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SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-Q/A
(Amendment No. 2)

(Mark One)

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

For the Quarterly Period Ended June 30, 2001

OR

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

For the transition period from _____ to _____

Commission file number 0-19125

ISIS PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

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

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

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

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

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

(1) Yes /x/ No / / (2) Yes /x/ No / /

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

Common stock $.001 par value	**42,247,956 shares**
(Class)	(Outstanding at June 30, 2001)

Explanatory Note

This amendment to the Form 10-Q for the quarterly period ended June 30, 2001, is being filed solely to amend Part II, Item 6(a), Exhibit 10.1, the Agreement between the Registrant and Merck & Co., Inc., dated May 22, 2001 (with certain confidential information deleted). The Merck Agreement includes a redacted Schedule 5.1, a Clinical Supply Agreement, which is being supplemented to include a list of schedules thereto.

PART II—OTHER INFORMATION

ITEM 6. EXHIBITS AND REPORTS ON FORM 8-K

a.

Exhibits

Exhibits	
3.1*	Bylaws of Isis Pharmaceuticals, Inc.
3.2*	Amended and Restated Certificate of Incorporation filed April 9, 2001
10.1	Agreement between the Registrant and Merck & Co., Inc., dated May 22, 2001 (with certain confidential information deleted)
10.2*	Master Agreement between the Registrant and Hybridon, Inc., dated May 24, 2001, (with certain confidential information deleted)
10.3*	Agreement between the Registrant and PE Corporation through the Celera Genomics Group, dated July 9, 2001 (with certain confidential information deleted)

* Previously filed.

b. *Reports on Form 8-K*

Not applicable.

ISIS PHARMACEUTICALS, INC.
SIGNATURES

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

ISIS PHARMACEUTICALS, INC.
(Registrant)

Date: October 11, 2001

By: /s/ B. LYNNE PARSHALL

B. Lynne Parshall
Executive Vice President, Chief Financial Officer and Director (Duly Authorized Officer and Principal Financial and Accounting Officer)

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*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

MERCK & CO., INC.

and

ISIS PHARMACEUTICALS, INC.

DEVELOPMENT AND LICENSE AGREEMENT

THIS AGREEMENT is effective as the date of the last party to sign this Agreement (the "Effective Date") between MERCK & CO., INC., a corporation organized and existing under the laws of the State of New Jersey ("MERCK") and ISIS PHARMACEUTICALS, INC. a corporation organized and existing under the laws of the State of Delaware ("ISIS").

RECITALS:

WHEREAS, ISIS has rights in and to ISIS Know-How and ISIS Patent Rights (as the foregoing are hereinafter defined); and,

WHEREAS, MERCK and ISIS desire to enter into an agreement to develop Compound (as hereinafter defined) upon the terms and conditions set forth herein; and,

WHEREAS, MERCK desires to obtain licenses under the ISIS Patent Rights and ISIS Know-How, and the technical assistance of ISIS for the purpose of preparing and manufacturing Compound and Product, upon the terms and conditions set forth herein, and ISIS desires to grant such licenses and such assistance to MERCK.

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

ARTICLE I

DEFINITIONS

Unless specifically set forth to the contrary herein, the following terms, whether used in the singular or plural, shall have the respective meanings set forth below:

1.1 "Affiliate" shall mean (i) any corporation or business entity of which fifty percent (50%) or more of the securities or other ownership interests representing the equity, the voting stock or general partnership interest are owned, controlled or held, directly or indirectly, by MERCK or ISIS; or (ii) any corporation or business entity which, directly or indirectly, owns, controls or holds fifty percent (50%) (or the maximum ownership interest permitted by law) or more of the securities or other ownership interests representing the equity, the voting stock or, if applicable, the general partnership interest, of MERCK or ISIS; or (iii) any corporation or business entity of which fifty percent (50%) or more of the securities or other ownership interests representing the equity, the voting stock or general partnership interest are owned, controlled or held, directly or indirectly, by a corporation or business entity described in (i) or (ii).

1.2 "Calendar Quarter" shall mean the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30 and December 31.

1.3 "Calendar Year" shall mean each successive period of twelve (12) months commencing on January 1 and ending on December 31.

1.4 "Clinical Development Program" shall mean the clinical development activities undertaken by MERCK as set forth in Article II herein

1.5 "Clinical Supply Agreement" shall mean the Clinical Supply Agreement entered into by the parties on the Effective Date in the form attached hereto as Schedule 1.

1.6 "Combination Product" shall mean a Product which includes one or more pharmaceutically active ingredients other than Compound in combination with Compound. All references to Product in this Agreement shall be deemed to include Combination Product.

1.7 "Compound" shall mean ISIS compounds ISIS 113715 and [*] that, as of the Effective Date and during the term of this Agreement, i) incorporate ISIS Core Technology and ii) target the genetic sequence of PTP-1B thereby reducing expression of PTP-1B protein in humans or animals.

1.8 "Compound Improvement" shall mean any and all enhancements, whether or not patentable, in the Compound. Compound Improvement shall include without limitation pharmaceutical formulations and dosage forms for administration discovered or invented solely or jointly by employees of MERCK, or acquired by MERCK, during the term of this Agreement. Compound Improvement shall not include pharmaceutical formulations or dosage forms for administration discovered or invented solely by employees of ISIS, or acquired by ISIS, during the term of this Agreement.

1.9 "Core Technology Improvement" shall mean any and all enhancements, whether or not patentable, in the ISIS Core Technology arising during the term of this Agreement.

1.10 "Field" shall mean the use of Compound and Product for any and all purposes.

1.11 "First Commercial Sale" shall mean, with respect to any Product, the first sale for end use or consumption of such Product in a country after all required approvals, including marketing and pricing approvals, have been granted by the governing Regulatory Authority of such country.

1.12 "FTE" shall mean the equivalent of a full-time scientist's work time over a twelve-month period (including normal vacations, sick days and holidays). The portion of an FTE year devoted by a scientist to the Preclinical Development Program, Technology Transfer, Clinical Supply Agreement, or any other activities under this Agreement which the parties may agree will be undertaken by ISIS on an FTE basis, shall be determined by dividing the number of days during any twelve-month period devoted by such employee to the Preclinical Development Program, Technology Transfer, Clinical Supply Agreement, or any other activities under this Agreement which the parties may agree will be undertaken by ISIS on an FTE basis, by the total number of working days during such twelve-month period (including normal vacations, sick days and holidays).

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

1.14 "ISIS Core Technology" shall mean technology owned or acquired by ISIS as of the Effective Date which claims, covers or relates to linkages and sugar units in an antisense oligonucleotide, wherein such linkages include phosphorothioate linkages and such sugar units include a combination of deoxy sugar units and 2'-O- (2-methoxy- ethyl)- (MOE-) modified sugar units with natural and methyl substituted heterocycle bases ("MOE Gapmer Technology"). ISIS Core Technology also includes technology owned or acquired by ISIS as of the Effective Date which claims, covers or relates to the cellular mechanisms of action by which MOE

*Confidential Treatment Requested

Gapmer Technology antisense oligonucleotides exert their effect. ISIS Core Technology does not include any target gene specific technology.

1.15 "ISIS Know-How" shall mean any and all information and materials including without limitation, Compound, Compound Improvements, ISIS Manufacturing Technology, ISIS Core Technology, Manufacturing Technology

Improvements, Core Technology Improvements, processes, methods, protocols, formulas, preclinical, manufacturing and other data, discoveries, inventions, know-how and trade secrets, patentable or otherwise, which during the term of this Agreement (i) are in the possession or control of ISIS or an ISIS Affiliate, (ii) are not generally known and (iii) are necessary or useful to MERCK in the Field including without limitation the development, manufacture, marketing, use or sale of Compound or Product.

1.16 "ISIS Patent Rights" shall mean any and all patents and patent applications in the Territory (which for the purposes of this Agreement shall be deemed to include certificates of invention and applications for certificates of invention) which during the term of this Agreement are owned by ISIS or to which ISIS through license or otherwise acquires rights which (a) claim, cover or relate to Compound and/or Product including without limitation those patents and patent applications which (i) are Compound patents and patent applications listed on Schedule 1.16 (a) (i); or (ii) are ISIS Core Technology patents and patent applications listed on Schedule 1.16 (a) (ii) (to the extent that such ISIS Core Technology patents and patent applications are necessary or useful to Merck in the Field) and patents and patent applications which claim, cover or relate to Core Technology Improvements (to the extent that such Core Technology Improvement patents and patent applications are necessary to Merck to practice effectively in the Field) ; or iii) are ISIS Manufacturing Technology patents and patent applications listed on Schedule 1.16 (a) (iii) (to the extent that such ISIS Manufacturing Technology patents and patent applications are necessary or useful to Merck in the Field) and patents and patent applications which claim, cover or relate to Manufacturing Technology Improvements, to the extent that such Manufacturing Technology Improvement patents and patent applications are necessary or useful to Merck in the Field; or (b) are divisions, continuations, continuations-in-part, reissues, renewals, extensions, supplementary protection certificates, and the like of any of the foregoing patents and patent applications and foreign equivalents thereof.

1.17 "ISIS Manufacturing Technology" shall mean any and all scientific and technical data and information including without limitation formulas, methods, techniques, protocols, and processes owned or acquired by ISIS or an ISIS Affiliate by license or otherwise as of the Effective Date which are necessary or useful to MERCK in the preparation, formulation, analysis, manufacturing or delivery of Compound and/or Product for the purpose of carrying out or implementing the manufacturing process defined generally as the process steps set forth in master batch records for the Compound ISIS 113715[*] including reasonable variants and extensions of process steps thereof.

1.18 "Major Market" shall mean any one of the following countries: United States, Japan, the United Kingdom, France, Germany, Italy or Spain.

1.19 "Manufacturing Technology Improvement" shall mean any and all enhancements, whether or not patentable, in the ISIS Manufacturing Technology arising during the term of this Agreement.

1.20 "Marketing Application" shall mean a New Drug Application (NDA), Worldwide Marketing Authorization (WMA), or Marketing Application Authorization (MAA) or similar application or submission for marketing authorization of a Product filed with a Regulatory Authority including without limitation the FDA.

1.21 "Net Sales" shall mean the gross invoice price of Product sold by MERCK, its Affiliates or sublicensees (which term does not include distributors) to the first independent third party after deducting, if not previously deducted, in the amount invoiced:

(a) trade and quantity discounts other than early pay cash discounts;

(b) returns, rebate, chargebacks and other allowances;

(c) retroactive price reductions;

(d) sales commissions paid to third party distributors;

(e) a fixed amount equal to [*] of the amount invoiced to cover bad debt, sales or excise taxes, early payment cash discounts, transportation and insurance charges, custom duties, and other governmental charges;

(f) the standard inventory cost of devices or delivery systems used for dispensing or administering Product.

With respect to sales of Combination Products, Net Sales shall be calculated on the basis of the invoice price of Product containing the same strength of Compound sold without other active ingredients. In the event that Product is sold only as a Combination Product, Net Sales shall be calculated on the basis of the invoice price of the Combination Product multiplied by a fraction, the numerator of which shall be the inventory cost of Compound in the Product and the denominator of which shall be the inventory cost of all of the active ingredients in the Combination Product. Inventory cost shall be determined in accordance with MERCK's regular accounting methods, consistently applied. The deductions set forth in paragraphs (a) through (f) above will be applied in calculating Net Sales for a Combination Product. In the event that Product is sold only as a Combination Product and either party reasonably believes that the calculation set forth in this Paragraph does not fairly reflect the value of the Product relative to the other active ingredients in the Combination Product, the parties shall negotiate, in good faith, other means of calculating Net Sales with respect to Combination Products.

1.22 "Phase I Clinical Trial" shall mean the first clinical trial in humans in any country including without limitation the first clinical trial in humans that is intended to evaluate the safety, tolerability, pharmacological and/or pharmocokinetic effect of a Compound in human subjects or that would otherwise satisfy the requirements of 21 CFR 312.21(a) or its foreign equivalent.

1.23 "Phase II Clinical Trial" shall mean a human clinical trial in any country that is intended to evaluate the effectiveness of a Compound for a particular indication or indications in human subjects with the disease or indication under study or that would otherwise satisfy the requirements of 21 CFR 312.21(b) or its foreign equivalent. Specifically, a Phase II (a) Clinical Trial shall mean a clinical trial which is the first assessment of efficacy in the target population (and specifically does not include a clinical trial in which the sole endpoints relate to safety or drug interaction), and a Phase II (b) Clinical Trial shall mean a clinical trial which is a definitive dose-ranging study.

1.24 "Phase III Clinical Trial" shall mean a pivotal human clinical trial in any country the results of which could be used to establish safety and efficacy of a Compound as a basis for a Marketing Application or that would otherwise satisfy the requirements of 21 CFR 312.21(c) or its foreign equivalent.

1.25 "Preclinical Development Program" shall mean the preclinical development activities undertaken by MERCK and/or by ISIS, at the direction of MERCK, as set forth in Article II herein and Schedule 2.2 attached hereto as may be amended by the parties from time to time.

1.26 "Product" shall mean preparation(s) in final form for sale by prescription, over-the-counter or any other method for any and all uses in the Field which contain Compound including without limitation any Combination Product.

1.27 "Regulatory Authority" shall mean any applicable government regulatory authority involved in granting approvals for the marketing, and/or pricing of a Product in the Territory, 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.

1.28 "Technology Transfer" shall have the meaning set forth in Section 7.2.1 herein.

1.29 "Territory" shall mean all of the countries in the world, and their territories and possessions.

1.30 "Valid Patent Claim" shall mean a claim of an issued and unexpired patent included within the ISIS Patent Rights listed on Schedule 1.16 (a) (i) hereto, which has not been revoked or held unenforceable or invalid by a decision of a court or other governmental agency of competent jurisdiction, unappealable or not appealed within the time allowed for appeal, and which has not been disclaimed, denied or admitted to be invalid or unenforceable through reissue or disclaimer or otherwise.

ARTICLE II

PRECLINICAL AND CLINICAL DEVELOPMENT PROGRAM

2.1 GENERAL. ISIS and MERCK shall undertake the Preclinical Development Program activities and MERCK shall undertake the Clinical Development activities upon the terms and conditions set forth in this Agreement.

2.2.1 CONDUCT OF PRECLINICAL DEVELOPMENT PROGRAM. a) The activities to be undertaken by ISIS and MERCK in the course of the Preclinical Development Program shall be at the direction of MERCK, and are set forth in Schedule 2.2. Promptly after the Effective Date, the parties will jointly develop a more detailed Schedule 2.2 relating to the activities, timeline, and budget agreed to in writing by the parties for the Preclinical Development Program, such amended Schedule 2.2 to be attached hereto and made a part of this Agreement. Schedule 2.2 may further be amended from time to time upon prior mutual written agreement of the parties. ISIS and MERCK shall conduct the Preclinical Development Program in a good scientific manner, and in compliance in all material respects with all requirements of applicable laws, rules and regulations to achieve the objectives efficiently and expeditiously. ISIS and MERCK shall proceed diligently with the work set out in Schedule 2.2 using good faith efforts to provide sufficient time, effort, equipment, facilities and skilled personnel to accomplish the objectives set forth in Schedule 2.2.

(b) In no event shall ISIS be entitled to utilize the services of any third party to carry out its obligation under the Preclinical Development Program without the prior written approval of MERCK. ISIS and MERCK hereby acknowledge that MERCK has approved the use by ISIS of third parties listed in the attached Schedule 2.2.1 (b) for the purpose of carrying out certain ISIS' obligations under the Preclinical Development Program as indicated in Schedule 2.2.1 (b). Notwithstanding such approval by MERCK for the use of third parties as set forth herein, ISIS shall remain fully liable for the performance of ISIS' obligations under the Preclinical Development Program. Further, where ISIS is permitted hereunder to utilize third parties to carry out ISIS's obligations under the Preclinical Development Program, ISIS hereby warrants that the terms of any and all agreements with such third parties applicable to activities under the Preclinical Development Program, including without limitation terms relating to confidentiality, record keeping and inspection, inventions and licensing shall be consistent with the terms of this Agreement between ISIS and MERCK. ISIS shall, at MERCK's request, provide MERCK with a copy of any such third party agreements. MERCK shall be entitled (but shall not be obligated), at its discretion, to assume ISIS' rights and responsibilities under such third party agreements applicable to activities under the Preclinical Research Program.

2.2.2 USE OF PRECLINICAL DEVELOPMENT PROGRAM FUNDING. ISIS shall apply the Preclinical Development Program funding it receives from MERCK under this Agreement solely to carry out its obligations under Schedule 2.2 in accordance with the terms of this Agreement and the budget established by the parties.

2.2.3 PRECLINICAL DEVELOPMENT PROGRAM PROJECT LEADERS. Each party shall appoint one (1) project leader who shall be the primary contact between the parties with respect to the Preclinical Development Program and who shall each have appropriate technical credentials, experience and knowledge, and ongoing familiarity with the Preclinical Development Program ("Project Leader"). The Preclinical Development Program shall be conducted under the direction of the Project Leaders. The parties may seek the advice of additional representatives or consultants from time to time, by mutual consent of the parties. In the event that the Project Leaders cannot or do not, after good faith efforts, reach agreement on an issue, the resolution and/or course of conduct shall be determined by MERCK, in its sole discretion, provided that ISIS shall not be required, without its prior written consent, to carry out any additional work not included in Schedule 2.2, as may be amended by the parties.

2.2.4 MEETINGS. The Project Leaders shall meet at least once each month with the location for such meetings alternating between ISIS and MERCK

facilities (or such other locations as is determined by the parties). Alternatively, the Project Leaders may meet by means of teleconference, videoconference or other similar communications equipment. The Project Leaders shall confer regarding the status of the Preclinical Development Program, review relevant data, consider and advise on any technical issues that arise, consider issues of priority, and review and advise on any budgetary and economic matters relating to the Preclinical Development Program.

2.2.5 PRECLINICAL DEVELOPMENT PROGRAM RESULTS AND INVENTIONS. ISIS shall promptly disclose to MERCK the development, making, conception or reduction to practice of all data, information, discoveries, and inventions, patentable or not, arising from the Preclinical Development Program. All such data, information, discoveries, and inventions including without limitations Compound Improvements, patentable or not, arising from the Preclinical Development Program shall be the sole and exclusive property of MERCK, subject to the provisions of Sections 3.4 and 7.2.6 with regard to Core Technology Improvements and Manufacturing Technology Improvements, respectively. MERCK shall promptly disclose to ISIS, prior to filing the relevant patent application, all Core Technology Improvements and Manufacturing Technology Improvements arising from the Preclinical Development Program which shall be subject to the license granted to ISIS hereunder in accordance with the requirements of Sections 3.4 and 7.2.6, respectively, in the event that such Core Technology Improvements or Manufacturing Technology Improvements become patented Core Technology Improvements or patented Manufacturing Technology Improvements.

2.2.6 RECORDS. ISIS shall maintain records, in sufficient detail and in good scientific manner appropriate for patent and regulatory purposes, which shall (a) fully and properly reflect all work done and results achieved in the performance of the Preclinical Development Program, and (b) permit ISIS to provide the CMC Items listed and attached hereto as Schedule 2.2.6 as required by MERCK.

2.2.7 COPIES AND INSPECTION OF RECORDS. MERCK shall have the right, during normal business hours and upon reasonable notice, to inspect and copy all such records of ISIS referred to in Section 2.2.6 including without limitation the CMC Items listed on Schedule 2.2.6 and all preclinical information and data necessary or useful for MERCK for the purposes of filing with Regulatory Authorities hereunder. MERCK shall maintain such records and the information disclosed therein in confidence in accordance with Section 4.1. MERCK shall have the right to arrange for its employees and/or consultants involved in the activities contemplated hereunder to visit the offices and laboratories of ISIS and its third party contractors listed in Schedule 2.2.1 (b) during normal business hours and upon reasonable notice, and to discuss the Preclinical Development Program work and its results in detail with the technical personnel and consultants of ISIS.

2.2.8 QUARTERLY REPORTS. Within thirty (30) days following the end of each Calendar Quarter during the Preclinical Development Program, ISIS shall provide to MERCK, upon MERCK's request, a written progress report which shall describe the work performed to date on the Preclinical Development Program, evaluate the work performed in relation to the goals of the Preclinical Development Program and provide such other information required by the Preclinical Development Program or reasonably requested by

MERCK relating to the progress of the goals or performance of the Preclinical Development Program ("Quarterly Report"). Upon request, ISIS shall provide copies of the records described in Section 2.2.6 above. Further, ISIS shall provide the CMC Items listed in Schedule 2.2.6 in accordance with the timeline to be agreed to by the parties.

2.2.9 COMPLIANCE. ISIS hereby certifies that it has not and will not employ or otherwise use in any capacity any person debarred under Section 21 USC 335(a) in performing any Preclinical Development Program activities.

2.3.1 CLINICAL DEVELOPMENT PROGRAM. MERCK may, at its sole discretion, undertake, and shall solely own the results of, the Clinical Development Program. MERCK shall have the sole responsibility to make any and all regulatory filings for Compound and Product in the Territory as MERCK, in its sole discretion, deems appropriate, and MERCK shall be the sole owner of all regulatory submissions and government approvals therefor. Similarly, MERCK shall have and conduct any and all communications and interactions with regulatory agencies with respect to the Compound and Product, including without limitation

Regulatory Authorities, and other government authorities. ISIS shall cooperate with MERCK in all of these activities whenever and to the extent requested by MERCK, and shall supply MERCK with any and all information necessary or useful to MERCK in preparing and filing regulatory and other government submissions, and in obtaining regulatory and other governmental approvals.

2.3.2 DEVELOPMENT AND COMMERCIALIZATION. MERCK shall use reasonable efforts, consistent with the usual practice followed by MERCK in pursuing the commercialization and marketing of its other similar pharmaceutical products, at its own expense, to develop and commercialize a Product on a commercially reasonable basis in such countries in the Territory where in MERCK's opinion it is commercially viable to do so.

2.3.3 EXCUSED PERFORMANCE. In addition to the provisions of Section 10.1 hereof, the obligations of MERCK with respect to any Product under Section 2.3.2 are expressly conditioned upon the continuing absence of any adverse condition or event relating to the safety or efficacy of the Product, and the obligation of MERCK to develop or market any such Product shall be delayed or suspended so long as in MERCK's opinion any such condition or event exists. All judgments as to safety and efficacy shall be made by MERCK in its sole discretion.

2.3.4 CLINICAL DEVELOPMENT PROGRAM RESULTS AND INVENTIONS. All data, information, inventions and discoveries including without limitation Compound Improvements, patentable or not, resulting from the Clinical Development Program shall be the sole and exclusive property of MERCK, subject to the provisions of Sections 3.4 and 7.2.6 with regard to Core Technology Improvements and Manufacturing Technology Improvements, respectively.

2.4 REPORTING REQUIREMENTS. ISIS and MERCK hereby agree to comply with the reporting requirements set forth in Schedule 2.4 attached hereto, as may be amended in writing by the parties from time to time. In the event of changes to regulatory reporting requirements worldwide, each party agrees to comply with revised notification requirements as reasonably requested in writing by the other party. Notwithstanding the foregoing, MERCK shall have the sole right to report to the Regulatory Authorities any such information relating to the Compound or Product.

ARTICLE III
LICENSE; DISCLOSURE OF INFORMATION

3.1 LICENSE GRANT.

(a) ISIS hereby grants to MERCK an exclusive (exclusive even as to ISIS), sublicensable, royalty-bearing license in the Territory to practice under the ISIS Patent Rights and to utilize the ISIS Know-How to develop, make, have made, use, sell, offer to sell and import Compound and Product in the Field and to otherwise carry out the activities contemplated by this Agreement.

(b) Notwithstanding the foregoing, in the case of ISIS Patent Rights or ISIS Know-How consisting of Core Technology Improvements, MERCK shall be granted an exclusive license to such ISIS Patent Rights and ISIS Know-How in the Field to the extent that such Core Technology Improvements are necessary for MERCK to practice effectively in the Field, and, in the case of such Core Technology Improvements acquired by ISIS from third party(ies) during the term of this Agreement, where such third party rights are sublicensable and MERCK has agreed with ISIS to comply with all obligations relating to such sublicense by ISIS. Further, in the case of ISIS Patent Rights or ISIS Know-How consisting of Manufacturing Technology Improvements acquired by ISIS from third party(ies) during the term of this Agreement, MERCK's shall be granted an exclusive license to such ISIS Patent Rights and ISIS Know-How in the Field where such third party rights are sublicensable and MERCK has agreed with ISIS to comply with all obligations relating to such sublicense by ISIS.

(c) ISIS shall retain the right to practice under the ISIS Patent Rights and to utilize the ISIS Know-How licensed to MERCK hereunder solely as necessary to carry out ISIS' obligations under this Agreement.

(d) For clarification purposes, the parties hereby acknowledge that

MERCK shall have no liability or responsibility for, and ISIS shall be fully liable and responsible for, any payments of any kind whatsoever payable by ISIS to its third party licensors of intellectual property licensed to MERCK by ISIS hereunder.

(e) In addition to the representations and warranties set forth in this Agreement, ISIS hereby agrees, with regard to the ISIS Patent Rights licensed from third parties as set forth in Patent Schedule 1.16(a)(ii), to the following terms and conditions:

(i) ISIS warrants that it will take all actions reasonably necessary to maintain the relevant third party licenses in good standing as to the ISIS Patent Rights sublicensed to MERCK under this Agreement; and

(ii) ISIS shall make all reasonable efforts to notify MERCK as soon as practicable of any notice given or received by ISIS to terminate such third party license(s), and, in the event that such third party license(s) should be terminated for any reason, make all reasonable efforts to obtain for MERCK the right to directly license with the relevant ISIS' third party licensor(s) for the rights sublicensed to MERCK hereunder as of the Effective Date; and,

(iii) In the event that MERCK, due to termination of the relevant license between ISIS and its third party licensor, enter into a direct license with such third party licensor, MERCK shall be entitled to deduct any payments payable by MERCK to such third party licensor from payments due to ISIS under this Agreement.

3.2 NON-EXCLUSIVE LICENSE GRANT. In the event the development, making, having made, use, sale or import by MERCK, its Affiliates and/or sublicensees of Compound (or Product, due to its incorporation of Compound) would infringe during the term of this Agreement a claim of issued letters patent which ISIS owns or has the rights to license and which patents are not covered by the grant in Section 3.1, ISIS hereby grants to MERCK, to the extent ISIS is legally able to do so, a non-exclusive, royalty-free, sublicensable license in the Territory under such issued letters patent solely for MERCK to develop, make, have made, use, sell, offer for sale or import Compound and Product in the Field in the Territory.

3.3 DISCLOSURE OF INFORMATION. During the term of this Agreement, ISIS shall promptly disclose to MERCK in English and in writing on an ongoing basis all ISIS Know-How and other useful information not previously disclosed.

3.4 CORE TECHNOLOGY IMPROVEMENTS. The entire right, title, and interest in and to all Core Technology Improvements, patentable or not, developed or invented solely by employees of ISIS during the term of this Agreement shall be the sole and exclusive property of ISIS, subject to the licenses granted to MERCK under this Agreement. The entire right, title, and interest in and to all Core Technology Improvements, patentable or not, developed or invented solely by employees of MERCK during the term of this Agreement shall be the sole and exclusive property of MERCK, and MERCK hereby grants to ISIS a

worldwide, non-exclusive, sublicensable, royalty-free license to any such patented sole MERCK Core Technology Improvements solely for use outside of the Field. The entire right, title, and interest in and to all Core Technology Improvements, patentable or not, developed or invented jointly by employees of ISIS and MERCK during the term of this Agreement shall be the joint property of ISIS and MERCK, subject to the licenses granted to MERCK under this Agreement. The parties shall promptly disclose to each other the development, making, conception or reduction to practice of all Core Technology Improvements.

3.5 COMPOUND IMPROVEMENTS. The entire right, title, and interest in and to all Compound Improvements, patentable or not, developed or invented solely or jointly by employees of ISIS and/or MERCK during the term of this Agreement shall be the sole and exclusive property of MERCK. ISIS shall promptly disclose to MERCK the development, making, conception or reduction to practice of all Compound Improvements.

3.6 TARGET EXCLUSIVITY. ISIS hereby agrees that, until such time as the approval of the first marketing application for a Compound in a Major Market pursuant to this Agreement, ISIS will work exclusively (even as to ISIS itself) with MERCK with regard to any and all activities for

the research, discovery, development and/or commercialization of antisense compounds and products that target the genetic sequence of PTP-1B.

ARTICLE IV

CONFIDENTIALITY AND PUBLICATION

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

(a) is known by recipient at the time of its receipt, and not through a prior disclosure by the disclosing party, as documented by business records;

(b) is properly in the public domain;

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

(d) is developed by the receiving party independently of Information received from the other party;

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

(f) is deemed necessary by MERCK to be disclosed to MERCK sublicensees, agents, consultants, Affiliates 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 third parties agree to be bound by the confidentiality obligations contained this Agreement, PROVIDED the term of confidentiality for such third parties shall be no less than seven (7) years; or

(g) is required to be disclosed by law or 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.

4.2 PUBLICATION. MERCK shall be entitled to publish on the subject matter of this Agreement, PROVIDED THAT, MERCK shall deliver to ISIS a copy of any proposed publication or an outline of any oral disclosure involving ISIS Manufacturing Technology or ISIS Core Technology at least sixty (60) days prior to submission for publication or presentation, and ISIS shall have the right to request a reasonable delay in such publication or presentation in order to protect patentable information. If ISIS requests a delay, MERCK shall delay submission or presentation for a period of up to thirty (30) days after such planned submission date to enable patent applications to be filed by ISIS in accordance with Article VIII below.

Upon expiration of such thirty-day (30)period, MERCK shall be free to proceed with the publication or presentation. Further, MERCK hereby agrees to provide ISIS, for informational purposes only, with a copy of any proposed MERCK publication involving the Compound once such proposal has been submitted for publication. ISIS shall be permitted to publish on matters relating to the Compound or Product during the term of this Agreement including without limitation any ISIS Know-How only upon the prior written approval of MERCK, which may be given at MERCK's sole discretion. Notwithstanding the foregoing, MERCK acknowledges that, prior to the Effective Date, ISIS and its third party research collaborator(s) have generated data relating to the Compound that ISIS is contractually required to permit such third party research collaborator(s) to publish or present during the term of this Agreement. ISIS agrees to provide MERCK, in advance of the proposed publication or presentation, with copies of any such proposed publication or presentation intended for publication or presentation during the term of this Agreement, and ISIS warrants to MERCK that ISIS

shall not grant such third party collaborators any rights to publish or present such data beyond the rights ISIS is contractually required to grant such third parties as of the Effective Date, and in no case shall ISIS grant such third parties any rights to publish or present data which could negatively impact Compound or Product.

4.3 PUBLICITY. No disclosure of the existence of, or the terms of, this Agreement may be made by either party, and no party shall use the name, trademark, trade name or logo of the other party or its employees in any publicity, news release or disclosure relating to this Agreement, or its subject matter, without the prior express written permission of the other party, except as may be required by law.

ARTICLE V

PAYMENTS; ROYALTIES AND REPORTS

5.1 PROGRAM FUNDING. a) In consideration for ISIS' performance of certain preclinical development activities in connection with the Compound as of [*] such reimbursement to take place within thirty (30) days of the Effective Date and upon receipt of invoice from ISIS. In consideration for ISIS' performance of certain preclinical development activities in connection with the Compound [*] for the performance of such activities, such reimbursement to take place within thirty (30) days of receipt of invoice from ISIS. [*]

b) In consideration for ISIS' performance of its obligations under the Preclinical Development Program, upon the terms and conditions contained herein, MERCK shall pay ISIS for such performance in accordance with the requirements of Schedule 2.2. The FTE rate for Preclinical Development Program work performed directly by ISIS shall be [*] per FTE for any of the following activities undertaken directly by ISIS pursuant to the Preclinical Development Program: drug substance manufacturing; analytical chemistry; process chemistry; formulation; raw material ordering and handling; quality control; or manufacturing technology transfer. The FTE rate for Preclinical Development Program work performed directly by ISIS shall be [*] per FTE for any of the following activities undertaken pursuant to the Preclinical Development Program: toxicology; pharmocokinetics/metabolism; regulatory; clinical development and data management. MERCK shall reimburse ISIS for payments to third parties who have been approved by MERCK to conduct the Preclinical Development Program activities hereunder. ISIS shall invoice MERCK [*] for the amounts payable in accordance with Schedule 2.2. Payments under this Section. 5.1 (b) shall be due thirty (30) days after receipt of each invoice by MERCK. With each [*] invoice after the first [*] invoice provided to MERCK under this Paragraph, ISIS will provide MERCK with copies of third party invoices supporting the invoice amounts charged to MERCK in the prior [*] invoice to MERCK, and ISIS will make any adjustments for overpayment or underpayment therein. If one party is owing the other party as result of such reconciliation process, the owing party will issue a payment to the other party within thirty (30) days. Total payments under this Section shall not exceed [*] without the prior written approval of MERCK for performance of activities under Schedule 2.2.

c) In connection with the Technology Transfer efforts by ISIS hereunder, ISIS shall utilize [*] In consideration for ISIS' performance of its obligations under the Technology Transfer, upon the terms and conditions contained herein, MERCK shall pay ISIS for such performance in accordance with the

requirements of Article VII herein and Schedule 7. 2. ISIS shall invoice MERCK, [*] for all activities performed in accordance with Article VII and the Schedule 7.2. Such invoice shall itemize the activities as set forth in Schedule 7.2. Merck will pay each invoice within thirty (30) days after receipt of invoice and all relevant documentation.

d) In consideration of ISIS' performance of CMC activities in connection with the Compound as set forth in Schedule 2.2.6, and other Compound-specific activities including without limitation specifications development for in-process and release testing of Compound and formulated Compound (including standards, stability programs, and formulation development) and other activities requested by MERCK in support of registration efforts and in

response to regulatory questions and regulatory inspections, where the foregoing activities are required under this Agreement but fall outside ISIS' activities pursuant to the Preclinical Development Program, Technology Transfer and [*] MERCK shall compensate ISIS for such performance at the FTE rate of [*] for any of the following activities undertaken directly by ISIS: analytical chemistry; process chemistry; formulation; drug substance manufacturing, raw material ordering and handling; or manufacturing technology transfer; and, at the FTE rate of [*] for the following activities performed directly by ISIS under this Paragraph (d): toxicology; pharmocokinetics/metabolism; regulatory; clinical development and data management.

Further, where ISIS undertakes other activities such as analytical methods development for raw materials, API, drug product testing and release, and process development in connection with other phosphorothioate 2' deoxyoligonucelotides and MOE Gapmer Technology drugs which support the activities of ISIS with regard to Compound as required pursuant to this Agreement, MERCK will compensate ISIS [*] The FTE rate shall be [*] for any of the following activities undertaken directly by ISIS pursuant to this Section 5.1 (d): analytical chemistry; process chemistry; formulation; drug substance manufacturing, raw material ordering and handling; or manufacturing technology transfer. The FTE rate shall be [*] per FTE for any of the following activities undertaken by ISIS pursuant to this Section 5.1 (d); toxicology; pharmocokinetics/metabolism; regulatory; clinical development and data management.]

5.2 CONSIDERATION FOR RESEARCH FUNDING. [*]

5.3 MILESTONE PAYMENTS.

a) Subject to the terms and conditions of, and during the term of, this Agreement, MERCK shall pay to ISIS [*] each, each such milestone payable only once, upon satisfactory performance of the Preclinical Development Program activities in accordance with the requirements of Schedule 2.2 as Schedule 2.2 may be amended by mutual agreement of the parties. The Preclinical Development milestones set forth in this Section 5.3 (a) shall become payable [*] Notwithstanding the foregoing, in the event that MERCK provides ISIS with a notice of Agreement termination in accordance with the terms of Article 9 herein prior to any such anniversary date, any milestone payment for a milestone achieved during [*] and MERCK shall have no obligation to make any such milestone payment to ISIS.

b) Subject to the terms and conditions of, and during the term of, this Agreement, MERCK shall pay to ISIS the following Development milestone payments with respect to each Compound in development for diabetes, each milestone payment to be made no more than once with respect to such Compound:

(i) [*]

(ii) [*]

(iii) [*]

(iv) [*]

(v) [*]

c) Subject to the terms and conditions of, and during the term of, this Agreement, MERCK shall pay to ISIS the following Development milestone payments with respect to each Compound for obesity, each milestone payment to be made no more than once with respect to each such Compound:

(i) [*]

(ii) [*]

(iii) [*]

MERCK shall notify ISIS in writing within thirty (30) days upon the achievement of each Development milestone set forth in Sections 5.3 (b) and (c), such notice to be accompanied by payment of the appropriate

milestone payment. The milestone payment shall be payable only upon the initial achievement of such milestone and no amounts shall be due hereunder for subsequent or repeated achievement of such milestone. Should the development of a Compound for an indication be discontinued, any Development milestone payment(s) previously paid hereunder for a Compound for such indication shall not be payable by MERCK for any other Compound developed by MERCK hereunder for the same indication. In the event that MERCK achieves any Developmental Milestone set forth in Sections 5.3 (b) or (c) without having achieved prior Developmental Milestone(s) set forth in the relevant Section for the same indication, Merck shall be obligated to pay all such prior Developmental Milestones not previously paid, upon achievement of such subsequent Developmental Milestone for the same indication.

ROYALTIES.

5.4.1 ROYALTIES PAYABLE BY MERCK. Subject to the terms and conditions of, and during the term of, this Agreement, MERCK shall pay to ISIS royalties in an amount equal to:

(a) [*] of the aggregate annual worldwide Net Sales of each Product by MERCK, its Affiliates or sublicensees where such aggregate annual worldwide Net Sales are less than [*] as set forth below, provided the sale of the Product would, but for the license hereunder, infringe a Valid Patent Claim in the country of sale, or

(b) [*] of the aggregate annual worldwide Net Sales of each Product by MERCK, its Affiliates or sublicensees where such aggregate annual worldwide Net Sales are equal to or greater than [*] as set forth below, provided the sale of the Product would, but for the license hereunder, infringe a Valid Patent Claim in the country of sale, or

(c) For Net Sales of Products by MERCK, its Affiliates or sublicensees other than those covered by Subsection 5.4.1. (a) or 5.4.1 (b), the royalty rate shall be [*] but in no event shall such royalty pursuant to this Subsection 5.4.1 (c) [*]

Royalties on each Product at the rate set forth above shall be effective as of the date of First Commercial Sale of Product in a country and shall continue until either (i) the expiration of the last applicable patent on such Product in such country in the case of sales under Subsection 5.4.1(a) and (b), [*] in the case of sales of Product under Subsection 5.4.1(c) above. Notwithstanding the foregoing, under Subsection (ii) of this Paragraph, [*] However, in no event shall such pass through royalties be payable by Merck after such ISIS' royalty obligations to such third party licensor(s) have terminated. Royalty payments pursuant to Subsection 5.4.1 are subject to the following conditions:

(x) that only one royalty shall be due with respect to the same unit of Product;

(y) that no royalties shall be due upon the sale or other transfer among MERCK, its Affiliates or sublicensees, but in such cases the royalty shall be due and calculated upon MERCK's or its Affiliate's or its sublicensee's Net Sales to the first independent third party; and (z) no royalties shall accrue on the disposition of Product in reasonable quantities by MERCK, Affiliates or its sublicenses as samples (promotion or otherwise) or as donations (for example, to non-profit institutions or government agencies for a non-commercial purpose).

In the event that MERCK sells Product for end use or consumption prior to receiving all required approvals from the governing Regulatory Authority of the country of sale, including without limitation for compassionate use purposes, the first such sale for end use or consumption of such Product in such country shall be deemed a First Commercial Sale hereunder for the purpose of establishing the effective date for the initiation of payment of royalties in such country as set forth above, however, [*]set forth in Section (ii) above shall commence upon the date of First Commercial Sale after all required approvals have been granted, as set forth in Section 1.11 of this Agreement.

5.4.2 ROYALTY PAYABLE UNDER MANAGED PHARMACEUTICAL CONTRACT. It is understood by the parties that MERCK may sell Product to an independent third party (such as a retailer or wholesaler) and may subsequently perform services relating to Product and other products under a managed pharmaceutical benefits contract or other similar contract. In such cases, it is agreed by the parties that Net Sales shall be based on the invoice price to such independent retailer or wholesaler, as set forth in Section 1.21, notwithstanding that MERCK or its Affiliates may receive compensation arising from the performance of such services.

5.4.3 CHANGE IN SALES PRACTICES. The parties acknowledge that during the term of this Agreement, MERCK's sales practices for the marketing and distribution of Product may change to the extent to which the calculation of the payment for royalties on Net Sales may become impractical or even impossible. In such event the parties agree to meet and discuss in good faith new ways of compensating ISIS to the extent currently contemplated under Section 5.4.1.

5.4.4 ROYALTIES FOR BULK FORMULATED COMPOUND. In those cases where MERCK sells bulk formulated Compound, rather than Product in packaged form, to an independent third party, the royalty obligations of this Article V shall be applicable to the bulk formulated Compound.

5.4.5 COMPULSORY LICENSES. If a compulsory license is granted to a third party with respect to Product in any country in the Territory with a royalty rate lower than the royalty rate provided by Section 5.4.1., then the royalty rate to be paid by MERCK on Net Sales in that country under Section 5.4.1 shall be reduced to the rate paid by the compulsory licensee.

5.4.6 THIRD PARTY LICENSES. In the event that one or more patent licenses from other third parties are required by MERCK, its Affiliates and sublicensees to practice the ISIS Patent Rights or to utilize the ISIS Know-How in order to develop, make, have made, use, import, offer to sell or sell Compound (or Product, due to the incorporation of Compound) (hereinafter "Third Party Patent Licenses"). [*] In the event that MERCK acquires patent license(s) from third parties pursuant to this Subsection 5.4.6, and such license(s) are both sublicensable, and useful outside the Field, MERCK hereby grants ISIS a non-exclusive, royalty-free sublicense under such patent license(s) solely for use outside the Field, such sublicense to be subject to the obligations of such third party license(s) to MERCK.]

5.5 REPORTS; PAYMENT OF ROYALTY. During the term of the Agreement following the First Commercial Sale of a Product, MERCK shall furnish to ISIS a [*] written report for the [*] showing the Net Sales of all Products subject to royalty payments sold by MERCK, its Affiliates and its sublicensees in the Territory during the reporting period and the royalties payable under this Agreement. MERCK shall provide ISIS, for ISIS' convenience, [*] Reports of actual information as required in this Subsection 5.5 above shall be due on the [*] following the close of each [*] Royalties shown to have accrued by each such [*] royalty report shall be due and payable on the date such royalty report is due [*] following the close of each [*] MERCK shall keep complete and accurate records in sufficient detail to enable the royalties payable hereunder to be determined.

5.6 AUDITS.

(a) Upon the written request of ISIS and not more than once in each Calendar Year, MERCK shall permit an independent certified public accounting firm of nationally recognized standing selected by ISIS and reasonably acceptable to MERCK, at ISIS's expense, to have access during normal business hours to such of the records of MERCK as may be necessary to verify the accuracy of the royalty reports hereunder for any year ending not more than twenty-four (24) months prior to the date of such request. Such records shall consist of the Net Sales figure for each Product, and the Coefficient for each Product, as reported on a quarterly basis within MERCK's internal worldwide accounting system. The accounting firm shall disclose to ISIS only whether the royalty reports are correct or incorrect and the specific details concerning any discrepancies. No other information shall be provided to ISIS.

(b) If such accounting firm correctly concludes that additional royalties were owed during such period, MERCK shall pay the additional royalties within thirty (30) days of the date ISIS delivers to MERCK such accounting firm's written report so correctly concluding. The fees charged by such accounting firm shall be paid by ISIS [*]

(c) MERCK shall include in each sublicense granted by it pursuant to this Agreement a provision requiring the sublicensee to make reports to MERCK, to keep and maintain records of sales made pursuant to such sublicense and to grant access to such records by ISIS's independent accountant to the same extent required of MERCK under this Agreement.

(d) Upon the expiration of [*] months following the end of any year, the calculation of royalties payable with respect to such year shall be binding and conclusive upon ISIS, and MERCK and its sublicensees shall be released from any liability or accountability with respect to royalties for such year.

(e) ISIS shall treat all financial information subject to review under this Section 5.6 or under any sublicense agreement as MERCK Information in accordance with the confidentiality and non-use provisions of this Agreement, and shall cause its accounting firm to enter into an acceptable confidentiality agreement with MERCK and its sublicensees obligating such accounting firms to retain all such financial information in confidence pursuant to such confidentiality and non-use provisions.

5.7 PAYMENT EXCHANGE RATE. All payments to be made by MERCK to ISIS under this Agreement shall be made in United States dollars and may be paid by check made to the order of ISIS or bank wire transfer in immediately available funds to such bank account in the United States designated in writing by ISIS from time to time. In the case of sales invoiced in a foreign currency, exchange conversion of such sales into United States dollars shall be made on a monthly basis and shall be made at the rate of exchange utilized by MERCK in its worldwide accounting system prevailing on the third to the last business day preceding the month in which sales are recorded by MERCK.

5.8 INCOME TAX WITHHOLDING. If laws, rules or regulations require withholding of income taxes or other taxes imposed upon payments set forth in this Article V, MERCK shall make such withholding payments as required and subtract such withholding payments from the payments set forth in this Article V. MERCK shall submit appropriate proof of payment of the withholding taxes to ISIS within a reasonable period of time.

ARTICLE VI

REPRESENTATIONS, WARRANTIES AND INDEMNITY

6.1 REPRESENTATION AND WARRANTY. ISIS represents and warrants to MERCK that, as of the date of this Agreement:

(a) to the best of ISIS' knowledge, the ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology and ISIS Know-How are subsisting and are not invalid or unenforceable, in whole or in part;

(b) it has the full right, power and authority to enter into this Agreement, to perform the Preclinical Development Program and Technology Transfer, and to grant the licenses granted under Article III hereof;

(c) it has not previously assigned, transferred, conveyed or otherwise encumbered its right, title and interest in ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology or ISIS Know-How in a manner that would interfere with ISIS' ability to grant the licenses granted to MERCK under this Agreement;

(d) it is the sole and exclusive owner of the Compound and the patent applications claiming Compound set forth in Schedule 1.16 (a) (i) herein, and has the rights in and to the ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology and ISIS Know-How necessary and sufficient to grant to MERCK the rights licensed to MERCK under this Agreement all of which are free and clear of any liens, charges and encumbrances, and no

other person, corporate or other private entity, or governmental entity or subdivision thereof, has or shall have any claim of ownership with respect to the ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology and ISIS Know-How licensed to MERCK under this Agreement that would interfere with the licenses granted to MERCK under this Agreement, whatsoever;

(e) to the best of ISIS' knowledge, the licensed ISIS Patent Rights, ISIS Core Technology, ISIS Manufacturing Technology and ISIS Know-How and the development, manufacture, use, sale and import of Compound and Product do not interfere with or infringe any intellectual property rights owned or possessed by any third party;

(f) 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, ISIS Core Technology, ISIS Manufacturing Technology or ISIS Know-How; and

(g) ISIS has disclosed to MERCK all reasonably relevant information regarding ISIS Patent Rights, ISIS Manufacturing Technology, ISIS Core Technology and ISIS Know-How licensed under this Agreement, including all patent opinions obtained by ISIS related thereto.

6.2 INDEMNITY. a) ISIS shall indemnify, defend and hold MERCK and its Affiliates, and their respective directors, officers, employees and agents harmless against any and all losses, costs, liabilities and expenses (including reasonable attorneys' fees), actions, suits, claims, demands and prosecution that may be brought or instituted to the extent based upon or arising out of i) the 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.

b) MERCK shall indemnify, defend and hold ISIS and its Affiliates, and their respective directors, officers, employees and agents harmless against any and all losses, costs, liabilities and expenses (including reasonable attorneys' fees), actions, suits, claims, demands and prosecution that may be brought or instituted to the extent based upon or arising out of i) the negligence or willful misconduct of MERCK under this Agreement, ii) the material breach by MERCK of any warranty, representation or obligation of MERCK under this Agreement, or iii) the use, manufacture or sale by MERCK of Compound or Product.

ARTICLE VII

CLINICAL SUPPLY AND TECHNOLOGY TRANSFER

7.1 CLINICAL SUPPLY. ISIS hereby agrees to supply MERCK with its worldwide requirements for API, Intermediate Compound, Placebo and Clinical Product (as the foregoing terms are defined in the Clinical Supply Agreement) in accordance with the terms of the Clinical Supply Agreement. In the event that ISIS does not have sufficient manufacturing capacity to meet MERCK's requirements in accordance with the terms of the Clinical Supply Agreement, ISIS may use a third party toll manufacturer to manufacture all or part of MERCK's requirements, upon the prior written approval of MERCK. MERCK shall supply its own requirements for Compound and Products for development and commercialization on a worldwide

basis upon completion of the Technology Transfer in accordance with the terms of this Agreement. Concurrently with the execution of this Agreement, the parties shall execute the Clinical Supply Agreement attached hereto as Schedule 1.5.

7.2.1 TECHNOLOGY TRANSFER. Commencing with the Effective Date and for a time period thereafter to be determined by the Committee (the "Technology Transfer Term") and in accordance with the terms and conditions set forth in this Agreement, ISIS promptly shall (a) disclose to and transfer to MERCK all of the ISIS Know-How and ISIS Technology including the items listed in Schedule 7.2 and those items more fully detailed in the Technology Transfer Work Plan to be agreed to by the parties within thirty (30) days after the Effective Date and (b) provide to MERCK the training and support described in Schedule 7.2 and the Technology Transfer Work Plan and elsewhere in this Agreement to enable MERCK to efficiently and economically optimize use of the ISIS Know-How, ISIS Technology and ISIS Patent Rights, in the

formulation, development, registration, manufacture, marketing and sale of Compound and Product in the Field (the "Technology Transfer"). ISIS shall perform the Technology Transfer in accordance with the Procedures established by the Committee in accordance with Section 7.2.3. The parties shall cooperate so that the Technology Transfer may be completed as expeditiously as possible.

7.2.2 TECHNOLOGY TRANSFER COMMITTEE. The Technology Transfer shall be coordinated and implemented under the supervision of a joint committee (the "Committee") comprised of an agreed number of employees appointed by the parties having appropriate technical credentials, experience and knowledge and co-chaired by an employee of each party. The advice of additional employees or consultants of either party may by mutual consent of the parties be obtained. Decisions of the Committee shall 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 shall be determined in good faith by the Executive Vice President, Science and Technology, and President of MERCK Research Laboratories, and the Executive Vice President of ISIS; provided, however, in the event that they do not, after good faith efforts, reach agreement on an issue, the issue shall be submitted to arbitration pursuant to Section 10.6. Throughout the entire Technology Transfer Term, the Committee shall meet at least once each month in person or by teleconference, videoconference or by other mutually acceptable means. The Committee shall establish the Procedures, confer regarding the status of the Technology Transfer and compliance with the Procedures, review relevant data and results achieved, consider and advise on any technical issues that arise, consider issues of priority, and review and advise on any matters relating to the Technology Transfer referred to the Committee.

7.2.3 PROCEDURES FOR TECHNOLOGY TRANSFER. Promptly after the Effective Date, the Committee shall commence to monitor compliance with the procedures set forth in Schedule 7.2 and the Technology Transfer Work Plan which shall detail the procedures for the prompt and efficient Technology Transfer, and shall describe the events necessary to accomplish the Technology Transfer and detail the training and support to be provided by ISIS during the Technology Transfer (the "Procedures"). The Procedures shall be designed to ensure, and shall be refined by the Committee as necessary to ensure, MERCK's optimal use of the ISIS Know-How, ISIS Technology and ISIS Patent Rights in developing, manufacturing and commercializing Compound and Product, all in accordance with the terms of this Agreement.

7.2.4 TRAINING AND SUPPORT. The training and support to be provided by ISIS to MERCK throughout the Technology Transfer Term shall include without limitation training and support in a mutually acceptable MERCK facility in all of the methods necessary to practice the ISIS Know-How, ISIS Technology and ISIS Patent Rights in the development, manufacturing and commercialization of Compound and Product, and this shall include without limitation (a) demonstration and training during the installation, operational and performance qualifications of the technology, (b) technical support for the operational startup of manufacturing equipment, and (c) demonstration of the manufacturing processes. In addition, a reasonable number of employees of MERCK and its Affiliates shall 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 shall provide technical consultation on an as-needed basis following NDA approval of Product for a time period to be established by the Committee. ISIS also shall 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.

7.2.5 RECORDS. ISIS shall maintain records, in sufficient detail and in good scientific manner appropriate for patent, regulatory and manufacturing purposes, which shall 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 shall be available to the Committee and Merck shall have the right, during normal business hours and upon reasonable notice, to inspect and copy all such Records. MERCK also shall 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.

7.2.6 MANUFACTURING TECHNOLOGY IMPROVEMENTS. The entire right, title, and interest in and to all Manufacturing Technology Improvements, patentable or not, developed or invented solely by employees of ISIS during the term of this Agreement shall be the sole and exclusive property of ISIS, subject to the licenses granted to MERCK under this Agreement. The entire right, title, and interest in and to all Manufacturing Technology Improvements, patentable or not, developed or invented solely by employees of MERCK during the term of this Agreement shall be the sole and exclusive property of MERCK, and MERCK hereby grants to ISIS a worldwide, non-exclusive, sublicensable, royalty-free license to any such patented sole MERCK Manufacturing Technology Improvements solely for use outside of the Field. The entire right, title, and interest in and to all Manufacturing Technology Improvements, patentable or not, developed or invented jointly by employees of ISIS and MERCK during the term of this Agreement shall be the joint property of ISIS and MERCK, subject to the licenses granted to MERCK under this Agreement. The parties shall promptly disclose to each other the development, making, conception or reduction to practice of all Manufacturing Technology Improvements.

ARTICLE VIII

PATENT PROVISIONS

8.1 FILING, PROSECUTION AND MAINTENANCE OF PATENTS. ISIS and MERCK hereby agree that, during the term of this Agreement, the ISIS Patent Rights which claim, cover or relate to the Compound in the Territory shall, at MERCK's expense, be filed, prosecuted and maintained by independent patent legal counsel chosen by MERCK and reasonably acceptable to ISIS. Such independent counsel shall keep ISIS and MERCK advised of the status of the actual and prospective patent filings and upon the request of the party(ies), shall provide advance copies of any papers related to the filing, prosecution and maintenance. The parties shall consult as to patent filings by such independent counsel which shall be subject to the prior mutual agreement of the parties. ISIS agrees to file, prosecute and maintain in the Territory the ISIS Patent Rights which claim, cover or relate to Core Technology, Core Technology Improvements, Manufacturing Technology or Manufacturing Technology Improvements owned in whole or in part by ISIS and licensed to MERCK under this Agreement. ISIS shall keep MERCK advised of the status of the actual and prospective patent filings on a semi-annual basis and upon the request of MERCK, provide copies of any papers related to the filing, prosecution and maintenance of such patent filings. MERCK shall have the exclusive right during the term of this Agreement to file, prosecute and maintain, in the Territory, patent applications that claim, cover or relate to Compound Improvements. With respect to all filings hereunder, the filing party shall be responsible for payment for all costs and expenses related to such filings.

8.2 ISIS PATENT RIGHTS PATENT SCHEDULES. ISIS hereby agrees to provide MERCK with updated patent schedules in a timeframe agreed to by the parties.

8.3 INTERFERENCE, OPPOSITION, REEXAMINATION AND REISSUE. Either party shall, within ten (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 ISIS Patent Rights in the Field. MERCK and ISIS shall thereafter consult and cooperate fully to determine a course of action with respect to any such proceeding subject to the following:

(a) Any interference, opposition, reissue, or reexamination proceeding relating to ISIS Patent Rights which claim, cover or relate to Compound in the Territory shall be conducted at MERCK's expense by independent patent legal counsel chosen by MERCK and reasonably acceptable to

ISIS. MERCK and ISIS will cooperate fully and will provide each other and the independent patent legal counsel with any information or assistance that any party may reasonably request. Outside patent legal counsel shall keep MERCK and 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, shall be made by mutual agreement of ISIS and MERCK.

(b) Any interference, opposition, reissue, or reexamination proceeding relating to ISIS Patent Rights which claim, cover or relate to the Core Technology, Core Technology Improvements, Manufacturing Technology or Manufacturing Technology Improvements in the Territory, shall be conducted by ISIS at ISIS' expense. To the extent that such interference, opposition, reissue, or reexamination proceeding materially impacts MERCK's rights within the Field, MERCK and ISIS will cooperate fully and will provide each other with any information or assistance that either may reasonably request. ISIS shall keep MERCK 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 MERCK's consent to any settlement terms which affect MERCK's freedom to operate in the Field under the licenses granted to MERCK under this Agreement.

8.4 ENFORCEMENT AND DEFENSE.

(a) ISIS shall give MERCK notice of (i) any infringement of ISIS Patent Rights in the Field, or (ii) any misappropriation or misuse of ISIS Know-How in the Field, that may come to ISIS's attention. MERCK and ISIS shall thereafter consult and cooperate fully to determine a course of action, including without limitation the commencement of legal action by either or both MERCK and ISIS, to terminate any infringement of ISIS Patent Rights or any misappropriation or misuse of ISIS Know-How in the Field. However, ISIS, upon notice to MERCK, shall have the first right to initiate and prosecute such legal action at its own expense and in the name of ISIS and MERCK, or to control the defense of any declaratory judgment action relating to ISIS Patent Rights or ISIS Know-How in the Field. ISIS shall promptly inform MERCK if it elects not to exercise such first right and MERCK shall 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 MERCK and, if necessary, ISIS.

(b) In the event that ISIS elects not to initiate and prosecute an action as provided in paragraph (a), and MERCK elects to do so, the costs of any agreed-upon course of action to terminate infringement of ISIS Patent Rights or misappropriation or misuse of ISIS Know-How, including the costs of any legal action commenced or the defense of any declaratory judgment, shall be shared equally by ISIS and MERCK, except that the cost of any such action related solely to the Compound shall be borne by MERCK.

(c) For any action to terminate any infringement of ISIS Patent Rights or any misappropriation or misuse of ISIS Know-How, in the event that MERCK 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 MERCK to initiate litigation to prosecute and maintain such action. In connection with any action, MERCK and ISIS will cooperate fully and will provide each other with any information or assistance that either may reasonably request. Each party shall 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.

(d) Any recovery obtained by either or both MERCK and ISIS in connection with or as a result of any action contemplated by this section, whether by settlement or otherwise, shall be shared in order as follows:

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

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

(iii) the amount of any recovery remaining shall then be allocated between the parties on a PRO RATA basis under which ISIS shall receive a proportion based on the royalties it lost and MERCK shall receive a proportion based on its lost profits.

(e) ISIS shall inform MERCK of any certification regarding any ISIS Patent Rights it has received pursuant to either 21 U.S.C. Sections 355(b)(2)(A)(iv) or (j)(2)(A)(vii)(IV) or under Canada's Patented medicines (Notice of Compliance) Regulations Article 5 and shall provide MERCK with a copy of such certification within five (5) days of receipt. ISIS's and MERCK's rights with respect to the initiation and prosecution of any legal action as a result of such certification or any recovery obtained as a result of such legal action shall be as defined in paragraphs (a)-(d) hereof; provided, however, that ISIS shall exercise its first right to initiate and prosecute any action and shall inform MERCK of such decision within ten (10) days of receipt of the certification, after which time MERCK shall have the right to initiate and prosecute such action.

8.5 CERTIFICATION UNDER DRUG PRICE COMPETITION AND PATENT RESTORATION ACT. ISIS and MERCK each shall 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 ISIS Patent Rights covering Compound or Product are invalid or that infringement will not arise from the manufacture, use or sale of Compound(s) or Product(s) by a third party. If ISIS or MERCK (depending on which party is defending the ISIS Patent Rights) decides not to bring infringement proceedings against the entity making such a certification, such party shall give notice to the other party of its decision not to bring suit within twenty-one (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 MERCK or ISIS shall either be in the name of MERCK or in the name of ISIS, or jointly by MERCK and ISIS. For this purpose, the party not bringing suit shall execute such legal papers necessary for the prosecution of such suit as may be reasonably requested by the party bringing suit.

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

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

ARTICLE IX

TERM AND TERMINATION

9.1 TERM AND EXPIRATION. This Agreement shall be effective as of the Effective Date and unless terminated earlier pursuant to Sections 9.2 or 9.3 below, the term of this Agreement shall continue in effect until expiration of all royalty obligations hereunder. Upon expiration of this Agreement due to expiration of all royalty obligations hereunder, MERCK's licenses pursuant to Section 3.1 and 3.2 shall become fully paid-up, perpetual licenses.

9.2 TERMINATION BY MERCK. a) Notwithstanding anything contained herein to the contrary, MERCK shall have the right to terminate this Agreement at any time in its sole discretion a) during the Preclinical Development Program by giving thirty (30) days advanced written notice to ISIS, and b) thereafter by giving ninety (90) days advance written notice to ISIS. b) In the event of such termination by MERCK, the rights and obligations hereunder, including any payment obligations not due and owing as of the termination date, shall terminate, subject to the provisions of Section 9.4 herein, provided that MERCK shall be obligated to pay all non-cancelable commitments to undertake Preclinical Development Program studies in accordance with Schedule 2.2 and the terms of this Agreement, and all other non-cancelable Agreement commitments undertaken by ISIS in accordance with the terms of this Agreement, where such non-cancelable commitments exist as of the date of notice of termination is provided by MERCK. c) In the

event that MERCK terminates this Agreement pursuant to this Section 9.2 after the commencement of Clinical Development studies by MERCK for reasons other than safety, and ISIS notifies MERCK within ninety (90) days after such termination that ISIS wishes to commercialize the Compound, the parties hereof agree to enter into negotiations for a

commercially reasonable arrangement to permit ISIS to undertake development and commercialization of the Compound utilizing summaries of Clinical Development Program data developed by MERCK under this Agreement. [*]

9.3 TERMINATION.

9.3.1 TERMINATION FOR CAUSE. This Agreement may be terminated by 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 by causes and reasons within its control and has not cured such breach within ninety (90) days after 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 ninety (90) day cure period shall be stayed until such time as the dispute is resolved pursuant to Subsection 10.6 hereof; and

(b) upon the filing or institution of bankruptcy, reorganization, liquidation or receivership proceedings, 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 shall only become effective if the party consents to the involuntary bankruptcy or such proceeding is not dismissed within ninety (90) days after the filing thereof.

9.3.2 EFFECT OF TERMINATION FOR CAUSE ON LICENSE.

(a) In the event MERCK terminates this Agreement under Section 9.3.1(a), MERCK's licenses pursuant to Sections 3.1 and 3.2 shall become perpetual licenses. It is understood that in the event MERCK contends it suffers damages as a result of the breach, MERCK may place a portion of the payments to be made by MERCK pursuant to Article 5 that would reasonably cover MERCK's alleged damages into an interest-bearing escrow account pending resolution of any dispute between the parties relating to the material breach or termination of the agreement, including a dispute over damages, pursuant to paragraph 10.6. In the event that ISIS terminates this Agreement under Section 9.3.1(a), MERCK's licenses pursuant to Sections 3.1 and 3.2 shall terminate as of such termination date.

(b) In the event this Agreement is terminated by MERCK under Section 9.3.1(b) or due to the rejection of this Agreement by or on behalf of ISIS under Section 365 of the United States Bankruptcy Code (the "Code"), all licenses and rights to licenses granted under or pursuant to this Agreement by ISIS to MERCK are, and shall otherwise be deemed to be, for purposes of Section 365(n) of the Code, licenses of rights to "intellectual property" as defined under Section 101(35A) of the Code. The parties agree that MERCK, as a licensee of such rights under this Agreement, shall retain and may fully exercise all of its rights and elections under the Code, and that upon commencement of a bankruptcy proceeding by or against ISIS under the Code, MERCK shall be entitled to a complete duplicate of or complete access to (as MERCK deems appropriate), any such intellectual property and all embodiments of such intellectual property. Such intellectual property and all embodiments thereof shall be promptly delivered to MERCK (i) upon any such commencement of a bankruptcy proceeding upon written request therefore by MERCK, unless ISIS elects to continue to perform all of its obligations under this Agreement or (ii) if not delivered under (i) above, upon the rejection of this Agreement by or on behalf of ISIS upon written request therefore by MERCK. Where MERCK does retain and is able to fully exercise all licenses and rights to licenses granted under this Agreement, MERCK's payment obligations to ISIS for milestones and royalties in accordance with Section 5.3 and/or Section 5.4 of this Agreement in connection with such exercise by MERCK of MERCK's licenses hereunder shall continue in effect.

The foregoing is without prejudice to any rights MERCK may have arising under the Code or other applicable law.

9.4 EFFECT OF EXPIRATION OR TERMINATION. (a) Expiration or termination of the Agreement shall not relieve the parties of any obligation accruing

prior to such expiration or termination, Sections 2.2.5, 2.2.6, 2.2.7, 2.3.4, 3.1 (d), 3.4, 3.5, 7.2.5, 7.2.6, 9.1, 9.2, 9.3.2, 9.4, 10.4, 10.5 and 10.6 shall survive expiration or termination of the Agreement, the provisions of Article IV shall survive the termination or expiration of the Agreement and shall continue in effect for ten (10) years thereafter, and the provisions of 2.4 and Schedule 2.4 shall continue in effect in accordance with the application timetable set forth therein. Any expiration or early termination of this Agreement shall 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 or Compound sold prior to such termination.

(b) Upon any termination of this Agreement by MERCK pursuant to Subsection 9.2, or by ISIS pursuant to Subsection 9.3.1, MERCK shall be entitled, during the twelve (12) months following the termination date, to finish any work-in-progress and to sell any inventory of Compound and Product which remains on hand.

ARTICLE X

MISCELLANEOUS

10.1 FORCE MAJEURE. Neither party shall 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 shall notify the other party of such force majeure circumstances as soon as reasonably practical and shall make every reasonable effort to mitigate the effects of such force majeure circumstances.

10.2 ASSIGNMENT. This Agreement shall 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 MERCK 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 related to the Product or the business, or in the event of its merger or consolidation or change in control or similar transaction, and PROVIDED, HOWEVER, that ISIS may, without such consent, assign the Agreement and its rights and obligations hereunder 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 shall assume all obligations of its assignor under the Agreement. Any attempted assignment not in accordance with this Section 10.2 shall be void.

10.3 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 shall 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 shall 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.

10.4 NOTICES. All notices which are required or permitted hereunder shall be in writing and sufficient if delivered personally, sent by facsimile (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

with a copy to: Attention: General Counsel
Fax No.: (760) 603-3820

if to MERCK, to: Merck & Co., Inc.
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100
Attention: Vice President,
Corporate Development and Licensing

with a copy to: Attention: Office of the Secretary

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 shall be deemed to have been given when delivered if personally delivered or sent by telecopier 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.

10.5 APPLICABLE LAW. The Agreement shall be governed by and construed in accordance with the laws of the State of New Jersey without reference to any rules of conflict of laws or renvoi.

10.6 DISPUTE RESOLUTION. The parties shall negotiate in good faith and use reasonable efforts to settle any dispute, controversy or claim arising from or related to this Agreement or the breach thereof. If the parties do not fully settle, and a party wishes to pursue the matter, each such dispute, controversy or claim that is not an "Excluded Claim" shall be finally resolved by binding arbitration in accordance with the Commercial Arbitration Rules and Supplementary Procedures for Large Complex Disputes of the American Arbitration Association ("AAA"), and judgment on the arbitration award may be entered in any court having jurisdiction thereof. The arbitration shall be conducted by a panel of three persons experienced in the pharmaceutical business: within 30 days after initiation of arbitration, each party shall select one person to act as arbitrator and the two party-selected arbitrators shall select a third arbitrator within 30 days of their appointment. If the arbitrators selected by the parties are unable or fail to agree upon the third arbitrator, the third arbitrator shall be appointed by the AAA. The place of arbitration shall be Denver, Colorado. Either party may apply to the arbitrators for interim injunctive relief until the arbitration award is rendered or the controversy is otherwise resolved. Either party also may, without waiving any remedy under this Agreement, seek from any court having jurisdiction any injunctive or provisional relief necessary to protect the rights or property of that party pending the arbitration award. The arbitrators shall have no authority to award punitive or any other type of damages not measured by a party's compensatory damages. Each party shall bear its own costs and expenses and attorneys' fees and an equal share of the arbitrators' and any administrative fees of arbitration. Except to the extent necessary to confirm an award or as may be required by law, neither a party nor an arbitrator may disclose the existence, content, or results of an arbitration without the prior written consent of both parties. In no event

shall an arbitration be initiated after the date when commencement of a legal or equitable proceeding based on the dispute, controversy or claim would be barred by the applicable New York statute of limitations. As used in this Section, the term "Excluded Claim" shall mean a dispute, controversy or claim that concerns (a) the validity or infringement of a patent, trademark or copyright; or (b) any antitrust, anti-monopoly or competition law or regulation, whether or not statutory.

10.7 ENTIRE AGREEMENT. This Agreement and the Clinical Supply Agreement

contain the entire understanding of the parties with respect to the license, development and commercialization of Compound 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.

10.8 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.

10.9 INDEPENDENT CONTRACTORS. It is expressly agreed that ISIS and MERCK shall be independent contractors and that the relationship between the two parties shall not constitute a partnership, joint venture or agency. Neither ISIS nor MERCK shall have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on the other, without the prior consent of the other party.

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

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

10.12 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 shall be construed against the drafting party shall not apply.

IN WITNESS WHEREOF, the parties have executed this Agreement as of the date(s) set forth below.

Merck & Co., Inc.	Isis Pharmaceuticals, Inc.
BY:_____	BY:_____
TITLE: _____	TITLE: _____
DATE: _____	DATE: _____

SCHEDULE 1.5

[*]

SCHEDULE 1

[*]

SCHEDULE 2

[*]

SCHEDULE 2.1

[*]

SCHEDULE 3

[*]

SCHEDULE 4.3

[*]

*Confidential Treatment Requested 24

ISIS PATENT RIGHTS

SCHEDULE 1.16 (a)(i)

[*]

and 1.16 (a)(ii)

[*]

and 1.16 (a)(iii)

[*]

*Confidential Treatment Requested 25

SCHEDULE 2.2

[*]

*Confidential Treatment Requested 26

SCHEDULE 2.2.1 (b)

[*]

*Confidential Treatment Requested 27

SCHEDULE 2.2.6

[*]

*Confidential Treatment Requested 28

SCHEDULE 2.4

[*]

*Confidential Treatment Requested 29

SCHEDULE 7.2

[*]

*Confidential Treatment Requested 30