Company determines in good faith that to do so would reasonably be expected to have a material adverse effect on any proposal or plan by the Company to engage in any financing, acquisition or disposition of assets (other than in the ordinary course of business) or any merger, consolidation, tender offer or similar transaction or would require the disclosure

of any information that the board of directors of the Company determines in good faith the disclosure of which would be detrimental to the Company, it being understood that the period for which the Company is obligated to keep the Registration Statement effective shall be extended for a number of days equal to the number of days the Company delays amendments or supplements pursuant to this provision. Upon receipt of any notice pursuant to this Section 6(e), the Holders shall suspend all offers and sales of securities of the Company and all use of any prospectus until advised by the Company that offers and sales may resume, and shall keep confidential the fact and content of any notice given by the Company pursuant to this Section 6(e);

(f) cause all such Registrable Securities to be listed on each securities exchange on which similar securities issued by the Company are then listed;

(g) provide a transfer agent and registrar for all such Registrable Securities not later than the effective date of such registration statement;

(h) enter into such customary agreements (including underwriting agreements in customary form) and take all such other actions as the Holders of a majority of the Registrable Securities being sold or the underwriters, if any, reasonably request in order to expedite or facilitate the disposition of such Registrable Securities;

(i) at reasonable times and as reasonably requested make available for inspection by a representative of the Holders of Registrable Securities included in the registration statement, any underwriter participating in any disposition pursuant to such registration statement and any attorney, accountant or other agent retained by any such seller or underwriter, all pertinent financial and other records, pertinent corporate documents and properties of the Company, and use commercially reasonable efforts to cause the Company's officers, directors, employees and independent accountants to supply all information reasonably requested by any such seller, underwriter, attorney, accountant or agent in connection with such registration statement;

(j) otherwise use its reasonable efforts to comply with all applicable rules and regulations of the Commission, and make available to its security holders, as soon as reasonably practicable, an earnings statement covering the period of at least 12 months beginning with the first day of the Company's first full calendar quarter after the effective date of the registration statement, which earnings statement shall satisfy the provisions of Section 12(a) of the Securities Act and Rule 158 thereunder;

(k) in the event of the issuance of any stop order suspending the effectiveness of a registration statement, or of any order suspending or preventing the use of any related prospectus or suspending the qualification of any Common Stock included in such registration statement for sale in any jurisdiction, use all reasonable efforts promptly to obtain the withdrawal of such order; and

(l) if the registration is an underwritten offering, use all reasonable efforts to obtain a so-called "cold comfort" letter from the Company's independent public accountants in

customary form and covering such matters of the type customarily covered by cold comfort letters.

7. OBLIGATIONS OF HOLDERS. Whenever the Holders of Registrable Securities sell any Registrable Securities pursuant to a Registration, such Holders shall be obligated to comply with the applicable provisions of the Securities Act, including the prospectus delivery requirements thereunder, and any applicable state securities or blue sky laws.

8. INDEMNIFICATION. (a) In connection with any registration statement for any Registration in which a Holder of Registrable Securities is participating, the Company agrees to indemnify, to the fullest extent permitted by applicable law, each such Holder of Registrable Securities, its officers and directors and each Person who controls such Holder (within the meaning of the Securities Act) against all losses, claims, damages, liabilities, reasonable and documented expenses or any amounts paid in settlement of any litigation, investigation or proceeding commenced or threatened to which each such indemnified party may become subject under the Securities Act including, without limitation, reasonable attorneys fees and disbursements (collectively, "Claims") insofar as such Claim arose out of (i) any untrue or alleged untrue statement of material fact contained, on the effective date thereof, in any such registration statement, prospectus or preliminary prospectus or any amendment thereof or supplement thereto or (ii) any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the

statements therein not misleading, except insofar as the same are caused by or contained in any information furnished in writing to the Company by such Holder expressly for use therein or by such Holder's failure to deliver a copy of the registration statement or prospectus or any amendments or supplements thereto after the Company has furnished such Holder with a sufficient number of copies of the same. In connection with an underwritten offering, the Company will indemnify the underwriters, their officers and directors and each Person who controls the underwriters (within the meaning of the Securities Act) to the same extent as provided above with respect to the indemnification of the Holders of Registrable Securities.

(b) In connection with any registration statements for any Registration in which a Holder of Registrable Securities is participating, each such Holder will furnish to the Company in writing such customary information as the Company reasonably requests for use in connection with any such registration statement or prospectus (the "Seller's Information") and, to the fullest extent permitted by applicable law, will indemnify the Company, its directors and officers and each Person who controls the Company (within the meaning of the Securities Act) against any and all Claims to which each such indemnified party may become subject under the Securities Act insofar as such Claim arose out of (i) any untrue or alleged untrue statement of material fact contained, on the effective date thereof, in any such registration statement, prospectus or preliminary prospectus or any amendment thereof or supplement thereto or (ii) any omission or alleged omission to state therein a material fact required to be stated therein or necessary to make the statements therein not misleading; provided that with respect to a Claim arising pursuant to clause (i) or (ii) above, the material misstatement or omission is contained in such Seller's Information; provided, further, that the obligation to indemnify will be individual to each Holder (not joint and several among Holders) and will be limited to the amount of proceeds received by such Holder from the sale of Registrable Securities pursuant to such registration statement.

(c) Any Person entitled to indemnification hereunder will (i) give prompt written notice to the indemnifying party of any claim with respect to which it seeks indemnification (but the failure to provide such notice shall not release the indemnifying party of its obligation under paragraphs (a) and (b), unless and then only to the extent that, the indemnifying party has been prejudiced by such failure to provide such notice) and (ii) unless in such indemnified party's reasonable judgment a conflict of interest between such indemnified and indemnifying parties may exist with respect to such claim, permit such indemnifying party to assume the defense of such claim with counsel reasonably satisfactory to the indemnified party. An indemnifying party who is not entitled to, or elects not to, assume the defense of a claim will not be obligated to pay the fees and expenses of more than one counsel for all parties indemnified by such indemnifying party with respect to such claim, unless in the reasonable judgment of any indemnified party a conflict of interest may exist between such indemnified party and any other of such indemnified parties with respect to such claim.

(d) The indemnifying party shall not be liable to indemnify an indemnified party for any settlement, or consent to judgment of any such action effected without the indemnifying party's written consent (but such consent will not be unreasonably withheld). Furthermore, the indemnifying party shall not, except with the prior written approval of each indemnified party, consent to entry of any judgment or enter into any settlement which does not include as an unconditional term thereof the giving by the claimant or plaintiff to each indemnified party of a release from all liability in respect of such claim or litigation without any payment or consideration provided by each such indemnified party.

(e) If the indemnification provided for in this Section 8 is unavailable to an indemnified party under clauses (a) and (b) above in respect of any losses, claims, damages or liabilities referred to therein, then each indemnifying party, in lieu of indemnifying such indemnified party, shall contribute to the amount paid or payable by such indemnified party as a result of such losses, claims, damages or liabilities in such proportion as is appropriate to reflect the relative fault of the Company, the underwriters, the sellers of Registrable Securities and any other sellers participating in the registration statement in connection with the statement or omission which resulted in such losses, claims, damages or liabilities, as well as any other relevant equitable considerations. The relative fault of the Company, the underwriters, the sellers of Registrable Securities and any other sellers participating in the registration statement shall be determined by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission or alleged omission to state a material fact relates to information supplied by the Company or by the sellers of Registrable Securities and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission. Notwithstanding anything herein to the contrary, the obligation of any Holder to contribute as

provided herein shall be limited to the amount of net proceeds received by such Holder from the sale of Registrable Securities pursuant to the registration statement.

(f) The indemnification provided for under this Agreement will remain in full force and effect regardless of any investigation made by or on behalf of the indemnified party or any officer, director or controlling person of such indemnified party.

9. PARTICIPATION IN UNDERWRITTEN REGISTRATIONS. No Holder may participate in any registration hereunder which is underwritten unless such Holder (a) agrees to sell such

Holder's securities on the basis provided in any underwriting arrangements approved by the Holder or Holders entitled hereunder to approve such arrangements, (b) as expeditiously as possible notifies the Company of the occurrence of any event as a result of which any prospectus contains an untrue statement of material fact or omits to state a material fact required to be stated therein or necessary to make the statements therein not misleading and (c) completes and executes all questionnaires, powers of attorney, indemnities, underwriting agreements and other documents reasonably required under the terms of such underwriting arrangements.

10. TRANSFER OF REGISTRATION RIGHTS. The rights to cause the Company to register Registrable Securities pursuant to this Agreement may be assigned by a Holder to an affiliate of Lilly and to not more than two other transferees or assignees of such Registrable Securities pursuant to a private placement transaction as permitted by the Purchase Agreement; provided that (i) such transferee or assignee was a Holder of Registrable Securities prior to such transfer or such transferee or assignee acquires at least 200,000 Registrable Securities (subject to appropriate adjustment for stock splits, stock combinations and similar events) and the transferring Holder gives the Company written notice of such transfer or assignment within a reasonable time after consummation thereof, which notice states the name and address of the transferee or assignee and identifies the Registrable Securities with respect to which such registration rights are being transferred or assigned; (ii) such transferee or assignee assumes the obligations of the Holder with respect to the transferred Registrable Securities pursuant to this Agreement; (iii) immediately following such transfer or assignment, the further disposition of such Registrable Securities by the transferee or assignee is restricted under the Securities Act; and (iv) no more than a maximum of three such transferees or assignees in the aggregate shall be assigned or hold the rights to cause the Company to register Registrable Securities pursuant to this Agreement.

11. INFORMATION BY HOLDER. Each Holder shall furnish to the Company such written information regarding such Holder and any distribution proposed by such Holder as the Company may reasonably request in writing and as shall be reasonably required in connection with any registration, qualification or compliance referred to in this Agreement and shall promptly notify the Company of any changes or updates in such information.

12. EXCHANGE ACT COMPLIANCE. The Company shall comply with all of the reporting requirements of the Exchange Act then applicable to it and shall comply with all other public information reporting requirements of the Commission which are conditions to the availability of Rule 144 for the sale of the Registrable Securities. The Company shall cooperate with each Holder in supplying such information as may be necessary for such Holder to complete and file any information reporting forms presently or hereafter required by the Commission as a condition to the availability of Rule 144.

13. TERMINATION OF REGISTRATION RIGHTS. All registration rights granted under this Agreement shall terminate and be of no further force and effect, as to any particular Holder, at such time as all Registrable Securities held by such Holder or contingently issuable to such Holder upon conversion of the Note (i) represent, in the aggregate, less than 2% of the Common Stock then outstanding and (ii) can be sold by such Holder within a three-month period without compliance with the registration requirements of the Securities Act pursuant to Rule 144 (including Rule 144(k)) promulgated thereunder.

14. STANDSTILL.

(a) Provided that nothing contained herein will prevent or prohibit Lilly from acquiring Voting Stock (as defined below) of the Company pursuant to the Purchase Agreement or pursuant to conversion of the Note, Lilly will not, directly or indirectly, without the prior consent of a majority of the Board of Directors of the Company (the "Board"), (i) acquire (or offer or agree

to acquire) any Voting Stock if, as a result, Lilly would beneficially own more than 20% of the then outstanding Voting Stock; (ii) directly or indirectly solicit proxies or consents or become a participant in a solicitation (as such terms are defined in Regulation 14A under the Exchange Act) in opposition to the recommendation of the majority of the Board for a Takeover Event (as defined below); or (iii) transfer to any third party (other than to its "affiliates," "associates" (as such terms are defined in Rule 12b-2 under the Exchange Act), officers, directors or employees and other than pursuant to a proxy solicitation conducted by or on behalf of the Board), the right to vote any Voting Stock except in connection with the transfer of ownership of such Voting Stock for fair value. Lilly also agrees that it will not advise, assist or encourage any third party to do any of the foregoing. Notwithstanding the foregoing, (x) Lilly will not be obligated to dispose of any Voting Stock it owns if its percentage ownership is increased as a result of a decrease in the number of shares of Voting Stock outstanding, and (y) in the event of any bona fide third party tender or exchange offer for at least 50% of the outstanding Voting Stock of the Company, Lilly will be free to tender or exchange any or all of its Voting Stock and/or take such other actions as it deems advisable, in its sole discretion. The covenants in this Section 14(a) shall expire upon the later of (i) the fifth anniversary of the date hereof and (ii) the first anniversary of the termination of the Collaboration Agreement, dated as of the date hereof, between the Company and Lilly (the "Collaboration Agreement").

(b) The Company will give Lilly prompt notice of the receipt by the Company of any written notice couched in such terms as to put the Company reasonably on notice of the likelihood that a person or group has acquired or is proposing to acquire an aggregate position of at least 10% of the Voting Stock, the Company's receiving any bona fide offer to purchase or acquire 20% or more of the Voting Stock or all or substantially all of the assets of the Company, and any Board determination to seek an acquiror for in excess of 50% of the Voting Stock.

(c) Lilly will cause its affiliates and associates to comply with the provisions of this Section 14, whether directly or indirectly, individually or as part of a "group" (as such term is defined in Rule 13d-5 under the Exchange Act). When used in this Section 14, the term Lilly includes Lilly together with its affiliates and associates.

(d) For purposes of this Section 14, the term "TAKEOVER EVENT" means any proposal for any merger or business combination involving the Company or any of its subsidiaries, the purchase or sale of all or substantially all of the assets of the Company or any of its subsidiaries, or the purchase of at least 20% of the Voting Stock, by tender offer or otherwise (except pursuant to the exercise of rights, warrants, options or similar securities distributed by the Company to holders of Voting Stock generally), and the term "VOTING STOCK" means the Common Stock and any preferred stock of the Company possessing voting rights and eligible to participate in votes of all of the Company's stockholders pursuant to the Company's Certificate of Incorporation and Delaware law, and includes any options, convertible securities or other rights to acquire such stock.

15. COOPERATION UPON SALE OF SECURITIES. In the event that Lilly or any affiliate transferee of Lilly proposes to sell, transfer or otherwise dispose of any securities of the Company prior to the termination of the Collaboration Agreement, Lilly or any such affiliate transferee shall notify the Company in writing at least fifteen (15) days prior to such proposed sale, transfer or other disposition thereof and further agrees to cooperate and coordinate with the Company in the development by Lilly or such affiliate transferee, as applicable, and the Company of a standby statement to be used in responding to any inquiries from third parties (or if deemed appropriate by the Company or Lilly or such affiliate transferee, as applicable, a press release of that party) that would, as appropriate, indicate the continuing strong support by Lilly or such affiliate transferee, as applicable, of the collaboration activities, and the Company, notwithstanding the decision of Lilly or such affiliate transferee, as applicable, to dispose of some of its holdings of the Company's securities. Subject to the required notice above, the Company and Lilly or such affiliate transferee, as applicable, shall provide each other with comments on any such proposed standby statement or press release in such manner as is necessary to not cause a delay in Lilly's or such affiliate transferee's, as applicable, proposed sale, transfer or other disposition of such securities.

16. MISCELLANEOUS.

(a) NO INCONSISTENT AGREEMENTS. The Company will not hereafter enter into any agreement with respect to its securities which is inconsistent with or violates the rights granted to the Holders of Registrable Securities in this Agreement without the prior written consent of a majority in interest of such Registrable Securities.

(b) REMEDIES. Any Person having rights under any provision of this Agreement will be entitled to enforce such rights specifically to recover damages caused by reason of any breach of any provision of this Agreement and to exercise all other rights granted by law. The parties hereto agree and acknowledge that money damages may not be an adequate remedy for any breach of the provisions of this Agreement and that any party may in its sole discretion apply to any court of law or equity of competent jurisdiction (without posting any bond or other security) for specific performance and for other injunctive relief in order to enforce or prevent violation of the provisions of this Agreement; provided, however, that in no event shall any Holder have the right to enjoin, delay or interfere with any offering of securities by the Company which is not in violation of the provisions of Section 5(a) above.

(c) AMENDMENTS AND WAIVERS. Except as otherwise provided herein, the provisions of this Agreement may be amended or waived only with the prior written consent of the Company and Holders of at least 50% of the Registrable Securities; provided, however, that without the prior written consent of all the Holders, no such amendment or waiver shall reduce the foregoing percentage required to amend or waive any provision of this Agreement. Notwithstanding the foregoing, Section 14 may be amended or waived only with the prior written consent of the Company and Lilly.

(d) SUCCESSORS AND ASSIGNS. All covenants and agreements in this Agreement by or on behalf of any of the parties hereto will bind and inure to the benefit of the respective successors and assigns of the parties hereto, and shall inure to the benefit and be enforceable by each Holder of Registrable Securities from time to time.

(e) SEVERABILITY. Whenever possible, each provision of this Agreement will be interpreted in such manner as to be effective and valid under applicable law, but if any provision of this Agreement is held to be prohibited by or invalid under applicable law, such provision will be ineffective only to the extent of such prohibition or invalidity, without invalidating the remainder of this Agreement.

(f) COUNTERPARTS. This Agreement may be executed simultaneously in two or more counterparts, any one of which need not contain the signatures of more than one party, but all such counterparts taken together will constitute one and the same Agreement.

(g) DESCRIPTIVE HEADINGS. The descriptive headings of this Agreement are inserted for convenience only and do not constitute a part of this Agreement.

(h) GOVERNING LAW. All questions concerning the construction, validity and interpretation of this Agreement will be governed by the laws of the State of Delaware without regard to principles of conflicts of laws, except that all issues concerning the relative rights of the Company and its stockholders shall be governed by the Delaware General Corporation Law, without giving effect to the principles thereof relating to conflicts of laws.

(i) NOTICES. All notices, demands and requests of any kind to be delivered to any party in connection with this Agreement shall be in writing and shall be deemed to have been duly given if personally delivered or if sent by nationally-recognized overnight courier or by registered or certified airmail, return receipt requested and postage prepaid or by facsimile transmission (with receipt confirmed by telephone), addressed as follows:

(i) if to the Company, to:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
Facsimile: (760) 931-9639
telephone confirmation required at (760) 603-2460
Attention: B. Lynne Parshall

with a copy to:

Cooley Godward LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121
Facsimile: (858) 453-3555
telephone confirmation required at (858) 550-6000
Attention: Julie M. Robinson, Esq.

(ii) if to Lilly, to:
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
Facsimile: (317) 433-3000
telephone confirmation required at (317) 276-2703
Attention: Rebecca O. Kendall, Esq., Senior Vice President and General Counsel

with a copy to:

Facsimile: (317) 277-7979
telephone confirmation required at (317) 276-5624
Attention: Richard D. Dimarchi, Ph.D., Group Vice President, Lilly Research Center

(j) ENTIRE AGREEMENT. This Agreement constitutes the full and entire understanding and agreement between the parties with regard to the subject matter hereof.

[Signature page follows]

IN WITNESS WHEREOF, the parties have executed this Registration Rights and Standstill Agreement as of the date first written above.

ISIS PHARMACEUTICALS, INC.

By: /s/ B. Lynne Parshall

Name: B. Lynne Parshall
Title: Executive Vice President and Chief Financial Officer

ELI LILLY AND COMPANY

By: /s/ Sidney Taurel

Name: Sidney Taurel
Title: Chairman of the Board, Chief Executive Officer and President

Exhibit 2.4

*Text Omitted and Filed Separately
Confidential Treatment Requested
Under 17 C.F.R. Sections 200.80(b)(4)
200.83 and 240.24b-2

COLLABORATION AGREEMENT

BETWEEN

ELI LILLY AND COMPANY

AND

ISIS PHARMACEUTICALS, INC.

AUGUST 17, 2001

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COLLABORATION AGREEMENT

THIS COLLABORATION AGREEMENT (the "AGREEMENT") is entered into as of August 17, 2001 and effective as of the Effective 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.

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 [*] All decisions related to selection and advancement of Lilly Products being developed by Lilly outside the scope of the Collaboration Programs shall be made by Lilly.

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.

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 INITIAL OPERATING COMMITTEES. Without limiting the generality of the foregoing, the Joint Research Committee shall establish the following three (3) 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; and

(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.

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.

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

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 RESULTS OF LILLY FIRST PASS IN VITRO ANALYSIS. [*]

4.4 PROTECTED REAGENT TARGETS. [*]

4.5 ISIS USE OF REAGENT TARGETS AND REAGENT ASO COMPOUNDS. Except as provided otherwise in this Agreement, [*]

4.6 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. [*]

(i) [*]

(ii) [*]

(iii) [*]

[*]

4.7 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.

*Confidential Treatment Requested

4.8 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, (c) in accordance with Section 4.3 hereof or (d) as otherwise expressly permitted by this Agreement, but for no other purpose.

4.9 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 [*]

5.5.2 Isis shall provide written notice to Lilly [*]

5.6 REJECTED VALIDATION TARGETS. [*]

5.6.1 [*]

5.6.2 [*]

5.7 LILLY RIGHTS REGARDING OTHER TARGETS. [*]

*Confidential Treatment Requested

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, (c) in accordance with Section 4.3 hereof or (d) 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. 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. 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, 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.

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6.4.2 AFTER THE ANTISENSE DRUG DISCOVERY TERM. Subject to Section 6.5, after the Antisense Drug Discovery Term, Lilly shall make the decision of whether a Drug Discovery ASO Compound corresponding to a Drug Discovery Target that is the subject of an Active Program shall be designated a Development Candidate, using criteria substantially similar to those used by the Joint Research Committee during the Antisense Drug Discovery Term. Lilly shall have the option to license each Development Candidate in accordance with Section 8.2.3.

6.5 CONTINUED DEVELOPMENT OF DRUG DISCOVERY TARGETS AFTER THE ANTISENSE DRUG DISCOVERY TERM. Within ten (10) days following expiration or termination (subject to Article 13) of the Antisense Drug Discovery Term and again on the 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 until the [*] anniversary of the expiration or termination (subject to Article 13) of the Antisense Drug Discovery Term, Lilly

shall provide Isis with semiannual written reports describing the work conducted in the previous six (6) months on each such Drug Discovery Target and Drug Discovery ASO Compounds directed thereto in sufficient detail to permit Isis to verify that Lilly is maintaining an Active Program with respect thereto and notifying Isis of any such Drug Discovery Target with respect to which Lilly has discontinued an Active Program; PROVIDED, HOWEVER, such reports shall be given annually once such Drug Discovery Target has been licensed by Lilly under Section 8.2.3. Subject to the provisions of Article 13, for so long as Lilly maintains an Active Program with respect to a Drug Discovery Target after the expiration or termination of the Antisense Drug Discovery Term (but in no event to exceed [*] years after such expiration or termination), Lilly shall have the right to continue to perform research and development on such Drug Discovery Target and Drug Discovery ASO Compounds directed thereto.

6.6 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 not [*] PROVIDED,

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HOWEVER, that 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. 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. Within [*] days 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 above [*] in any one order Lilly shall pay for such extra quantity in an amount equal to [*] per gram or fraction thereof within [*] after receipt of such additional quantities of 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

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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 solely to the extent necessary or appropriate to carry out Lilly's responsibilities under the Collaborative Research Plan; 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 [*] days following the Section 8.2.2 Exercise Notice Date for a Reagent Target or Validation Target, Isis shall notify Lilly whether or not Isis has granted or assigned any rights to any Third Party as permitted by this Agreement with respect to such Reagent Target or Validation Target, or any ASO Compounds directed thereto as of the Section 8.2.2 Exercise Notice Date and the nature of the rights so granted, if any, or whether Isis has an Isis Internal Program with respect to such Reagent Target or Validation Target. Isis shall have no obligation to disclose to Lilly the identity of any such Third Party to which rights or licenses have been granted. If Isis has not granted any such rights or license and does not have an Isis Internal Program with respect to such Target as of the Section 8.2.2 Exercise Notice Date, then Isis shall grant to Lilly, and is hereby deemed to grant to Lilly, the license described above in this Section 8.2.2 with respect to such Reagent Target or Validation Target as of the Section 8.2.2 Exercise Notice Date and Lilly shall be obligated to make payments to Isis with respect to such Reagent ASO Product or Validation ASO Product directed to such Reagent Target or Validation Target, as applicable, in accordance

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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 six (6) months of such notice from Lilly, or within six (6) 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 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

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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 [*] months, 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 six (6) 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 six (6) 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:

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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) [*] 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

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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:

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(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 [*] months [*] 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.

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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.

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

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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 REAGENT TARGETS. For any Reagent ASO Compound delivered to Lilly by Isis under this Agreement that is directed to a Target that Lilly chooses to make a Protected Reagent Target pursuant to Section 4.4, Isis shall charge the Collaboration Funds an amount that is [*] above the amount that would otherwise be charged by Isis under Section 9.1.2 with respect to Reagent ASO Compounds to such Protected Reagent Target.

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.

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

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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.

9.2 TECHNOLOGY ACCESS FEE. If Lilly is conducting any research, development or commercialization activities relating to any Lilly Product as of the fourth (4th) 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 (4th) 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:

*Confidential Treatment Requested

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MILESTONE
EVENT
MILESTONE
PAYMENT
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[*] - --

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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 of the date that Lilly or the Collaboration, as applicable, performs the equivalent of the Lilly First Pass In Vitro Analysis with respect to 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, as reasonably evidenced by Lilly's laboratory notebooks or other scientific records.

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

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

(ii) [*] on the annual Net Sales of a Validation Non-ASO Product or Drug Discovery Non-ASO Product until the expiration of the last to expire Isis Collaboration Patent Right or Isis Patent Right that includes a Valid Claim that Covers such Validation Non-ASO Product or Drug Discovery Non-ASO Product.

9.3.3 REAGENT ASO PRODUCTS AND VALIDATION ASO PRODUCTS.

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

(b) MILESTONE PAYMENTS. Lilly will pay to Isis the following milestone payments for a Reagent ASO Compound being developed as a Reagent ASO Product or a Validation ASO Compound being developed as a Validation ASO Product within thirty (30) days after achievement of each of the following events in the first Major Market Country; PROVIDED, HOWEVER, that no milestone payment shall be due or owing for any Reagent ASO Compound or a Validation ASO Compound that has as its site of activity the same Target that is

the site of activity of any Lilly Product with respect to which such milestone payment has already been paid:

MILESTONE EVENT

MILESTONE PAYMENT
-- [*] -

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

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

WORLDWIDE ANNUAL SALES OF THE PRODUCT ROYALTY RATE
[*]

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

9.3.4 DRUG DISCOVERY ASO PRODUCTS.

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

DRUG DISCOVERY

ASO TARGET LICENSE FEE
[*]
[*]
[*]
[*]
[*]

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

MILESTONE PAYMENT
[*]
[*]
[*]
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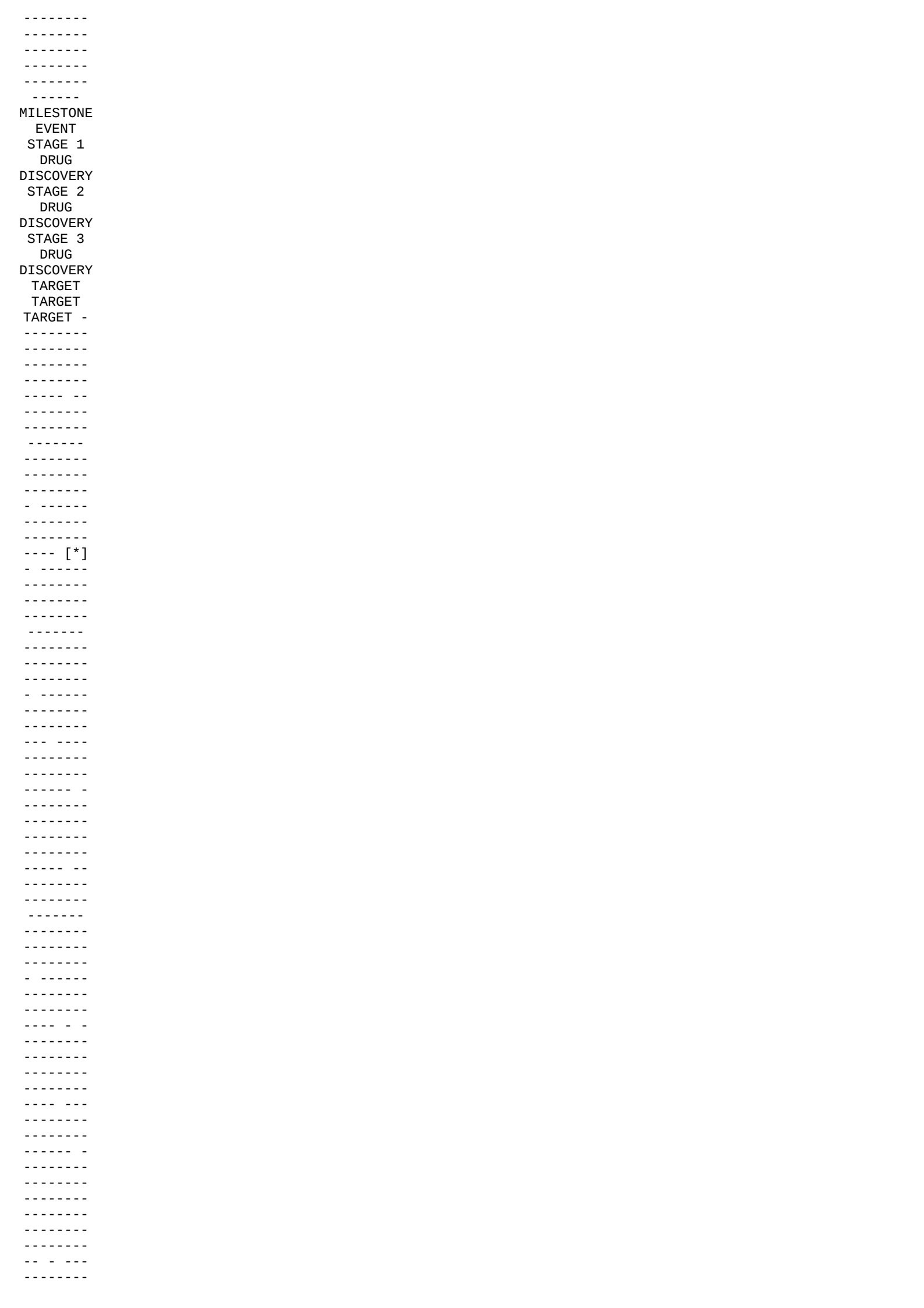
MILESTONE EVENT
STAGE 1 DRUG DISCOVERY
STAGE 2 DRUG DISCOVERY
STAGE 3 DRUG DISCOVERY
TARGET
TARGET
TARGET -
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PROVIDED, HOWEVER, that with respect to any Combination Product that contains more than one (1) Drug Discovery ASO Compound, Lilly shall be 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. 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	
STAGE 2 DRUG DISCOVERY	
STAGE 3 DRUG TARGET	
TARGET DISCOVERY	

TARGET -

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[*] - --

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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 [*]

9.5 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 exceed [*] of Net Sales in the aggregate; and

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

-- STAGE AT WHICH LILLY'S LICENSE TO A ISIS DRUG DISCOVERY ASO ROYALTY RATE PRODUCT WAS

TERMINATED

[*]

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 ROYALTY RATE PRODUCT WAS TERMINATED

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

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

9.10 INFLATION. The increments of annual Net Sales tiers set forth in Sections 9.3.3(c) or 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; or (f) 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 (f) 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; or (f) 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 (f) 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 for [*] 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

*Confidential Treatment Requested

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. 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.

13.2 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 (4th) 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 [*] days following the date of termination of this Agreement by Lilly under Section 13.4 or 13.5, and such Validation Targets shall be deemed licensed by Lilly under Section 8.2.2; PROVIDED, HOWEVER, that: (i) with respect to each such Validation Target, no license fee shall be payable by Lilly under Section 9.3.2(a) until the date that is [*] years after the Effective Date and, prior to such date, Lilly may terminate its license with respect to any such Validation Target by providing written notice to Isis and no license fee shall be owed by Lilly with respect to such Validation Target; (ii) the provision regarding diligence set forth in Section 8.2.2(c) shall not apply until [*] years after the Effective Date; and (iii) Lilly's milestone payment obligations set forth in Section 9.3.3(b) and royalty payment obligations set forth in Section 9.3.3(c) shall continue; PROVIDED, HOWEVER, that the amounts of the milestone and royalty payments shall be decreased to reflect the nature of Isis' breach and the damages caused thereby by amounts to be agreed upon by the Parties or, if the Parties are unable to reach agreement, by an independent Third Party with the requisite expertise selected by the Parties, the expense of which shall be borne by Isis;

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(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) Lilly's obligations under Section 4.3 shall cease;

(j) 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;

(k) 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

(l) 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

HART-SCOTT-RODINO FILING

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 if [*] 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, 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.

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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 Counsel
Telephone: 317-276-2703
Facsimile: 317-277-3977

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/ Sidney Taurel	By: /s/ B. Lynne Parshall
Sidney Taurel	B. Lynne Parshall
Chairman of the Board, Chief Executive Officer and President	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.

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"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 ASO PRODUCT" means a Drug Discovery ASO Product or Validation ASO Product.

"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 inflammation, bone, and metabolism (E.G., diabetes and obesity).

"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 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.

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"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 the last date on which the last Party executes this Agreement or, if later, the next day following the expiration or earlier termination of any notice and waiting period under The Hart-Scott-Rodino

Antitrust Improvements Act of 1976, as amended.

"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 or [*] hours per year (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" means [*]

"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

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which can reasonably be screened within three to six months using Isis' combined RTS and HTS resources.

"HTS STANDARD COST" [*]

"IDT AGREEMENT" means that certain agreement between Isis and Integrated DNA Technologies, Inc., effective March 12, 1999, and any amendments thereto.

"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.

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"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 FIRST PASS IN VITRO ANALYSIS" means [*]

"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 this 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.

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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.

"NOVARTIS AGREEMENT" means that certain agreement between Isis and Ciba-Geigy Limited (now Novartis AG) effective June 3, 1996, and all amendments thereto.

"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.

"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.

"PHASE III STUDY INITIATION" means the first human clinical trial conducted in patients and designed to establish Product safety and efficacy and required to obtain clinical registration of a product with health regulatory authorities such as the FDA.

"PRODUCT" shall mean a Lilly Product or an Isis Product, as applicable.

"PROGRAM SANCTION APPROVAL" means [*]

"PROJECT SANCTION APPROVAL" means [*]

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"PROPOSED VALIDATION TARGET" has the meaning set forth in Section 5.2.

"PROTECTED REAGENT 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.

"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

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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

DELETE IN ENTIRETY

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

DELETED IN ENTIRETY

SCHEDULE 8.8

TECHNOLOGY TRANSFER TERMS

DELETED IN ENTIRETY

SCHEDULE A

EXISTING ISIS INTERNAL PROGRAMS

DELETED IN ENTIRETY

SCHEDULE B

ISIS MANUFACTURING PATENT RIGHTS

DELETED IN ENTIRETY

SCHEDULE C

ISIS CORE TECHNOLOGY PATENT RIGHTS

DELETED IN ENTIRETY

Exhibit 2.5

*Text Omitted and Filed Separately
Confidential Treatment Requested
Under 17 C.F.R. Sections 200.80(b)(4)
200.83 and 240.24b-2

DEVELOPMENT AND LICENSE AGREEMENT

BETWEEN

ELI LILLY AND COMPANY

AND

ISIS PHARMACEUTICALS, INC.

DEVELOPMENT AND LICENSE AGREEMENT

THIS DEVELOPMENT AND LICENSE AGREEMENT (the "Agreement") is made as of August 14, 2001 (the "Signing Date") between Eli Lilly and Company, a corporation organized and existing under the laws of the State of Indiana ("LILLY") and Isis Pharmaceuticals, Inc., a corporation organized and existing under the laws of the State of Delaware ("ISIS").

RECITALS

WHEREAS, ISIS has discovered ISIS 3521, an antisense oligonucleotide, and is developing a product containing ISIS 3521 for the treatment of cancer; and

WHEREAS, LILLY and ISIS desire to enter into an agreement whereby LILLY will complete the development of, and commercialize the ISIS 3521 product upon the terms and conditions set forth herein;

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

ARTICLE 1

DEFINITIONS

Capitalized terms used in this Agreement have the meanings set forth in Exhibit A.

ARTICLE 2

DEVELOPMENT PROGRAM

2.1 GENERAL.

(a) ISIS will use commercially reasonable efforts to complete ongoing clinical trials and studies of the Product for non-small cell lung cancer and non-Hodgkin's lymphoma, as further described in the Development Plan set forth in Exhibit C hereto, and will participate in related activities, including the provision of consulting support to LILLY, in furtherance of the Development Program under the terms and conditions set forth in this Agreement.

(b) LILLY will undertake all future clinical trials and studies of the Product as further described in the Development Plan. LILLY will provide financial and other support for the Development Program and, other than as provided in subsection (a) above, will be responsible for implementing the Development Plan.

(c) While the parties will endeavor to reach a consensus with respect to amendments to the Development Plan and decisions affecting the Development Program, all final decisions regarding the content of the Development Plan and conduct of the Development Program will be made by LILLY after consideration of ISIS' input as provided in Section 2.2(a) below; provided, however, that ISIS cannot be compelled by LILLY to perform any studies or other tasks without its consent; and provided further that LILLY will provide ISIS with reasonable advance notice of any proposed changes to the Development Plan relating to ISIS's participation.

2.2 JOINT DEVELOPMENT COMMITTEE.

(a) For so long as ISIS is performing work pursuant to the Development Plan, the Development Program will be conducted under the overall oversight of a joint development committee ("JDC") comprised of 2 representatives each from LILLY and ISIS. Each party will designate a representative as a project leader to serve as the contact person for that party. The parties may agree to add additional members to the JDC, as long as equal representation is maintained. LILLY will designate one of its representatives as chairman of the JDC. In the event of a tied vote, the JDC chairman will have final decision-making authority.

(b) The JDC will be responsible for overseeing the parties' performance of the Development Program and for making strategic decisions related to that program. The JDC will be responsible for approving or disapproving any amendments to the Development Plan proposed by either party. The JDC will provide to the parties copies of the amended Development Plan promptly after approval by the JDC.

(c) During the term of ISIS's participation in the Development Program, the JDC will meet on a regular basis, and at least quarterly, either in person, or as the parties otherwise may agree. The JDC will review the progress of the activities carried out under the Development Program and will consider proposed modifications to the strategy and goals of that program. The frequency, dates and times of all meetings will be mutually agreed upon by the parties, as will the location for face-to-face meetings, alternating between Indianapolis, Indiana and Carlsbad, California, or such other location as members of the JDC will agree. At its first meeting, the JDC will decide upon the organizational rules under which it will operate during the term of this Agreement.

(d) Upon completion of the activities required to be performed by ISIS under the Development Plan, the JDC will be disbanded, and LILLY will assume full control over the conduct of the Development Program. However, ISIS and LILLY will meet to discuss the plans for and the progress of development of the Product on a semi-annual basis for the duration of the clinical development of the Product. Such meetings may be held in conjunction with the meetings of LILLY's Therapeutic Area Steering Committee for Oncology (or any successor committee or group charged with the oversight of the development of the Product).

2.3 DEVELOPMENT PROGRAM; ROLES AND RESPONSIBILITIES OF ISIS AND LILLY.

(a) ISIS' RESPONSIBILITIES.

(i) The activities to be undertaken by ISIS in the course of the Development Program are set forth in the Development Plan attached hereto as Exhibit C, as amended from time to time by the JDC. ISIS will not initiate any activities with the Product not provided for in the Development Plan, except with the approval of the JDC.

(ii) A budget estimate and related assumptions for certain activities to be undertaken by ISIS in the course of the Development Program and certain other activities to be undertaken by ISIS pursuant to the Supply Agreement are set forth in Exhibit E. The budget is a good faith estimate only of the activities described in the assumptions, and actual labor and expenses will be determined by more detailed work plans and approved by the JDC.

(iii) ISIS will conduct its portion of the Development Program in a

good scientific manner and in compliance in all material respects with all requirements of applicable laws, rules and regulations, including cGCPs, cGLPs and cGMPs, to achieve the objectives efficiently and expeditiously. ISIS will proceed diligently with the ISIS projects set out in the Development Plan using commercially reasonable efforts, such efforts to be at least equivalent to those efforts that ISIS uses on its own products of similar commercial potential value and at a similar stage of the product life cycle, to provide sufficient time, effort, equipment, facilities and skilled personnel.

(iv) ISIS will perform CMC activities, technology transfer activities, and various additional activities in support of the Development Program and the NDA, all as further described in the Supply Agreement.

(v) ISIS will provide LILLY with all reasonable assistance and take all actions reasonably requested by LILLY, at LILLY's expense and without changing the allocation of responsibilities assigned in the Development Plan, that are necessary or desirable to enable LILLY to comply with the terms and intent of this Agreement.

(b) LILLY'S RESPONSIBILITIES.

(i) The activities to be undertaken by LILLY in the course of the Development Program are set forth in the Development Plan attached hereto as Exhibit C, as amended from time to time by the JDC. LILLY will use commercially reasonable efforts, such efforts to be at least equivalent to those efforts that LILLY uses on its own products of similar commercial potential value and at a similar stage of the product life cycle, to develop and obtain Marketing Approval for the Product in all Major Markets and to maximize the commercial value of the Product.

(ii) LILLY will conduct its portion of the Development Program in a good scientific manner and in compliance in all material respects with all requirements of applicable laws, rules and regulations, including cGCPs, cGLPs and cGMPs, to achieve the objectives efficiently and expeditiously. LILLY will proceed diligently with the LILLY projects set out in the Development Plan using commercially reasonable efforts, such efforts to be at least equivalent to those efforts that LILLY uses on its own products of similar commercial potential value and at a similar stage of the product life cycle, to provide sufficient time, effort, equipment, facilities and skilled personnel.

(iii) LILLY will provide ISIS with all reasonable assistance and take all actions reasonably requested by ISIS, at LILLY's expense and without changing the allocation of responsibilities assigned in the Development Plan, that are necessary or desirable to enable ISIS to comply with the terms and intent of this Agreement.

2.4 FUNDING OF DEVELOPMENT PROGRAM.

(a) LILLY will pay to ISIS US$20,000,000 for the conduct and conclusion of preclinical and clinical studies relating to Product and conducted by ISIS, including the pivotal, on-going Phase III study. Such payment will be made within [*] days after the Effective Date, and LILLY will use its best efforts to make such payment no later than September 30, 2001.

(b) LILLY will pay to ISIS [*] for the budgeted expenses in the third Calendar Quarter of 2001 and [*] for the budgeted expenses in the fourth Calendar Quarter of 2001 for work performed by ISIS through December 31, 2001. Such payment will be made within [*] days after the Effective Date, and LILLY will use its best efforts to make such payment no later than September 30, 2001.

(c) LILLY will pay for all activities as described in the Development Plan or as approved by the JDC and performed by ISIS in the course of the Development Program beginning January 1, 2002 on a time and materials basis, including Cost of Manufacture of API used by ISIS in the performance of the Development Program. Labor will be billed at the ISIS FTE Rate, and Out-of-Pocket Expenses will be passed through to LILLY at actual cost on a dollar-for-dollar basis.

(d) LILLY will pay ISIS for such activities referred to in Article 2.4(c) on a quarterly basis [*] for the time and Out-of-Pocket Expenses budgeted to be expended by ISIS in the performance of the Development Plan during the [*] Calendar Quarter. ISIS will submit an invoice for such expenditures to LILLY [*] days prior to the beginning of each Calendar Quarter beginning in 2002, and LILLY will pay such invoices within [*] days from date of invoice. Within [*]days after the end of each Calendar Quarter, ISIS will provide to LILLY a statement reconciling the budgeted expenditures and the actual expenditures incurred by ISIS in the performance of the Development Plan during the preceding Calendar Quarter. Any amounts over- or underpaid by LILLY will be credited

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against or charged to LILLY with the next invoice prepared by ISIS as provided above. Interest will be charged on late payments as provided in Section 5.6.

(e) Materials for use in clinical studies conducted by or for LILLY will be paid in accordance with Section 5.1 of the Supply Agreement as described in Exhibit 7 of the Supply Agreement.

(f) LILLY will pay all costs of the Development Program, whether incurred by ISIS (in accordance with the Development Plan or as approved by the JDC) or by LILLY, and will perform and pay for any other activities LILLY desires to conduct or which are required to fulfill its obligations hereunder.

2.5 COMMERCIALIZATION.

(a) Prior to the launch of a Product, LILLY will prepare a global integrated Product plan outlining the key aspects of market launch and commercialization (the "Integrated Product Plan" or IPP). The Integrated Product Plan will contain information customarily contained in LILLY's commercialization plans, including Product charter, strategic intent, a market analysis (event maps - demographics, market dynamics), label need and wants (based on the Development Plan), Product life overview, geographic overview and financial overview. In addition, a global marketing plan will be developed which includes analysis of market (disease overview, Product profile, archetype, patient segmentation), strategic ends (strategic intent, product positioning, brand character, core messages, critical success factors, marketing objectives), strategic means (global Product, place, price, promotion, launch, market research programs), operational plan (implementation plan, marketing activities) and budget for the execution of the plan. Each plan will be updated annually in accordance with LILLY's internal planning and budgeting process.

(b) LILLY will provide to ISIS a copy of the final draft of the IPPs (original and updates) for each Major Market. LILLY and ISIS will meet to discuss the draft IPPs and LILLY will consider, in its discretion, any proposals and comments made by ISIS for incorporation in the final Commercialization Plan.

(c) As soon as is commercially reasonable and practicable after Marketing Approval and pricing approval, if necessary, have been obtained in a particular country, LILLY will commence and continuously market, promote, sell and distribute the Product in each such country. As used in this Article 2.5, "commercially reasonable" means efforts at least equivalent to those efforts that LILLY uses on its own products of similar commercial potential value and at a similar stage of the product life cycle.

(d) LILLY will use commercially reasonable efforts to Manufacture, market, promote, distribute and sell the Product on a worldwide basis, and LILLY will apply resources and expend funds in connection with such activities in a manner and to an extent consistent with and comparable to LILLY's own oncology pharmaceutical products of similar commercial potential at a similar stage of the product life cycle.

2.6 REGULATORY COOPERATION

(a) The parties will provide each other with all reasonable assistance and take all actions reasonably requested by the other party, at LILLY's expense and without changing the allocation of responsibilities assigned in the Development Plan, that is necessary or desirable to enable the other party to comply with the terms and conditions of this Agreement, and any law or regulation applicable to the Product, including the parties meeting their reporting and other obligations to (i) obtain, maintain, and update Marketing Approval application or Marketing Approval for the Product and any filings under this Agreement or the Development Plan, (ii) report adverse drug experience reports and serious adverse drug experience reports to the FDA and/or other governmental or Regulatory Authorities and (iii) submit or file promotional materials with the FDA and/or other governmental or Regulatory Authorities.

(b) Such assistance and actions will include keeping the other party informed, commencing within 48 hours of notification of any action by, or notification or other information which it receives from, the FDA or any other governmental or Regulatory Authority, which (a) raises any material concerns regarding the safety or efficacy of the Product, (b) which indicates or suggests a potential material liability for either party to third parties arising in connection with the Product, or (c) which is reasonably likely to lead to a recall or market withdrawal of the Product.

(c) Information that will be disclosed pursuant to this Section 2.6 will include:

1. governmental or Regulatory Authority inspections of Manufacturing, distribution or other related facilities; inquiries by governmental or Regulatory Authorities concerning clinical investigation activities (including inquiries of investigators, clinical monitoring organizations and other related parties); any communication from governmental or Regulatory Authorities involving the Manufacture, sale, promotion or distribution of Product or any other governmental or Regulatory Authority reviews or inquiries relating to the Product;

2. receipt of a warning letter or other notice of alleged non-compliance with FDA laws or regulations from the FDA relating to the Product; and

3. an initiation of any governmental or Regulatory Authority investigation, detention, seizure or injunction concerning the Product.

2.7 RECORDS.

(a) Each party will maintain records, in sufficient detail and in good scientific manner, which will fully and properly reflect all work done and results achieved in the performance of its responsibilities under the Development Plan. Each party will have the right, during normal business hours and upon reasonable prior notice, to inspect and copy those records of the other party referred to herein that are necessary or useful to the inspecting party for the purposes of making any required filings with Regulatory Authorities in

order to obtain Manufacturing Approvals and/or Marketing Approvals. Each party will maintain such records and the information disclosed therein in confidence in accordance with Article 4.

(b) In addition to the foregoing, LILLY will have the right to arrange for its employees and/or consultants involved in the activities contemplated hereunder to visit the offices, laboratories and other facilities of ISIS where activities of the Development Program are being performed during normal business hours and upon reasonable notice, subject to any restrictions imposed by ISIS in order to protect the confidentiality of programs, activities and information unrelated to the Development Program or ISIS 3521.

ARTICLE 3

GRANT OF RIGHTS; REPLACEMENT PRODUCT; TARGET EXCLUSIVITY

3.1 LICENSE GRANTS.

(a) ISIS hereby grants to LILLY an exclusive, worldwide, sublicensable, royalty-bearing license under the ISIS Patent Rights to make, have made, use, import, offer for sale and sell the Product.

(b) ISIS hereby grants to LILLY a non-exclusive, worldwide, sublicensable, royalty-bearing license under the Core Technology Patent Rights only to the extent such license is required for LILLY to effectively practice the license granted to LILLY under subsection (a) above and to fulfill its duties and obligations hereunder.

(c) ISIS retains the right to practice under the ISIS Patent Rights as necessary to carry out ISIS' obligations under this Agreement and the Supply Agreement, and for any purpose other than to make, have made, use, import, offer for sale and sell the Product. LILLY will not practice the ISIS Patent Rights and the Core Technology Patent Rights other than as expressly licensed in subsection (a) and (b) above.

(d) Any sublicense granted by LILLY under this Agreement is subject to and will be consistent with the terms and conditions of this Agreement. The grant of any such sublicense hereunder will not relieve LILLY of responsibility for its obligations under this Agreement, including ensuring that such sublicensees will perform such obligations as required. LILLY will promptly provide ISIS with copies of those sublicenses as well as Sublicensee contact information.

3.2 UPSTREAM LICENSES AND ACQUISITION OF PATENT RIGHTS.

(a) The parties will consult about the need to license any patents Controlled by Third Parties that claim the composition of matter of ISIS 3521 or the method of use of ISIS 3521 in the field of oncology. If it is agreed that there is a need for a license or to acquire any such patent, the parties will negotiate in good faith regarding (i) the share of the financial

obligations relating to the license or acquisition that each party will bear; (ii) the compensation of any acquisition costs incurred in connection with obtaining the patent rights; and (iii) an agreement by the parties to abide by all terms of the agreement under which the patent rights are granted.

(b) In the event that (i) ISIS has obtained Control of a Patent claiming Core Technology Improvements during the term of this Agreement, or (ii) a change in the Manufacturing Process requires access of LILLY to Manufacturing Patent Rights or Manufacturing Technology Improvements Controlled by ISIS that were not practiced in the Manufacture of the Product prior to such change (the "Additional Rights"), and LILLY wishes to obtain access to such Additional Rights under this Agreement, then the license from ISIS to LILLY of such Additional Rights pursuant to Section 3.1(a) and (b) (the "Downstream License") is conditioned on the prior agreement to be negotiated in good faith by the parties regarding (1) the assumption by LILLY of all financial obligations to ISIS' licensors or collaborators, if any, arising from the grant to LILLY of the Downstream License and the practice under such Downstream License by LILLY, its Affiliates or Sublicensees; (2) the compensation of a reasonable portion of any acquisition costs paid by ISIS to its licensors or collaborators in connection with obtaining Control of such Additional Rights; and (3) an agreement by LILLY to abide by all terms that ISIS is obligated to have any person that accesses such Additional Rights abide by under the agreement under which ISIS has obtained or retained Control of such Additional Rights.

3.3 REPLACEMENT PRODUCT OPTION.

(a) In the event LILLY decides to abandon the Development of the Product because of an unfavorable outcome of a Pivotal Trial or other technical failure, failure to obtain a Marketing Approval of the Product or unfavorable market conditions associated with commercialization of the Product, LILLY will have the right to terminate this Agreement and the Supply Agreement with written notice to ISIS, and all rights to ISIS 3521 will be returned to ISIS.

(b) Upon such termination, all licenses granted under this Agreement terminate, and LILLY will assign and transfer to ISIS all its rights and Information relating specifically to ISIS 3521 obtained or generated by LILLY during the term of the Agreement. For clarification, data relating to other LILLY products, including Gemzar and Alimta will

not be returned, provided that ISIS will have the right to access and reference data obtained in combination trials of ISIS 3521 and other LILLY products after consultation with LILLY to ensure a reasonable use of such data in compliance with applicable laws and regulations.

(c) Upon termination of this Agreement pursuant to subsection (a) above, LILLY will have the right to obtain a license to another antisense therapeutic compound Controlled by ISIS that is not further advanced in development than ISIS 3521 as of the Effective Date. The terms of the license agreement under which such license is granted will be substantially similar to the terms of this Agreement, except that ISIS will waive any up-front license fees.

3.4 TARGET EXCLUSIVITY.

ISIS will not commercialize any antisense compounds and products that target the genetic sequence of [*] This obligation will expire upon the earlier of (i) expiration of the Agreement, or (ii) termination by LILLY of its activities directed to the development or commercialization of the Product.

ARTICLE 4

CONFIDENTIALITY AND PUBLICATION

4.1 NONDISCLOSURE OBLIGATION.

All Proprietary Information disclosed by one party to the other party hereunder will be maintained in confidence by the receiving party and will not be disclosed to a Third Party or Affiliate or used for any purpose except as set forth below.

4.2 PERMITTED DISCLOSURES.

A party may disclose Proprietary Information received from the other party:

(a) to governmental or other regulatory agencies in order to obtain Patents, for SEC or tax purposes as required by law, to obtain approval to conduct clinical trials, or to gain Marketing Approval; provided that such disclosure may be made only to the extent reasonably necessary to obtain such patents, purposes or approvals;

(b) to Affiliates, Sublicensees, agents, consultants, and/or other Third Parties for the development, Manufacturing and/or marketing of the Product (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 obligations contained in this Agreement, provided the term of confidentiality for such Affiliates and Third Parties will be no less than 7 years; or

(c) if such disclosure is required by law, including without limitation disclosures required by court order, provided that notice is promptly delivered to the other party in order to provide an opportunity to challenge or limit the disclosure obligations.

4.3 PUBLICATION.

(a) LILLY agrees that it is customary in the industry to publish results obtained from clinical trials and other studies of the Product, and that ISIS may publish such information obtained by ISIS in the performance of the Development Program, subject to the provisions of this Section 4.3.

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(b) Except as provided otherwise herein, the parties will be entitled to publish or present on the results of the Development Program, ISIS 3521 and the Product, provided that the party seeking to publish will deliver to the other party for its review a copy of any proposed publication or an abstract of any oral presentation of clinical results at scientific meetings involving ISIS 3521, the Product, or the Proprietary Information of the other party, at least [*] prior to submission of scientific publications and [*] with respect to abstracts

of oral presentations. The reviewing party will have the absolute right to request that any of its Proprietary Information be deleted from such publication or presentation, and the disclosing party will comply with that request. If the disclosing party does not receive any feedback from the reviewing party within that [*] period, respectively, the disclosing party will be free to proceed with the publication or presentation, with the following limitations:

(i) ISIS will be permitted to publish on matters relating to ISIS 3521 or Product during the term of this Agreement only upon the prior written approval of LILLY, which may be reasonably withheld by LILLY unless such publication is permitted to be made under any publication rights granted by ISIS to clinical investigators of the 3521 Product prior to the Effective Date.

(ii) LILLY will be permitted to publish on matters relating to any Manufacturing Technology or Manufacturing Technology Improvements during the term of this Agreement only upon the prior written approval of ISIS, which may be given at ISIS' sole discretion.

(c) The parties recognize that it may not be practical under all circumstances to comply with the [*] notice requirements for review of publications and abstracts as provided in subsection (b) above. Each party will reasonably review proposed publications and abstracts submitted by the other party as promptly as possible and will not unreasonably withhold its consent to such publications or presentations that have been submitted for review with less than the required notice period.

4.4 PUBLICITY.

(a) The parties will issue a joint press release regarding the execution of this Agreement.

(b) Except as otherwise provided herein or required by law, neither party will originate any publication, news release or other public announcement, written or oral, whether in the public press, or otherwise, about this Agreement, and neither party will use the name, trademark, trade name, logo or likeness of the other party or its employees in any publicity, news release or disclosure about this Agreement without the prior express written permission of the other party.

(c) The parties will inform each other of any press releases relating to the Product permitted hereunder or required to be made by law in advance of general release to the public.

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ARTICLE 5

PAYMENTS, ROYALTIES AND REPORTS

5.1 LICENSE FEE.

LILLY will pay to ISIS an up-front license fee of [*] Such payment will be made within [*] days after the Effective Date, and LILLY will use its best efforts to make such payment no later than September 30, 2001.

5.2 MILESTONE PAYMENTS.

(a) LILLY will pay to ISIS the following milestone payments with respect to the Product developed for the first Major Tumor within 30 days of the achievement of the corresponding milestone events:

MILESTONE EVENT	MILESTONE PAYMENT
[*]	

(b) LILLY will pay to ISIS the following milestone payments with respect to the Product developed for each Major Tumor subsequent to the first

Major Tumor within [*] of the achievement of the corresponding milestone events:

MILESTONE EVENT	MILESTONE PAYMENT
[*]	

(c) LILLY will inform ISIS within 10 days of achieving each milestone.

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5.3 ROYALTIES.

(a) LILLY will pay ISIS a royalty on Net Sales of the Product according to the schedule set forth below:

CONSOLIDATED WORLDWIDE ANNUAL NET SALES OF THE PRODUCT	ROYALTY RATE
[*]	

(b) The increments of the annual Net Sales tiers set forth in subsection (a) above will be adjusted for the immediately preceding Calendar Year as follows: the annual Net Sales of the Product set out above are in 2001 U.S. dollars. Such numbers will be adjusted upward on a Calendar Year basis commencing January 1, 2002 (and on January 1 of each year thereafter during the term of this Agreement) using the CPI for all urban consumer series ID CUUR0000SA0 as published from time to time by the US Bureau of Labor Statistics, where June 2001 was 178.

(c) If the Product is Manufactured in a country where such Manufacture does not infringe on any ISIS Patent Rights or Core Technology Patent Rights, and is sold in a country where the Manufacture, use, importation, offer for sale or sale of the Product does not infringe any ISIS Patent Rights or Core Technology Patent Rights in the country of sale, [*]

(d) If the royalty payable by LILLY [*]

(e) [*].

(f) The royalty payment obligation of LILLY under this Section will expire on a country-by-country basis upon the later of (i) expiration of a period of [*] from the date of First Commercial Sale in a particular country and (ii) the expiration of the last to expire Patent within ISIS Patent Rights and Core Technology Patent Rights in a particular country.

5.4 PAYMENT OF ROYALTY; REPORTS.

LILLY will provide to ISIS within [*] after the end of each Calendar Quarter a written report [*] LILLY will make royalty payments to ISIS for the Product sold during a Calendar Quarter within [*] of the last day of that Calendar Quarter. Each royalty payment will be accompanied by a written report for that Calendar Quarter showing the cumulative Net Sales of the Product sold by LILLY, its Affiliates and its Sublicensees on a country-by-country basis worldwide during the quarterly reporting period and the corresponding royalties payable under this Agreement.

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5.5 AUDITS.

(a) Upon the written request of ISIS and not more than once in each Calendar Year, LILLY will permit an independent certified public accounting firm of nationally recognized standing selected by ISIS and reasonably acceptable to LILLY, at ISIS' expense, to have access during normal business hours to those records of LILLY that may be necessary

to verify the accuracy of the royalty reports hereunder for any year ending not more than 24 months prior to the date of such request. ISIS will submit an audit plan, including audit scope, to LILLY for LILLY's approval, which will not be unreasonably withheld, prior to audit implementation. The accounting firm will disclose to ISIS only whether the royalty reports of LILLY are correct or incorrect, the specific details concerning any discrepancies, and the corrected amount of Net Sales. No other information will be provided to ISIS.

(b) At the request of ISIS, LILLY will direct its Affiliates to permit audits of the Affiliates' records in accordance with the provisions of subsection (a) above. Further, LILLY will include in each sublicense granted by it pursuant to this Agreement a provision requiring the Sublicensee to submit reports to LILLY, to keep and maintain records of sales made pursuant to such sublicense and to grant access to such records by ISIS' independent accounting firm, to the same extent required of LILLY under Sections 5.4 and 5.5. ISIS' independent accounting firm will be granted access to such reports in LILLY'S possession as part of the audit referenced in subparagraph (a) above.

(c) If ISIS' independent accounting firm determines that Net Sales were underreported or overreported and additional royalties are owed or have been overpaid, LILLY or ISIS will pay or repay the additional royalties within [*] days of the date ISIS delivers to LILLY such accounting firm's written report. The fees charged by such accounting firm will be paid by ISIS provided that, if the audit determines that the additional royalties payable by LILLY for such period exceed [*] of the royalties actually paid for such period, then LILLY will pay the reasonable fees and expenses charged by such accounting firm. If the audit conducted on behalf of ISIS reveals an overpayment by LILLY, LILLY will pay the fees and expenses charged by the accounting firm upon receipt of the payment by ISIS of such overpaid royalties.

(d) ISIS will treat all financial information subject to review under this Section 5.5 or under any sublicense agreement as Proprietary Information of LILLY in accordance with Article 4, and will cause its accounting firm to enter into an acceptable confidentiality agreement with LILLY and its Sublicensees obligating such accounting firms to retain all such financial information in confidence pursuant to such confidentiality and non-use provisions.

5.6 PAYMENT MODALITIES; FOREIGN CURRENCY CONVERSION; LATE PAYMENT CHARGES.

(a) All payments to be made by LILLY to ISIS under this Agreement will be made by LILLY in United States dollars and may be paid by bank wire transfer in immediately available funds to such bank account in the United States designated in writing by ISIS

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from time to time. If the payment is made from outside the U.S., LILLY will make the payment in a manner that will not result in a tax liability for ISIS larger than it would be if the payment were made from inside the U.S with no additional delays in payment when compared to the timing of payment made in the U.S.

(b) For purposes of calculating royalties due on Net Sales generated outside the United States, all Net Sales amounts in non-US currency will be converted into US dollars using LILLY's then current standard exchange rate methodology. This methodology is used by LILLY in the translation of its foreign currency operating results, is consistent with generally accepted accounting principles, is audited by LILLY's independent certified public accountants in connection with the audit of the consolidated financial statements of LILLY, and is used for external reporting of foreign currency operating results.

(c) LILLY will pay a late payment service charge of [*] per month [*] on all past-due amounts owed under this Agreement.

5.7 INCOME TAX WITHHOLDING.

ISIS will be responsible for its own tax liabilities resulting from the payments received from LILLY under this Agreement. If laws, rules or regulations require withholding of income taxes or other taxes imposed upon payments set forth in this Article 5, LILLY will make such withholding payments as required and subtract such withholding payments from the payments set forth in this Article 5. LILLY will submit appropriate proof of payment of the withholding taxes to

ISIS within a reasonable period of time.

ARTICLE 6

REPRESENTATIONS, WARRANTIES AND INDEMNIFICATION

6.1 REPRESENTATIONS AND WARRANTIES OF ISIS.

ISIS represents and warrants to LILLY that, as of the date of this Agreement:

(a) it has the full right, power and authority to enter into this Agreement, to perform the Development Program, to grant the licenses granted under Article 3 hereof, and to consummate the transaction contemplated herein;

(b) it has duly and properly taken all action required by its articles of incorporation and its bylaws to authorize the execution, delivery, and performance by it of this Agreement;

(c) this Agreement has been duly executed and delivered by ISIS and constitutes a legal, valid, and binding agreement of ISIS enforceable against it in accordance with its terms, except as enforcement may be affected by bankruptcy, insolvency, or other similar laws and by general principles of equity as applied by a court of competent jurisdiction;

*Confidential Treatment Requested

(d) it has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in ISIS Patent Rights in a manner that would interfere with ISIS' ability to grant the licenses granted to LILLY under this Agreement;

(e) it is the sole and exclusive owner the Compound Patent Rights, all of which are free and clear of any liens, claims and encumbrances;

(f) all Patents Controlled by ISIS as of the Effective Date that specifically claim the composition of matter or the use of ISIS 3521 are listed in Exhibit D under the heading of "Compound Patent Rights";

(g) all Patents Controlled by ISIS as of the Effective Date that are necessary for performing the process steps set forth in master batch records for ISIS 3521 in the version existing as of the Effective Date are listed in Exhibit D under the heading of "Manufacturing Patent Rights";

(h) to the best of ISIS' knowledge, the Manufacture, use and sale of ISIS 3521 and the Product do not infringe any Patents owned by any Third Party;

(i) there are no claims, judgments or settlements against or owed by ISIS or pending or threatened claims or litigation relating to the ISIS Patent Rights; and

(j) ISIS has disclosed to LILLY all patent opinions obtained by ISIS regarding ISIS Patent Rights.

6.2 REPRESENTATIONS AND WARRANTIES OF LILLY.

LILLY represents and warrants to ISIS that, as of the date of this Agreement:

(a) it has the full right, power and authority to enter into this Agreement, to perform the Development Program and to consummate the transaction contemplated herein;

(b) it has duly and properly taken all action required by its articles of incorporation and its bylaws to authorize the execution, delivery, and performance by it of this Agreement; and

(c) this Agreement has been duly executed and delivered by LILLY and constitutes a legal, valid, and binding agreement of LILLY enforceable against it in accordance with its terms, except as enforcement may be affected by bankruptcy, insolvency, or other similar laws and by general principles of equity as applied by a court of competent jurisdiction.

6.3 INDEMNIFICATION.

(a) ISIS will indemnify, defend and hold LILLY and its Affiliates, and their respective directors, officers, employees and agents ("LILLY Indemnitees") harmless against any and all losses, costs, liabilities and expenses (including reasonable attorneys' fees) ("Losses"), arising in connection with actions, suits, claims, demands and prosecution

that may be brought or instituted by Third Parties ("Third Party Claims") against LILLY Indemnitees to the extent based upon or arising out of (i) the gross negligence or willful misconduct of ISIS under this Agreement, or (ii) the material breach by ISIS of any warranty, representation or obligation of ISIS under this Agreement, except to the extent that such Losses are the result of (i) the gross negligence or willful misconduct of LILLY under this Agreement, or (ii) the material breach by LILLY of any warranty, representation or obligation of LILLY under this Agreement.

(b) LILLY will indemnify, defend and hold ISIS and its Affiliates, and their respective directors, officers, employees and agents ("ISIS Indemnitees"), harmless against any and all Losses arising in connection with Third Party Claims that may be brought or instituted against ISIS Indemnitees to the extent based upon or arising out of (i) the gross negligence or willful misconduct of LILLY under this Agreement, (ii) the material breach by LILLY of any warranty, representation or obligation of LILLY under this Agreement, or (iii) the Manufacture, use, import or sale by LILLY, its Affiliates or Sublicensees of ISIS 3521 or Product, except to the extent that such Losses are the result of (i) the gross negligence or willful misconduct of ISIS under this Agreement, or (ii) the material breach by ISIS of any warranty, representation or obligation of ISIS under this Agreement.

(c) A party that intends to claim indemnification under this Section (the "Indemnitee") will (i) notify the other party (the "Indemnitor") in writing of any Losses and Third Party Claims with respect to which the Indemnitee intends to claim indemnification as soon as practicable after the Indemnitee becomes aware of any such losses and claims; (ii) permit the Indemnitor to assume the defense thereof with counsel selected by the Indemnitor; and (iii) cooperate with the Indemnitor, at the Indemnitor's expense, in the defense thereof.

(d) Indemnitee will have the right to participate and be represented (at the Indemnitor's expense) by legal counsel of the Indemnitee's choice in all proceedings and negotiations, if representation by counsel retained by Indemnitor would be inappropriate due to actual or potential differing interests between the Indemnitee and any other party represented by such counsel in such proceedings.

(e) The indemnity agreement in this Section will not apply to amounts paid in settlement of any Third Party Claim if such settlement is effected without the consent of the Indemnitor, which consent will not be unreasonably withheld. The Indemnitor will not settle or compromise any Third Party Claim in any manner that admits fault on the part of the Indemnitee without the express prior written consent of the Indemnitee, which consent may be withheld for any reason or no reason.

(f) Failure of the Indemnitee to deliver notice to the Indemnitor within a reasonable time after becoming aware of potential Losses will not relieve the Indemnitor of any liability to the Indemnitee pursuant to this Section, except to the extent such delay prejudices the Indemnitor's ability to defend the Third Party Claim.

ARTICLE 7

INTELLECTUAL PROPERTY

7.1 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.

7.2 COMPOUND IMPROVEMENTS.

(a) The entire right, title, and interest in and to all Compound 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. LILLY hereby grants ISIS a worldwide, royalty-free, nonexclusive license to practice under LILLY's rights to any such LILLY Compound Improvements to carry out the activities contemplated by this Agreement.

(b) The entire right, title, and interest in and to all Compound 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, subject to the license granted to LILLY under Section 3.1.

(c) The entire right, title, and interest in and to all Compound 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 Compound Improvements, and may license its rights under such Compound Improvements for its own account and without the consent of the other party, subject to the license granted to LILLY under Section 3.1.

(d) Promptly after the filing of a patent application claiming a Compound Improvement, the filing party will disclose to the other party each Patent claiming such improvements.

7.3 CORE TECHNOLOGY IMPROVEMENTS.

(a) The entire right, title, and interest in and to all Core Technology 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. LILLY hereby grants ISIS a worldwide, royalty-free, sublicensable, perpetual, nonexclusive license to practice under LILLY's rights to any such LILLY Core Technology Improvements to carry out the activities contemplated by this Agreement, and to make, have made, use, import, offer for sale and sell products other than the Product.

(b) The entire right, title, and interest in and to all Core Technology 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, subject to the license granted to LILLY under Section 3.1.

(c) The entire right, title, and interest in and to all Core Technology 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 Core Technology Improvements, and may license its rights under such Core Technology Improvements for its own account and without the consent of the other party, subject to the license granted to LILLY under Section 3.1.

(d) Promptly after the filing of a patent application claiming Core Technology Improvements, the filing party will disclose to the other party each Patent claiming such improvements.

7.4 MANUFACTURING TECHNOLOGY IMPROVEMENTS.

(a) The entire right, title, and interest in and to all Manufacturing Technology 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. LILLY hereby grants ISIS a worldwide, royalty-free, sublicensable, perpetual, nonexclusive license to practice under LILLY'S rights to any such Manufacturing Technology Improvements to carry out the activities contemplated by this Agreement and to make, have made, use, import, offer for sale and sell products other than the Product.

(b) The entire right, title, and interest in and to all Manufacturing

Technology 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, subject to the license granted to LILLY under Section 3.1.

(c) The entire right, title, and interest in and to all Manufacturing Technology 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 Technology Improvements, and may license its rights under such Manufacturing Technology Improvements for its own account and without the consent of the other party, subject to the license granted to LILLY under Section 3.1.

(d) Promptly after the filing of a patent application claiming a Manufacturing Technology Improvement, the filing party will disclose to the other party each Patent claiming such improvements.

7.5 FILING, PROSECUTION AND MAINTENANCE OF PATENTS AND PATENT APPLICATIONS UNDER ISIS PATENT RIGHTS.

(a) During the term of this Agreement, LILLY will file, prosecute and maintain the Compound Patent Rights, any Patents filed on Compound Improvements owned solely by LILLY or jointly by ISIS and LILLY, and any Patents filed on Core Technology Improvements and Manufacturing Technology Improvements owned solely by LILLY (the "LILLY Patent Portfolio"), at its own expense, using patent counsel of its choice, but reasonably acceptable to ISIS. LILLY will keep ISIS advised of the status of the actual and prospective patent filings pursuant to this subsection (a) on a semi-annual basis and upon the request of ISIS, LILLY will provide copies of any papers related to the filing, prosecution and maintenance of such patent filings. If LILLY decides to discontinue the prosecution or maintenance of a Patent within the LILLY Patent Portfolio entirely or in a particular country, it will inform ISIS thereof with sufficient time for ISIS to assume the prosecution or maintenance of such Patent, and, if ISIS continues such prosecution or maintenance, such Patent in such country will thereafter be included in the ISIS Patent Rights hereunder, including, without limitation, for purposes of calculating royalties due and owing to ISIS hereunder.

(b) ISIS will be responsible for filing, prosecuting and maintaining worldwide the Manufacturing Patent Rights and any Patents filed on Core Technology Improvements and Manufacturing Technology Improvements owned jointly by ISIS and LILLY (the "ISIS Patent Portfolio"), at its expense, using patent counsel of its choice, but reasonably acceptable to LILLY. ISIS will keep LILLY advised of the status of the actual and prospective patent filings of Patents within the ISIS Patent Portfolio on a semi-annual basis and upon the request of LILLY, ISIS will provide copies of any papers related to the filing, prosecution and maintenance of such patent filings. If ISIS decides to discontinue the prosecution or maintenance of any Patent within the ISIS Patent Portfolio entirely or in a particular country, it will inform LILLY thereof with sufficient time for LILLY to assume the prosecution or maintenance of such Patent, and LILLY may assume such prosecution or maintenance if such Patent provides a substantial competitive advantage to LILLY with respect to any Product in the applicable country in coordination with any Third Party to whom ISIS has granted rights under such Patent if such Patent also provides a substantial competitive advantage to such Third Party in the applicable country.

7.6 INTERFERENCE, OPPOSITION, REEXAMINATION AND REISSUE.

(a) Either party will, within 10 days of learning of such event, inform the other party of any request for, or filing or declaration of, any interference, opposition, or reexamination relating to Patents within the LILLY Patent Portfolio and the ISIS Patent Portfolio. LILLY and ISIS will thereafter consult and cooperate fully to determine a course of action with respect to any such proceeding subject to the provisions of this Section set forth below.

(b) Any interference, opposition, reissue, or reexamination proceedings

relating to the LILLY Patent Portfolio will be conducted at LILLY'S expense. LILLY and ISIS will cooperate fully and will provide each other with any information or assistance that any party may reasonably request. LILLY will keep ISIS informed of developments in any such action or proceeding. Decisions on whether to initiate such a proceeding and the course of action in such proceeding, including settlement negotiations and terms, will be made by mutual agreement of ISIS and LILLY.

(c) Any interference, opposition, reissue, or reexamination proceeding relating to the ISIS Patent Portfolio will be conducted by ISIS at ISIS' expense. To the extent that such interference, opposition, reissue, or reexamination proceeding materially impacts the commercial value of the Product in the marketplace, LILLY and ISIS will cooperate fully and will provide each other with any information or assistance that either may reasonably request. ISIS will keep LILLY informed of developments in any such action or proceeding, including, to the extent permissible, the status of any settlement negotiations and the terms of any offer related thereto, except that ISIS must obtain LILLY'S consent to any settlement terms which materially affect LILLY'S freedom to operate under the licenses granted to LILLY under this Agreement.

7.6 ENFORCEMENT AND DEFENSE.

(a) Either party will, within 10 days of learning of such event, inform the other party of any infringement of Patents within the LILLY Patent Portfolio or the ISIS Patent Portfolio. LILLY and ISIS will thereafter consult and cooperate fully to determine a course of action including, without limitation, the commencement of legal action by either or both LILLY and ISIS, to terminate any infringement, subject to the provisions of this Section 7.6 set forth below.

(b) If there is any infringement of Patents within the LILLY Patent Portfolio, LILLY will have the first right to initiate and prosecute such legal action at its own expense and in the name of ISIS and LILLY, or to control the defense of any declaratory judgment action relating to Compound Patent Rights. LILLY will promptly inform ISIS if it elects not to exercise such first right and ISIS will thereafter have the right to either initiate and prosecute such action or to control the defense of such declaratory judgment action in the name of ISIS and, if necessary, LILLY.

(c) In the event that LILLY elects not to initiate and prosecute an action as provided in subsection (b), and ISIS elects to do so, the costs of any agreed-upon course of action to terminate infringement of Patents within the LILLY Patent Portfolio, including the costs of any legal action commenced or the defense of any declaratory judgment, will be borne by ISIS, except that the cost of any such action related solely to ISIS 3521 will be borne by LILLY.

(d) For any action by LILLY pursuant to subsection (b) above, in the event that LILLY is unable to initiate or prosecute such action solely in its own name, ISIS will join such action voluntarily and will execute and cause its Affiliates to execute all documents

necessary for LILLY to initiate litigation to prosecute and maintain such action. In connection with any action, LILLY and ISIS will cooperate fully and will provide each other with any information or assistance that either may reasonably request. Each party will keep the other informed of developments in any action or proceeding, including, to the extent permissible by law, the status of any settlement negotiations and the terms of any offer related thereto.

(e) If there is any infringement of Patents within the ISIS Patent Portfolio, ISIS will have the first right to initiate and prosecute such legal action at its own expense and in the name of ISIS and LILLY, or to control the defense of any declaratory judgment action relating to Patents within the ISIS Patent Portfolio. To the extent that infringement materially impacts the commercial value of the Product in the marketplace, ISIS will promptly inform LILLY if it elects not to exercise such first right and LILLY will thereafter have the right to either initiate and prosecute such action or to control the defense of such declaratory judgment action in the name of LILLY and, if necessary, ISIS.

(f) In the event that ISIS elects not to initiate and prosecute an action

as provided in subsection (e) above, and LILLY elects to do so, the costs of any agreed-upon course of action to terminate infringement of Patents within the ISIS Patent Portfolio, including the costs of any legal action commenced or the defense of any declaratory judgment, will be shared equally by ISIS and LILLY.

(g) For any action to terminate any infringement of Patents within the ISIS Patent Portfolio, in the event that ISIS is unable to initiate or prosecute such action solely in its own name, LILLY will join such action voluntarily and will execute and cause its Affiliates to execute all documents necessary for ISIS to initiate litigation to prosecute and maintain such action. In connection with any action, ISIS and LILLY will cooperate fully and will provide each other with any information or assistance that either may reasonably request. Each party will keep the other informed of developments in any action or proceeding, including, to the extent permissible by law, the status of any settlement negotiations and the terms of any offer related thereto.

(h) Except as provided otherwise herein, any recovery obtained by either or both LILLY and ISIS in connection with or as a result of any action contemplated by this Section, whether by settlement or otherwise, will be shared in order as follows:

(i) the party which initiated and prosecuted the action will recoup all of its costs and expenses incurred in connection with the action;

(ii) the other party will then, to the extent possible, recover its costs and expenses incurred in connection with the action;

(iii) the amount of any recovery remaining from actions relating to Compound Patents Rights, Manufacturing Technology Patents, Patents claiming Manufacturing Technology Improvements or Patents claiming Compound Improvements will then be allocated between the parties on a PRO RATA basis based on the amounts of

proportionate lost royalties of ISIS and lost profits of LILLY under which ISIS will receive a proportion based on the royalties it lost and LILLY will receive a proportion based on its lost profits.

7.7 PROSECUTION, MAINTENANCE, ENFORCEMENT AND DEFENSE OF PATENTS CONTROLLED BY ISIS.

ISIS will have the sole and exclusive right, in its sole discretion, to file, prosecute, enforce and defend any Patents within Core Technology Patent Rights and Patents claiming Compound Improvements, Manufacturing Technology Improvements and Core Technology Improvements Controlled by ISIS.

7.8 THIRD PARTY PATENTS.

If either party receives notice that a Product infringes a Third Party Patent, and the parties hereto agree to settle with and pay royalties to such Third Party, [*] If all the foregoing conditions are met, additional royalties payable to such Third Party [*]

7.9 CERTIFICATION UNDER DRUG PRICE COMPETITION AND PATENT RESTORATION ACT.

ISIS and LILLY each will immediately give notice to the other of any certification of which they become aware filed under the United States "Drug Price Competition and Patent Term Restoration Act of 1984" claiming that Compound Patent Rights or Manufacturing Patent Rights covering ISIS 3521 or Product are invalid or that infringement will not arise from the Manufacture, use or sale of ISIS 3521(s) or Product(s) by a Third Party. If ISIS or LILLY (depending on which party is defending the relevant ISIS Patent Rights) decides not to bring infringement proceedings against the entity making such a certification, such party will give notice to the other party of its decision not to bring suit within 21 days after receipt of notice of such certification. The party receiving such notice may then, but is not required to, bring suit against the party that filed the certification. Any suit by LILLY or ISIS will either be in the name of LILLY or in the name of ISIS, or jointly by LILLY and ISIS. For this purpose, the party not bringing Suit will execute such legal papers necessary for the prosecution of such suit as may be reasonably requested by the party bringing suit.

7.10 ABANDONMENT.

ISIS will promptly give notice to LILLY of the grant, lapse, revocation, surrender, invalidation or abandonment of any ISIS Patent Rights licensed to LILLY for which ISIS is responsible for the filing, prosecution and maintenance.

7.11 PATENT TERM RESTORATION.

The parties hereto will cooperate with each other in obtaining patent term restoration or supplemental protection certificates or their equivalents in any country worldwide where applicable to ISIS Patent Rights. In the event that elections with respect to obtaining such patent term restoration are to be made, LILLY will have the right to make the election and ISIS agrees to abide by such election.

7.12 PATENT STATUS.

At least 60 days before projected Marketing Approval of a Product, the parties will agree on which ISIS Patent Rights cover the manufacture, use or sale of such Product on a country-by-country basis, and such Patents will be deemed to be "relevant" to such Product. Within 60 days after each calendar year-end beginning upon Marketing Approval of a Product, ISIS will provide LILLY with a report describing the status of the ISIS Patent Rights relevant to such Product. Such report will include, at a minimum, the patent country, patent and application numbers, filing date, issue date, expiration date and any other relevant information for ISIS Patent Rights relevant to such Product. Such report will be mailed to:

Eli Lilly and Company
Attention: Royalty Administration D.C. 1064
Lilly Corporate Center
Indianapolis, IN 46285

ARTICLE 8

TERM AND TERMINATION

8.1 TERM AND EXPIRATION.

This Agreement will be effective as of the Effective Date and unless terminated earlier pursuant to Section 8.2 below, the term of this Agreement will continue in effect until expiration of all royalty obligations hereunder.

8.2 TERMINATION FOR CAUSE.

(a) This Agreement may be terminated upon written notice by either party to the other at any time during the term of this Agreement if the other party is in material breach of its obligations hereunder and has not cured such breach within 90 days after written notice requesting cure of the breach; providing, however, that in the event of a good faith dispute with respect to the existence of a material breach, the 90-day cure period will be stayed until such time as the dispute is resolved pursuant to Subsection 9.6 hereof.

(b) Upon material breach by ISIS of its obligations in the performance of the Development Program, if LILLY decides not to terminate the Agreement, LILLY will have the right to offset any costs it may incur as a result of curing such breach against the amounts payable to ISIS for the performance of such obligations. Further, to the extent that a party prevails in a law suit brought against the other party for material breach of this Agreement, such prevailing party will be entitled to collect from the other party reasonable attorneys' fees and legal costs incurred in connection with such law suit commensurate with extent that its claim is upheld.

8.3 EFFECT OF EXPIRATION OR TERMINATION.

(a) In the event this Agreement is terminated by either party under Section 8.2(a), LILLY's license pursuant to Section 3.1 will terminate as of such termination date. Promptly upon termination, the parties will

prepare a transition plan to ensure the seamless transition of any clinical studies and distribution and sales activities relating to the Product. Further, LILLY will transfer all Marketing Approvals to ISIS, and will instruct its patent counsel to coordinate transfer of the relevant patent files with ISIS. Once all such files and responsibilities have been assigned and/or transferred back to ISIS, LILLY will have no further obligation to pay for the filing, prosecution or maintenance of such patents and patent applications. In addition, LILLY will provide ISIS with any and all data relating to ISIS 3521 and/or to the ISIS Patent Rights that are in LILLY's possession or control. Further, the licenses granted by LILLY to ISIS under Compound Improvements, Core Technology Improvements and Manufacturing Technology Improvements pursuant to Section 7.2(a), 7.3(a) and 7.4(a) will each convert to a worldwide, royalty-free, sublicensable, perpetual, nonexclusive license to practice under such LILLY's rights to any such improvements, and to make, have made, use, import, offer for sale and sell products and Products.

(b) In the event this Agreement is terminated by ISIS under Section 8.2(a), if LILLY has granted any sublicenses under this Agreement, those sublicenses will continue, provided that such sublicenses are consistent with the terms of this Agreement and further provided that Sublicensees make all royalty payments directly to ISIS effective as of the termination date of this Agreement.

(c) The foregoing rights and remedies of the parties are non-exclusive and without prejudice to any rights that either party may have arising under applicable law or equity.

8.4 SURVIVAL OF CERTAIN RIGHTS AND OBLIGATIONS.

Expiration or termination of the Agreement will not relieve the parties of any obligation accruing prior to such expiration or termination. The provisions of following Sections will survive expiration or termination of the Agreement: 3.3(b) and (c); 5.5 to 5.7; 6.3; 7.2(c), 7.3(c) and 7.4(c), other than the reference to Section 3.1 therein; 8.3 to 8.5; 9.5; 9.7 to 9.13. The provisions of Section 4.1 and 4.2 will survive the termination or expiration of the Agreement and will continue in effect for 10 years thereafter. Any expiration or early termination of this Agreement will be without prejudice to the rights of either party against the other accrued or accruing under this Agreement prior to termination, including the obligation to pay royalties for Product sold prior to such termination.

8.5 RIGHTS IN BANKRUPTCY.

All rights and licenses granted under or pursuant to this Agreement by ISIS and LILLY are, and will otherwise be deemed to be, for purposes of Section 365(n) of the United States Bankruptcy Code, licenses of rights to "intellectual property" as defined under Section 101 of the United States Bankruptcy Code. The parties agree that the parties, as licensees of such rights under this

Agreement, will retain and may fully exercise all of their rights and elections under the United States Bankruptcy Code. The parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against a party under the United States 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, which, if not already in the non-subject party's possession, will be promptly delivered to it (a) upon any such commencement of a bankruptcy proceeding upon the non-subject party's written request therefor, unless the party subject to such proceeding continues to perform all of its obligations under this Agreement or (b) if not delivered under clause (a) 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.

ARTICLE 9

MISCELLANEOUS

9.1 FORCE MAJEURE.

Neither 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 when such failure or delay is caused by or results from causes beyond the reasonable control of the affected

party including, without limitation, embargoes, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, or acts of God. The affected party will notify the other party of such force majeure circumstances as soon as reasonably practical and will make every reasonable effort to mitigate the effects of such force majeure circumstances.

9.2 ASSIGNMENT.

This Agreement will inure to the benefit and be binding upon each party, its successors and assigns. The Agreement may not be assigned or otherwise transferred, nor, except as expressly provided hereunder, may any right or obligation hereunder be assigned or transferred by either party without the prior 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 an Affiliate or in connection with the transfer or sale of all or substantially all of its assets, or in the event of its merger or consolidation or change in control or similar transaction. Any permitted assignee will assume all obligations of its assignor under the Agreement. Any attempted assignment not in accordance with this Section 9.2 will be void.

9.3 SEVERABILITY.

In the event any one or more of the provisions contained in this Agreement should be 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 in such an instance use their best efforts to replace the invalid, illegal or unenforceable provision(s) with valid, legal and enforceable provision(s) which, insofar as practical, maintains the balance of the rights and obligations of the parties under this Agreement.

9.4 NOTICES.

All notices which are required or permitted hereunder will be in writing and sufficient if delivered personally, sent by facsimile or email (and promptly confirmed by personal delivery, registered or certified mail or overnight courier), sent by nationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

if to ISIS, to:	Isis Pharmaceuticals, Inc. Carlsbad Research Center 2292 Faraday Avenue Carlsbad, CA 92008 Attention: Executive Vice President Fax No.: (760) 931-9639 E-Mail: lparshall@isisph.com
with a copy to:	Attention: General Counsel Fax No.: (760) 603-3820 E-Mail: gbryce@isisph.com
if to LILLY, to:	Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285 Attention: General Patent Counsel Fax No.: (317) 277-1917 E-Mail: armitage_robert_a@lilly.com

or to such other address as the party to whom notice is to be given may have furnished to the other party in writing in accordance herewith. Any such notice will be deemed to have been given when delivered if personally delivered or sent by facsimile on a business day, on the business day after dispatch if sent by nationally-recognized overnight courier and on the third business day following the date of mailing if sent by mail.

9.5 APPLICABLE LAW.

The Agreement will be governed by and construed in accordance with the laws of the State of Delaware without reference to any rules of conflict of laws.

9.6 DISPUTE RESOLUTION; OVERSIGHT COMMITTEE.

The parties recognize that disputes may from time to time arise between the parties during the term of this Agreement. In the event of such a dispute, either party, by written notice to the other

party, may have such dispute referred to the Oversight Committee, the function of which is to attempt resolution of any disputes arising under this Agreement by good faith negotiations. The Oversight Committee will endeavor to resolve such disputes within 30 days after such notice is received. The Oversight Committee will be comprised of two designated executive officers (or their successors), one from each party. Said designated officers are as follows:

For ISIS:	Chief Executive Officer
For LILLY:	Executive Vice President

9.7 REMEDIES.

In the event the parties are unable to resolve any disputes hereunder pursuant to the dispute resolution measures provided herein, each party may pursue its rights and remedies in law or equity in any court of competent jurisdiction.

9.8 ENTIRE AGREEMENT.

This Agreement and the Supply Agreement contain the entire understanding of the parties with respect to the license, development and commercialization of ISIS 3521 and Product. All express or implied agreements and understandings, either oral or written, heretofore made by the parties on the same subject matter are expressly superseded by this Agreement. The Agreement may be amended, or any term hereof modified, only by a written instrument duly executed by both parties hereto.

9.9 HEADINGS.

The captions to the several Articles and Sections hereof are not a part of the Agreement nor affect the interpretation of any of its provisions, but are merely a convenience to assist in locating and reading the several Articles and Sections hereof.

9.10 INDEPENDENT CONTRACTORS.

It is expressly agreed that ISIS and LILLY will be independent contractors and that the relationship between the two parties will not constitute a partnership, joint venture or agency. Neither ISIS nor LILLY 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, without the prior consent of the other party.

9.11 WAIVER.

The waiver by either party hereto of any right hereunder, or the failure to perform, or a breach by the other 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.

9.12 COUNTERPARTS.

The 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.

9.13 WAIVER OF RULE OF CONSTRUCTION.

Each party has had the opportunity to consult with counsel in connection with the review, drafting and negotiation of this Agreement. Accordingly, the rule of construction that any ambiguity in this Agreement will be construed against the drafting party will not apply.

ARTICLE 10

HART-SCOTT-RODINO FILING

10.1 HSR ACT COMPLIANCE.

Notwithstanding anything to the contrary in this Agreement, the Effective Date of this Agreement and the rights and obligations of the parties hereunder shall not occur until such time as (a) the parties shall have complied with all applicable requirements of the Hart Scott Rodino Antitrust Improvements Act of 1976, as amended (the "HSR Act"); (b) the waiting period under the HSR Act shall have expired or earlier been terminated; (c) no judicial or administrative proceeding opposing consummation of all or any part of this Agreement shall be pending; (d) 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 (e) no requirements or conditions shall have been imposed in connection therewith which are not reasonably satisfactory to the parties (the "HSR Conditions"). Upon satisfaction of the HSR Conditions, the parties shall enter into the Supply Agreement.

10.2 COOPERATION ON FILING.

Both LILLY and ISIS shall file, as soon as reasonably practicable after the Signing 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 will use reasonable best 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 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, because of 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 litigation is commenced, either party may terminate this Agreement.

IN WITNESS WHEREOF, the parties have executed this Agreement as of the Effective Date.

ELI LILLY AND COMPANY	ISIS PHARMACEUTICALS, INC.
By: /s/ AUGUST M. WATANABE	By:/s/ B. LYNNE PARSHALL
Name: August M. Watanabe	Name: B. Lynne Parshall
Title: Executive Vice President	Title: Executive Vice President and CFO

EXHIBIT A

DEFINITIONS

Each of the capitalized terms used in this Agreement (other than the headings of the Articles and Sections), whether used in the singular or the plural, will have the meaning as set forth below or, if not listed below, the meaning as designated in places throughout this Agreement.

1.1 "AFFILIATE" with respect to either party means any person, organization, corporation or other business entity (collectively, "Person") controlling, controlled by, or under common control with such party. For purposes of this definition, "control" refers to (a) the possession, directly or indirectly, of the power to direct the management or policies of a Person, whether through the ownership of voting securities, by contract or otherwise, and (b) the ownership, directly or indirectly, of at least 50% of the voting securities or other ownership interest of a Person.

1.2 "CALENDAR QUARTER" means the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30 and December 31.

1.3 "CALENDAR YEAR" means each successive period of 12 months commencing on January 1 and ending on December 31.

1.4 "COMBINATION PRODUCT" means any pharmaceutical product that comprises ISIS 3521 and at least one other active compound(s) and/or ingredients. All references to the Product in this Agreement will be deemed to include Combination Product.

1.5 "COMPOUND IMPROVEMENT" means any and all modifications and enhancements that specifically and solely relate to the composition of matter of ISIS 3521 or the method of use of ISIS 3521, except pharmaceutical formulations and dosage forms for administration of the Product, developed by or coming under Control of a party after the Effective Date.

1.6 "COMPOUND PATENT RIGHTS" means the Patents Controlled by ISIS as of the Effective Date that specifically claim the composition of matter or the use of ISIS 3521 that are Valid and would be infringed by the Manufacture, use, importation, offer for sale or sale of ISIS 3521 by an unlicensed Third Party. The Compound Patent Rights are listed in Exhibit D.

1.7 "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.

1.8 "CORE TECHNOLOGY PATENT RIGHTS" means the Patents Controlled by ISIS as of the Effective Date that are Valid and would be infringed by the Manufacture, use,

importation, offer for sale or sale of ISIS 3521 by an unlicensed Third Party that do not constitute Compound Patent Rights or Manufacturing Patent Rights, such as Patents which claim, cover or relate to the cellular mechanisms of action by which phosphorothioate antisense oligonucleotides exert their effect, or to methods of treatment using such oligonucleotides. The Core Technology Patent Rights are listed in Exhibit D.

1.9 "CORE TECHNOLOGY IMPROVEMENT" means any and all modifications and enhancements of antisense technology Controlled by ISIS or LILLY, as appropriate, after the Effective Date that claim, cover or relate to the cellular mechanisms of action by which phosphorothioate antisense oligodeoxynucleotides exert their effect, or to methods of treatment using such oligodeoxynucleotides, and that are necessary or useful for the Manufacture or use of the Product. The definition of Core Technology Improvements does not include any modifications or enhancements that are Compound Improvements or Manufacturing Technology Improvements.

1.10 "COST OF MANUFACTURE" means the cost incurred by ISIS in the Manufacture of API as described in Exhibit 7 of the Supply Agreement.

1.11 "CS17 STUDY" means the Phase III clinical trial conducted by ISIS that is ongoing as of the Effective Date, as further described in the Development Plan.

1.12 "DEVELOPMENT PLAN" means the plan for the development of ISIS 3521 attached hereto as Exhibit C.

1.13 "DEVELOPMENT PROGRAM" means the activities undertaken by ISIS and LILLY as set forth in the Development Plan.

1.14 "EC APPROVAL" means approval of a Product for marketing in the European Union by the European Commission ("EC") upon recommendation by the European Medicines Evaluation Agency ("EMEA") or, if LILLY seeks approval through mutual recognition therein, by the Ministry of Health of the United Kingdom, France, Germany, Italy or Spain (each a "Major European Country"), without the requirement for price having been approved. If a Product is sold in a Major European Country without EC or Ministry of Health approval, EC Approval will be deemed to have been obtained on the date of first sale of a Product in a Major European Country.

1.15 "EFFECTIVE DATE" means the latest of (a) the date on which the last party executes this Agreement and shall be the Signing Date or, (b) if applicable, the next day following the Required Approval (as defined in Section 10.2).

1.16 "FIRST COMMERCIAL SALE" means the first sale of a Product by LILLY, its Affiliates or a Sublicensee to an independent Third Party in a particular country after Marketing Approval has been obtained.

1.17 "FTE" means the equivalent of the scientific or technical work of at least a total of [*] hours per year on or directly related to the Development Program carried out by a qualified employee or consultant. [*]

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1.18 "INFORMATION" means any information exchanged by the parties under the confidentiality agreement executed by the parties on December 5, 2000 or generated by a party during the term of this Agreement and includes, but is not limited to, any and all inventions, know-how, developments, improvements, materials, data, analyses, and the like, regardless of whether the information is stored or transmitted in oral, documentary, or electronic form. "Information" also includes, without limitation, information relating to research and development plans, experiments, results, compounds, therapeutic leads, candidates and products, clinical and preclinical data, trade secrets and Manufacturing, marketing, financial, regulatory, personnel and other business information and plans, all scientific, clinical, regulatory, marketing, financial and commercial information or data.

1.19 "ISIS 3521" means the phosphorothioate oligodeoxyribonucleotide that targets human protein kinase C alpha disclosed and claimed (as SEQ ID NO 2) in U.S. Patent No. 5,703,054.

1.20 "ISIS FTE RATE" means [*]

1.21 "ISIS PATENT RIGHTS" means Compound Patent Rights, Manufacturing Patent Rights, and ISIS' rights and interest in Patents claiming Compound Improvements and Manufacturing Technology Improvements.

1.22 "JAPANESE APPROVAL" means the approval of a Product for marketing in Japan by the Japanese Ministry of Health and Welfare (or any future equivalent process), together with any other approval necessary to make and sell Product commercially in Japan without the requirement for price having been approved. If a Product can be sold in Japan without Ministry of Health and Welfare approval, Japanese Approval will be deemed to have been obtained on the first sale of a Product in Japan.

1.23 "MAJOR MARKET" means any one of the following countries: United States, Japan, the United Kingdom, France, Germany, Italy or Spain.

1.24 "MAJOR TUMOR" means one of following tumors: non-small cell lung cancer, pancreatic, ovarian, lymphoma, hepatoma, breast, colon, prostate, and bladder.

1.25 "MANUFACTURE" OR "MANUFACTURING" OR "MANUFACTURED" means all operations involved in the manufacturing, quality control testing (including in-process, release and stability testing, if applicable), releasing, and shipping the Product.

1.26 "MANUFACTURING APPROVAL" means the act of a Regulatory Authority necessary for the Manufacture of the Product in a country or regulatory jurisdiction.

1.27 "MANUFACTURING PATENT RIGHTS" means Patents Controlled by ISIS that claim the Manufacturing Technology that are Valid and would be infringed by the Manufacture, use, importation, offer for sale or sale of ISIS 3521 by an unlicensed Third Party. The Manufacturing Patent Rights are listed in Exhibit D.

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1.28 "MANUFACTURING PROCESS" means the process steps set forth in master batch records for ISIS 3521 in the version existing as of the Effective Date, including reasonable minor variants and extensions of process steps thereof.

1.29 "MANUFACTURING TECHNOLOGY" means any and all scientific and technical data and information including without limitation formulas, methods, techniques, protocols, and processes Controlled by ISIS as of the Effective Date which are necessary for performing the Manufacturing Process.

1.30 "MANUFACTURING TECHNOLOGY IMPROVEMENT" means any and all modifications and enhancements in the Manufacturing Technology, developed by or coming under Control of a party after the Effective Date.

1.31 "MARKETING APPROVAL" means the act of a Regulatory Authority necessary for the marketing and sale of the Product in a country or regulatory jurisdiction, including, without limitation, the approval of the NDA by the FDA, EC Approval, and Japanese Approval.

1.32 "NDA" means a new drug application or other application filed with the FDA to obtain approval for marketing a Product in the United States, or any future equivalent process.

1.33 "NET SALES" means the gross amount invoiced by LILLY, its Affiliates, or any Sublicensee 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) Refunds or credits for actual Product returns;
(d) the cost of drug delivery systems used for the administration of the Product;
(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.

Such amounts will be determined from the books and records of Lilly or sublicensee, maintained in accordance with U. S. Generally Accepted Accounting Principles or, in the case of sublicensees, such similar accounting principles, 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; and

(ii) Use by LILLY or its Affiliates or Sublicensees of Product for any use connected with the securing of regulatory approval or validating of the Manufacturing

Process or the obtaining of other necessary Marketing Approvals for Product (unless such Product is subsequently sold).

In the event that the Product is sold as part of a Combination Product (where "Combination Product" means any pharmaceutical product which comprises the Product and other active compound(s) and/or ingredients), the Net Sales of the Product, for the purposes of determining royalty payments, will be determined by multiplying the Net Sales of the 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 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 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 will 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 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 will 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 and the other product(s) in the Combination Product cannot be determined, the Net Sales of the Product will be negotiated by the parties in good faith. If the parties cannot reach agreement on the appropriate allocation, the Net Sales of the Product will 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 will be calculated once each Calendar Year and such price will be used during all applicable royalty reporting periods for the entire following Calendar Year. When determining the weighted average sale price of a Product, other product(s), or Combination Product, the weighted average sale price will 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) of the preceding Calendar Year for the respective Product, other product(s), or Combination Product. In the initial Calendar Year, a forecasted weighted average sale price will be used for the Product, 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.

1.34 "OUT-OF-POCKET EXPENSES" means costs, other than labor costs, that are directly related to the activities outlined in the Development Plan and the Supply Agreement, including, without limitation, costs of travel, supplies, outside services and consultants.

1.35 "PATENT" or "PATENTS" 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 prosecution applications, continuations-in-part, or divisions of or to any of the foregoing; and (e) term extension or other governmental action which provide exclusive rights to a Product beyond the original patent expiration date.

1.36 "PIVOTAL TRIAL" means a pivotal human clinical trial in any country, the results of which could be used to establish safety and efficacy of a ISIS 3521 as a basis for an application for a Marketing Approval or

that would otherwise satisfy the requirements of 21 CFR 312.21(c) or its foreign equivalent.

1.37 "PRODUCT" means preparation(s) containing ISIS 3521 or a Compound Improvement.

1.38 "PROPRIETARY INFORMATION" means any and all Information, whether communicated in writing, orally or by any other means, which is provided by one party to the other party in connection with this Agreement. Proprietary 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, subsequent to the disclosure by the disclosing party, 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 Proprietary Information received from the other party , as documented by written records.

1.39 "REGULATORY AUTHORITY" means any applicable government regulatory authority involved in granting approvals for the marketing, and/or pricing of a Product worldwide, including without limitation, in the United States, the Food and Drug Administration ("FDA"), and any successor government authority having substantially the same function, and foreign equivalents thereof.

1.40 "SUBLICENSEE" means any Third Party (including a distributor) to which LILLY or any of its Affiliates grants any right to make, use, market, or import and sell a Product. A Third

Party who is granted only the right to import and sell a Product (such as a wholesaler) will not be considered a Sublicensee.

1.41 "SUPPLY AGREEMENT" means the supply agreement for ISIS 3521 to be entered into by the parties on the Effective Date in the form attached hereto as Exhibit B.

1.42 "THIRD PARTY" means any party other than ISIS or LILLY and their respective Affiliates.

1.43 "VALID" means (a) with respect to an issued patent that such patent is issued and unexpired, has not been revoked, held unenforceable or invalid by an unappealed or unappealable decision of a court or other governmental agency of competent jurisdiction, and has not been admitted by the owner of such patent to be invalid or unenforceable, and (b) with respect to a patent application that such patent application has been pending for no more than seven (7) years.

EXHIBIT B
ISIS 3521 CLINICAL SUPPLY AGREEMENT

(See Exhibit 2.6 to this 8-K)

EXHIBIT C

DEVELOPMENT PLAN

DELETE IN ENTIRETY

[*]

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EXHIBIT D

COMPOUND PATENT RIGHTS

[*]

MANUFACTURING PATENT RIGHTS

[*]

CORE TECHNOLOGY PATENT RIGHTS

[*]

*Confidential Treatment Requested

EXHIBIT E

BUDGET ESTIMATE AND ASSUMPTIONS

DELETE IN ENTIRETY

[*]

*Confidential Treatment Requested

EXHIBIT 2.6
(EXHIBIT B TO EXHIBIT 2.5 HEREOF)

EXHIBIT B

ISIS 3521 CLINICAL SUPPLY AGREEMENT

This ISIS 3521 Clinical Supply Agreement ("Agreement") is made and entered into as of August 29, 2001 (the "Effective Date") between Eli Lilly and Company, a corporation organized and existing under the laws of the State of Indiana ("LILLY") and Isis Pharmaceuticals, Inc., a corporation organized and existing under the laws of the State of Delaware ("ISIS").

WITNESSETH

WHEREAS, ISIS and LILLY have entered into the Development and License Agreement relating to the development and commercialization of ISIS 3521, and the conditions to entering into this Agreement described in the Development and License Agreement have been satisfied; and

WHEREAS, ISIS will initially manufacture, release and deliver ISIS 3521 API to LILLY for support of ongoing clinical trials and will also perform CMC activities and transfer to LILLY or a third party selected by LILLY the technology to manufacture ISIS 3521 for commercial uses, pursuant to the terms set forth herein;

NOW, THEREFORE, in consideration of the covenants herein contained, the parties hereto agree as follows:

ARTICLE 1

DEFINITIONS

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

ARTICLE 2

MANUFACTURE AND SUPPLY OF API

2.1 Subject to the terms and conditions set forth herein, LILLY will provide ISIS with estimates of LILLY's requirements of API for support of ongoing clinical trials prior to the start of Calendar Years 2002 and 2003. ISIS will supply API to LILLY, in amounts agreed upon by the parties, based on LILLY's requirements and ISIS' Annual Capacity, in accordance with the terms of this Agreement.

2.2 ISIS will provide bulk API to LILLY for use in Clinical Products. LILLY will be responsible for the formulation, filling, finishing, labeling and packaging of the Clinical Products, including stability studies; provided, however, that, in accordance with

Section 6.2, until the Release Technology Transfer is completed, ISIS will perform Clinical Product release.

2.3 The parties acknowledge that as of the Effective Date, a third party manufacturer performs the formulation, filling and finishing of Clinical Product for ISIS. Following the Effective Date, LILLY will be responsible for the formulation, filling and finishing of Clinical Product and will use commercially reasonable efforts to promptly establish, itself or through a third party manufacturer, the manufacturing process for formulating, filling, and finishing Clinical Product. If requested by LILLY, ISIS will cooperate with LILLY, as appropriate, to enable LILLY to enter into an agreement with the third party manufacturer used by ISIS to perform the formulation, filling and finishing of Clinical Product.

ARTICLE 3

ORDERS AND LIMITATION OF SUPPLY

3.1 PRODUCTION AND DELIVERY PLANS AND ORDERS.

(a) Not later than July 1 of each year, except 2001, in which this Agreement is in effect, LILLY will provide ISIS with a written estimate of the amount of API LILLY will require during the subsequent Calendar Year, which estimate will indicate the quantity of API to be utilized in Clinical Products. [LILLY's API order estimate for Calendar Year 2002 is set forth on Exhibit 2. [*]

(b) At the time of delivery of each such estimate (but within 30 days after the Effective Date with regard to the estimate for Calendar Year 2002), LILLY representatives will meet with ISIS representatives to discuss and agree upon a production and delivery plan for the next Calendar Year (the "Production and Delivery Plan"). Each year's agreed-upon Production and Delivery Plan will specify the quantity of API to be utilized in Clinical Product that ISIS will supply to LILLY during the subsequent Calendar Year, taking into account all relevant factors including, without limitation, ISIS' Annual Capacity and its obligations to other parties. Each such Production and Delivery Plan will be deemed a firm purchase order of LILLY for the quantities of API specified therein, and a firm commitment of ISIS to Manufacture and supply such quantities of API to LILLY.

(c) The Production and Delivery Plan will further specify one or more dates upon which Delivery of the API to be supplied by ISIS will occur during the relevant Calendar Year. ISIS will use commercially reasonable efforts to Deliver the API to LILLY according to the agreed-upon Delivery schedule set forth in the Production and Delivery Plan. The Production and Delivery Plan will provide for Delivery of API promptly after completion of Manufacture and release. The date on which the parties agree upon a Production and Delivery Plan for the following Calendar Year will be referred to herein as the "API Order Date."

(d) Based on various considerations, including its obligations to Third Parties and to its own drug development efforts, ISIS' Annual Capacity will vary from year to year. ISIS'

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annual capacity for the Manufacture of API for Calendar Years 2002 and 2003 (the "Annual Capacity"), indicating the maximum amount of API that LILLY may order from ISIS during each such Calendar Year, is set forth in Exhibit 3.

(e) ISIS will purchase the Raw Materials used in the Manufacture. At its sole discretion, LILLY will have the option to purchase some or all of the Raw Materials used in the Manufacture. If Lilly so decides, LILLY will notify ISIS, and the parties will work together to establish appropriate procedures for order and delivery of and payment for such Raw Materials to be purchased by LILLY.

3.2 COMMERCIAL MANUFACTURING .

LILLY and ISIS will work together to complete a plan for commercial supply of API. LILLY and ISIS will work together to identify and investigate other sources for the manufacture of API to be utilized for Commercial Product. LILLY will inform ISIS in writing by July 1, 2002 of LILLY's decision, at its sole discretion, regarding whether LILLY, ISIS and/or a third party will manufacture API to be utilized for Commercial Product, and which of them shall be the primary source and the back-up source of API to be utilized for Commercial Product. If, in such notice, LILLY elects to have ISIS manufacture API to be utilized for Commercial Product, LILLY and ISIS will negotiate in good faith, and ISIS hereby commits, for ISIS to manufacture API to be utilized for Commercial Product on substantially the terms set forth in Exhibit 8. In such notice, LILLY will also provide LILLY's API order estimates for Calendar Years 2003, 2004 and 2005.

3.3 LIMITATIONS OF SUPPLY.

In the event that at any time ISIS anticipates that it will be unable to supply in whole or in part the quantities of API set forth in an agreed-upon Production and Delivery Plan for any reason, including without limitation force majeure, ISIS will notify LILLY in writing as soon as possible of such anticipated shortfall. ISIS will also notify LILLY of the underlying reason for the shortfall, proposed remedial

measures, the date such inability to supply the full order of API is expected to end, and a proposed amount of API to be Delivered to LILLY. [*] The proposed amount of API to be made available to LILLY hereunder will be no less than [*] of the amount of raw materials or other resources required for the Manufacture of API, taking into consideration the amount of such raw materials or other resources required by (i) LILLY under this Agreement and (ii) ISIS and its other programs.

If ISIS cannot Manufacture as set forth in this Agreement, ISIS shall so inform LILLY immediately upon the prediction or occurrence such non-supply. In such event, LILLY shall have the right to Manufacture or have Manufactured API for LILLY's needs and ISIS shall provide all assistance and relevant information, know-how and data necessary for LILLY in establishing and beginning the Manufacture of API.

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ARTICLE 4

QUALITY STANDARDS; MANUFACTURING WORKING GROUP

4.1 QUALITY STANDARDS.

(a) With respect to API in process prior to the time the Quality Agreement is adopted, ISIS will Manufacture such API in accordance with cGMP and the same specifications as applied to the Manufacture of API for use in Clinical Product used in the CS17 Study. Subject to the preceding sentence, ISIS will Manufacture API for use in Clinical Product in accordance with the API Specifications, cGMP, the DRD, the Quality Agreement and other applicable rules and regulations of all Regulatory Authorities and other regulatory agencies with jurisdiction over the manufacture, use or sale of the API, as then in effect. If cGMP for the U.S. and its foreign equivalent differ, LILLY will specify in writing which cGMP will apply to each quantity of API ordered from ISIS by LILLY. ISIS will be responsible for Manufacturing issues related to API safety and regulatory compliance. Each party will promptly notify the other party of any relevant new instructions or specifications required by a Regulatory Authority, and of other applicable and regulations of which that party becomes aware. The parties will confer with each other with respect to the best means to comply with such requirement and will allocate any costs of implementing such changes on an equitable basis. The parties acknowledge that frequent change-over in the Manufacture of API as may be necessary to comply with differing cGMP in the US and abroad will reduce the Annual Capacity, and that any costs incurred by ISIS in connection with such change-overs will be included in the calculation of API Supply Cost.

(b) ISIS will perform quality control testing, as is specified (i) in the Quality Agreement and API Specifications; and (ii) as required by a Regulatory Authority and by the mutual written consent of the parties, on each lot of API supplied for use in Clinical Product, prior to shipment.

4.2 CERTIFICATE OF ANALYSIS.

(a) ISIS will provide a Certificate of Analysis to LILLY or its designated agent with each lot of API supplied hereunder. Such Certificate of Analysis will contain the results of the analysis of API as required in the API Specifications, and will certify with respect to each shipment and lot (identified by lot number): (i) the quantity of the shipment, (ii) that the API delivered was Manufactured in accordance with the API Specifications and in conformance with cGMP. The Certificate of Analysis will contain any information in addition to that required pursuant to subsection (a) above as may be required by the Regulatory Authority of the country of destination of API or Product; provided, that LILLY provides to ISIS sufficient documentation and information necessary or useful to enable ISIS to conform with such requirements. ISIS will provide the results of such analysis to LILLY, along with any supporting data.

(b) LILLY will be under no obligation to accept any Delivered lot of API without an accompanying Certificate of Analysis that conforms to subsection (a) above. Each

Certificate will contain the results of testing per the API Specifications and a statement that the batch was prepared in compliance with cGMP. ISIS will also make available for LILLY's review ISIS' Manufacturing records for the API, including its master and production batch records, for the purposes of assuring product quality and compliance with agreed-upon Manufacturing procedures as per the following Section 9.3, Quality Assurance Audits.

4.3 CHANGES TO MANUFACTURING PROCESS; MANUFACTURING WORKING GROUP.

(a) During the term of this Agreement, if ISIS proposes to make a material change in Manufacturing materials, equipment, processes, procedures, or to the API Specifications, the parties will discuss and address such proposals as follows. Prior to implementing such a material change, ISIS will notify the Manufacturing Working Group (the "MWG") of ISIS' proposed material change, for consideration by the MWG pursuant to Section 4.6. ISIS will provide information to the MWG regarding the change at a level sufficient to allow the MWG members to evaluate such changed Manufacturing process.

(b) The MWG will consist of 3 members from LILLY and 3 members from ISIS and will be established promptly after the Effective Date. The members will be individuals who are capable of responding to the technical, financial, quality, and other issues that could arise under this Agreement. The MWG can consult with, and receive assistance from, LILLY and ISIS employees who are not MWG members. The additional objectives of the MWG are (i) with the parties' quality units, to adopt the initial Quality Agreement and Development Responsibilities Document and subsequent amendments (if any) to each; and (ii) monitor the parties' performance under this Agreement, including reviewing, on a periodic basis, forecast accuracy and on-time delivery. The MWG shall report to the parties at least once each calendar quarter and more frequently as requested.

4.4 QUALITY AGREEMENT.

(a) Promptly (and in any event within 60 days) after the Effective Date, the MWG will adopt the initial Quality Agreement for API for Clinical Product (the "Quality Agreement").

(b) The MWG will, at least annually, review the Quality Agreement and will amend it from time to time as necessary through the issuance of a revised section incorporating the modification and stating the effective date of the modification, signed by a duly authorized representative from each party who is a member of the quality control/quality assurance group, as evidenced by a signed, revised Quality Agreement incorporating the revision number that sets forth the effective date of the modifications and reason for the revision.

(c) The Quality Agreement will describe the parties' quality control, quality assurance and regulatory responsibilities relating to the Manufacture and release of the API by ISIS. The Quality Agreement will include as an exhibit the current standard operating procedures of ISIS, as may be amended by ISIS from time to time, listed in Exhibit 4. ISIS will provide to LILLY not less than once per calendar year an updated set of such

standard operating procedures. All standard operating procedures used by ISIS in connection with the Manufacture of API will comply with cGMP.

(d) In the event of an inconsistency between the Quality Agreement and the terms of this Agreement, the terms of this Agreement will apply.

4.5 DEVELOPMENT RESPONSIBILITY DOCUMENT.

(a) Promptly after the Effective Date, and in any event before initiation of LILLY-sponsored clinical trials of the Product, the MWG will adopt the initial Development Responsibilities Document ("DRD").

(b) The MWG will, at least annually, review the DRD and will amend it from time to time through the issuance of a revised section incorporating the modification and stating the effective date of the modification,

signed by a duly authorized representative of each party.

(c) The DRD will be similar to, but shorter than, a Manufacturing Responsibilities Document and will provide specific guidance to the parties to ensure the logistics for supply of Clinical Product to support the Development Program.

(d) In the event of an inconsistency between the DRD and the terms of this Agreement, the terms of this Agreement will apply.

4.6 PROCEDURES REGARDING CHANGES TO MANUFACTURING PROCESS.

(a) At its initial meeting, the MWG will consider and agree upon the guidelines to be used to determine the approval process to be applied to any material change in Manufacturing materials, equipment, processes, procedures, or to the API Specifications proposed by ISIS. ISIS will prepare and submit the guidelines to the MWG for consideration, using the following 3 categories and providing examples of the types of material changes that will be included in each category:

(i) changes in production of API that may affect the filing of an application for Marketing Approval or require prior Regulatory Approval and will thus require LILLY's approval prior to implementation;

(ii) changes that will require ISIS to notify LILLY prior to implementation, but which do not require LILLY's approval; and

(iii) changes that do not require ISIS to notify LILLY prior to implementation.

(b) If ISIS proposes to make a material change described in subsection (a)(i), ISIS will notify the MWG and provide information to the MWG regarding such change at a level sufficient to allow the MWG members to evaluate the impact of such change on the Manufacturing Process, and to form a basis for LILLY to determine whether or not to approve such material change. If there are any additional questions regarding notification

and approval that arise during the term of this Agreement, ISIS will submit the questions to the MWG or, if an immediate response is required, will contact LILLY's Quality Assurance function to determine the level of review/notification that may be required by the proposed change. The parties will obtain the prior Regulatory Approval and any other required approvals, if such approval is required, before any such material change is implemented.

4.7 COMPLIANCE WITH LAWS.

In performing its obligations under this Agreement, ISIS will comply with all applicable present and future orders, regulations, requirements and laws ("Legal Requirements") of any and all U.S. authorities and agencies, including without limitation laws and regulations applicable to the transportation, storage, use, handling and disposal of hazardous materials (the "U.S. Legal Requirements"), and any Legal Requirements of other countries ("Foreign Legal Requirements") of which it is informed by LILLY. If the U.S. Legal Requirements conflict with the Foreign Legal Requirements, the parties will discuss and agree on how to resolve such conflict.

4.8 DOCUMENTATION AND RECORD KEEPING.

ISIS will keep complete, accurate and authentic accounts, notes, data and records of all of ISIS' work performed under this Agreement, including, but not limited to, complete and adequate records pertaining to the methods and facilities used for the Manufacture in accordance with master production records, batch production records, product history documents (e.g., master formulae, validation packages, specifications, CT batch history documents, batch specific deviation reports, COAs) Standard Operating Procedures ("SOPs"), as well as the applicable regulations, including in the United States, so that API may be used in the production of a substance to be used in humans. ISIS will maintain these records for 2 years after expiration of the Clinical Product that incorporates the particular API. LILLY will notify ISIS in writing of the expiration of Products that incorporate

specific API pursuant to the procedures described in the DRD, and if LILLY changes the expiration date on any Clinical Product. SOPs will be maintained for 5 years after the document is superseded or deleted. Upon expiration of the retaining periods for the respective records as provided in this Section and in case ISIS wishes to cease retention of such records, ISIS will notify LILLY so that LILLY may, at its cost, retain such records.

4.9 REVIEWS.

ISIS will generate and provide annual summary reviews for API Manufacturing and control as well as supporting documents or other information for annual product reviews as agreed by the parties.

ARTICLE 5

SUPPLY PRICE; PAYMENT AND TERMS OF SALE

5.1 SUPPLY PRICE.

(a) The API Clinical Supply Price will apply to all API supplied to LILLY intended for use in a Clinical Product.

(b) Except as provided in Section 3.1 (a), for each calendar quarter, ISIS will invoice LILLY for the API Clinical Supply Price of API Delivered to LILLY during such calendar quarter. LILLY will pay each invoice within [*] after receipt, subject to the provisions of Section 5.3. Interest will be charged on late payments consistent with the provisions of subsection (c) below.

(c) All payments due hereunder will be paid by wire transfer in U.S. Dollars to such bank account designated in writing by ISIS from time to time. LILLY will pay a late payment service charge of [*] per month [*] on all past-due amounts.

5.2 DELIVERY.

(a) ISIS will deliver API to a carrier designated by LILLY FCA ISIS' Facility (Incoterms 2000). The shipping and packaging specifications will be agreed upon by the parties.

(b) In the event of a loss of work in process or API prior to the transfer of title pursuant to the Delivery of API as provided in subsection (a) above, any uninsured portion of the loss will be shared by LILLY and ISIS as follows: [*] Any deductible will be applied ratably against all items damaged or lost.

5.3 ACCEPTANCE AND CLAIMS; MATERIALS REVIEW BOARD.

(a) If LILLY claims that any sample of API did not meet the warranty specified in Article 8, LILLY will notify ISIS in writing within 30 days of such Delivery, and a joint Materials Review Board formed under subsection (b) below will review the test data generated by LILLY and ISIS under QA approved procedures mutually agreed by the parties within 30 days after LILLY's notice to ISIS.

(b) Promptly after the Effective Date, ISIS and LILLY will each select 2 members of their in-house materials review boards (or other senior personnel with appropriate qualifications) to participate in a joint Materials Review Board ("MRB") that will review and consider any test data generated by LILLY and ISIS with respect to the Delivered lot of API.

(c) If the members of the MRB are thereafter unable to agree as to whether the API met the warranty specified in Article 8, the parties will cooperate and have the test data reviewed by an independent third party selected by LILLY and approved by ISIS, which approval will not be unreasonably withheld. If the independent third party reviewer cannot determine whether the Delivered API in dispute met the warranty of Article 8, a sample

of the batch of the Delivered API in dispute retained by ISIS will be analyzed in accordance with the API Specifications, under QA approved procedures, by an independent testing laboratory of recognized repute selected by LILLY and approved by ISIS, which approval will not be unreasonably withheld. The results of such laboratory testing will be final and binding on the parties on the issue of compliance of the API with such warranty.

(d) If the Delivered API is determined to meet the warranty set forth in Article 8, LILLY will bear the cost of any third party review and/or independent laboratory testing performed pursuant to subsection (c) above and will pay for the API in accordance with the terms of this Agreement. If the API is determined not to meet the warranty set forth in Article 8, ISIS will bear the cost of any third party review and/or independent laboratory testing performed pursuant to subsection (c) above.

(e) If ISIS agrees, or if it is determined pursuant to subsection (c) above, that API did not conform to the warranty set forth in Article 8, ISIS will use commercially reasonable efforts to Manufacture and Deliver a replacement batch of API to LILLY for the batch of API that did not conform to such warranty, and LILLY will pay ISIS for any such replacement batch of API, including without limitation, all costs and expenses associated with such Manufacture, consistent with the provisions of Section 5.1 herein. [*]

(f) Any Delivered API which ISIS agrees did not meet, or which was determined not to have met, the Article 8 warranty that is in LILLY's control will, at ISIS' option, either be returned to ISIS or will be destroyed pursuant to ISIS' instructions and with LILLY's approval, which approval will not be unreasonably withheld, at ISIS' expense.

(g) Failure by LILLY to notify ISIS within [*] after Delivery of API which does not meet the warranty under Article 8 will be a waiver of the remedies available to LILLY under this Section 5.3.

(h) Should either party identify any possible latent defect of API that is not revealed by the procedures set forth above within [*] of receipt of any shipment by LILLY, it will so notify the other party immediately upon discovery. LILLY and ISIS will discuss in good faith and agree upon the appropriate measures to be taken by the parties related to such latent defect.

5.4 TERMS OF SALE.

The terms and conditions of this Agreement will be controlling over any inconsistent terms or conditions included in any agreed-upon order for API or any other sales acknowledgment or document. No provision of any LILLY forms purporting to be orders for API that may impose different conditions than those herein referenced upon ISIS, LILLY or their respective Affiliates will be of any force or effect unless expressly agreed to in writing by both parties.

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5.5 RECORD KEEPING AND AUDIT.

ISIS will keep accurate records in sufficient detail to enable the API Clinical Supply Price to be verified. Upon written request of LILLY and not more than once in each Calendar Year, ISIS will permit representatives of LILLY to have access during normal business hours to such records as may be reasonably necessary to verify the API Clinical Supply Price. Once specific records have been audited under this Section 5.5, no further audit of such records may be made. If such audit correctly concludes that any amounts are due to either party, such payment will be made within [*] days after the determination by the parties. The parties will treat all financial information subject to review under this Section 5.5 in accordance with the confidentiality provisions of the Development and License Agreement, which are incorporated herein and made part of this Agreement by reference.

ARTICLE 6

TECHNOLOGY TRANSFER

6.1 TECHNOLOGY TRANSFER TEAM.

(a) The Technology Transfer will be coordinated and implemented under the MWG. The MWG will form a team (the "Technology Transfer Team") comprised of the members of the MWG and such additional employees of each of the parties selected by the MWG as it deems appropriate to effect the Technology Transfer (with equal representation of each of the parties). Members of the Technology Transfer Team will each have appropriate technical credentials, experience and knowledge; the Technology Transfer Team will be co-chaired by a LILLY representative and an ISIS representative from the MWG. The advice of additional employees or consultants of either party may by mutual consent of the parties be obtained.

(b) Decisions of the Technology Transfer Team will be made by unanimous decision of the two-co-chairs; provided however, in the event that the co-chairs do not, after good faith efforts, reach agreement on an issue, the resolution and/or course of conduct in issue will be determined in good faith by the MWG. In the event that the MWG does not, after good faith efforts, reach agreement on such issue, the resolution and/or course of conduct in issue will be determined in good faith by the Product Leader at LILLY with respect to Product, who shall hold at least an Executive Director position at LILLY, after consultation with the Executive Vice President of ISIS.

(c) Throughout the entire Technology Transfer Term, the Technology Transfer Team will meet at least once each month in person or by teleconference, videoconference or by other mutually acceptable means, as necessary to implement effectively and efficiently the Release Technology Transfer Plan and the API Technology Transfer Plan.

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6.2 TECHNOLOGY TRANSFER FOR CLINICAL PRODUCT RELEASE.

(a) Promptly after the Effective Date, the Technology Transfer Team will establish a plan (the "Release Technology Transfer Plan") for the transfer to LILLY of the Release Technology as specified in the Release Technology Transfer Plan (the "Release Technology Transfer"). The goal of the Release Technology Transfer Plan is to effect the Release Technology Transfer at the same time that Clinical Product release is conducted for the second Phase III clinical trial of the Clinical Product and in no event later than December 31, 2002.

(b) The Release Technology Transfer Plan will include INTER ALIA (i) procedures designed to effect the prompt and efficient Release Technology Transfer, (ii) a list of events necessary to accomplish the Release Technology Transfer, (iii) a description of the training and support to be provided by ISIS to LILLY during the Release Technology Transfer, and (iv) the time period during which ISIS will perform the Release Technology Transfer.

(c) During the Technology Transfer Term with respect to the Release Technology Transfer, ISIS will (i) disclose and transfer to LILLY all of the Release Technology as specified in the Release Technology Transfer Plan and (ii) provide to LILLY the training and support described in the Release Technology Transfer Plan and in this Agreement.

(d) ISIS will use commercially reasonable efforts to perform the Release Technology Transfer in accordance with the Release Technology Transfer Plan and the terms of this Agreement. The parties will cooperate so that the Release Technology Transfer may be completed as expeditiously as possible.

(e) LILLY will use commercially reasonable efforts to implement the Release Technology to be transferred by ISIS pursuant to this Section 6.2, and to make available all reasonably necessary personnel and other resources to enable such transfer without delay.

6.3 TECHNOLOGY TRANSFER PLAN FOR MANUFACTURE OF API.

(a) Promptly after LILLY notifies ISIS of its decision regarding the manufacture of API to be utilized in Commercial Products as provided in Section 3.2, the Technology Transfer Team will establish a plan (the "API Technology Transfer Plan") for the transfer of the Manufacturing Process and the Manufacturing Technology for the Manufacture of API from ISIS to LILLY, its Affiliates or a third party designated by LILLY

(the "API Technology Transfer"). The goal of the API Technology Transfer Plan is to enable LILLY to apply the Manufacturing Technology, implement the Manufacturing Process and Manufacture API as soon as practicable thereafter and in no event later than December 31, 2003.

(b) The API Technology Transfer Plan will include INTER ALIA (i) procedures designed to effect the prompt and efficient API Technology Transfer, (ii) a list of events necessary to accomplish the API Technology Transfer, (iii) a description of the training and support to

be provided by ISIS to LILLY during the API Technology Transfer, and (iv) the time period during which ISIS will perform the API Technology Transfer.

(c) During the Technology Transfer Term with respect to the API Technology Transfer, ISIS will (i) disclose and transfer to LILLY all of the Manufacturing Process and the Manufacturing Technology as specified in the API Technology Transfer Plan and (ii) provide to LILLY the training and support described in the API Technology Transfer Plan and in this Agreement.

(d) ISIS will use commercially reasonable efforts to perform the API Technology Transfer in accordance with the API Technology Transfer Plan and the terms of this Agreement. The parties will cooperate so that the API Technology Transfer may be completed as expeditiously as possible.

(e) LILLY and/or its third party manufacturer will use commercially reasonable efforts to establish the Manufacturing Process for the Manufacture of API to be transferred by ISIS pursuant to this Section 6.3, and to make available all reasonably necessary personnel and other resources to enable such transfer without delay.

6.4 TRAINING AND SUPPORT.

The training and support to be provided by ISIS to LILLY in connection with the Release Technology Transfer and the API Technology Transfer (the "Technology Transfer") will include without limitation training and support in a mutually acceptable facility in all of the methods necessary to practice the Release Technology and the Manufacturing Technology, as detailed in the Release Technology Transfer Plan and the API Technology Transfer Plan. In addition, a reasonable number of employees of LILLY and its Affiliates will be entitled to visit ISIS facilities including without limitation pilot and commercial scale facilities and testing laboratories to observe relevant processes in operation. Moreover, ISIS will provide technical consultation on an as-needed basis following NDA approval of Product for a time period to be established by the Technology Transfer Team. ISIS also will be available, if requested, for consultation during any regulatory inspection or to assist in responding to regulatory questions that may occur during Product registration activities.

6.5 PAYMENT OF TECHNOLOGY TRANSFER COSTS.

The Technology Transfer Team will submit a plan for resourcing the Technology Transfer to the MWG. A budget for ISIS and LILLY resources to be used in the performance of the Technology Transfer will be developed to ensure effective forward planning and cost management. LILLY will compensate ISIS [*] ISIS will invoice LILLY on a quarterly basis for all activities performed and expenses incurred in accordance with this Article. LILLY will pay each invoice within [*] days after receipt. Interest will be charged on late payments consistent with the provisions of Section 5.1(c).

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6.6 RECORDS.

ISIS will maintain records, in sufficient detail and in good scientific manner appropriate for patent, regulatory and manufacturing purposes, which will fully and properly reflect all of the work done and the progress achieved in the performance of the Technology Transfer (the "Records"). The Records at all times will be available to the

Technology Transfer Team and LILLY will have the right, during normal business hours and upon reasonable notice, to inspect and copy all such Records. LILLY also will have the right to arrange for its employees and/or consultants to visit ISIS at its offices and laboratories and other facilities during normal business hours on reasonable notice concerning or in furtherance of the Technology Transfer and/or to discuss the progress of the Technology Transfer and its results in detail with the technical personnel and consultants of ISIS.

ARTICLE 7

ISIS CMC AND DEVELOPMENT ACTIVITIES

7.1 ISIS CMC ACTIVITIES.

(a) As part of its activities under the Development Plan set forth in the Development and License Agreement, ISIS will perform the CMC items set forth in Exhibit 5 hereto. ISIS will perform the listed activities and such other activities as approved by the JDC in support of the preparation and filing of the NDA according to the schedule set forth in the Development Plan.

(b) In consideration of ISIS' performance of CMC activities in connection with ISIS 3521 as set forth in Exhibit 5, LILLY will compensate ISIS [*] ISIS will invoice LILLY on a quarterly basis for all activities performed in accordance with this Article and related expenses. Payments due under this Section will be due [*] days after receipt of each invoice by LILLY. Interest will be charged on late payments consistent with the provisions of Section 5.1(c).

7.2 ISIS DEVELOPMENT ACTIVITIES.

(a) As of the Effective Date, LILLY will also compensate ISIS for additional development efforts undertaken by ISIS, such as analytical methods development for raw materials, API and drug product testing and release, and process development in connection with other phosphorothioate oligodeoxynucleotides, which additional activities support the activities of ISIS with regard to ISIS 3521 as approved by the JDC and required pursuant to this Agreement and the Development and License Agreement.

(b) In consideration of ISIS' performance of such additional activities in connection with ISIS 3521, LILLY will compensate ISIS [*] used in activities allocated to ISIS 3521 development, manufacture or support, [*] Payments due under this Section will be due [*] days after receipt of each invoice by LILLY. Interest will be charged on late payments consistent with the provisions of Section 5.1(c).

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ARTICLE 8

PRODUCT WARRANTY

8.1 API SPECIFICATIONS; CGMPS; APPLICABLE LAWS.

Subject to Section 8.2 below, ISIS warrants that the API will, at the time of Delivery, be Manufactured in accordance with and meet (a) the API Specification; (b) cGMP; (c) requirements of the DRD and Quality Agreement, and (d) the Legal Requirements.

8.2 FOREIGN MANUFACTURING REQUIREMENTS.

If the cGMP or the Legal Requirements applicable to the Manufacture of API for use in the U.S. (the "U.S. Manufacturing Requirements") are different from those applicable outside to the Manufacture of API for use in countries other than the U.S. (the "Foreign Manufacturing Requirements"), the warranty of subsection (a) will include such Foreign Manufacturing Requirements only if LILLY has informed ISIS thereof in writing as provided in Section 4.1, the parties have resolved any conflicts as provided in Section 4.6, and have adapted the Manufacturing Process, if necessary, as provided in Section 4.3.

8.3 MRB APPROVED API.

Notwithstanding anything in this Agreement, API will be deemed to conform with API Specifications at the time of Delivery if approved by the MRB pursuant to Section 5.3 for release and further processing into

Clinical Product.

ARTICLE 9

QUALITY CONTROL

9.1 SPECIFICATIONS AND PROCESS CHANGES.

The API Specification may not be materially amended, changed or supplemented, except as provided in Section 4.3 and 4.6 above. Unless otherwise specified in that Section, material changes required to comply with applicable laws and regulations and Agency requirements will be mutually agreed upon by ISIS and LILLY.

9.2 MATTERS RELATING TO THE FACILITY.

(a) ISIS will Manufacture API supplied by ISIS hereunder at the Facility, which ISIS represents and warrants has passed inspections of the U.S. and EU Agencies. ISIS will perform release testing of API at the Facility and/or the facility of subcontractors

(b) ISIS will arrange for one or more qualified technical specialists from LILLY, upon reasonable prior notice and during normal business hours, to conduct inspections of the Facility. Observations and conclusions of LILLY's audits or inspections will be issued to and promptly discussed with ISIS and such corrective action as LILLY determines to be

reasonably required will be promptly implemented by ISIS. ISIS will maintain complete and accurate records of all reasonably relevant information relating to the performance by ISIS of its obligations hereunder. ISIS will permit LILLY to review, during the inspection at the Facility, relevant cGMP documentation. The total number of inspections under this Section 9.2(b) and audits under Section 9.3 per Calendar Year will not exceed two.

9.3 QUALITY ASSURANCE AUDITS.

ISIS will perform inspections of its facilities to review its manufacturing operations and assess its compliance with cGMP. In addition, upon LILLY's written request and at mutually agreeable times during normal business hours, ISIS will permit representatives of LILLY to review ISIS' manufacturing operations and records and assess its compliance with cGMP and quality assurance standards and to discuss any manufacturing issues with ISIS' manufacturing and management personnel. Under the Production and Delivery Plan, LILLY will have notice of how many production runs ISIS may conduct in a given Calendar Year, which will permit LILLY personnel to observe any such production run, if LILLY so chooses, after providing notice to ISIS (and at its own expense). In the event of a regulatory inspection that directly involves the API, ISIS will immediately inform LILLY of the issuance of the Notice of Inspection (or an equivalent notice from a non-U.S. Regulatory Authority) will provide LILLY with copies of all communications relating thereto and LILLY will be allowed to participate.

9.4 TESTING.

(a) ISIS will perform such tests as are indicated in the API Specification. Such testing methods will be qualified by ISIS prior to use and certain of such tests will be stability indicating. No production lot of API will be released for Delivery unless such tests show the API to meet the API Specification. Should any production lot fail to meet API Specification limits, such lot will not be released, unless the failure is identified following release, in which case the identifying party will immediately notify the other party and they will cooperate on the actions to be taken as described in Section 5.3.

(b) ISIS is responsible for obtaining and retaining, at LILLY's expense, the amount of API required for quality control release testing as indicated in the API Specification, as applicable. Such amounts will be retained for a period of not less than 1 year from the last retest date prescribed by ISIS, and thereafter shipped at LILLY's request for longer term storage at a designated LILLY facility.

(c) At LILLY's expense and approval, ISIS will perform an on-going program of stability testing, as required in the stability plan to be agreed by the parties, and provide a stability report to support the

transportation of API to a LILLY-designated facility. The stability study period will be for a period specified by LILLY following completion of Manufacture of such production lots and such stability testing will be stability indicating. In the event that ISIS will detect a change in a degradant in excess of the amount specified in the stability plan of API in connection with such testing, ISIS will notify LILLY, and as a part of each stability test of such lot thereafter, ISIS will specifically

incorporate additional testing and controls (e.g., storage condition changes), as LILLY may reasonably specify.

(d) In consideration of ISIS' performance of testing as set forth in subsection (c) above, LILLY will compensate ISIS for such performance at the ISIS FTE Rate and will pay for any Out-of-Pocket Expenses incurred in connection with such testing. ISIS will invoice LILLY on a quarterly basis for all activities performed in accordance with this Section 9.4 and related expenses. Payments due under this Section will be due [*] after receipt of each invoice by LILLY. Interest will be charged on late payments consistent with the provisions of Section 5.1(c).

9.5 INFORMATION RELATING TO MANUFACTURING CONDITIONS.

(a) Each party will notify the other immediately of any health hazards with respect to API of which it becomes aware which may impact employees involved in the Manufacture of API.

(b) Each party will promptly advise the other of any safety or toxicity problem that is not part of the knowledge base readily available in chemical manufacturing facilities of which either party becomes aware regarding the API.

9.6 AGENCY INSPECTIONS.

ISIS hereby agrees to advise LILLY of any visit or inspection by an Agency of the Facility relating to the Manufacture of API, provide copies of all communications relating thereto and will permit one or more qualified representative(s) of LILLY to be present, when possible. If LILLY is not present during such a visit or inspection for any reason, ISIS will promptly provide a copy of the actual report of the results of the inspection to LILLY. ISIS will furnish LILLY copies of all reports, documents or correspondence with respect to any such Agency inspections of the Facility.

9.7 STORAGE AND DELIVERY.

ISIS will store and Deliver API in accordance with the DRD and Quality Agreement, API Specifications and label requirements set forth by the MWG and cGMP.

ARTICLE 10

REGULATORY MATTERS

10.1 ISIS will prepare and promptly provide necessary and useful information, including without limitation Manufacturing information, as is needed to support filings of Registrations by LILLY, its Affiliates, sublicensees or distributors of Product. In addition, ISIS will participate as required in resolving regulatory concerns. ISIS will be responsible for maintaining current technical information needed to support such submissions of Registrations, and accordingly will promptly provide LILLY with advance notification of all changes in such technical information required to be filed as

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amendment to CMC. All such activities will be at LILLY's expense, which will be agreed to in advance by the parties.

10.2 The mutual goal of ISIS and LILLY will be to maintain an integrated approach to the content and timing of all submissions of Registrations made by LILLY in an effort to obtain and maintain regulatory approvals of a Product. To ensure this mutual goal is met, with respect to issues

pertaining to API or to a Product, ISIS will provide to LILLY the right to review and reference all authorizations, certificates, methodologies and specifications in the possession or under the control of ISIS relating to the pharmaceutical/technical development and Manufacture or any component thereof to the extent needed for LILLY's filings of Registrations.

ARTICLE 11

INDEMNIFICATION AND INSURANCE

11.1 INDEMNIFICATION.

(a) ISIS will defend, indemnify and hold harmless LILLY, its Affiliates and their respective directors, officers, employees and agents, and their respective successors and permitted assigns, from any and all claims, actions, causes of action, liabilities, losses, damages, costs or expenses, including reasonable attorney's fees, which arise out of or relate to claims that may be brought or instituted against them by third parties to the extent based upon or arising out of (i) the failure by ISIS to meet the warranties set forth in Article 8; (ii) a material breach by ISIS of its obligations set forth in this Agreement; or (iii) gross negligence or willful misconduct of ISIS, its officers, employees and agents in the performance of its obligations hereunder.

(b) LILLY will defend, indemnify and hold harmless ISIS, its Affiliates and their respective directors, officers, employees and agents, and their respective successors and permitted assigns, from any and all claims, actions, causes of action, liabilities, losses, damages, costs or expenses, including reasonable attorney's fees, which arise out of or relate to claims that may be brought or instituted against them by third parties to the extent based upon or arising out of (i) a material breach by LILLY of its obligations set forth in this Agreement; or (ii) gross negligence or willful misconduct of LILLY, its officers, employees and agents in the performance of its obligations hereunder.

11.2 CLAIMS.

(a) If a claim is made against a party entitled to indemnification under this Article 11, and if that party intends to seek indemnification with respect thereto under this Article 11, the party seeking indemnification (the "Indemnitee") will promptly notify the indemnifying party (the "Indemnifying Party") of such claim. The Indemnifying Party will defend, negotiate and settle such claim, and the Indemnitee will cooperate with the Indemnifying Party in connection therewith. The Indemnitee may participate in the defense of any claim with counsel of its own choice and at its own expense. Neither party will settle or compromise any such claim without the other party's prior written consent, which

consent will not be unreasonably withheld. The indemnity agreement in this Article 11 will not apply to amounts paid in settlement of any claim if such settlement is effected without the consent of the Indemnifying Party, which consent will not be unreasonably withheld. Failure of the Indemnitee to deliver notice to the Indemnifying Party within a reasonable time after becoming aware of a claim will not relieve the Indemnifying Party of any liability to the Indemnitee pursuant to this Article 11, except to the extent such delay prejudices the Indemnifying Party's ability to defend such claim.

11.3 INSURANCE.

Each party will maintain during the term of this Agreement and for [*] thereafter, at its own expense, (i) commercial general liability insurance, including contractual liability coverage, with a minimum limit of [*] per occurrence and [*] annual aggregate; (ii) property insurance with a minimum limit of [*]; and (iii) statutory workers' compensation coverage as required by law.

ARTICLE 12

TERM AND TERMINATION

12.1 TERM.

This Agreement will be effective as of the Effective Date, and unless sooner terminated as provided herein, will continue in effect until

December 31, 2003; provided that LILLY may, in its sole discretion, extend the term of this Agreement for up to two additional, consecutive one-year periods by providing ISIS with written notice of such extension at least six months prior to the then scheduled expiration date of this Agreement (using ISIS' Annual Capacity for 2003 for any such additional year). The term of this Agreement may be further extended by mutual written agreement of the parties.

12.2 TERMINATION BY EITHER PARTY.

This Agreement may be terminated with written notice by either party at any time during the term of this Agreement:

(a) if the other party is in breach of its material obligations hereunder and has not cured such breach within 90 days after written notice requesting cure of the breach has been given; provided, however, in the event of a good faith dispute with respect to the existence of a material breach, the 90-day cure period will be tolled until such time as the dispute is resolved pursuant to Section 14.6; or

(b) upon the filing or institution of bankruptcy, reorganization, liquidation or receivership proceedings by the other party or upon an assignment of a substantial portion of the assets for the benefit of creditors by the other party; provided, however, in the case of any involuntary bankruptcy proceeding such right to terminate will only become effective if the party consents to the involuntary bankruptcy or such proceeding is not dismissed within 90 days of the filing thereof.

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12.3 TERMINATION OF DEVELOPMENT AND LICENSE AGREEMENT.

This Agreement will automatically terminate in the event the Development and License Agreement is terminated for any reason.

12.4 PAYMENT OF OUTSTANDING DEBTS.

Upon expiration or termination of this Agreement for whatever reason, LILLY and ISIS will settle all outstanding invoices or monies owed to the other party in accordance with the terms of this Agreement.

12.5 EFFECT OF TERMINATION OR EXPIRATION.

(a) If this Agreement is terminated by LILLY pursuant to Section 12.2(a), all orders will be automatically cancelled and ISIS will terminate the Manufacture of API as soon as practicable. LILLY will have the option but not the obligation to (i) purchase all quantities of API stored at ISIS by paying the API Clinical Supply Price as provided in Section 5.1, and (ii) undertake the Manufacture of API or seek a third party to do such Manufacture. If LILLY undertakes to Manufacture or have Manufactured API, then ISIS will continue the transfer of technology pursuant to Article 6 on an expedited basis, at LILLY's expense.

(b) If this Agreement is terminated by LILLY pursuant to Section 12.2(b), LILLY (i) will purchase all quantities of API stored at ISIS by paying the API Clinical Supply Price as provided in Section 5.1, and (ii) will have the right to undertake the Manufacture of API or seek a third party to do such Manufacture.

(c) If this Agreement is terminated by ISIS pursuant to Section 12.2(a), ISIS will have the option but not the obligation to supply under all outstanding quantities set forth in the Production and Delivery Plan at the API Clinical Supply Price or the API Commercial Supply Price, as applicable. If ISIS elects to so supply, LILLY's payment obligations relating thereto including, without limitation, those set forth in Section 5.1 will continue to apply until all outstanding obligations of LILLY to ISIS are fulfilled.

(d) If this Agreement is terminated pursuant to Section 12.3, all outstanding quantities of API set forth in the Production and Delivery Plan will be automatically cancelled and ISIS will terminate the Manufacture of API as soon as practicable. In addition, LILLY will be responsible for all other Manufacturing costs associated with API pursuant to Section 5.1 at the time of termination. Notwithstanding the foregoing, ISIS will use its best efforts to mitigate any costs payable by LILLY under this Section 12.5(d).

(e) If this Agreement expires pursuant to Section 12.1, LILLY will purchase

all API ordered by LILLY during the term of this Agreement. ISIS will Deliver such API in accordance with Section 5.2.

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ARTICLE 13

DAMAGE LIMITATIONS

NOTWITHSTANDING ANYTHING TO THE CONTRARY CONTAINED HEREIN, IN NO EVENT WILL EITHER PARTY HERETO, OR ITS DIRECTORS, OFFICERS, EMPLOYEES, AGENTS OR AFFILIATES BE LIABLE TO THE OTHER PARTY OR SUCH OTHER PARTY'S DIRECTORS, OFFICERS, EMPLOYEES, AGENTS, AFFILIATES OR SUBLICENSEES FOR ANY INDIRECT, CONSEQUENTIAL, INCIDENTAL OR SPECIAL DAMAGES, COSTS OR EXPENSES (INCLUDING, BUT NOT LIMITED TO, LOST PROFITS, LOST REVENUES AND/OR LOST SAVINGS) SUFFERED OR INCURRED BY THE OTHER PARTY, WHETHER BASED UPON A CLAIM OR ACTION OF CONTRACT, WARRANTY, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE, ARISING FROM THIS AGREEMENT.

ARTICLE 14

MISCELLANEOUS

14.1 FORCE MAJEURE.

Neither 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 when such failure or delay is caused by or results from causes beyond the reasonable control of the affected party including without limitation embargoes, war, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, or acts of God. The affected party will notify the other party of such force majeure circumstances as soon as reasonably practical and will make every reasonable effort to mitigate the effects of such force majeure circumstances.

14.2 ASSIGNMENT.

This Agreement will inure to the benefit and be binding upon each party, its successors and assigns. The 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 either party without the prior 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 an Affiliate or in connection with the transfer or sale of all or substantially all of its assets, or in the event of its merger or consolidation or change in control or similar transaction. Any permitted assignee will assume all obligations of its assignor under the Agreement. Any attempted assignment not in accordance with this Section 14.2 will be void.

14.3 SEVERABILITY.

In the event any one or more of the provisions contained in this Agreement should be 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 in such an instance use their best efforts to 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.

14.4 NOTICES.

All notices which are required or permitted hereunder will be in writing and sufficient if delivered personally, sent by facsimile or electronic mail (and promptly confirmed), sent by nationally-recognized overnight courier or sent by registered or certified mail, postage prepaid, return receipt requested, addressed as follows:

if to ISIS, to: Isis Pharmaceuticals, Inc.

Carlsbad Research Center
2292 Faraday Avenue
Carlsbad, CA 92008
Attention: Executive Vice President
Fax No.: (760) 931-9639
E-Mail: lparshall@isisph.com

with a copy to: Attention: General Counsel
Fax No.: (760) 603-3820
E-Mail: gbryce@isisph.com

if to LILLY, to: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
Attention: General Patent Counsel
Fax No.: (317) 277-1917
E-Mail: armitage_robert_a@lilly.com

or to such other address as the party to whom notice is to be given may have furnished to the other party in writing in accordance herewith. Any such notice will be deemed to have been given when delivered if personally delivered or sent by facsimile or electronic mail on a business day, on the business day after dispatch if sent by nationally-recognized overnight courier and on the third business day following the date of mailing if sent by mail.

14.5 GOVERNING LAW.

This Agreement will be governed by and construed in accordance with the laws of the State of Delaware without reference to any rules of conflict of laws.

14.6 DISPUTE RESOLUTION; OVERSIGHT COMMITTEE.

The parties recognize that disputes may from time to time arise between the parties during the term of this Agreement. In the event of such a dispute, either party, by written notice to the other party, may have such dispute referred to the Oversight Committee, the function of which is to attempt resolution of any disputes arising under this Agreement by good faith negotiations. The Oversight Committee will endeavor to resolve such disputes within 30 days after such notice is received. The Oversight Committee will be comprised of two designated executive officers (or their successors), one from each party. Said designated officers are as follows:

For ISIS: Chief Executive Officer

For LILLY: Executive Vice President

14.7 REMEDIES.

In the event the parties are unable to resolve any disputes hereunder pursuant to the dispute resolution measures provided herein, each party may pursue its rights and remedies in law or equity in any court of competent jurisdiction.

14.8 ENTIRE AGREEMENT.

This Agreement and the Development and License Agreement contain the entire understanding of the parties with respect to the license, development and commercialization of Products containing API and the Manufacture and supply of API. All express or implied agreements and understandings, either oral or written, heretofore made by the parties on the same subject matter are expressly superseded by this Agreement and the Development and License Agreement. This Agreement may be amended, or any term hereof modified, only by a written instrument duly executed by both parties hereto.

14.9 HEADINGS.

The captions to the several Articles and Sections hereof are not a part of the Agreement, but are merely a convenience to assist in locating and reading the several Articles and Sections hereof.

14.10 INDEPENDENT CONTRACTORS.

It is expressly agreed that ISIS and LILLY will be independent contractors and that the relationship between the two parties will not constitute a partnership, joint venture or agency. Neither ISIS nor LILLY 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, without the prior consent of the other party.

14.11 WAIVER.

The waiver by either party hereto of any right hereunder, or the failure to perform, or a breach by the other 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.

14.12 COUNTERPARTS.

The 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.

14.13 WAIVER OF RULE OF CONSTRUCTION.

Each party has had the opportunity to consult with counsel in connection with the review, drafting and negotiation of this Agreement. Accordingly, the rule of construction that any ambiguity in this Agreement will be construed against the drafting party will not apply.

IN WITNESS WHEREOF, the parties have executed this Agreement as of the Effective Date.

ELI LILLY AND COMPANY	ISIS PHARMACEUTICALS, INC.
By:/s/ AUGUST M. WATANABE	By:/s/ B. LYNNE PARSHALL
Name: August M. Watanabe	Name: B. Lynne Parshall
Title: Executive Vice President	Title: Executive Vice President & CFO

EXHIBIT 1

DEFINITIONS

1.1 "AFFILIATE" with respect to either party means any person, organization, corporation or other business entity (collectively, "Person") controlling, controlled by, or under common control with such party. For purposes of this definition, "control" refers to (a) the possession, directly or indirectly, of the power to direct the management or policies of a Person, whether through the ownership of voting securities, by contract or otherwise, and (b) the ownership, directly or indirectly, of at least 50% of the voting securities or other ownership interest of a Person.

1.2 "AGENCY" means the U.S. Food and Drug Administration. In the event LILLY provides written notice to ISIS that LILLY intends to conduct Development Program activities outside of the United States, the term "Agency" will mean with respect to such activities outside the United

States the Regulatory Authority (as defined below) of the country specified in such notice involved in granting any approvals relating to such Development Program activities.

1.3 "ANNUAL CAPACITY" has the meaning as defined in Section 3.1(d).

1.4 "API" means the bulk drug substance ISIS 3521 as described in Exhibit 6.

1.5 "API SPECIFICATION" will mean the specification comprising methods, tests and acceptance criteria or release limits of API, which may be amended from time to time by the MWG. The current API Specification is attached as Exhibit 6.

1.6 "API CLINICAL SUPPLY PRICE" means [*] of the API Supply Cost.

1.7 API SUPPLY COST" means the cost of Manufacture of API described in Exhibit 7.

1.8 "API ORDER DATE" means the date on which the parties agree upon a Production and Delivery Plan for the following Calendar Year, as set forth in Section 3.1(c).

1.9 "CALENDAR YEAR" means each successive period of 12 months commencing on January 1 and ending on December 31.

1.10 "cGMP" means the current good manufacturing practices described in Q7A ICH Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients and 21 CFR Parts 210 ET SEQ. as applicable to the Manufacture of API in the U.S., as are in effect on the Effective Date or as may subsequently be modified or supplemented. In the event LILLY provides written notice to ISIS that LILLY intends to conduct the Development Program activities in countries outside of the United States, the term "cGMP" will also include corresponding good manufacturing practices in such countries, provided that to the extent any conflict exists between cGMP applicable in the U.S. and in such countries, the cGMP of the U.S. will apply, unless the parties agree otherwise as provided in Section 4.1, 4.3, 4.6 and 8.2.

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1.11 "CLINICAL PRODUCT" means a formulated pharmaceutical product containing API in finished form for use in conducting clinical trials prior to Regulatory Approval.

1.12 "COMMERCIAL PRODUCT" means a formulated pharmaceutical product containing API for all uses after Regulatory Approval has been obtained for the Product.

1.13 "COMBINATION PRODUCT" means any pharmaceutical product that comprises the API and at least one other active compound(s) and/or ingredients. All references to Product in this Agreement will be deemed to include Combination Product.

1.14 "CS17 STUDY" means the Phase III clinical trial conducted by ISIS that is ongoing as of the Effective Date, as further described in the Development Plan.

1.15 "DELIVER" OR "DELIVERY" means the delivery of API by ISIS to the carrier pursuant to Section 5.2.

1.16 "DEVELOPMENT AND LICENSE AGREEMENT" means the agreement for the development and commercialization of ISIS 3521 entered into by ISIS and LILLY on August 14, 2001.

1.17 "DEVELOPMENT PLAN" means the plan for the development of ISIS 3521 attached as Exhibit C to the Development and License Agreement.

1.18 "DEVELOPMENT PROGRAM" means the activities undertaken by ISIS and LILLY as set forth in the Development Plan.

1.19 "DRD" has the meaning as defined in Section 4.5.

1.20 "FACILITY" means the Manufacturing facility of ISIS located in 2282 Faraday Avenue, Carlsbad, California.

1.21 "FTE" means the equivalent of the scientific or technical work of at

least a total of [*] hours per year on or directly related to the Manufacture, the Technology Transfer, CMC activities or any other activities contemplated under this Agreement, carried out by a qualified employee or consultant. Scientific or technical work can include, but is not limited to, [*]

1.22 "ISIS 3521" means the phosphorothioate oligodeoxyribonucleotide that targets human protein kinase C disclosed and claimed (as SEQ ID NO 2) in U.S. Patent No. 5,703,054.

1.23 "ISIS FTE RATE" means [*]

1.24 "JDC" means the joint development committee established under the Development and License Agreement.

1.25 "LEGAL REQUIREMENTS" has the meaning as defined in Section 4.7.

1.26 "MANUFACTURE" or "MANUFACTURED" or "MANUFACTURING" means all operations involved in the manufacturing, quality control testing (including in-process, release and

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stability testing, if applicable), releasing, packaging and shipping of API under this Agreement.

1.27 "MANUFACTURING PROCESS" means the process steps set forth in master batch records for ISIS 3521 in the version existing as of the Effective Date, including reasonable minor variants and extensions of process steps thereof.

1.28 "MANUFACTURING TECHNOLOGY" means any and all scientific and technical data and information including without limitation formulas, methods, techniques, protocols, and processes controlled by ISIS as of the Effective Date which are necessary for performing the Manufacturing Process.

1.29 "MANUFACTURING WORKING GROUP" or "MWG" has the meaning set forth in Section 4.3 herein.

1.30 "MATERIALS REVIEW BOARD" has the meaning set forth in Section 5.3(b) herein.

1.31 "MARKETING APPROVAL" means the act of a Regulatory Authority necessary for the marketing and sale of the Product in a country or regulatory jurisdiction, including, without limitation, the approval of the NDA by the FDA.

1.32 "MRD" means the Manufacturing Responsibilities Document for the supply of Commercial Product that includes key contacts, supply chain diagrams, forecasting processes, the details of shipping and receiving, and a process for informing ISIS of the batch numbers and expiration date of Product referencing the batch numbers of API contained therein.

1.33 "NDA" means a new drug application or other application filed with the FDA to obtain approval for marketing a Product in the United States, or any future equivalent process.

1.34 "OUT-OF-POCKET EXPENSES" means costs, other than labor costs, that are directly related to the activities outlined in the Development Plan and this Agreement, including, without limitation, costs of travel, supplies, outside services and consultants.

1.35 "OVERSIGHT COMMITTEE" has the meaning set forth in Section 14.6 herein.

1.36 "PRODUCT" means preparation(s) containing API for the treatment of cancer in humans, including preparations for use in clinical trials ("Clinical Product") and preparations for sale by prescription, over-the-counter or any other method ("Commercial Product").

1.37 "PRODUCTION AND DELIVERY PLAN" has the meaning a defined in Section 3.1(b).

1.38 "QUALITY AGREEMENT" has the meaning as defined in Section 4.4.

1.39 "RAW MATERIALS" means any raw materials intended for use in the Manufacture of the Product, including those that may not appear in the Product.

1.40 "REGISTRATIONS" means the technical, medical and scientific licenses, registrations, authorizations and/or approvals of API or Product (including, without limitation, IND, DMF, NDA or other prerequisite manufacturing approvals or authorizations, and marketing authorization based upon such approvals or authorizations) that are required by any national, supranational (e.g., the European Commission or the Council of the European Union), regional, state or local regulatory agency, department, bureau or other governmental entity, as amended or supplemented from time to time.

1.41 "REGULATORY AUTHORITY" means any applicable government regulatory authority involved in granting approvals for the marketing, and/or pricing of a Product worldwide, including without limitation, in the United States, the Food and Drug Administration ("FDA"), and any successor government authority having substantially the same function, and foreign equivalents thereof.

1.42 "REGULATORY APPROVAL" means the act of a Regulatory Authority necessary for the Manufacture of Product in a country or regulatory jurisdiction.

1.43 "RELEASE TECHNOLOGY" means any and all scientific and technical data and information including without limitation formulas, methods, techniques, protocols, and processes controlled by ISIS as of the Effective Date regarding Clinical Product release.

1.44 "TECHNOLOGY TRANSFER" has the meaning set forth in Section 6.4 herein.

1.45 "TECHNOLOGY TRANSFER TEAM" has the meaning set forth in Section 6.1 herein.

1.46 "TECHNOLOGY TRANSFER TERM" means the time period following the Effective Date, as determined by the Technology Transfer Team, during which the Technology Transfer will take place.

EXHIBIT 2

LILLY'S API ORDER ESTIMATE FOR CALENDAR YEAR 2002

DELETE IN ENTIRETY

[*]

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EXHIBIT 3

MANUFACTURING CAPACITY OF ISIS

DELETE IN ENTIRETY

[*]

*Confidential Treatment Requested

EXHIBIT 4

LIST OF ISIS SOPS

DELETE IN ENTIRETY

[*]

*Confidential Treatment Requested

EXHIBIT 5

ISIS CMC ACTIVITIES

DELETE IN ENTIRETY

[*]

*Confidential Treatment Requested

EXHIBIT 6

API SPECIFICATIONS

DELETE IN ENTIRETY

[*]

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EXHIBIT 7

CALCULATION OF API SUPPLY COST

DELETE IN ENTIRETY

[*]

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EXHIBIT 8

TERMS OF COMMERCIAL SUPPLY OF API BY ISIS

DELETE IN ENTIRETY

[*]

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EXHIBIT 99.1

[LILLY LETTERHEAD]

DATE: August 22, 2001

FOR RELEASE: Immediately
REFER TO: (317) 276-5795 - Terra L. Fox (Lilly)
(760) 603-2521 - Kristina Peterson (Isis)

LILLY AND ISIS PHARMACEUTICALS ANNOUNCE STRATEGIC ALLIANCE THAT INCLUDES LICENSE OF ISIS' PHASE III ANTISENSE CANCER DRUG AND BROAD ANTISENSE DRUG DISCOVERY COLLABORATION

Eli Lilly and Company (NYSE: LLY) and Isis Pharmaceuticals, Inc. (NASDAQ: ISIP) announced today that they have entered into a strategic alliance that includes the license of Isis' novel antisense cancer compound and the formation of a broad collaboration to discover antisense drugs.

The licensed compound, ISIS 3521, is a selective inhibitor of protein kinase C-alpha (PKC-alpha) expression and is in early Phase III trials for the treatment of non-small cell lung cancer. In an ongoing Phase II trial in combination with chemotherapy, ISIS 3521 is currently showing a median patient survival of 15.9 months as compared with a typical 8 to 9 months median survival of standard chemotherapy alone and is being well tolerated with minimal side effects. ISIS 3521 is also being evaluated in combination with the Lilly oncolytic Gemzar(R). Lilly will have exclusive worldwide commercialization rights to ISIS 3521. Non-small cell lung cancer represents a significant market as it affects approximately one million people worldwide and is the leading cause of cancer death.

In addition to the license of ISIS 3521, the companies have formed a four-year collaboration to discover antisense drugs for metabolic and inflammatory diseases. The companies will also use the Isis GeneTrove(TM) antisense technology as a tool to rapidly determine the functional role of up to 1,000 human genes in disease. More than 300 of those genes will be validated as potential drug targets for the antisense drug discovery collaboration. The functional genomics efforts will support the companies' drug discovery programs across multiple therapeutic areas.

Lilly has committed more than $200 million in funding to Isis over a four-year period. Lilly will make a $75 million equity investment in Isis through the purchase of stock at $18 per share,

resulting in approximately a 9 percent ownership of outstanding common stock. In addition, Lilly will loan Isis $100 million, repayable in cash or stock at $40 per share at the end of the four-year term, to fund the research collaboration. For the license of ISIS 3521, Isis will receive $25 million in upfront fees and will be reimbursed for remaining Phase III development and registration costs. Isis may also receive approximately $50 million in milestone payments plus royalties on product sales for the non-small cell lung cancer indication, as well as additional milestones and royalties for other indications and for successes related to the gene functionalization and antisense drug discovery programs. Assuming success of ISIS 3521 and the success of multiple drugs from the collaboration, the cumulative contingent funds over the life of the development process have the potential to exceed total committed funds. The transactions relating to ISIS 3521 and relating to the collaboration and stock purchase are each subject to the approval of the United States Federal Trade Commission under the Hart-Scott-Rodino Antitrust Improvements Act of 1976.

"As an antisense drug, ISIS 3521 represents a potential new method of treating non-small cell lung cancer. This late-stage compound complements our growing oncology portfolio and represents a significant market opportunity," said August M. Watanabe, M.D., executive vice president, science and technology, for Lilly. "We are also keenly interested in antisense technology as both a novel class of highly selective drugs and as a tool to leverage genomics and accelerate target validation in support of our diverse drug discovery programs. We look forward to continuing our strong partnership with Isis, the antisense leader."

"The formation of this strategic partnership with Lilly is a pivotal event for Isis. This transaction fortifies our financial position and enables us to

intensify our drug discovery, drug development and technology development efforts, which we believe will generate substantial value for our shareholders," said Stanley T. Crooke, M.D., Ph.D., Isis chairman and chief executive officer. "Lilly's leadership in oncology and in the creation of innovative therapies makes Lilly an ideal partner to commercialize ISIS 3521 and to help us establish antisense technology as an important new class of drugs. Already we have established a strong working relationship and are looking forward to a long and productive alliance."

Antisense inhibitors work at the genetic level by binding to messenger RNA to interrupt the process by which disease-related proteins are produced. Antisense inhibitors can be used as

functional genomics tools or as drugs. The effects of antisense gene inhibition help identify what a gene does in a biological process (gene functionalization) and help determine whether a specific gene is a good target for drug discovery (target validation). The same antisense inhibitor that is used as a functional genomics tool can be scaled up and studied as a drug candidate in animals and ultimately tested in man in clinical trials, making antisense drug discovery very rapid and efficient. Antisense drugs can be designed to treat a wide range of diseases. Due to their gene selectivity, they have the potential to be highly effective and less toxic than traditional small molecule drugs.

Isis will conduct a live webcast conference call to discuss this release on Wednesday, August 22, at 11 a.m. Eastern time. To participate over the Internet, go to WWW.STREETFUSION.COM. A replay of the webcast will be available at this address for up to 90 days. Richard D. DiMarchi, Ph.D., group vice president, research technologies and product development for Lilly, will be a guest on Isis' conference call.

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Additional information about Lilly is available at WWW.LILLY.COM.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene(TM) (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 11 products in its development pipeline with 2 in late-stage development and 5 in Phase II human clinical trials. ISIS 3521, an inhibitor of PKC-alpha, is in Phase III trials for non-small cell lung cancer. Isis is preparing to initiate a Phase III program for ISIS 2302 (alicaforsen), an ICAM-1 inhibitor, in Crohn's disease. Isis has a broad patent estate as the owner or exclusive licensee of more than 800 issued patents worldwide. Isis' GeneTrove division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services and access to an extensive gene function database. Ibis Therapeutics(TM) is a division focused on the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at www.isip.com.

This press release contains forward-looking statements about the potential of the investigational compound ISIS 3521 in the treatment of non-small cell lung cancer and the potential of antisense drug discovery and development efforts that reflect the current beliefs of Lilly and Isis. However, as with any pharmaceutical under development, there are substantial risks and uncertainties in the process of pharmaceutical discovery, development and regulatory review. There are no guarantees that future clinical trials will confirm the preliminary results referred to in this release or that ISIS 3521 or any other products that may result from the collaboration will receive regulatory approvals or prove to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly and Isis' filings with the United States Securities and Exchange Commission. Lilly and Isis undertake no duty to update forward-looking statements.

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Gemzar(R)(gemcitabine hydrochloride, Lilly)
GeneTrove(TM)and Ibis Therapeutics(TM)are trademarks of
Isis Pharmaceuticals, Inc.
Vitravene(TM)(fomivirsen) is a trademark of Novartis AG