SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

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

Date of report (Date of earliest event reported): **December 13, 2001**

ISIS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Charter)

Delaware
(State or Other Jurisdiction of Incorporation)

000-19125	**33-0336973**
(Commission File No.)	(IRS Employer Identification No.)

2292 Faraday Avenue
Carlsbad, CA 92008
(Address of Principal Executive Offices and Zip Code)

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

Item 5. Other Events.

On December 13, 2001 Isis Pharmaceuticals, Inc. and Amgen, Inc. announced a three-year collaboration agreement to discover new antisense drugs. The collaboration will utilize Isis' proprietary second-generation chemistry to develop antisense drugs which inhibit several gene targets. Amgen will have the right to develop and commercialize antisense drugs resulting from the collaboration. Isis will receive milestone payments upon key clinical and commercial achievements, and royalties for successful antisense drugs.

On December 19, 2001 Isis Pharmaceuticals, Inc. and Circadian Technologies Limited, an Australian biotechnology commercialization firm, announced the formation of Antisense Therapeutics Limited (ATL). ATL was established to focus on the discovery and development of antisense drugs. ATL is listed on the Australian Stock Exchange and has successfully completed its initial public offering. As part of the formation of ATL, Isis has licensed to ATL ISIS 107248, an antisense inhibitor to CD 49d, a sub-unit of VLA-4. In addition, Isis and ATL will participate in a five-year antisense drug discovery and development collaboration, which includes the use of GeneTrove's gene functionalization services. ATL will pay royalties on antisense drugs discovered and developed within the partnership.

On December 27, 2001 Isis Pharmaceuticals, Inc. announced the establishment of a supply agreement with Integrated DNA Technologies, Inc. (IDT). In addition, Isis expanded its existing licensing agreement with IDT on certain antisense patents. The agreement calls for IDT to manufacture research-scale antisense inhibitors and research reagents to Isis specifications.

Item 7. Exhibits.

10.1*	Collaboration Agreement dated December 11, 2001 between Isis Pharmaceuticals, Inc. and Amgen, Inc.
10.2*	Oligonucleotide Manufacturing and Supply Agreement dated December 4, 2001 between Isis Pharmaceuticals, Inc. and Integrated DNA Technologies, Inc.
10.3*	Amended and Restated IDT-Isis Licensing Agreement dated December 4, 2001 between Isis Pharmaceuticals, Inc. and Integrated DNA Technologies, Inc.
10.4	Master Agreement dated October 30, 2001 between Isis Pharmaceuticals, Inc. and Antisense Therapeutics Ltd.
10.5*	Collaboration and License Agreement dated October 30, 2001 between Isis Pharmaceuticals, Inc. and Antisense Therapeutics Ltd.
10.6*	Clinical Supply Agreement dated October 30, 2001 between Isis Pharmaceuticals, Inc. and Antisense Therapeutics Ltd.
10.7	Stock Purchase Agreement dated October 30, 2001 between Isis Pharmaceuticals, Inc. and Antisense Therapeutics Ltd.
99.1	Press Release dated December 13, 2001 regarding Amgen, Inc. and Isis Pharmaceuticals, Inc.
99.2	Press Release dated December 19, 2001 regarding Antisense Therapeutics Limited and Isis Pharmaceuticals, Inc.
99.3	Press Release dated December 27, 2001 regarding Integrated DNA Technologies, Inc. and Isis Pharmaceuticals, Inc.

* Confidential treatment has been requested with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

SIGNATURE

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

Isis Pharmaceuticals, Inc.

Dated: January 4, 2002

By: /s/ B. Lynn Parshall

B. Lynne Parshall
Executive Vice President, Chief Financial Officer and Director

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

COLLABORATION AGREEMENT

BETWEEN

AMGEN INC.

AND

ISIS PHARMACEUTICALS, INC.

DECEMBER 11, 2001

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COLLABORATION AGREEMENT

THIS COLLABORATION AGREEMENT (the "AGREEMENT") is entered into as of December 11, 2001 (the "EFFECTIVE DATE") by and between AMGEN INC., a Delaware corporation having an address of One Amgen Center Drive, Thousand Oaks, California 91320-1799 ("AMGEN"), and ISIS PHARMACEUTICALS, INC., a Delaware corporation having an address of 2292 Faraday Avenue, Carlsbad, California 92008 ("ISIS").

RECITALS

WHEREAS, Isis is engaged in the discovery and development of antisense oligonucleotides and has accumulated considerable knowledge in the field of antisense technology, including processes and techniques relating to the design, synthesis and development of antisense oligonucleotides as drugs;

WHEREAS, Amgen is engaged in the discovery, development, manufacturing and marketing of human therapeutics; and

WHEREAS, Isis and Amgen desire to enter into a collaborative relationship to discover and develop antisense drugs for the treatment of [***], on the terms and subject to the conditions set forth herein.

NOW, THEREFORE, in consideration of the foregoing premises and the mutual covenants contained herein and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties agree as follows:

ARTICLE 1

DEFINITIONS

Capitalized terms used but not otherwise defined herein have the meanings provided in EXHIBIT A hereto.

ARTICLE 2

COLLABORATION GOVERNANCE

2.1 RESEARCH MANAGEMENT COMMITTEE. Promptly after the Effective Date, the parties will form a Research Management Committee (the "RMC") comprised of three (3) representatives each of Isis and Amgen. The party hosting an RMC meeting will designate one of its RMC members to serve as chairperson for that meeting. The RMC will oversee and manage the Collaboration, as more fully described in Section 2.2. A primary objective of the RMC is to reach unanimous decisions, with each party having one (1) vote, arrived at through open discussions amongst the representatives of each of the parties. In the event the RMC is unable to unanimously decide or resolve an issue, such issue shall be resolved in accordance with Section 2.3 below. The RMC will meet at least quarterly during the Collaboration Term, with the meeting location alternating between the principal offices of each party, at mutually-agreed times. Promptly following the Effective Date the RMC will hold an organizational meeting to

establish the operational requirements for the RMC. A reasonable number of additional representatives of a party may attend meetings of the RMC in a non-voting capacity.

2.2 RESEARCH MANAGEMENT COMMITTEE FUNCTIONS AND POWERS. The RMC generally shall have the responsibility of managing, directing and overseeing the Collaboration including, without limitation, the following responsibilities:

(a) managing and monitoring the progress and results of the Collaboration and the parties' diligence in carrying out their responsibilities thereunder;

(b) determining future Collaboration activities to be conducted under the Research Plan;

(c) allocating responsibility for the various Collaboration activities between the parties;

(d) reviewing and approving the Research Plan;

(e) amending and/or supplementing the Research Plan upon any addition, substitution or discontinuation of an Amgen Gene Target pursuant to Section 4.2, 4.3 or 4.4, upon any decision by Amgen to advance an Amgen Gene Target into Level 2 Research or as otherwise deemed appropriate by the RMC;

(f) developing an estimate of resources needed for activities related to Level 2 Research to be performed by Isis pursuant to the Research Plan for each year of the Collaboration Term (including any renewal or extension thereof);

(g) maintaining and, on a regular basis, updating and providing to the parties a list or lists of all Collaboration ASO Compounds identified or developed in the course of the Collaboration;

(h) determining when each of the Level 1 Research and Level 2 Research with respect to an Amgen Gene Target and Collaboration ASO Compounds directed thereto has been completed in accordance with the Research Plan or as otherwise mutually agreed and providing each party with notice of

such completion;

(i) maintaining records of the completion date of each of Level 1 Research and Level 2 Research with respect to each Amgen Gene Target; and

(j) approving the number of Isis researchers performing work under the Collaboration (and with respect to Level 2 Research, subject to Section 6.2).

2.3 RMC DISPUTE RESOLUTION. If the RMC is unable to unanimously decide or resolve an issue, the issue will be referred to the Executive Vice President, R&D of Amgen or another Amgen officer (not a member of the RMC) appointed by the Executive Vice President, R&D and to the Chief Executive Officer of Isis. Such officers of the parties will promptly meet (in person, by teleconference or otherwise) thereafter and negotiate in good faith to resolve such issue. If they cannot resolve such issue within fifteen (15) days of commencing such negotiations, then

Amgen will make the final decision regarding such matter, provided that Amgen will not have the right to unilaterally amend or modify the terms and conditions of this Agreement, or to obligate Isis to perform additional work outside the scope of the Research Plan or incur significant costs beyond those provided for in this Agreement or the Research Plan.

ARTICLE 3

CONDUCT OF THE COLLABORATION

3.1 OBJECTIVES. The parties hereby agree to establish and conduct the Collaboration in accordance with the Research Plan and with the terms of this Agreement with the goal of discovering and developing Products. The initial Research Plan for conducting the Collaboration with respect to the Amgen Gene Targets through Level 1 Research is attached hereto as EXHIBIT B. The RMC chairperson will promptly provide to the parties copies of any amendment or supplement to the Research Plan approved by the RMC pursuant to Section 2.2.

3.2 TECHNICAL ASSISTANCE. During the course of the Collaboration, each party will provide the other party with reasonable technical assistance relating to the use of such party's technology, solely to the extent permitted under the license(s) granted to the other party in this Agreement. In addition, during the Term each party shall make its employees, consultants and agents reasonably available upon reasonable notice during normal business hours at their respective places of employment to consult with the other party on issues arising during or from the Collaboration and in connection with any request from any regulatory agency, including those relating to regulatory, scientific and technical issues.

3.3 PERFORMANCE STANDARDS. Isis shall use reasonable best efforts, and shall commit the personnel, facilities and resources, to discover and supply the Collaboration ASO Compounds and to perform its other obligations under the Research Plan. Amgen will use reasonable best efforts to perform its obligations under the Research Plan. Each party will conduct its activities under the Collaboration in good scientific manner and in compliance in all material respects with applicable laws and regulations and with applicable good laboratory practices ("GLP") and good manufacturing practices ("GMP"). Each party will prepare and maintain complete and accurate written records with respect to its activities under the Research Plan consistent with industry standards including, for purposes of patent and regulatory matters, prompt signing and corroboration of laboratory notebooks and conception documents. Upon Amgen's written request and within twenty (20) business days after such request, Isis shall make the source data (including laboratory notebook records) of the Collaboration Know-How available for inspection by an authorized representative of Amgen at any reasonable time during Isis' regular working hours, and copies of all or any part of such data and all records (whether in tangible or electronic form) shall be furnished to Amgen upon request.

3.4 RESEARCH REPORTS. Each party will keep the other party fully informed as to all discoveries and technical developments (including, without limitation, any inventions) made in the course of performing activities under the Collaboration. In particular, prior to each RMC meeting Isis and Amgen each will prepare and distribute to all members of the RMC (no later than five (5) business days prior to each such RMC meeting) a reasonably detailed written summary report, in such form and format and setting forth such information regarding the results

and progress of performance of the Collaboration (since the last report) as determined from time to time by the RMC. The information contained in the report shall be accurate in the reporting party's best scientific judgment. In addition, Isis shall promptly make available and disclose to Amgen Collaboration Know-How and Isis Know-How relating to Collaboration ASO Compounds. At Amgen's request, at any time during the Term Isis shall provide written reports of any studies performed by Isis as part of the Collaboration, including, without limitation, data and information related to the synthesis and analytical methods used in preparing Collaboration ASO Compounds, which Amgen may need to support its regulatory submissions relating to Products and shall allow Amgen to use the data included in such reports to support such submissions. Nothing herein will require either party to disclose information received from a Third Party that remains subject to bona fide confidentiality obligations to such Third Party.

3.5 SUBCONTRACTS. Neither party shall subcontract to a Third Party any of its obligations under the Research Plan without the prior approval of the RMC. Any approved subcontracting must be performed pursuant to a written agreement containing appropriate provisions as determined by the RMC, including, without limitation, provisions of confidentiality and non-use and intellectual property provisions at least as restrictive as set forth in Section 3.9.

3.6 MATERIALS TRANSFER. In order to facilitate the Collaboration, either party may provide to the other party certain biological materials or chemical compounds including, but not limited to, Collaboration ASO Compounds, Amgen ASO Compounds, Amgen Gene Targets, screens, animal models, cell lines, cells, nucleic acids, receptors and reagents (collectively, "MATERIALS") Controlled by the supplying party for use by the other party in furtherance of the Collaboration. Except as otherwise provided under this Agreement (e.g., Amgen's rights pursuant to Sections 4.5, 4.6 and 5.1(a)(ii)), all such Materials delivered to the other party shall remain the sole property of the supplying party, shall be used only in furtherance of the Collaboration in accordance with this Agreement and remain solely under the control of the other party, shall not be used or delivered to or for the benefit of any Third Party without the prior written consent of the supplying party, and shall not be used in research or testing involving human subjects, except to the extent permitted by applicable law and permitted by the licenses granted hereunder. The Materials supplied under this Section 3.6 must be used with prudence and appropriate caution in any experimental work, because not all of their characteristics may be known. Except as expressly set forth in this Agreement (including, without limitation, Sections 3.7, 3.10 and 10.2), THE MATERIALS ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

3.7 MATERIALS AND EQUIPMENT. Other than with respect to Materials provided by Amgen pursuant to the Research Plan, Isis shall be responsible for the procurement and documentation of the quality of all materials, equipment and facilities used for the preparation and analysis of Collaboration ASO Compounds. Isis covenants that the materials, equipment and facilities to be used by Isis under this Agreement shall be of the same quality as Isis in its experience and best scientific judgment uses in its own research of similar nature. At its own

expense, Isis shall be responsible for storing, handling, transporting and disposing of chemical synthesis by-products generated by Isis during the performance of the Collaboration.

3.8 ISIS RESEARCHERS. Amgen and Isis acknowledge the importance of having personnel devoted full-time to work in the Collaboration. Accordingly, in order to maximize the effective conduct of the Collaboration, Isis shall use reasonable best efforts to maximize the continuity of Isis researchers conducting the Collaboration.

3.9 EMPLOYEE OBLIGATIONS. Prior to beginning work on the Collaboration and/or being given access to Isis Know-How, Amgen Know-How, Collaboration Know-How or Joint Know-How, each employee, consultant or agent

of Isis and Amgen shall have signed or shall be required to sign a non-disclosure and invention assignment agreement pursuant to which each such person shall agree to comply with all of the obligations of Isis or Amgen, as appropriate, substantially including: (a) promptly reporting any invention, discovery, process, software program or other intellectual property right, as appropriate within Isis Know-How, Amgen Know-How, Collaboration Know-How or Joint Know-How; (b) assigning to Isis or Amgen, as appropriate, all of his or her right, title and interest in and to any such invention, discovery, process, software program or other intellectual property right; (c) cooperating in the preparation, filing, prosecution, maintenance and enforcement of any patent rights; (d) performing all acts and signing, executing, acknowledging and delivering any and all papers, documents and instruments required for effecting the obligations and purposes of this Agreement and (e) abiding by the obligations of confidentiality and non-use set forth in this Agreement. It is understood and agreed that any such non-disclosure and invention assignment agreement need not be specific to this Agreement.

3.10 THIRD PARTY INTELLECTUAL PROPERTY. Isis covenants not to practice the Isis Standard Chemistry in a manner which Isis believes would infringe the claim of any issued patent or fall within the scope of other intellectual property rights, including but not limited to the claims of published patent applications, of a Third Party without Amgen's prior written consent.

ARTICLE 4

DISCOVERY, DEVELOPMENT AND COMMERCIALIZATION OF PRODUCTS

4.1 AMGEN GENE TARGETS. The Amgen Gene Targets are set forth in EXHIBIT C hereto, which exhibit will be updated upon any substitution or discontinuation of a Gene Target in accordance with Sections 4.2, 4.3 and 4.4.

4.2 SUBSTITUTION OF AMGEN GENE TARGETS. Amgen, in its sole discretion, shall have the right to decide whether to substitute a Gene Target for any of the then-current Amgen Gene Targets. At any time prior to completion of Level 2 Research (as determined by the RMC) with respect to a particular Amgen Gene Target, Amgen may provide written notice to Isis that Amgen wishes to substitute a different Gene Target (each, a "PROPOSED SUBSTITUTION TARGET") for such Amgen Gene Target, which notice shall specify both the Proposed Substitution Target and the existing Amgen Gene Target proposed to be replaced thereby. Prior to Isis providing written notice to Amgen as set forth below, the parties will engage in discussions relating to such Proposed Substitution Target as described in Point 1 of the Level 1 Research Plan, attached

hereto as Exhibit B. Amgen shall have the right to withdraw such Proposed Substitution Target within five (5) business days of such discussions. Within ten (10) business days after such notice from Amgen, Isis will provide written notice to Amgen (the "ISIS NOTICE") indicating whether such Proposed Substitution Target is subject to any agreement between Isis and a Third Party under which such Third Party has or may acquire rights to ASO Compounds directed to such Proposed Substitution Target or whether Isis has an existing Internal Program with respect to such Proposed Substitution Target or any ASO Compound directed thereto.

(a) If both (i) such Proposed Substitution Target is not subject to any agreement between Isis and a Third Party under which such Third Party has or may acquire rights to ASO Compounds directed to such Proposed Substitution Target and (ii) Isis does not have an existing Internal Program with respect to such Proposed Substitution Target or any ASO Compound directed thereto, then, effective upon the Isis Notice, such Proposed Substitution Target will be deemed an Amgen Gene Target and the original Amgen Gene Target replaced by such Proposed Substitution Target will cease to be an Amgen Gene Target and Exhibit C shall be updated by the RMC.

(b) Amgen will have the right to make only two (2) such substitutions of Amgen Gene Targets under this Section 4.2. For purposes of clarification, at no time may there be more than [***] Amgen Gene Targets under this Agreement. Isis acknowledges that only Proposed Substitution Targets deemed Amgen Gene Targets in accordance with Section 4.2(a) shall be considered a substitution.

4.3 LEVEL 1 RESEARCH.

(a) Isis shall conduct the Level 1 Research with respect to each Amgen Gene Target and Collaboration ASO Compounds, as more fully described

in the Research Plan. With respect to each Amgen Gene Target, Isis shall promptly, from the date such Amgen Gene Target is listed on Exhibit C, apply the appropriate level of resources in order to complete the Level 1 Research within [***] months from the date of such listing.

(b) During the [***] days following the RMC's determination that the Level 1 Research with respect to an Amgen Gene Target has been completed, Amgen may notify Isis in writing (the "Notice of Intent to Initiate Level 2 Research") of its desire to advance such Amgen Gene Target to Level 2 Research, which notice shall be accompanied by the payment set forth in Section 6.3(a)(i). If Amgen does not notify Isis of its desire to advance such Amgen Gene Target to Level 2 Research within such [***] period, or if Amgen notifies Isis that it does not desire to advance such Amgen Gene Target to Level 2 Research, then such Gene Target will cease to be an Amgen Gene Target, with the consequences of termination set forth in Section 12.5, and Exhibit C shall be updated by the RMC.

4.4 LEVEL 2 RESEARCH.

(a) Promptly following any election by Amgen pursuant to Section 4.3 to advance an Amgen Gene Target to Level 2 Research, the RMC will develop and approve an amendment and/or supplement to the Research Plan setting forth the activities to be performed by the parties, and the corresponding FTE requirements, with respect to such Amgen Gene

Target and Collaboration ASO Compounds directed thereto as part of the Level 2 Research. The parties will conduct such Level 2 Research with respect to each such Amgen Gene Target and Collaboration ASO Compounds directed thereto in accordance with the Research Plan, as so amended and/or supplemented. With respect to each such Amgen Gene Target so advanced, the parties shall apply the appropriate level of resources in order to complete the Level 2 Research within [***] months of the Notice of Intent to Initiate Level 2 Research.

(b) During the [***] months following RMC's determination that the Level 2 Research with respect to an Amgen Gene Target has been completed, Amgen may provide Isis with written notice (the "DEVELOPMENT NOTICE") that Amgen desires to advance such Amgen Gene Target to IND-enabling toxicology studies, accompanied by the payment set forth in Section 6.3(a)(ii). If Amgen does not notify Isis of its desire to advance such Amgen Gene Target to IND-enabling toxicology studies within such [***] period, or if Amgen notifies Isis that it does not desire to advance such Amgen Gene Target to IND-enabling toxicology studies, then such Gene Target will cease to be an Amgen Gene Target, with the consequences of termination set forth in Section 12.5, and Exhibit C shall be updated by the RMC.

4.5 FURTHER RESEARCH, DEVELOPMENT AND COMMERCIALIZATION.

(a) RESPONSIBILITY. Amgen shall have sole and full control, authority, discretion and right to conduct (by itself or via a Third Party) and make all decisions regarding continued research activities and all development (e.g., pre-clinical development, nomination of clinical candidates, clinical trial design), regulatory (e.g., interaction with all governmental authorities and preparation of any Regulatory Filings), manufacturing, commercialization (e.g., determination of price, sales and distribution, packaging, labeling, language to be included on the package insert, promotion, detailing and selection of trademarks and Phase IV clinical trials) for each Amgen Gene Target, Collaboration ASO Compounds, Amgen ASO Compounds and/or Products directed thereto from and after any election by Amgen pursuant to Section 4.4 to advance an Amgen Gene Target to IND-enabling toxicology studies. However, in addition to Isis' obligations under Article 3, Isis shall provide reasonable assistance to Amgen in connection with any such additional research or development as mutually agreed by the parties (which assistance may include consulting services), at Amgen's expense.

(b) OWNERSHIP. Amgen shall own all Regulatory Filings and Regulatory Approvals.

(c) DILIGENCE. Amgen will use Commercially Reasonable Efforts to pursue development and commercialization with respect to each Amgen Gene Target and Products directed thereto. Any alleged failure by Amgen to use Commercially Reasonable Efforts under this Section 4.5(c) will entitle Isis to seek redress solely under Section 12.3 below. Other than as expressly set forth hereinabove in this Section 4.5(c), it shall be in Amgen's sole discretion as to which and how many Product(s) and indications for Product(s) with respect to an Amgen Gene Target will be developed under this Agreement. By way of example, but not by way of minimum requirement, if Amgen pursues development of one (1) Product with respect to each Amgen Gene Target it shall be deemed to have used

Commercially Reasonable Efforts with respect to such Amgen Gene Target and Products directed thereto.

(d) EXCHANGE OF INFORMATION. Following completion of the Level 2 Research with respect to any Amgen Gene Target and Collaboration ASO Compounds directed thereto, and for so long as Amgen has a license with respect thereto under Section 5.1(a)(iii), Amgen will keep Isis reasonably informed about Amgen's research, development and commercialization efforts with respect to any Collaboration ASO Compound, Amgen ASO Compound or Product directed to such Amgen Gene Target. Without limiting the generality of the foregoing, Amgen shall be deemed to have met its obligation under this Section 4.5(d) by providing Isis with annual written reports that summarize the research, development and commercialization activities by Amgen with respect to any Amgen Gene Target, Collaboration ASO Compound, Amgen ASO Compound or Product and written notice of development and Regulatory Approval results with respect to any Collaboration ASO Compound, Amgen ASO Compound and Product that would trigger milestone payments under Section 6.3.

4.6 RESEARCH SUPPLY OF COLLABORATION ASO COMPOUNDS.

(a) Isis shall supply all Collaboration ASO Compounds synthesized by Isis, in quantities and to specifications agreed upon by the RMC in accordance with Section 2.1 above, to Amgen (or a Third Party designated by Amgen) for use in the Collaboration as set forth in the Research Plan. Together with each such Collaboration ASO Compound, Isis shall present to Amgen a certificate of analysis that meets the agreed-upon specifications regarding such shipment of Collaboration ASO Compound. For any Collaboration ASO Compound that Amgen advances to IND-enabling toxicology studies, Isis shall present to Amgen data and information corresponding to such Collaboration ASO Compound for use in IND-enabling toxicology and subsequent studies, including, but not limited to, end-of-compound preparation reports (e.g., detailed synthesis and analytical procedures), synthesis completion dates and lot numbers, batch identifications and a copy of all analytical data obtained. Amgen shall have the right, within thirty (30) days after receipt, to accept or reject such Collaboration ASO Compounds as follows: in the event Amgen determines that such Collaboration ASO Compound fails to meet the agreed-upon specifications, Amgen shall have the right to reject the shipment in whole or part, and Isis shall promptly resynthesize and provide Amgen with the rejected quantities of such ASO Collaboration Compounds. The cost of such requirements of Collaboration ASO Compounds for use in the Collaboration through completion of Level 1 Research is included in the up-front fee payable by Amgen pursuant to Section 6.1. Upon Amgen's written request, Isis shall promptly provide additional quantities of Collaboration ASO Compounds for use in Level 1 Research to be conducted at Amgen beyond the activities set forth in the Research Plan and all quantities of Collaboration ASO Compounds for use in Level 2 Research at a charge to Amgen of [***] per gram (inclusive of all shipping, freight and other delivery charges), with a minimum charge of [***] per order. For any quantities of Collaboration ASO Compound requested and delivered pursuant to the preceding sentence, Amgen will pay Isis for such quantities within thirty (30) days after receipt of such Collaboration ASO Compound, provided that Amgen shall have the right, within thirty (30) days after receipt, to accept or reject such quantity of such Collaboration ASO Compound as follows: in the event Amgen determines that such Collaboration ASO Compound fails to meet the agreed-upon specifications, Amgen shall have the right to reject the shipment in whole or part. Isis shall promptly resynthesize and provide Amgen with the rejected quantities of such ASO Collaboration Compound. Amgen shall pay only for such quantity of such Collaboration ASO Compounds that Amgen accepts.

(b) The parties will confer, prior to any delivery of any Collaboration ASO Compounds to Amgen, regarding the container and shipping details, the analytical results and other related data. Title in all quantities of each of the Collaboration ASO Compounds delivered under this Agreement shall pass to Amgen free and clear of any security interest, lien or other encumbrance. Risk of loss for all quantities of each of the Collaboration ASO Compounds shall remain with Isis until each such Collaboration Compound has been transferred to a carrier designated by Amgen in writing.

4.7 CLINICAL SUPPLY OF COLLABORATION ASO COMPOUNDS AND AMGEN ASO COMPOUNDS. If Amgen decides, following completion of Level 2 Research, to advance any Collaboration ASO Compound, Amgen ASO Compound and/or Product to IND-enabling toxicology studies, then, if requested by Amgen, Isis and Amgen

will negotiate in good faith a clinical supply agreement pursuant to which Isis will supply all of Amgen's requirements of such Collaboration ASO Compound or Amgen ASO Compound through the completion of Phase IIA Clinical Trials on such Collaboration ASO Compound or Amgen ASO Compound, which agreement will contain customary terms, including, without limitation, the following:

(a) In no event will Isis be obligated to provide more than [***] of any one Collaboration ASO Compound or Amgen ASO Compound;

(b) Isis shall also provide Amgen with any information and documentation on such Collaboration ASO Compound or Amgen ASO Compound in Isis' possession that Amgen deems necessary to meet or address regulatory requirements, at Amgen's request and expense; and

(c) Isis shall supply any such Collaboration ASO Compound or Amgen ASO Compound in accordance with mutually agreed-upon specifications, including, without limitation, current GMP, and at a price per gram equal to Isis' cost of manufacturing such Collaboration ASO Compound or Amgen ASO Compound plus [***].

If Isis is not able to supply up to [***] of any such Collaboration ASO Compound or Amgen ASO Compound to Amgen then Isis shall, at its expense, promptly transfer all necessary technology, documentation and technical assistance and grant all necessary rights and licenses to permit Amgen, its Affiliates, its Sublicensees or a Third Party manufacturer reasonably acceptable to Amgen to manufacture and supply such Collaboration ASO Compound or Amgen ASO Compound on behalf of Amgen, its Affiliates or Sublicensees. In anticipation of Amgen's post-Phase IIA clinical requirements or if Amgen otherwise determines to itself manufacture or to obtain a supply of any such Collaboration ASO Compound or Amgen ASO Compound from a Third Party, then Isis shall, at Amgen's request and expense, promptly transfer all necessary technology, documentation and technical assistance and grant all necessary rights and licenses to permit Amgen, its Affiliates, its Sublicensees or a Third Party manufacturer to manufacture and supply such Collaboration ASO Compounds or Amgen ASO Compounds on behalf of Amgen, its Affiliates or Sublicensees. The parties acknowledge that a separate agreement with a Third Party would be required to fill and finish Products containing any such Collaboration ASO Compound or Amgen ASO Compound and, upon request by Amgen, Isis agrees to facilitate the negotiations thereof with the Third Party used by Isis for such finishing activities.

4.8 GENETROVE DATABASE. Isis shall be prohibited from including any information regarding the Amgen Gene Targets in the GeneTrove Database and such information shall not be used for any other purpose except as expressly permitted by this Agreement.

4.9 TARGET EXCLUSIVITY. Isis agrees that Isis shall work exclusively with Amgen on each Amgen Gene Target during the Collaboration Term and for so long thereafter as the license under Section 5.1(a)(iii) with respect to such Amgen Gene Target or Products directed thereto remains in force. Except as otherwise expressly permitted by this Agreement, Isis shall not directly or indirectly (i) conduct any research on any Amgen Gene Target or any ASO Compound directed thereto, outside the course of the Collaboration either on its own or for a Third Party; (ii) grant or assign any rights to a Third Party with respect to any Amgen Gene Target or ASO Compound directed thereto, in each case, while such Amgen Gene Target is included within the Collaboration or (iii) either by itself and/or with or through a Third Party, make, have made, use, sell, lease, offer to sell or lease, import, export or otherwise exploit, or transfer physical possession of or title in (or otherwise directly or indirectly engage in any activity or take any action with respect to), any and all ASO Compounds and/or Products directed to any Amgen Gene Target for any purpose anywhere in the world.

ARTICLE 5

LICENSE GRANTS

5.1 LICENSE GRANTS.

(a) BY ISIS.

(i) RESEARCH LICENSE. Isis hereby grants to Amgen during the Collaboration Term (1) an exclusive, worldwide, royalty-free license, with the right to sublicense to subcontractors approved pursuant to Section 3.5, under the Isis ASO Compound Patent Rights, Isis' interest in the Joint Patent Rights, Collaboration Know-How and Isis' interest in Joint

Know-How solely to perform Amgen's responsibilities under the Collaboration, and (2) a non-exclusive, worldwide, royalty-free license, with the right to sublicense to subcontractors approved pursuant to Section 3.5, under the Isis Core Technology Patent Rights, the Isis Manufacturing Patent Rights and the Isis Know-How, solely to perform Amgen's responsibilities under the Collaboration; PROVIDED, HOWEVER, that the license to Amgen under this Section 5.1(a)(i) with respect to Isis' rights under the [***] License is limited to the scope of permissible licenses under the [***] License (a copy of the relevant portion of which has been provided to Amgen). Notwithstanding the foregoing or any other provision of this Agreement to the contrary, Isis retains the right to practice under the Isis ASO Compound Patent Rights and Collaboration Know-How solely to perform its responsibilities under the Collaboration, and Isis retains the right to practice under the Joint Patent Rights and the Joint Know-How to perform its responsibilities under the Collaboration and under the Joint Patent Rights not claiming any Amgen Gene Target or any ASO Compound directed thereto and Joint Know-How not directed to any Amgen Gene Target or any ASO Compound directed thereto for any and all other purposes except to the extent that Isis has granted Amgen an exclusive license under any of the foregoing pursuant to this Section 5.1(a).

(ii) INTERNAL USE LICENSE. In addition to the exclusive license and other rights granted to Amgen in this Agreement, Isis grants to Amgen a non-exclusive, irrevocable, perpetual, compensation-free and unrestricted worldwide right and license, without the right to sublicense, to make, have made, and use Isis Know-How and Collaboration Know-How, for Amgen's internal research and development purposes. Nothing in this Section 5.1(a)(ii) shall be construed to give Amgen any rights to commercialize products under Isis Patent Rights outside of the licenses granted by Isis pursuant to Section 5.1(a)(iii).

(iii) DEVELOPMENT AND COMMERCIALIZATION LICENSES. Isis hereby grants to Amgen (1) an exclusive (even as to Isis), worldwide license, with the right to sublicense, under the Isis ASO Compound Patent Rights, Isis' interest in the Joint Patent Rights, Collaboration Know-How and Isis' interest in Joint Know-How to research, develop, make, have made, use, sell, offer for sale, have sold, import, export or otherwise exploit, or transfer physical possession of or title in, Products in the Field, and (2) a non-exclusive, worldwide license, with the right to sublicense, under the Isis Core Technology Patent Rights, the Isis Manufacturing Patent Rights and the Isis Know-How to research, develop, make, have made, use, sell, offer for sale, have sold, import, export or otherwise exploit, or transfer physical possession of or title in, Products in the Field; PROVIDED, HOWEVER, that the license to Amgen under this Section 5.1(a)(iii) with respect to Isis' rights under the [***]License is limited to the scope of permissible licenses under the [***] License, and Amgen acknowledges that this Section 5.1(a) does not grant to Amgen any sublicense under the [***] License with respect to [***]. For purposes of clarification, the foregoing licenses will only be effective with respect to any Products directed to a Gene Target for so long as such Gene Target remains an Amgen Gene Target under this Agreement. Such licenses shall be royalty-bearing as expressly provided in Section 6.4 of this Agreement.

(b) BY AMGEN.

(i) RESEARCH LICENSE. Amgen hereby grants to Isis, during the Collaboration Term, a non-exclusive, worldwide, royalty-free license, without the right to sublicense, under the Amgen Technology solely to perform Isis' obligations under the Collaboration. Amgen retains the right to practice under Joint Patent Rights not claiming any Amgen Gene Target or any ASO Compound directed thereto and Joint Know-How not directed to any Amgen Gene Target or any ASO Compound directed thereto for any and all purposes.

(ii) INTERNAL USE LICENSE. Amgen grants to Isis a non-exclusive, irrevocable, perpetual, compensation-free and unrestricted worldwide right and license, without the right to sublicense, to make, have made, and use Amgen Know-How (limited to that which has been provided to Isis) for Isis' internal research and development purposes. Nothing in this Section 5.1(b)(ii) shall be construed to give Isis any rights to commercialize products under Amgen Patent Rights.

5.2 MANUFACTURING IMPROVEMENTS.

(a) Isis hereby grants to Amgen an option, exercisable upon written notice to Isis, to obtain a license to Manufacturing Improvements, under the following terms and conditions ("MANUFACTURING IMPROVEMENT OPTION"):

(i) The Manufacturing Improvement Option shall be exercisable at any time beginning upon the Effective Date and extending thirty (30) days thereafter.

(ii) In the event Amgen exercises the Manufacturing Improvement Option, during the first ten (10) years of the Term the parties will meet at least annually to review Manufacturing Improvements developed by either of the parties (or with respect to Isis, those certain Third Parties described hereinbelow). The parties will disclose all such Manufacturing Improvements Controlled by such party in reasonable detail so as to enable the other party to use such Manufacturing Improvements in the manufacture of ASO Compounds as permitted by this Section 5.2. Isis will have the right to disclose and sublicense any Manufacturing Improvements Controlled by Amgen to any Third Party that is a licensee of Isis with respect to the commercialization of one or more ASO Compounds only if (i) such Third Party has a then-existing contractual relationship with Isis whereby such Third Party is required to disclose to Isis on at least an annual basis any Manufacturing Improvements developed by such Third Party, (ii) Isis has the right to license such Third Party's Manufacturing Improvements to Amgen under this Agreement and (iii) such Third Party is manufacturing an ASO Compound on its own behalf (i.e., not using a Third Party manufacturer to manufacture ASO Compounds) or, in the event that such Third Party is using a Third Party manufacturer to manufacture an ASO Compound, such Third Party manufacturer is contractually obligated to provide access to any Manufacturing Improvements developed over the course of the relationship with such Third Party, and the Information disclosed in any such discussions, and any Patent Rights Controlled by such Third Party relating thereto, will be licensable to Amgen under this Agreement as Manufacturing Improvements under Section 5.2(d). Isis warrants, represents and covenants that the rights and obligations of the parties under this Section 5.2 are, and will be, the same in substance as those rights granted to and those obligations required of a Third Party to which Isis has the right to sublicense pursuant to this subsection.

(b) The entire right, title, and interest in and to all Manufacturing Improvements developed or invented solely by employees or consultants of Amgen during the Term shall be the sole and exclusive property of Amgen. In the event Amgen exercises the Manufacturing Improvement Option, Amgen hereby grants Isis a worldwide, royalty-free, perpetual, non-exclusive license under Information or Patent Rights Controlled by Amgen or its Affiliates that claim Manufacturing Improvements to make and have made products (other than the Products) containing, consisting of, based on or incorporating ASO Compounds. The license granted under this Section 5.2(b) shall be sublicensable by Isis solely in connection with the grant of a license to develop, make, have made, use, sell, offer for sale, have sold, import, export or otherwise exploit, or transfer physical possession of or title in, an ASO Compound discovered by Isis alone or in collaboration with a Third Party to which Isis has the right to sublicense pursuant to Section 5.2(a)(ii) above, subject to the exclusive licenses granted to Amgen under Section 5.1(a) and Isis' obligation of exclusivity with respect to Amgen Gene Targets under Section 4.9.

(c) The entire right, title, and interest in and to all Manufacturing Improvements developed or invented solely by employees or consultants of Isis during the Term shall be the sole and exclusive property of Isis. In the event Amgen exercises the Manufacturing Improvement Option, Isis hereby grants Amgen a worldwide, royalty-free (except as otherwise expressly provided in Section 6.4 of this Agreement), perpetual, non-exclusive license under

Information or Patent Rights Controlled by Isis or its Affiliates that claim Manufacturing Improvements to make and have made Products. The license granted under this Section 5.2(c) shall be sublicensable by Amgen solely in connection with the grant of a license to develop, make, have made, use, sell, offer for sale, have sold, import, export or otherwise exploit, or transfer physical possession of or title in, Products.

(d) The entire right, title, and interest in and to all Manufacturing Improvements developed or invented jointly by employees or consultants of Isis and Amgen during the Term shall be the joint property of Isis and Amgen. Each party shall have an undivided joint ownership interest in such Manufacturing Improvements, and may license its rights under such Manufacturing Improvements for its own account and without the consent of the

other party, subject to the exclusive licenses granted to Amgen under Section 5.1(a) and Isis' obligation of exclusivity with respect to Amgen Gene Targets under Section 4.9.

ARTICLE 6

FEES AND PAYMENTS

6.1 UP-FRONT FEE. Within five (5) business days following the Effective Date, Amgen will pay to Isis (i) a non-refundable, non-creditable up-front technology access fee of [***], and (ii) a non-refundable, non-creditable up-front fee of [***], which payment will cover the entire cost of Level 1 Research activities performed by Isis in accordance with the Research Plan.

6.2 RESEARCH FUNDING. During the Collaboration Term, commencing with initiation of Level 2 Research on an Amgen Gene Target-by-Amgen Gene Target basis, Amgen shall make research funding payments to Isis for such number of FTEs as Isis devotes to Collaboration activities with respect to an Amgen Gene Target in accordance with the Research Plan, at the FTE Rate, and shall reimburse Isis for the cost of materials and outside services incurred in connection with such Collaboration activities and approved by the RMC. Amgen will fund a minimum of [***] FTEs to conduct the Level 2 Research, with the exact number to be determined solely by Amgen but decided in a timely manner so as to allow Isis time to resource and staff appropriately. Subject to the FTE limitations set forth above, Amgen will pay Isis quarterly, in advance, for the number of FTEs projected to be devoted to Collaboration activities with respect to an Amgen Gene Target during such Calendar Quarter as set forth in the Research Plan, at the FTE Rate; PROVIDED, HOWEVER, that for the purpose of allowing the parties sufficient time to determine the applicable adjustment to the FTE Rate each year, with respect solely to the first quarter of each calendar year beginning in January 2003, such payment will be made within 15 days of the start of the quarter. Isis shall deliver written reports (certified by Isis' Vice President of Finance or Director of Finance) to Amgen on a quarterly basis within thirty (30) days after the end of such Calendar Quarter setting forth the number of FTEs actually devoted by Isis to Collaboration activities and a summary of all such FTE-funded activities with respect to such Amgen Gene Target during such Calendar Quarter. Isis or Amgen, as applicable, shall remit to the other party the amount of any overpayment or underpayment, respectively, within thirty (30) days of receipt thereof. In no event shall Amgen be obligated to pay Isis for FTEs beyond that number of FTEs approved by Amgen for such Calendar Quarter.

6.3 MILESTONE PAYMENTS.

(a) RESEARCH MILESTONES. On an Amgen Gene Target-by-Amgen Gene Target basis, Amgen shall pay to Isis the one-time, non-refundable, non-creditable milestone payment set forth below concurrently with the events set forth below, as provided in Section 4.3 or 4.4, as applicable:

	MILESTONE EVENT	MILESTONE PAYMENT
(i)	[***].....	[***] per Amgen Gene Target
(ii)	[***].....	[***] per Amgen Gene Target

(b) CLINICAL MILESTONES. On an Amgen Gene Target-by-Amgen Gene Target basis, within thirty (30) days following the first occurrence or achievement by the performance of Amgen, its Affiliate or Sublicensee of each of the clinical milestones set forth below with respect to the first Product to each Amgen Gene Target, Amgen shall pay to Isis the one-time, non-refundable, non-creditable milestone payment set forth below:

MILESTONE EVENT	MILESTONE PAYMENT
[***]	

(c) NET SALES MILESTONE. On an Amgen Gene Target-by-Amgen Gene Target basis, Amgen shall pay to Isis a one-time, non-refundable, non-creditable milestone payment of [***] upon the first achievement of cumulative Net Sales exceeding [***] of a Product approved for two or more indications, beginning with Net Sales occurring on or after the approval of the second indication. For purposes of this Section 6.3(c), a second (or subsequent) "indication" is defined as an addition to the indication section of the package insert for the Product only after a clinical program separate and distinct from the first clinical program is undertaken. Any such addition to the indication section shall represent a distinct disease category from the previously approved indication (i.e., additions to treat subpopulations within the previously approved indication or new or different treatment regimens for the previously approved indication do not apply).

(d) MILESTONE PAYMENTS. For purposes of clarification, (i) if any of the milestones set forth above in Sections 6.3(b)(i), 6.3(b)(ii) or 6.3(b)(iii) is achieved prior to or in the absence of the achievement of a preceding milestone, then, effective upon achievement of any of such milestones, any previously unpaid milestone shall also become due and payable and (ii) each milestone is payable pursuant to this Section 6.3 on an Amgen Gene Target-by-Amgen Gene Target basis only, and once one milestone has been paid with respect to a particular Amgen Gene Target no additional such milestone shall be paid with respect to such Amgen Gene Target, regardless of the number of Collaboration ASO Compounds, Amgen ASO Compounds and/or Products relative to each Amgen Gene Target which subsequently achieves such milestone event.

6.4 ROYALTIES.

(a) ROYALTIES PAYABLE BY AMGEN. During the Royalty Term of each Product, Amgen shall pay to Isis, on a country-by-country basis, incremental royalties on total annual worldwide Net Sales of each such Product by Amgen, its Affiliates and its Sublicensees at the following rates:

(i) [***] of that portion of total annual Net Sales of each such Product that is less than [***];

(ii) [***] of that portion of total annual Net Sales of each such Product that is greater than or equal to [***] and less than [***]; and

(iii) [***] of that portion of total annual Net Sales of each such Product that is greater than or equal to [***].

(b) ROYALTY TERM. Royalties for sales of any Product shall be paid for a period equal to the Royalty Term for such Product.

(c) [***] LICENSES. Amgen acknowledges that Isis may be obligated to pay royalties under the [***] License and the [***] License with respect to Net Sales of Products and agrees that, in addition to the royalties set forth in Section 6.4(a) above but subject to Section 6.4(e) below, Amgen shall pay to Isis a total of [***] of Net Sales of Products by Amgen, its Affiliates and its Sublicensees, which represents [***] of the total combined royalties payable by Isis under the [***] License and the [***] License with respect to Net Sales of Products by Amgen, its Affiliates and its Sublicensees. Upon the expiration or termination, on a country-by-country basis, of the obligation by Isis to pay royalties (or equivalent payments) to [***] under the [***] License or [***] under the [***] License, Amgen shall have the right to decrease the amount of its quarterly payment under Section 8.1 to Isis by [***] of the amount Amgen would have otherwise paid to Isis for such license in such country. After the expiration of the Royalty Term, Amgen agrees to pay [***] of the total combined royalties payable by Isis under the [***] License and/or the [***] License with respect to Net Sales of each Product for so long as such royalties are due and payable under the [***] License and/or the [***] License. Isis acknowledges and agrees that Isis is solely responsible for any and all obligations that may have accrued or may accrue in the future with respect to the [***] License and the [***] License; PROVIDED, HOWEVER, that Amgen shall be obligated to pay Isis the applicable amount under this

Section 6.4(c) with respect to any sale of a Product that would obligate Isis to make a royalty payment to [***] under the [***] License or to [***] under

the [***] License.

(d) THIRD PARTY LICENSES. If Amgen reasonably determines in its sole discretion, authority and right that one or more licenses (other than the [***] License and the [***] License) to access the intellectual property rights of a Third Party or Parties are required for Amgen, its Affiliates and/or its Sublicensees to research, develop, make, have made, use, import, offer to sell and/or sell, export or otherwise exploit, or transfer physical possession of or title in Collaboration ASO Compounds and/or Amgen ASO Compounds ("THIRD PARTY LICENSE(S)"), then: [***] of any compensation (including, without limitation, up-front payments, milestones and royalties) actually paid by Amgen, its Affiliates and Sublicensees with respect to the sale of any Product containing such Collaboration ASO Compound and/or Amgen ASO Compound under any such Third Party License(s) entered into by Amgen, its Affiliates or Sublicensees shall be creditable against the royalty payments to be paid to Isis by Amgen with respect to the sale of such Product; PROVIDED HOWEVER, that, on a Product-by-Product basis, Isis' royalty rate due under Section 6.4(a) in any given year will not be reduced to less than [***] of Net Sales of such Product as a consequence of any compensation (including, without limitation, up-front payments, milestones and royalties) actually paid by Amgen under any Third Party License(s) being creditable against the royalty payments to be paid to Isis by Amgen; FURTHER PROVIDED HOWEVER, that unused credits in any period may be carried forward against royalties due in future periods.

(e) ELIMINATION OR REDUCTION OF THIRD PARTY ROYALTIES. Isis shall notify Amgen if Isis eliminates or reduces the royalty payments required under the [***] License or the [***] License that may be required in order for Amgen, its Affiliates and/or Sublicensees to develop, make, have made, use, import, offer to sell and/or sell or otherwise export, or transfer physical possession of or title in any Collaboration ASO Compound, Amgen ASO Compound and/or Product. Thereafter, Amgen shall have the option, exercisable upon written notice to Isis, to reduce the amount of royalties payable to Isis with respect to the [***] License and the [***] License pursuant to Section 6.4(c) for any Product by an amount that is equal to the portion of the pass-through royalty payments eliminated or reduced by Isis by paying to Isis an amount equal to [***] of the dollar amount paid by Isis to such Third Party to eliminate or reduce such pass-through royalty. In the event that non-monetary consideration is exchanged between Isis and the Third Party to eliminate or reduce such pass-through royalties, the parties will negotiate in good faith an adequate payment by Amgen to Isis for elimination or reduction of such pass-through royalty to Amgen. If the parties fail to determine an acceptable amount for such a payment by Amgen, or if Amgen does not exercise its option under this Section 6.4(e), then the royalty rate determined in accordance with Sections 6.4(a), (c) and (d) will remain in full force and effect as though Isis had not eliminated or reduced such pass-through royalty with respect to Isis' agreement with such Third Party.

(f) INFLATION. The increments of annual Net Sales tiers set forth in Section 6.4(a)(i)-(iii) and the cumulative Net Sales milestone set forth in Section 6.3(c) shall be adjusted upward on a Calendar Year basis commencing January 1, 2003 (and on January 1 of each year thereafter during the term of this Agreement) by an amount equal to the percentage change, if any, in the Consumer Price Index for the preceding year.

(g) ORAL PREPARATION OR FORMULATION TECHNOLOGY. Any oral preparation or formulation technology, other than oral preparation and formulation technology within Collaboration Know-How or Joint Know-How, that is applicable to Collaboration ASO Compounds and/or Amgen ASO Compounds and is Controlled by Isis or its Affiliates shall be made available to Amgen under the following terms and conditions. The parties will negotiate a license in good faith for use of such technology in connection with the license granted to Amgen in Section 5.1(a)(iii) above, on terms and conditions no less favorable than those made available by Isis to Third Party collaborators of Isis in similar transactions, including reasonable compensation to Isis.

(h) CUMULATIVE ROYALTIES. The obligation under Article 6 to pay royalties on the Net Sales of a Product shall be imposed only once with respect to the same unit of said Product e.g., regardless of the number of claims within Isis Patent Rights which would, but for this Agreement, be infringed by the making, having made, using, selling, leasing, offering to sell or lease, importing, exporting or otherwise exploiting, or transferring physical possession of or title in, said Product in the Field anywhere in the world.

(i) PAID-UP LICENSE. Upon the expiration of Amgen's obligation under this Section 6.4 to pay royalties on Net Sales of a Product in a country, Amgen shall have a fully paid-up, non-exclusive license, with the right to

sublicense, to make, have made, use, sell, lease, offer to sell or lease, import, export or otherwise exploit, transfer physical possession of or otherwise transfer title in such Product in the Field in that country.

(j) NO OTHER COMPENSATION. Other than as explicitly set forth (and as applicable) in this Article 6, and in Sections 4.6 and 13.1(a), Amgen shall not be obligated to pay any additional fees, milestone payments, royalties or any additional payments to Isis under this Agreement.

(k) CROSS LICENSE. In the event that Amgen, in its sole business judgment, shall determine it is necessary to grant a sublicense, or a covenant not to sue under Isis ASO Compound Patent Rights or Joint Patent Rights, to any Third Party in a country in the world in order for Amgen to make, have made, use, sell, lease, offer to sell or lease, or import, export or otherwise exploit, transfer physical possession of or otherwise transfer title in a Product in the Field, and wherein no compensation or consideration other than the cross-licenses is exchanged between Amgen and such Third Party as a result thereof, Amgen shall have the right to grant such sublicense or covenant not to sue to such Third Party solely in connection with Amgen's commercialization of Products. For purposes of this Section 6.4(k), the determination of Net Sales of Products for purposes of calculating the royalties payable by Amgen to Isis under Section 6.4(a) shall not include sales of products (other than Products of Sublicensees) by such Third Party receiving such sublicense or covenant not to sue.

ARTICLE 7

COMPETITION

7.1 COMPETITION. In the event that one or more Competitive ASO Compounds are commercially available in the same country of sale as a Product (hereinafter referred to as

"Competition"), the applicable royalty rates due under Article 6 above shall be reduced by [***], subject to Section 7.3 below.

7.2 COMPETITION CALCULATION. For the purpose of calculating incremental royalties on total annual worldwide Net Sales of said Product, Net Sales of such Product in a country where no Competition exists and Net Sales of such Product in a country where Competition exists shall be allocated among the Net Sales increments [***] on a country by country basis in accordance with the ratios between (i) each of (x) annual Net Sales of such Product in countries where no Competition exists, and (y) annual Net Sales of such Product in countries where Competition exists; and (ii) total annual Net Sales of such Product (i.e., the ratios of (i)(x)/(ii) and (i)(y)/(ii)).

7.3 [***] LICENSES. Notwithstanding Section 7.1 above, Amgen's obligation to pay royalties payable by Isis under the [***] License and the [***] License with respect to Net Sales of each Product in accordance with Section 6.4(c) above remains in effect and shall not be subject to reduction under Section 7.1.

7.4 EXAMPLE CALCULATION. An example royalty calculation is attached hereto as Exhibit E. The parties acknowledge and agree that the example does not contain all possible facts and circumstances that may apply at any given period and that the formulas used in such example may not be the only formulas that can be used to achieve the same result.

ARTICLE 8

PAYMENT; RECORDS; AUDITS

8.1 PAYMENT; REPORTS. Beginning with the Calendar Quarter after the First Commercial Sale of the first Product until the expiration of Amgen's obligation to pay royalties, royalty payments and reports of the sale of Products for each Calendar Quarter will be calculated and delivered to Isis under this Agreement within sixty (60) days of the end of each such Calendar Quarter, unless otherwise specifically provided herein. Notwithstanding the above, Amgen will provide within twenty-five (25) days of the end of each such Calendar Quarter an estimate of royalties due for such Calendar Quarter, such estimate being subject to change between the time reported and the time royalties are paid for such Calendar Quarter. Each payment of royalties will be accompanied by a report of Net Sales of Products in sufficient detail to permit confirmation of the accuracy of the royalty payment made, including, without limitation and on a country-by-country basis, the number of Products sold, the gross sales and Net Sales of Products, the royalties payable (in U.S. dollars),

the method used to calculate the royalty and the exchange rates used. Amgen will keep (and will cause its Affiliates and Sublicensees to keep) complete and accurate records pertaining to the development of Products and the sale or other disposition of Products in sufficient detail to permit Isis to confirm the accuracy of all payments due hereunder.

8.2 EXCHANGE RATE; MANNER AND PLACE OF PAYMENT. All payments hereunder will be payable in U.S. dollars. With respect to each Calendar Quarter, for countries other than the United States, whenever conversion of payments from any foreign currency will be required, such conversion will be made at the average rate of exchange during the Calendar Quarter to which such payments relate, as reported in BLOOMBERG PROFESSIONAL, a service of Bloomberg L.P.

during the royalty period of such Net Sales, or in the event BLOOMBERG PROFESSIONAL is not available then THE WALL STREET JOURNAL, for the currency of the country in which the sale is made. All payments owed under this Agreement will be made by wire transfer in immediately available funds to a bank and account designated in writing by Isis, unless otherwise specified in writing by Isis. If, for reasons beyond the control of Amgen, its Affiliates and/or Sublicensees, Amgen (or its Affiliate or Sublicensee) is unable to convert a foreign currency into United States Dollars in a country where neither Amgen nor its Affiliates or Sublicensees has operations, or is restricted by law, regulation or court order from remitting royalties from any country of sale in which neither Amgen nor its Affiliates or Sublicensees has operations, Amgen shall cause such payment to be made to Isis by deposit to the credit and account of Isis or its designated nominee in any commercial bank designated by Isis in the applicable country. Amgen will deliver to Isis proper evidence of such deposit.

8.3 LATE PAYMENTS. In the event that any payment, including up-front fee, royalty, milestone and research payment, due hereunder is not made when due, the payment will accrue interest from the due date at the rate of [***] per month, PROVIDED HOWEVER, that Isis will provide Amgen written notice of its alleged failure to make such a payment, and no such interest shall accrue if within [***] business days thereafter Amgen makes such payment; AND FURTHER PROVIDED HOWEVER, that in no event shall such rate exceed the maximum legal annual interest rate. The payment of such interest will not limit a party from exercising any other rights it may have as a consequence of the lateness of any payment. In the event that Amgen receives two such notices in a given calendar year, Isis will no longer be obligated to give Amgen written notice for the remainder of that calendar year.

8.4 INCOME TAX WITHHOLDING. If laws, rules or regulations require withholding of income taxes or other taxes imposed upon payments set forth in Article 6, Amgen will make such withholding payments as required and will subtract such withholding payments from the payments set forth in Article 6. Amgen will submit appropriate proof of payment of the withholding taxes to Isis within a reasonable period of time.

8.5 AUDITS.

(a) Amgen will keep complete and accurate records pertaining to the development of Products and the sale or other disposition of Products in sufficient detail to permit Isis to confirm the accuracy of all payments due hereunder, and such records will be open to inspection for three (3) years following the end of the period to which they pertain. Not more than once per year, Isis will have the right to cause an independent, certified public accountant reasonably acceptable to Amgen to audit such records to confirm Net Sales and royalty and other payments for a period covering not more than the preceding three (3) years.

(b) Such audits may be exercised during normal business hours upon reasonable prior written notice to Amgen (but in no event less than a 30-day prior written notice). Isis shall submit an audit plan, including audit scope, to Amgen for Amgen's approval, which shall not be unreasonably withheld, prior to audit implementation.

(c) The independent certified public accountant(s) shall keep confidential any information obtained during such inspection and shall report to Isis only the amounts of Net

Sales and royalties due and payable, but may include, in the event such accountant shall be unable to verify the correctness of any such payment, information relating to why such payment is unverifiable. Amgen shall receive a copy of each such report concurrently with receipt by Isis. In the event that such payment is unverifiable, Amgen and Isis shall use good faith efforts to arrive at an equitable solution. Prompt adjustments will be made by the parties to reflect the results of such audit. Isis shall bear the full cost of such audit unless such audit discloses an underpayment of more than [***] from the amount of the Net Sales or royalties or other payments due under this Agreement. In such case, Amgen shall bear the full cost of such certified public accountant to perform such audit and will promptly remit to Isis the amount of any underpayment. Upon the expiration of three (3) years following the end of any Calendar Year, the calculation of royalties payable with respect to such year shall be binding and conclusive upon Isis, Amgen and its Affiliates and Sublicensees shall be released from any liability or accountability with respect to royalties for such year, and Amgen shall no longer be required to retain such records for such year.

8.6 CONFIDENTIALITY. Isis shall treat all financial information subject to review under Article 8, or under any related sublicense agreement, as Amgen's Confidential Information. Isis shall be responsible for this financial information and shall cause its accounting firm to be bound to obligations of confidentiality at least as restrictive as Isis' obligations of confidentiality in this Agreement.

ARTICLE 9

INTELLECTUAL PROPERTY

9.1 OWNERSHIP OF INVENTIONS. Ownership of inventions shall be determined in accordance with the rules of inventorship under United States patent laws. Isis shall own all Isis Know-How, Collaboration Know-How and all Patent Rights claiming Isis Know-How or Collaboration Know-How. Amgen shall own all Amgen Know-How and all Patent Rights claiming Amgen Know-How. All Joint Know-How and Joint Patent Rights shall be owned jointly by Isis and Amgen.

9.2 PATENT PROSECUTION AND MAINTENANCE.

(a) It is the intention of the parties to secure broad patent protection for inventions. Without limiting the generality of the foregoing, the parties will use reasonable efforts to file patent applications containing Collaboration ASO Compound or Amgen ASO Compound composition of matter claims and claims directed to the use of such Collaboration ASO Compounds or Amgen ASO Compounds separately from patent applications containing claims directed to Isis Standard Chemistry and Isis Standard Chemistry Manufacturing Process.

(b) Isis shall be responsible for the preparation, filing, prosecution, maintenance and defense before all patent offices of all Isis Patent Rights, other than Isis ASO Compound Patent Rights, [***].

(c) Amgen shall be responsible for the preparation, filing, prosecution, maintenance and defense before all patent offices of Isis ASO Compound Patent Rights

exclusively licensed to Amgen pursuant to Section 5.1(a) [***]. Amgen shall have the sole right, but not the obligation, to prepare, file, prosecute, maintain and defend before all patent offices all Amgen Patent Rights [***].

(d) Amgen shall be responsible for the preparation, filing, prosecution, maintenance and defense before all patent offices of Joint Patent Rights using mutually acceptable outside counsel, and shall initially bear the costs, expenses and fees thereof, provided that Amgen shall be entitled to reimbursement by Isis of [***] of such documented costs, expenses and fees within thirty (30) days after presenting a bill to Isis. Amgen will consult with Isis as to the preparation, filing, prosecution, and maintenance of such Joint Patent Rights reasonably prior to any deadline or action with the U.S. Patent & Trademark Office or any foreign patent office, and will furnish to Isis copies of all relevant documents reasonably in advance of such consultation.

(e) The responsible party will keep the other party informed of progress with regard to the preparation, filing, prosecution, maintenance and defense before all patent offices of Isis Patent Rights subject to Sections 9.2(b), 9.2(c) and 9.2(d) that contain a claim which

would otherwise be infringed by the making, having made, using, selling, offering for sale or importing of a Collaboration ASO Compound, Amgen ASO Compound and/or Product being developed or commercialized by Amgen. Each party will consider in good faith the requests and suggestions of the other party with respect to strategies for filing and prosecuting such Patent Rights. In the event that (i) Isis under Section 9.2(b) elects not to prepare, file, prosecute, maintain or defend a patent application claiming an invention which would, but for the licenses granted herein, be infringed by the making, having made, using, selling, offering for sale or importing of a Collaboration ASO Compound, Amgen ASO Compound and/or Product being developed or commercialized by Amgen, or (ii) Amgen under Section 9.2(c) elects to discontinue prosecution, maintenance or defense of any Isis ASO Compound Patent Right claiming the manufacture, use, sale, offer for sale or import of a Product being developed or commercialized by Amgen, or (iii) either party under Section 9.2(d) elects to discontinue sharing expenses with respect to the preparation, filing, prosecution, maintenance and defense of any Joint Patent Rights, such party shall provide reasonable prior written notice to the other party of such intention to discontinue its efforts, and the other party (the "CONTINUING PARTY") shall have the right, at its expense, to prepare, file, prosecute, maintain and defend such Patent Right (the "DISCONTINUED PATENT"). The Continuing Party will own such Discontinued Patent and be solely responsible for all costs associated with the continuing activities described in the preceding sentence; PROVIDED, HOWEVER, that if Amgen is the Continuing Party, [***] of Amgen's reasonable documented costs associated with such continuing activities shall be creditable against the royalty payments to be paid to Isis by Amgen pursuant to Section 6.4(a), unless no such royalty payments are due thereunder with respect to the applicable Product in the applicable territory. Solely with respect to Discontinued Patents under the preceding clauses (i) and (ii) of this Section 9.2(e) (but, for the avoidance of doubt, not under the preceding clause (iii) of this Section 9.2(a)), the non-Continuing Party will have a non-exclusive, perpetual, irrevocable, fully-paid license to continue to practice such Discontinued Patent in the applicable territory where such Discontinued Patent is filed, including the right to sublicense solely in connection with the grant of a license to develop, make, have made, use, sell, offer for sale, have sold and import a product of such non-Continuing Party, except that if Isis is the non-Continuing Party, such license shall exclude the right to develop, make, have made, use, sell, offer for sale, have

sold and import products containing ASO Compounds that selectively modulate expression of an Amgen Gene Target. The non-Continuing Party shall execute such documents and perform such acts as may be reasonably necessary for the Continuing Party to prepare, file, prosecute, maintain or defend any such Discontinued Patent, including assigning ownership of such Discontinued Patent and the invention(s) claimed therein to the Continuing Party.

(f) A decision by a party not to prepare, file, prosecute, maintain or defend any patent application or patent shall not affect any of its rights to practice certain Patent Rights under the licenses granted to the parties in Article 5 of this Agreement; provided however, in the event Isis is the non-Continuing Party, or if Amgen is the non-Continuing Party but Isis does not elect to proceed with preparing, filing, prosecuting, maintaining or defending any such Discontinued Patent, Amgen shall cease to have any obligation to pay royalties to Isis under this Agreement with respect to such Discontinued Patent in respect of Amgen's manufacture, use, sale, offer for sale or import of Products in such territory.

9.3 COOPERATION OF THE PARTIES. Each party agrees to cooperate fully (and to cause any employee, consultant or agent who worked on the Collaboration to cooperate) in the preparation, filing, prosecution and defense of any Patent Rights under this Agreement. Such cooperation includes, but is not limited to:

(a) executing all papers and instruments, or requiring its employees or agents to execute such papers and instruments, so as to effectuate the ownership of inventions set forth in Section 8.1 and Patent Rights claiming such inventions, and to enable the other party to apply for and to prosecute patent applications in any country; and

(b) promptly informing the other party of any matters coming to such party's attention that may affect the preparation, filing, prosecution or defense of any such patent applications.

9.4 INFRINGEMENT BY THIRD PARTIES.

(a) Isis and Amgen will promptly notify the other in writing of any alleged or threatened infringement of any patent included in

the Isis Patent Rights, Amgen Patent Rights or Joint Patent Rights of which they become aware that is likely to have a materially adverse effect on any Product being developed or commercialized by Amgen, its Affiliates or Sublicensees pursuant to a license granted under Section 5.1(a)(iii).

(b) At its own expense and by counsel of its own choice, Amgen shall have the sole right, but not the obligation, to bring and control any action or proceeding, including, without limitation, the right to settle or compromise such proceedings, with respect to infringement of (i) any patent included in the Isis ASO Compound Patent Rights, (ii) any Joint Patent Rights claiming any Amgen Gene Target or any ASO Compound directed thereto, (iii) the Amgen Patent Rights and (iv) any right relating to the Collaboration Know-How, any Joint Know-How directed to an Amgen Gene Target or any ASO Compound directed thereto and the Amgen Know-How. Isis shall cooperate and, if Amgen finds it necessary or desirable, join Amgen as a party in such litigation, including the signing of any necessary legal papers, and shall provide Amgen with data or other information in support thereof, and shall use best efforts to

ensure the cooperation of any of its respective personnel as might reasonably be requested in any such matters.

(c) Amgen shall have the first right, but not the obligation, to bring and control any action or proceeding with respect to infringement of any patent included in the Joint Patent Rights not claiming any Amgen Gene Target or any ASO Compound directed thereto and of any right relating to Joint Know-How not directed to any Amgen Gene Target or any ASO Compound directed thereto, at its own expense and by counsel of its own choice, and Isis shall have the right, at its own expense, to be represented in any such action by counsel of its own choice, and if Amgen fails to bring such an action or proceeding within (i) sixty (60) days following the notice of alleged infringement by or to Isis pursuant to Section 9.4(a) or (ii) ten (10) business days before the time limit, if any, set forth in the appropriate laws and regulations for the filing of such actions, whichever comes first, Isis shall have the right to bring and control any such action at its own expense and by counsel of its own choice, and Amgen shall have the right, at its own expense, to be represented in any such action by counsel of its own choice. The mutual consent of both parties is required before either party has the right to settle or compromise any proceedings with respect to infringement of any patent included in Joint Patent Rights other than Joint Patent Rights claiming any Amgen Gene Target or ASO Compounds directed thereto.

(d) Isis shall have the sole right, but not the obligation, to bring and control any action or proceeding with respect to infringement of any patent included in the Isis Core Technology Patent Rights and Isis Manufacturing Patent Rights and of any right relating to Isis Know-How, at its own expense and by counsel of its own choice; PROVIDED HOWEVER, that with respect to infringement of any Isis Core Technology Patent Right or Isis Manufacturing Patent Right or of any right relating to Isis Know-How that is likely to have a materially adverse effect on any Product being developed or commercialized by Amgen, its Affiliates or Sublicensees pursuant to a license granted under Section 5.1(a)(iii), Amgen shall have the right, at its own expense, to be represented in any such action by counsel of its own choice, and if Isis fails to bring such an action or proceeding within (i) sixty (60) days following the notice of alleged infringement by or to Amgen pursuant to Section 9.4(a) or (ii) ten (10) business days before the time limit, if any, set forth in the appropriate laws and regulations for the filing of such actions, whichever comes first, Amgen shall have the right to bring and control any such action at its own expense and by counsel of its own choice, and Isis shall have the right, at its own expense, to be represented in any such action by counsel of its own choice.

(e) Except as otherwise agreed to by the parties as part of a cost-sharing arrangement, any recovery realized as a result of any such litigation described in Sections 9.4(b), 9.4(c) and 9.4(d) above (after reimbursement of reasonable attorneys' fees and litigation expenses of Isis and Amgen) shall be retained by the party that brought and controlled such litigation for purposes of this Agreement, except that any recovery realized by a party as a result of such litigation, after reimbursement of the parties' reasonable attorneys' fees and litigation expenses, shall, to the extent attributable to lost profits based on sales of Products, be allocated between the parties so as to [***].

9.5 INFRINGEMENT OF THIRD PARTY RIGHTS. Each party will promptly notify the other in writing of any allegation by a Third Party that the activity of either of the parties pursuant to this Agreement infringes or may infringe the intellectual property rights of such Third Party. Other than with respect to any claim for which Amgen has an indemnification obligation under Section 13.1(a), Isis shall have the sole right to control any defense of any such claim involving alleged infringement of Third Party rights by Isis' activities at its own expense and by counsel of its own choice, and Amgen shall have the right, at its own expense, to be represented in any such action by counsel of its own choice. Isis shall not settle any such action in a manner that would materially adversely affect Amgen, without Amgen's prior written consent. Other than with respect to any claim for which Isis has an indemnification obligation under Section 13.1(b), Amgen shall have the sole right to control any defense of any such claim involving alleged infringement of Third Party rights by Amgen's activities or with respect to any claim for which Amgen has an indemnification obligation under Section 13.1(a), at its own expense and by counsel of its own choice, and, solely to the extent such claim is based on any act or failure to act of Isis, Isis shall have the right, at its own expense, to be represented in any such action by counsel of its own choice. Amgen shall not settle any such action in a manner that would materially adversely affect Isis without Isis' prior written consent.

ARTICLE 10

REPRESENTATIONS AND WARRANTIES

10.1 MUTUAL REPRESENTATIONS AND WARRANTIES. Each party represents to the other that:

(a) CORPORATE POWER. It is duly organized and validly existing under the laws of its jurisdiction of incorporation or formation, and has full corporate or other power and authority to enter into this Agreement and to carry out the provisions hereof.

(b) DUE AUTHORIZATION. It is duly authorized to execute and deliver this Agreement and to perform its obligations hereunder, and the person or persons executing this Agreement on its behalf has been duly authorized to do so by all requisite corporate or partnership action.

(c) BINDING AGREEMENT. This Agreement is legally binding upon it, and enforceable in accordance with its terms. The execution, delivery and performance of this Agreement by it does not conflict with any agreement, instrument or understanding, oral or written, to which it is a party or by which it may be bound, nor violate any material law or regulation of any court, governmental body or administrative or other agency having jurisdiction over it. It is not aware of any action, suit, inquiry or investigation contemplated or instituted by any governmental agency which would question or threaten the validity of this Agreement.

(d) COMPLIANCE WITH LAWS. It shall carry out its activities under this Agreement in compliance with any applicable laws including, without limitation, federal, state or local laws, regulations or guidelines governing the work at the site where such work is being conducted. Moreover, it will carry out all work under the Collaboration in accordance with current GLP, good clinical practices and GMP, if applicable based on the specific work to be conducted.

(e) NO DEBARMENT. It shall comply at all times with the provisions of the Generic Drug Enforcement Act of 1992 and will upon request certify in writing to the other party that none of its employees nor any person providing services to it in connection with the Collaboration have been debarred under the provisions of such Act.

(f) NO CONFLICT. It shall not enter into any collaboration with, or render services for, a Third Party whereby such collaboration or service with or for a Third Party will negatively impact the timely accomplishment of the objectives of the Collaboration.

10.2 REPRESENTATIONS, WARRANTIES AND COVENANTS OF ISIS.

(a) GRANT OF RIGHTS. As of the Effective Date and to the best of Isis' knowledge, Isis has sufficient legal and/or beneficial title and ownership under the Isis Technology and Collaboration Know-How as is necessary to fulfill its obligations under this Agreement and to grant the licenses and options to license to Amgen pursuant to this Agreement and Isis has no reason to believe Isis Patents are invalid. As of the Effective Date

Isis has not granted, and shall not during the Term, grant any right, license, consent or privilege to any Third Party or otherwise undertake any action, either directly or indirectly, which would conflict with the rights granted to Amgen or interfere with any obligations of Isis set forth in this Agreement.

(b) MAINTENANCE OF AGREEMENTS; PATENTS. Isis has (or shall have at the time performance is due) maintained and shall maintain and keep in full force and effect all agreements (including license agreements, e.g. the [***] License and the [***] License) and filings (including patent filings) necessary to perform its obligations hereunder. Isis shall not consent to any termination, modification or amendment to the [***] License or [***] License that would adversely affect Amgen's rights under this Agreement, without first obtaining Amgen's prior written consent. As of the Effective Date Isis has not received any notice of default, and to the best of its knowledge is not in default, of its obligations under the [***] License or the [***] License.

(c) ABSENCE OF LITIGATION, INFRINGEMENT, MISAPPROPRIATION. As of the Effective Date and to the best of Isis' knowledge, there is no pending or threatened litigation and Isis has not received any communication relating thereto which alleges that Isis' activities with ASO Compounds or under this Agreement would infringe or misappropriate any intellectual property rights of any Third Party. To the best of Isis' knowledge, there is no material unauthorized use, infringement or misappropriation of any of its intellectual property rights that Isis believes is or would be likely to compete with the development or commercialization of Products hereunder.

(d) FULL DISCLOSURE. As of the Effective Date and to the best of Isis' knowledge, Isis has provided Amgen with all information that Amgen has requested for deciding the merits of entering into this Agreement including, without limitation, all information that Amgen has requested concerning Isis Standard Chemistry and Isis Standard Chemistry Manufacturing Process, and all such provided information is true and not misleading.

(e) EXHIBITS. Isis has exercised best efforts in ensuring that Exhibit D accurately lists, via one representative member, all relevant patent families (i.e., all patents

and/or applications which claim priority from a common patent application) included within Isis Patent Rights as of the Effective Date and, in the event it learns that any Patent Rights disclosed in Exhibit D are inaccurate (or that the list of patent families is incomplete), then it shall promptly correct or complete such list of Patent Rights disclosed in Exhibit D. It is understood that Exhibit D merely lists one representative member of each of the patent families set forth in Exhibit D and that Exhibit D in no way limits the licenses granted to Amgen in Article 5.

10.3 DISCLAIMER. EXCEPT AS EXPRESSLY SET FORTH IN THIS AGREEMENT, NEITHER PARTY MAKES ANY REPRESENTATION OR WARRANTY TO THE OTHER PARTY OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING, WITHOUT LIMITATION, ANY PURPOSE. Without limiting the generality of the foregoing, except as expressly set forth in this Agreement, each party expressly does not warrant (i) the success of any research, study or test commenced under the Collaboration or (ii) the safety or usefulness for any purpose of the technology it provides hereunder.

10.4 LIMITATION OF LIABILITY. NEITHER PARTY SHALL BE ENTITLED TO RECOVER FROM THE OTHER PARTY ANY INDIRECT, SPECIAL, INCIDENTAL, CONSEQUENTIAL OR PUNITIVE DAMAGES IN CONNECTION WITH THIS AGREEMENT OR ANY LICENSE GRANTED HEREUNDER.

ARTICLE 11

CONFIDENTIALITY; PUBLICATION

11.1 CONFIDENTIALITY.

(a) Except to the extent expressly authorized by this Agreement or otherwise agreed in writing by the parties, the parties agree that, during the Term and for five (5) years thereafter, the receiving party will keep the other party's Confidential Information confidential and will not publish or otherwise disclose such Confidential Information and will not use such Confidential Information for any purpose other than as expressly provided for in this Agreement. Each party may use the other party's Confidential Information only to the extent required to accomplish the purposes of this Agreement. Each party will use at least the same standard of care as it uses to protect proprietary or confidential information of its own

to ensure that its directors, employees, agents, consultants, other representatives, Affiliates and Sublicensees do not disclose or make any unauthorized use of the Confidential Information. Each party will promptly notify the other upon discovery of any unauthorized use or disclosure of the Confidential Information.

(b) Notwithstanding anything to the contrary in this Agreement, for purposes of this Agreement (i) Isis Know-How and all oral or written communications regarding Isis Know-How are, and shall be, the Confidential Information of Isis; (ii) Amgen Know-How and all oral or written communications regarding Amgen Know-How are, and shall be, the Confidential Information of Amgen; (iii) Collaboration Know-How and all oral or written communications regarding Collaboration Know-How are, and shall be, the Confidential Information of Amgen; (iv) Joint Know-How (directed to any Amgen Gene Target or any ASO Compound directed thereto) and all oral or written communications regarding such Joint Know-How are, and shall be, the Confidential Information of Amgen; and (v) Joint Know-How beyond the scope of any of the Amgen Gene Targets or ASO Compounds directed thereto and all oral or written communications regarding such Joint Know-

How are, and shall be, the Confidential Information of Amgen and Isis.

11.2 AUTHORIZED DISCLOSURE. Each party, unless otherwise specified below, may disclose Confidential Information belonging to the other party to the extent such disclosure is reasonably necessary in the following instances:

(a) filing or prosecuting patents relating to the Collaboration pursuant to Section 9.2;

(b) obtaining copyright protection with respect to proprietary algorithms and software code;

(c) prosecuting or defending litigation as expressly permitted under this Agreement;

(d) complying with applicable court orders or governmental regulations;

(e) (solely with respect to Amgen unless Isis undertakes development and commercialization activities in accordance with Sections 12.5(b) and 12.6(a)) conducting research, development, regulatory activities (including making Regulatory Filings), manufacturing or sales and marketing with respect to Collaboration ASO Compounds, Amgen ASO Compounds or Products as permitted by this Agreement; and

(f) disclosure to other Third Parties in connection with due diligence or similar investigations by such Third Parties, in each case who agree to be bound by similar terms of confidentiality and non-use at least equivalent in scope to those set forth in this Article 11.

Notwithstanding the foregoing, with respect to the authorized disclosures under Sections 11.2(c) and (d) in the event a party is required to make a disclosure of the other party's Confidential Information, it will, except where impracticable, give reasonable advance notice to the other party of such disclosure and use efforts to secure confidential treatment of such information at least as diligent as such party would use to protect its own confidential information, but in no event less than reasonable efforts. In any event, the parties agree to take all reasonable action to avoid disclosure of Confidential Information hereunder.

11.3 PUBLICATIONS. Amgen shall have the sole right, either directly or indirectly, to publish scientific results and other related information of work conducted with respect to Amgen Gene Targets, Collaboration ASO Compounds, Amgen ASO Compounds and/or Products directed thereto pursuant to this Agreement. Before any such paper is submitted for publication, Amgen will deliver a complete copy to Isis at least thirty (30) days prior to submitting the paper to a publisher. Isis will have the right to review any such paper and give its comments to Amgen within thirty (30) days of the delivery of such paper to Isis. With respect to oral presentation materials and abstracts, Isis will make reasonable efforts to expedite review of such materials and abstracts, and will return such items as soon as practicable to Amgen with appropriate comments, if any, but in no event later than thirty (30) days from the date of delivery to Isis. It is

understood and agreed that failure by Isis to notify Amgen within such thirty (30) day period shall be deemed consent by Isis to such publication. Amgen will comply with Isis's request to delete references to Isis' Confidential Information in any such paper and agrees to withhold publication of same for an additional thirty (30) days in order to permit the parties to obtain patent protection, if either of the parties deems it necessary, in accordance with the terms of this Agreement. Any such publication will include recognition of the contributions of Isis according to standard practice for assigning scientific credit, either through authorship or acknowledgment, as may be appropriate. Other than as explicitly set forth above, while each party to this Agreement recognizes that the publication of results of and other information regarding the Collaboration may be beneficial, each party shall have the right to review and approve any proposed publication by the other party, including papers, oral presentations and abstracts, which utilizes data generated from the Collaboration (it being acknowledged that pursuant to Section 4.9(i) Isis shall not generate information relating to Amgen Gene Targets or ASO Compounds directed thereto outside the Collaboration) and/or includes Confidential Information of the other party.

11.4 PUBLICITY. Neither party to this Agreement may release any information to any Third Party regarding the terms and existence of this Agreement or the reasons for any termination hereof, without prior written consent of the other party; PROVIDED HOWEVER, that (a) a party may disclose the terms or conditions of this Agreement on a need-to-know basis to its directors, employees, agents, consultants and other representatives (including legal and financial advisors), Affiliates and Sublicensees to the extent such disclosure is reasonably necessary in connection with such party's activities as expressly permitted by this Agreement and is in confidence under terms and conditions at least as restrictive as set forth in this Agreement, and (b) either party may disclose the terms and conditions of this Agreement to Third Parties in connection with due diligence or similar investigations by such Third Parties, in each case who agree to be bound by similar terms of confidentiality and non-use at least as restrictive as set forth in this Agreement. Without limitation, this prohibition applies to press releases, educational and scientific conferences, quarterly investor updates, promotional materials, governmental filings and discussions with public officials, the media, security analysts and investors. However, this provision does not apply to any disclosures regarding this Agreement or related information to regulatory agencies such as the FDA or Federal Trade Commission and/or Department of Justice for such disclosures which may be required by law, including requests for a copy of this Agreement or related information by tax authorities; PROVIDED HOWEVER, if any party to this Agreement determines that a release to such a regulatory agency of information regarding the existence or terms of this Agreement is required by law (including releases as may be required to be filed through the Securities and Exchange Commission or other government agency), that party will notify the other party as soon as practicable and give as much detail as possible in relation to the disclosure required. The parties will then cooperate with respect to determining what information should actually be released, including which terms of the Agreement shall be redacted in SEC filings. The parties hereby agree that release of a press release upon complete execution of this Agreement is appropriate and such press release shall be mutually agreed upon by the parties. In addition, following the initial joint press release announcing this Agreement, either party will be free to disclose, without the other party's prior written consent, the existence of this Agreement, the identity of the other party and those terms of the Agreement which have already been publicly disclosed in accordance herewith.

11.5 USE OF NAMES, LOGOS OR SYMBOLS. Subject to Section 11.4, no party hereto shall use the name, trademarks, logos, physical likeness, employee names or owner symbol of any other party for any purpose, including, without limitation, private or public securities placements, without the prior written consent of the affected party, such consent not to be unreasonably withheld or delayed so long as such use of name is limited to objective statement of fact rather than for endorsement purposes. Nothing contained in this Agreement shall be construed as granting either party any rights or license to use any of the other party's trademarks or trade names or the names of any employees thereof, without separate, express written permission of the owner of such trademark or trade name or name.

ARTICLE 12

12.1 TERM. The term of the Collaboration shall commence on the Effective Date and continue until expiration of the Collaboration Term, unless earlier terminated pursuant to Section 12.2, 12.3 or 15.9 or extended by mutual agreement of the parties. The term of this Agreement (the "TERM") shall commence on the Effective Date and continue until the expiration of the obligation by Amgen under Section 6.4 to pay royalties for all Products, unless earlier terminated pursuant to Section 12.2, 12.3 or 15.9 or extended upon terms mutually agreeable to both parties.

12.2 TERMINATION AT AMGEN'S ELECTION. Amgen shall have the right to elect at any time to discontinue any or all activities relating to the research, development or commercialization of any Amgen Gene Target and Products directed thereto, or to terminate this Agreement in its entirety, by providing 60 days' written notice (except as set forth in Sections 4.3(b) and 4.4(b)), to Isis setting forth Amgen's election; PROVIDED HOWEVER, notwithstanding the above in the event (i) Amgen desires to terminate the Collaboration during Level 1 Research, such notice shall take effect immediately; or (ii) Amgen desires to terminate the Collaboration during Level 2 Research conducted in accordance with Section 4.4(a), Amgen shall provide Isis with one hundred eighty (180) days prior written notice.

12.3 TERMINATION FOR CAUSE.

(a) In the event any material representation or warranty made hereunder by a party shall have been untrue in any material respect ("REPRESENTATION DEFAULT"), or upon or after the material breach of any material provision of this Agreement by a party ("PERFORMANCE DEFAULT"), the party not in default ("NON-DEFAULTING PARTY") must first give the other party ("DEFAULTING PARTY") written notice thereof ("NOTICE OF DEFAULT"), which notice must state the nature of the Representation Default or Performance Default in reasonable detail and must request the Defaulting Party cure such Representation Default or Performance Default within sixty (60) days. If the Defaulting Party shall dispute the existence, extent or nature of any default set forth in a Notice of Default, the parties shall use good faith efforts to resolve the dispute in accordance with the procedures set forth in Section 14.2.

(b) In the event of a Representation Default by Amgen that shall not have been cured within the period set forth above after Notice of Default has been given, Isis (in addition to any other remedies which may be available at law or equity), at its option, may

terminate this Agreement in its entirety. Prior to the completion of Level 2 Research with respect to any Amgen Gene Target, in the event of a Performance Default by Amgen that shall not have been cured within the period set forth above after Notice of Default has been given, Isis (in addition to any other remedies which may be available at law or equity), at its option, may terminate this Agreement either as to a particular Amgen Gene Target if such Performance Default relates specifically to such Amgen Gene Target or in its entirety if such Performance Default is not specific to any Amgen Gene Target. Upon or after completion of Level 2 Research with respect to any particular Amgen Gene Target, in the event of a Performance Default not specific to any Amgen Gene Target that shall not have been cured within the period set forth above after Notice of Default has been given, Isis shall no longer be entitled to terminate the Agreement in its entirety but, at its option, may terminate this Agreement as to the other Amgen Gene Targets for which Level 2 Research is not yet completed. Upon or after the completion of Level 2 Research with respect to any Amgen Gene Target, in the event of a Performance Default by Amgen regarding Amgen's obligations to pay fees, milestone payments or royalties hereunder or for failure to meet its obligations under Section 4.5(c) with respect to such particular Amgen Gene Target that shall not have been cured within the period set forth above after Notice of Default has been given, Isis (in addition to any other remedies which may be available at law or equity), at its option, may terminate this Agreement as to the applicable Amgen Gene Target; PROVIDED HOWEVER, that all other rights and obligations of the parties, including all rights and obligations with respect to the other Amgen Gene Targets, under this Agreement shall remain in full force and effect. Upon or after the completion of Level 2 Research with respect to any Amgen Gene Target, in the event of a Performance Default by Amgen other than regarding Amgen's obligations to pay fees, milestone payments or royalties hereunder or for failure to meet its obligations under Section 4.5(c) with respect to such particular Amgen Gene Target, Isis shall only be entitled to seek legal remedies, but shall not be entitled to seek termination of this Agreement, and all of Amgen's rights and

obligations under this Agreement shall remain in full force and effect.

(c) In the event of a Representation Default or a Performance Default by Isis that shall not have been cured within the period set forth above after a Notice of Default has been given, Amgen (in addition to any other remedies which may be available at law or equity), at its option, may (i) maintain this Agreement and seek remedies pursuant to Section 12.3(d) or (ii) terminate this Agreement.

(d) Upon material breach by a party of its obligations hereunder, if the non-breaching party decides not to or does not have the right to terminate this Agreement, such non-breaching party shall have the right to offset any costs it may incur as a result of curing such breach against the amounts then or in the future payable to the breaching party for the performance of such obligations. In the event that either party resorts to any legal action to pursue its legal remedies as described in Sections 12.4(b) and 12.4(c) above, the prevailing party in such action shall be entitled to recover reasonable attorneys' fees and litigation expenses which that party may incur as a result thereof.

12.4 TERMINATION OF COLLABORATION UPON CHANGE OF CONTROL OF ISIS. In the event of a Change of Control of Isis, Isis shall notify Amgen of such Change of Control specifying the effective date thereof and the name(s) of the acquiring Third Party(ies). Amgen shall have the

right to terminate the Collaboration at any time within sixty (60) days following such Change of Control, effective upon thirty (30) days written notice to Isis.

12.5 EFFECT OF TERMINATION OF COLLABORATION WITH RESPECT TO AN AMGEN GENE TARGET.

(a) Upon expiration or termination of the Collaboration with respect to an Amgen Gene Target (i) by Amgen pursuant to Section 12.2, (ii) by Isis pursuant to Section 12.3(b) or Section 15.9, prior to the completion of Level 2 Research with respect to such Amgen Gene Target, or (iii) by the occurrence of one of the events described in the last sentence of Section 4.3(b) or Section 4.4(b), then, in any such case, all rights and obligations in the following Sections shall terminate solely with respect to such Amgen Gene Target and Collaboration ASO Compounds, Amgen ASO Compounds and Products directed thereto:

Section 3.4 (Research Reports);
Section 4.3 (Level 1 Research);
Section 4.4 (Level 2 Research);
Section 4.5 (Further Research, Development and Commercialization);
Section 4.6 (Research Supply of Collaboration ASO Compounds);
Section 4.7 (Clinical Supply of Collaboration ASO Compounds and Amgen ASO Compounds);
Section 4.8 (GeneTrove Database), except that Isis shall be prohibited from including information regarding such Amgen Gene Target that was either provided by Amgen or developed during the Collaboration;
Section 4.9 (Target Exclusivity);
Section 5.1 (License Grants), except for the license granted in Section 5.1(a)(ii);
Section 6.2 (Research Funding) provided that Amgen shall not be entitled to any refund of amounts paid under this section prior to such termination, nor shall Amgen be released from its obligation to pay amounts accrued under this section prior to such termination;
Section 6.3 (Milestone Payments);
Section 6.4 (Royalties);
Section 8.1 (Payment; Reports);
Section 9.2 (Patent Prosecution and Maintenance);
Section 9.4 (Infringement by Third Parties);
Section 11.3 (Publications), solely with respect to the first sentence thereof.

(b) Upon the expiration or termination of the Collaboration with respect to an Amgen Gene Target as contemplated by Section 12.5(a), (i) any sublicenses granted hereunder by Amgen shall remain in effect, but shall be assigned to Isis where permitted by the agreement with such Sublicensee; and (ii) within sixty (60) days following any such termination, Isis may provide Amgen with written notice that Isis wishes to obtain an exclusive (even as to Amgen), worldwide, royalty-bearing license under the Amgen Patent Rights and Amgen Know-How (limited to that which has been provided to Isis) and Amgen's interest in the Joint Patent Rights and Joint Know-How to research, develop, make, have made, use, sell, offer for sale, have sold,

import, export or otherwise exploit or transfer physical possession of or title in, Collaboration ASO Compounds, Amgen ASO Compounds and Products directed to such Amgen Gene Target, in which event the parties will negotiate in good faith commercially reasonable terms for such license for up to [***] days, at which time Amgen shall be free to dispose of such rights, subject to Section 12.5(e). Such terms would include, without limitation, the transfer by Amgen to Isis

of material aspects of Information relating to preclinical studies, clinical trials, rights to all Regulatory Filings and Regulatory Approvals with respect to Collaboration ASO Compounds, Amgen ASO Compounds and Products directed to such Amgen Gene Target and all drug dossiers and master files with respect thereto, for all of which Amgen will be reasonably compensated.

(c) Upon termination of the Collaboration with respect to an Amgen Gene Target at any time by Amgen pursuant to Section 12.3(c), Section 12.4 or Section 15.9: (i) the licenses and other rights granted by Amgen to Isis under Section 5.1(b)(i) shall automatically terminate and revert to Amgen solely with respect to such Amgen Gene Target; and (ii) the licenses granted by Isis to Amgen under Section 5.1(a) shall remain in effect in accordance with their terms, subject to compliance by Amgen with all applicable provisions of this Agreement (including, without limitation, the payment obligations set forth in Article 6) and (iii) all rights and obligations in the following Sections shall terminate solely with respect to such Amgen Gene Target and Collaboration ASO Compounds, Amgen ASO Compounds and Products directed thereto:

Section 4.3 (Level 1 Research);
Section 4.4 (Level 2 Research);
Section 4.6 (Research Supply of Collaboration ASO Compounds);
Section 4.7 (Clinical Supply of Collaboration ASO Compounds and Amgen ASO Compounds);
Section 6.2 (Research Funding), provided that Amgen shall not be entitled to any refund of amounts paid under this section prior to such termination, nor shall Amgen be released from its obligation to pay amounts accrued under this section prior to such termination.

In the event Amgen shall terminate the Collaboration with respect to any Amgen Gene Target during Level 2 Research conducted in accordance with Section 4.4(a) and funded under Section 6.2, Isis shall neither increase the number of FTEs nor make any additional purchases (e.g., materials, supplies, equipment, chemicals or reagents) and shall take reasonable steps to mitigate FTE costs and expenses with respect to such Amgen Gene Target after such notice from Amgen has been given. All payments made by Amgen shall be subject to an accounting of Collaboration activities as set forth in Section 6.2; provided, however, that in no event will Amgen be responsible for any costs and expenses in excess of those Amgen would otherwise have been responsible for under Section 6.2 had Amgen not elected to terminate (subject to Section 12.7).

(d) Within sixty (60) days following the termination of Amgen's license right as to all Products relating to an Amgen Gene Target pursuant to Sections 12.5(a) or 12.5(c), except to the extent and for so long as Isis obtains a license under Section 12.5(b), Isis shall destroy Amgen's Materials and Information relating to such Amgen Gene Target in its possession, other than one (1) archival copy of Amgen's Information which may be retained for the sole purpose of determining its obligations hereunder.

(e) Except for those rights and obligations explicitly terminated as set forth in this Section 12.5, all rights and obligations under this Agreement shall remain in full force and effect.

12.6 EFFECT OF TERMINATION OF AGREEMENT IN ITS ENTIRETY.

(a) Upon termination of this Agreement by Amgen pursuant to Section 12.2, or by Isis pursuant to Section 12.3(b) or Section 15.9: (i) all licenses granted by either party to the other under Article 5, except for the licenses granted in Sections 5.1(a)(ii) and 5.1(b)(ii), shall automatically terminate (subject to the transition period under Section 12.7) and revert to the granting party; (ii) any sublicenses granted hereunder by Amgen shall remain in effect, but shall be assigned to Isis where permitted by the agreement with such Sublicensee; and (iii) within sixty (60) days following any such

termination, Isis may provide Amgen with written notice that Isis wishes to obtain an exclusive (even as to Amgen), worldwide, royalty-bearing license under the Amgen Patent Rights and Amgen Know-How (limited to that which has been provided to Isis) and Amgen's interest in the Joint Patent Rights and Joint Know-How to research, develop, make, have made, use, sell, offer for sale, have sold, import, export or otherwise exploit or transfer physical possession of or title in, Collaboration ASO Compounds, Amgen ASO Compounds and Products directed to Amgen Gene Targets, in which event the parties will negotiate in good faith commercially reasonable terms for such license for up to [***] days, at which time Amgen shall be free to dispose of such rights, subject to Section 12.6(c). Such terms would include, without limitation, the transfer by Amgen to Isis of material aspects of Information relating to preclinical studies, clinical trials, rights to all Regulatory Filings and Regulatory Approvals with respect to Collaboration ASO Compounds, Amgen ASO Compounds and Products directed to such Amgen Gene Targets and all drug dossiers and master files with respect thereto, for all of which Amgen will be reasonably compensated.

(b) Upon termination of this Agreement by Amgen pursuant to Section 12.3(c) or Section 15.9: (i) the licenses and other rights granted by Amgen to Isis under Article 5 shall automatically terminate and revert to Amgen; and (ii) the licenses granted by Isis to Amgen under Sections 5.1(a)(ii) and 5.1(a)(iii) shall remain in effect in accordance with its terms, subject to compliance by Amgen with all applicable provisions of this Agreement (including, without limitation, Section 4.5 and the payment obligations set forth in Article 6).

(c) In addition to the rights and obligations surviving under Sections 12.6(a) and 12.6(b), the obligations and rights of the parties under the following provisions of this Agreement shall survive expiration or termination of this Agreement:

Section 5.1(a)(ii) (Internal Use License)
Section 6.4(i) (Paid-Up License), except in the case of termination of this Agreement by Isis pursuant to Section 12.3(b)
Section 8.5 (Audits)
Section 9.1 (Ownership of Inventions)
Section 10.3 (Disclaimer)
Section 10.4 (Limitation of Liability)
Section 11.1 (Confidentiality)
Section 11.2 (Authorized Disclosure)
Section 11.3 (Publications), excluding the first sentence thereof in the case of termination of this Agreement by Isis pursuant to Section 12.3(b)
Section 11.4 (Publicity)
Section 11.5 (Use of Names, Logos or Symbols)

Section 12.6 (Effect of Termination of the Agreement in its Entirety; Surviving Obligations), including the provisions therein that are contemplated to continue following termination
Section 12.7 (Transition)
Section 12.9 (Exercise of Right to Terminate)
Section 12.10 (Damages; Relief)
Article 13 (Indemnification)
Article 14 (Dispute Resolution)
Article 15 (General Provisions)

(d) Within thirty (30) days following the expiration or termination of this Agreement, except to the extent and for so long as Isis obtains a license under Section 12.6(a), Isis shall destroy any and all Information and Materials of Amgen in its possession, other than one (1) archival copy of Amgen's Information which may be retained for the sole purpose of determining its obligations hereunder

(e) Except for those rights and obligations explicitly surviving expiration or termination, pursuant to this Section 12.6, all rights and obligations under this Agreement shall be terminated.

12.7 TRANSITION.

(a) During any sixty (60) day period after notice of termination has been given other than during Level 2 Research pursuant to Section 12.2, each party shall assist (and be responsible for its own expenses)

in the transition of affairs in a timely, reasonable and businesslike manner. During any such one hundred eighty (180) day period after notice of termination has been given during Level 2 Research pursuant to Section 12.2, each party shall assist (and be responsible for its own expenses) in the transition of affairs in a timely, reasonable and businesslike manner.

(b) During any sixty (60) day period after a Notice of Default has been given under Section 12.3 for which termination of this Agreement, in whole or in part, is a remedy, all of Amgen's rights and obligations under the affected parts of this Agreement, including but not limited to development, marketing, manufacturing, supply, and payment of fees and royalties, shall (to the extent applicable) remain in force and effect. After such first sixty (60) day period and in the event of any termination of rights under this Agreement, each party shall assist (and be responsible for its own expenses) in the transition of affairs in a timely, reasonable and businesslike manner, not to exceed an additional period of sixty (60) days; PROVIDED HOWEVER, that after such additional sixty (60) day period Amgen shall not be responsible for any further costs and expenses of any kind with respect to such transition.

(c) Should Isis provide Amgen with written notice that Isis wishes to obtain an exclusive license from Amgen to Collaboration ASO Compound(s), Amgen ASO Compound(s) and Products directed to any of the Amgen Gene Targets in accordance with Sections 12.5(b) or 12.6(a), and upon Amgen's approval, Isis shall be responsible for further costs and expenses incurred by Amgen in connection with the transition of affairs to Isis with respect to such Collaboration ASO Compound(s), Amgen ASO Compound(s) and Products, only

to the extent and for so long as the parties are negotiating or have entered into the license agreement.

12.8 PRODUCT SALES AFTER TERMINATION. Expiration or termination of this Agreement in whole or part shall not relieve the parties of any obligation accruing prior to such expiration or termination. Upon termination of this Agreement in its entirety or otherwise with respect to a particular Amgen Gene Target and Collaboration ASO Compounds, Amgen ASO Compounds and Products directed thereto in accordance with this Article 12, Amgen, its Affiliates and its Sublicensees shall thereupon have the right to sell that amount of Product(s) that Amgen, its Affiliates and its Sublicensees then have on hand, PROVIDED HOWEVER, that with respect to any Product for which a royalty is due under Article 6.4, Amgen shall pay the royalties thereon at the time provided for.

12.9 EXERCISE OF RIGHT TO TERMINATE. The lawful use by either party hereto of a termination right provided for under this Agreement will not give rise to the payment of damages or any other form of compensation or relief to the other party with respect thereto.

12.10 DAMAGES; RELIEF. Subject to Section 12.8 above, termination of this Agreement will not preclude either party from claiming any other damages, compensation or relief that it may be entitled to upon such termination as expressly set forth in this Agreement.

12.11 RIGHTS IN BANKRUPTCY. All rights and licenses granted under or pursuant to this Agreement by Isis or Amgen are, and shall otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code, licenses of right to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code. The parties agree that the parties, as licensees of such rights under this Agreement, shall retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code including, without limitation, Amgen's right to retain all licenses to Isis Technology, Collaboration Know-How, Joint Know-How, Joint Patent Rights, Manufacturing Improvements and Patent Rights that claim Manufacturing Improvements granted herein, subject to payments when due to Isis of all fees, milestone payments and royalties on Product(s). The parties further agree that, in the event of the commencement of a bankruptcy proceeding by or against either party under the U.S. Bankruptcy Code, the party hereto that is not a party to such proceeding shall be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, and same, if not already in their possession, shall be promptly delivered to them (i) upon any such commencement of a bankruptcy proceeding upon their written request therefor, unless the party subject to such proceeding elects to continue to perform all of its obligations under this Agreement, or (ii) if not delivered under (i) above, following the rejection of this Agreement by or on behalf of the party subject to such proceeding upon written request therefor by the non-subject party.

ARTICLE 13

INDEMNIFICATION

13.1 INDEMNIFICATION.

(a) During the Term and for a period of ten (10) years after the Term, Amgen hereby agrees to save, defend, indemnify and hold harmless Isis and its officers, directors, employees, consultants and agents from and against any and all losses, damages, liabilities, expenses and costs, including reasonable legal expenses and attorneys' fees ("LOSSES"), to which Isis may become subject as a result of any claim, demand, action or other proceeding by any Third Party to the extent such Losses arise directly or indirectly out of: (a) the breach of any representation or warranty made by Amgen pursuant to Article 10; (b) any material breach of this Agreement by Amgen; (c) the practice by Amgen of any license granted hereunder (other than with respect to any claims by [***] or [***] with respect to the subject matter of the [***] License and the [***] License); (d) the development, manufacture, use, handling, storage, sale or other disposition of any Collaboration ASO Compound, Amgen ASO Compound or Product by Amgen, its Affiliates or Sublicensees; (e) any Third Party claim that either party's use of an Amgen Gene Target infringes the intellectual property rights of such Third Party; or (f) violation of the trade secrets of any Third Party by Amgen; except, in each case, to the extent such Losses result from the gross negligence or willful misconduct of Isis or from the breach of any representation or warranty hereunder by Isis.

(b) During the Term and for a period of ten (10) years after the Term, Isis hereby agrees to save, defend, indemnify and hold harmless Amgen and its officers, directors, employees, consultants and agents from and against any and all Losses to which Amgen may become subject as a result of any claim, demand, action or other proceeding by any Third Party to the extent such Losses arise directly or indirectly out of: (a) the breach of any representation or warranty made by Isis pursuant to Article 10; (b) any material breach of this Agreement by Isis; (c) the practice by Isis of any license granted hereunder; (d) the development, manufacture, use, handling, storage, sale or other disposition of any product by Isis, its Affiliates or sublicensees; or (e) violation of the trade secrets of any Third Party by Isis; except, in each case, to the extent such Losses result from the gross negligence or willful misconduct of Amgen or from the breach of any representation or warranty hereunder by Amgen.

13.2 CONTROL OF DEFENSE. In the event a party (the "INDEMNIFIED PARTY") seeks indemnification under Section 13.1, it will inform the other party (the "INDEMNIFYING PARTY") of a claim as soon as reasonably practicable after it receives notice of the claim, it will permit the Indemnifying Party to assume direction and control of the defense of the claim (including the right to settle the claim solely for monetary consideration), and will cooperate as requested (at the expense of the Indemnifying Party) in the defense of the claim; PROVIDED HOWEVER, that the Indemnified Party shall have the right to retain its own counsel, with the fees and expenses to be paid by the Indemnified Party, if representation of such Indemnified Party by the counsel retained by the Indemnifying Party would be inappropriate due to actual or potential differing interests between such Indemnified Party and any other party represented by such counsel in such proceedings. The indemnity obligation in this Article 13 shall not apply to amounts paid in settlement of any loss, liability, damage, expense, claim, demand, action or other proceeding by

the Indemnified Party if such settlement shall be effected without the consent of the Indemnifying Party, which consent shall not be unreasonably withheld. The failure by the Indemnified Party to deliver notice to the Indemnifying Party within a reasonable time after commencement of any such action, if prejudicial to its ability to defend such action, shall relieve such Indemnifying Party of any liability to the Indemnified Party under this Section 13.2, but the omission to deliver notice to the Indemnifying Party will not relieve the Indemnifying Party of any liability that it may have to the Indemnified Party other than under this Section 13.2. The Indemnified Party under Section 13.2 and its employees and agents shall cooperate reasonably with the Indemnifying Party and its legal representatives in the

investigation of any action, claim or liability covered by this indemnification.

13.3 INSURANCE. Each party, at its own expense, will maintain product liability insurance (or self-insure) in an amount consistent with industry standards during the Term and will name the other party as an additional insured with respect to such insurance. Each party will provide the other party with a certificate of insurance (or evidence of self-insurance) evidencing such coverage.

ARTICLE 14

DISPUTE RESOLUTION

14.1 DISPUTES. Isis and Amgen shall deal with each other in good faith. The parties recognize that disputes as to certain matters may from time to time arise which relate to either party's rights and/or obligations hereunder. It is the objective of the parties to establish procedures to facilitate the resolution of such disputes in an expedient manner by mutual cooperation and without resort to litigation. To accomplish this objective, the parties agree to follow the procedures set forth in Section 14.2, if and when such a dispute arises between the parties.

14.2 PROCEDURES; DISCUSSIONS BETWEEN THE PARTIES. If any claim, dispute or controversy of whatever nature arises out of or relating to this Agreement including, without limitation, any action or claim based on tort, contract or statute (including any claims of breach or violation of statutory or common law protections from discrimination, harassment and hostile working environment), or concerning the interpretation, effect, termination, validity, performance and/or breach of this Agreement ("CLAIM"), arises between the parties and the parties cannot resolve the dispute within thirty (30) days after written notice of a Claim by a party, at the written request by either party to the other party, the parties agree to hold a meeting, attended by the Chief Executive Officer of Isis and the Executive Vice President, R&D or another Amgen officer appointed by the Executive Vice President, R&D of Amgen, to attempt in good faith to negotiate a resolution of the dispute prior to pursuing other available remedies. If, within thirty (30) days after such written request, the parties have not succeeded in negotiating a resolution of the dispute, such dispute may be resolved by litigation. Notwithstanding the foregoing, either party may at any time make a claim for temporary or immediate equitable relief without following the foregoing procedure.

ARTICLE 15

GENERAL PROVISIONS

15.1 GOVERNING LAW. This Agreement shall be governed by, and construed and enforced in accordance with, the laws of the State of California, excluding its conflicts of laws principles.

15.2 ENTIRE AGREEMENT; MODIFICATION. This Agreement is both a final expression of the parties' agreement and a complete and exclusive statement with respect to all of its terms. The Exhibits referred to in this Agreement are incorporated herein and made a part of this Agreement by this reference. This Agreement supersedes all prior and contemporaneous agreements and communications, whether oral, written or otherwise, concerning any and all matters contained herein; on the Effective Date, the Mutual Confidential Disclosure Agreement, effective September 12, 2001 (Amgen Reference No. 20017105) is hereby superseded, provided that all Confidential Information disclosed in such Non-Disclosure Agreement shall be treated as if disclosed under, and shall be subject to the terms of, this Agreement. No rights or licenses with respect to any intellectual property of either party are granted or deemed granted hereunder or in connection herewith, other than those rights expressly granted in this Agreement. No trade customs, courses of dealing or courses of performance by the parties will be relevant to modify, supplement or explain any term(s) used in this Agreement. This Agreement may not be modified or supplemented by any purchase order, change order, acknowledgment, order acceptance, standard terms of sale, invoice or the like. This Agreement may only be modified or supplemented in a writing expressly stated for such purpose and signed by the parties to this Agreement, except that the RMC may amend or update EXHIBITS B and C hereto as expressly permitted hereby.

15.3 RELATIONSHIP BETWEEN THE PARTIES. The parties' relationship, as established by this Agreement, is solely that of independent contractors.

This Agreement does not create any agency, distributorship, employee-employer, partnership, joint venture or similar business relationship between the parties. Neither party is a legal representative of the other party, and neither party can assume or create any obligation, representation, warranty or guarantee, express or implied, on behalf of the other party for any purpose whatsoever. Each party shall use its own discretion and shall have complete and authoritative control over its employees and the details of performing its obligations under this Agreement.

15.4 NON-WAIVER. The failure of a party to insist upon strict performance of any provision of this Agreement or to exercise any right arising out of this Agreement will neither impair that provision or right nor constitute a waiver of that provision or right, in whole or in part, in that instance or in any other instance. Any waiver by a party of a particular provision or right will be in writing, will be as to a particular matter and, if applicable, for a particular period of time and will be signed by such party.

15.5 ASSIGNMENT. Except as expressly provided hereunder, neither this Agreement nor any rights or obligations hereunder may be assigned or otherwise transferred by either party without the prior written consent of the other party (which consent will not be unreasonably withheld); PROVIDED HOWEVER, that either party may assign this Agreement and its rights and

obligations hereunder without the other party's consent to any directly or indirectly wholly-owned Affiliate if the assigning party remains liable and responsible for the performance and observance of all of the Affiliate's duties and obligations hereunder or, with prior notice, or in connection with the transfer or sale of all or substantially all of the business of such party to which this Agreement relates to a Third Party, whether by merger, sale of stock, sale of assets or otherwise. In the event of such transaction, however, intellectual property rights of the acquiring party to such transaction (if other than one of the parties to this Agreement) will not be included in the technology licensed hereunder. The rights and obligations of the parties under this Agreement will be binding upon and inure to the benefit of the successors and permitted assigns of the parties. Any assignment not in accordance with this Agreement shall be void.

15.6 NO THIRD PARTY BENEFICIARIES. This Agreement is neither expressly nor impliedly made for the benefit of any party other than those executing it.

15.7 SEVERABILITY. If, for any reason, any part of this Agreement is adjudicated invalid, unenforceable or illegal by a court of competent jurisdiction, such adjudication shall not affect or impair, in whole or in part, the validity, enforceability or legality of any remaining portions of this Agreement. Such adjudicated part of the Agreement shall be validly reformed to as nearly as possible approximate the intent of the parties and, if unreformable, shall be divisible and deleted in such jurisdiction. All remaining portions shall remain in full force and effect as if the original Agreement had been executed without the invalidated, unenforceable or illegal part.

15.8 NOTICES. Any notice to be given under this Agreement must be in writing and delivered either in person, by any method of mail (postage prepaid) requiring return receipt, or by overnight courier or facsimile confirmed thereafter by any of the foregoing, to the party to be notified at its address(es) given below, or at any address such party has previously designated by prior written notice to the other. Notice will be deemed sufficiently given for all purposes upon the earlier of: (a) the date of actual receipt; (b) if mailed, three (3) calendar days after the date of postmark; or (c) if delivered by overnight courier, the next business day such overnight courier regularly makes deliveries.

If to Isis, notices must be addressed to:

Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008
Attention: Executive Vice President
Telephone: (760) 931-9200
Facsimile: (760) 603-3861

with a copy to:

Attention: General Counsel
Telephone: (760) 931-9200

Facsimile: (760) 603-3820

If to Amgen, notices must be addressed to:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Attention: Vice President, Licensing
Telephone: (805) 447-1000
Facsimile: (805) 499-6058

with a copy to:

Attention: Senior Vice President, General Counsel
Telephone: (805) 447-1000
Facsimile: (805) 499-8011

15.9 FORCE MAJEURE. Except for the obligation to make payment when due, each party will be excused from liability for the failure or delay in performance of any obligation under this Agreement by reason of any event beyond such party's reasonable control including, but not limited to, Acts of God, fire, flood, explosion, earthquake, or other natural forces, war, civil unrest, accident, destruction or other casualty, any lack or failure of transportation facilities, any lack or failure of supply of raw materials, any strike or labor disturbance, or any other event similar to those enumerated above. Such excuse from liability will be effective only to the extent and duration of the event(s) causing the failure or delay in performance and provided that the party has not caused such event(s) to occur. Notice of a party's failure or delay in performance due to force majeure must be given to the other party within ten (10) calendar days after its occurrence. All delivery dates under this Agreement that have been affected by force majeure will be tolled for the duration of such force majeure. In no event will any party be required to prevent or settle any labor disturbance or dispute. Notwithstanding the foregoing, should the event(s) of force majeure suffered by a party extend beyond a 3-month period, the other party may then terminate the Collaboration or this Agreement by written notice to the non-performing party, with the consequences of such termination as set forth in Sections 12.5, 12.6, 12.7, 12.8, 12.9 and 12.10.

15.10 COUNTERPARTS. This Agreement may be executed in two or more counterparts, each of which will be deemed an original document, and all of which, together with this writing, will be deemed one instrument.

15.11 FURTHER ACTIONS. Each party agrees to execute, acknowledge and deliver such further instruments and to do all such other acts as may be necessary or appropriate in order to carry out the purposes and intent of this Agreement.

15.12 EXPORT REQUIREMENTS. Each party agrees to comply with all applicable laws and regulations. In particular, it is understood and acknowledged that the transfer of certain commodities and technical data is subject to United States laws and regulations controlling the export of such commodities and technical data, including all Export Administration Regulations of the United States Department of Commerce. Each party hereby agrees and by entering into this Agreement gives written assurance that it shall comply with all United States laws and

regulations controlling the export of commodities and technical data within Information and Materials, that it will be solely responsible for any violation of any such laws and regulations by itself, its Affiliates or its sublicensees, and that it will indemnify, defend and hold the other party harmless from any liability in the event of any legal action of any nature occasioned by such violation.

15.13 CAPTIONS. The captions to this Agreement are for convenience only and are to be of no force or effect in construing or interpreting any of the provisions of this Agreement.

15.14 EXHIBITS. All Exhibits referenced in and attached hereto are incorporated in this Agreement by reference. In case of any discrepancies between language incorporated from the Exhibits and the terms of the Sections, the terms of the Sections shall prevail; PROVIDED HOWEVER, where Sections of this Agreement make explicit reference to a substantive matter contained in an Exhibit, the substantive matter contained in such Exhibit shall prevail.

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

AMGEN INC.	ISIS PHARMACEUTICALS, INC.
By: /s/ Kevin W. Sharer	By: /s/ B. Lynne Parshall
Kevin W. Sharer	B. Lynne Parshall
Chairman and Chief Executive Officer	Executive Vice President

EXHIBIT A

DEFINED TERMS

A-1. "AFFILIATE" means any company or entity controlled by, controlling, or under common control with a party hereto. For purposes of this definition, "control" means (a) that an entity owns, directly or indirectly, more than fifty percent (50%) of the voting stock or participating profit interest of another entity and (b) that such entity has the actual ability to control and direct the management of the entity, whether by contract or otherwise.

A-2. "AMGEN ASO COMPOUND" means ASO Compounds characterized, conceived, developed, derived, discovered, generated or identified during the Term solely by employees of, or consultants to, Amgen through the practice of Isis Standard Chemistry and that selectively modulate expression of an Amgen Gene

Target.

A-3. "AMGEN GENE TARGET" means any of the Gene Targets listed in EXHIBIT C hereto, or a Gene Target substituted for any of the foregoing in accordance with Section 4.2 hereof.

A-4. "AMGEN KNOW-HOW" means, to the extent necessary for performance of the parties' obligations under the Research Plan, or the research, development, manufacturing and commercialization of Products, Information and Materials that Amgen Controls on the Effective Date or during the Term, including, without limitation, all such Information and Materials that are characterized, conceived, developed, derived, discovered, generated or identified solely by employees of or consultants to Amgen as part of the Collaboration, and, in each case, any replication or any part of such Information and Materials.

A-5. "AMGEN PATENT RIGHTS" means, to the extent necessary for Isis to perform its obligations under the Research Plan, all Patent Rights issued or existing as of the Effective Date or during the Term that Amgen Controls, including, without limitation, all Patent Rights that claim or disclose Amgen Know-How.

A.6. "AMGEN TECHNOLOGY" means the Amgen Patent Rights and Amgen Know-How.

A-7. "ASO COMPOUND" means an oligonucleotide or an analog thereof that selectively modulates protein synthesis at the nucleic acid level through the binding of such oligonucleotide or analog to a complementary sequence.

A-8. "CALENDAR QUARTER" means each respective period of 3 consecutive months ending on March 31, June 30, September 30 and December 31 of each Calendar Year.

A-9. "CALENDAR YEAR" means each successive period of 12 months commencing on January 1 and ending on December 31.

A-10. "CHANGE OF CONTROL OF ISIS" means the acquisition by a Third Party of fifty percent (50%) or more of the shares of Isis' capital stock the holders of which have general voting power under ordinary circumstances to elect at least a majority of Isis' Board of Directors or equivalent body.

A-11. "COLLABORATION" means the program of collaborative research in the field of treating or preventing [***] in humans, carried out by the parties during the Collaboration Term pursuant to Articles 2, 3 and 4 hereof, as more fully described in the Research Plan.

A-12. "COLLABORATION ASO COMPOUND" means an ASO Compound characterized, conceived, developed, derived, discovered, generated or identified in the course of the Collaboration either solely by employees of or consultants to Isis or jointly by employees of or consultants to Isis and employees of or consultants to Amgen through the practice of Isis Standard Chemistry that selectively modulates expression of an Amgen Gene Target as well as those ASO Compounds discovered or identified or Controlled outside of the Collaboration by Isis prior to and on the Effective Date of this Agreement.

A-13. "COLLABORATION KNOW-HOW" means Information and Materials directed to Collaboration ASO Compounds which are Controlled by Isis as of the Effective Date or are characterized, conceived, developed, derived, discovered, generated or identified solely by employees of or consultants to Isis in the course of the Collaboration and, in each case, any replication or any part of such Information or Materials, but excluding, in each case, the Isis ASO Compound Patent Rights.

A-14. "COLLABORATION TERM" means the 3 years following the Effective Date, subject to earlier termination in accordance with Article 12; PROVIDED HOWEVER, that if the Level 2 Research with respect to any Amgen Gene Target has not been completed (as determined by the RMC) prior to the 3rd anniversary of the Effective Date, then Amgen shall have the option to extend the Collaboration Term for such additional amount of time as the parties reasonably agree is necessary to complete such Level 2 Research, subject to mutual agreement of the parties on a written plan for completing such Level 2 Research, on terms similar to those set forth in this Agreement (including, without limitation, Section 6.2 hereof).

A-15. "COMMERCIALLY REASONABLE EFFORTS" means efforts and resources commonly used in the research-based pharmaceutical industry for a product of similar market potential at a similar stage in its product life taking into account efficacy, the competitiveness of alternative products and product candidates in development or in the marketplace (excluding other products owned or

controlled by Amgen), the patent and other proprietary position of the product, the likelihood of regulatory approval given the regulatory structure involved, the profitability of the product including the royalties payable to licensors of patent rights, alternative products and product candidates and other relevant factors. Commercially Reasonable Efforts shall be determined on a market-by-market basis for a particular product, and it is anticipated that the level of effort would change over time, reflecting changes in the status of the product and the market involved.

A-16. "COMPETITIVE ASO COMPOUND" means any ASO Compound using Isis Standard Chemistry that selectively modulates expression of an Amgen Gene Target through the binding of such ASO Compound to a complementary sequence in such Amgen Gene Target.

A-17. "CONFIDENTIAL INFORMATION" means any Information furnished to a party by the other party pursuant to this Agreement or any Information developed as part of the Collaboration hereunder; PROVIDED HOWEVER, that Confidential Information shall not include any information which the receiving party can prove by competent written evidence:

(a) is now, or hereafter becomes, through no act or failure to act on the part of the receiving party, generally known or available;

(b) is known by the receiving party at the time of receiving such information, as evidenced by its records;

(c) is hereafter furnished to the receiving party by a Third Party, as a matter of right and without restriction on disclosure;

(d) is independently discovered or developed by the receiving party without the use of Confidential Information belonging to the disclosing party; or

(e) is the subject of a written permission to disclose provided by the disclosing party.

A-18. "CONTROL" means, with respect to any Information, Material or intellectual property right (including Patent Rights), possession by a party of the ability (whether by ownership, license or otherwise) to grant access, a license or a sublicense to such Information, Material or intellectual property right as provided for in this Agreement without violating the terms of any agreement or other arrangement with any Third Party as of the time such party would first be required hereunder to grant the other party such access, license or sublicense.

A-19. "DEFAULT" has the meaning provided in Section 12.3.

A-20. "DEVELOPMENT NOTICE" has the meaning provided in Section 4.4.

A-21. "FDA" means the United States Food and Drug Administration, or any successor agency thereto having the administrative authority to regulate the marketing of human pharmaceutical products or biological therapeutic products, delivery systems and devices in the United States of America.

A-22. "FIELD" means all uses, including human therapeutic, prophylactic, palliative and diagnostic uses.

A-23. "FIRST COMMERCIAL SALE" means, with respect to any Product, the first sale for end-use or consumption of such Product in a country after the governing health regulatory authority of such country has granted Regulatory Approval. Sale to an Affiliate or Sublicensee will not constitute a First Commercial Sale unless the Affiliate or Sublicensee is the end user of the Product.

A-24. "FTE" means the equivalent of the work of one employee full time for one year [***]

A-25. "FTE RATE" means [***]

A-26. "GENE TARGET" means a transcriptional unit of a gene, and any RNA or protein product expressed by such transcriptional unit, including the pre-mRNA, all 5' untranslated regions, open reading frames, splice variants and 3' untranslated regions.

A-27. "GENETROVE DATABASE" means Isis' proprietary GeneTrove Human Gene Function Database consisting, without limitation, of data from the study of the effect of gene-specific

inhibition of up to ten thousand (10,000) human genes in a set of human cell-based pharmacology assays utilizing Isis' proprietary antisense technology, and software appropriate for storing, viewing and performing queries on the incorporated data.

A-28. [***]

A-29. "IND" means an Investigational New Drug application, as defined in 21 C.F.R. 312 or any successor regulation, or the equivalent application or filing filed with any equivalent agency or governmental authority outside the United States (including any supra-national agency such as in the European Union) necessary to commence human clinical trials in such jurisdiction.

A-30. "INFORMATION" means all tangible and intangible techniques, technology, practices, trade secrets, inventions (whether patentable or not), methods, knowledge, know-how, conclusions, skill, experience, test data and results (including pharmacological, toxicological and clinical test data and results), analytical and quality control data, results or descriptions, software and algorithms.

A-31. "INTERNAL PROGRAM" means an internal research effort on the development of ASO Compounds through the practice of Isis Standard Chemistry that selectively modulates expression of a Gene Target conducted by Isis outside the course of Collaboration whereby such internal research effort on such Gene Target has advanced at least to a stage that is equivalent to initiation of Level 2 Research, as reasonably evidenced by written documentation of Isis.

A-32. "ISIS ASO COMPOUND PATENT RIGHTS" means Patent Rights Controlled by Isis on the Effective Date or during the Term that claim the composition of matter of a Collaboration ASO Compound or a method of using such Collaboration ASO Compound, in each case to the extent in existence on the Effective Date or during the Collaboration Term. Isis ASO Compound Patent Rights shall include, but not be limited to, the patent applications and patents set forth in Exhibit D under the heading "Isis ASO Compound Patent Rights".

A-33. "ISIS CORE TECHNOLOGY PATENT RIGHTS" means Patent Rights Controlled by Isis on the Effective Date or during the Term that claim the practice of Isis Standard Chemistry in existence on the Effective Date or during the Collaboration Term, including Patent Rights that claim chemistries, motifs (patterns of arranging the chemical building blocks of an ASO Compound) and/or cellular mechanisms of action by which an oligonucleotide promotes RNA cleavage. Isis Core Technology Patent Rights shall include, but not be limited to, the patent applications and patents set forth in Exhibit D under the heading "Isis Core Technology Patent Rights".

A-34. "ISIS KNOW-HOW" means Information and Materials that are useful for purposes of the Collaboration or the research, development, manufacture and commercialization of Products, including, without limitation, such Information and Materials relating to Isis Standard Chemistry and Isis Standard Chemistry Manufacturing Process, that Isis Controls on the Effective Date or during the Collaboration Term, but not including Collaboration Know-How and Joint Know-How.

A-35. "ISIS MANUFACTURING PATENT RIGHTS" means Patent Rights Controlled by Isis on the Effective Date or during the Term that claim the practice of the Isis Standard Chemistry Manufacturing Process in existence on the Effective Date or during the Collaboration Term. Isis

Manufacturing Patent Rights shall include, but not be limited to, the patent applications and patents set forth in Exhibit D under the heading "Isis Manufacturing Patent Rights."

A-36. "ISIS PATENT RIGHTS" means the Isis ASO Compound Patent Rights, the Isis Core Technology Patent Rights and the Isis Manufacturing Patent Rights.

A-37. "ISIS STANDARD CHEMISTRY" means "2 MOE Gapmers" which are antisense phosphorothioate oligonucleotides wherein all of the backbone linkages are modified by adding a sulfur at one of the non-bridging oxygens (phosphorothioate) and a stretch of at least 5 consecutive nucleotides remain unmodified at the 2' position (deoxy sugars) and the remaining nucleotides contain a sugar moiety wherein the 2' position is substituted with

2'-methoxyethoxy (2'-O-CH2CH2OCH3), also known as 2'-O-(2-methoxyethyl) or 2'-MOE.

A-38. "ISIS STANDARD CHEMISTRY MANUFACTURING PROCESS" means the manufacturing process as of the Effective Date represented by Isis Batch Record No. [***] and the documents and electronic files referenced therein. Manufacturing for this purpose includes synthesis, purification and analysis.

A-39. "ISIS TECHNOLOGY" means the Isis Patent Rights and the Isis Know-How.

A-40. "JOINT KNOW-HOW" means Information and Materials characterized, conceived, developed, derived, generated or identified jointly by employees of or consultants to Isis and employees of or consultants to Amgen from the Effective Date through the end of the Term, including, without limitation, Information and Materials that are directed to Collaboration ASO Compounds.

A-41. "JOINT PATENT RIGHTS" means all Patent Rights that claim or disclose Joint Know-How.

A-42. "LEVEL 1 RESEARCH" means that portion of the research performed under the Research Plan with respect to an Amgen Gene Target through completion of experiments designed to [***]

A-43. "LEVEL 2 RESEARCH" means that portion of the research performed under the Research Plan with respect to an Amgen Gene Target after completion of the Level 1 Research and through completion of [***]

A-44. "MANUFACTURING IMPROVEMENTS" means any and all scientific and technical data, information, methods, techniques, protocols and processes that are useful in the manufacture of ASO Compounds developed by or coming under the Control of a party outside the course of the Collaboration, during the first 10 years of the Term.

A-45. "MATERIALS" has the meaning provided in Section 3.6.

A-46. "NDA" means a New Drug Application and all amendments and supplements thereto, or the equivalent thereof, filed with the FDA (as more fully defined in 21 C.F.R. 314.5 et seq.), or the equivalent application, including, without limitation, a Marketing Authorization Application ("MAA"), filed with any equivalent agency or governmental authority outside the United States (including any supra-national agency such as in the European Union (i.e., the CPMP and/or the

EMEA)) requiring such filing, including all documents, data, and other information concerning a pharmaceutical product which are necessary for gaining Regulatory Approval to market and sell such pharmaceutical product.

A-47. "NET SALES" means all revenues recognized in accordance with U.S. generally accepted accounting principles (GAAP) consistently applied, which are received from sales of Products sold by Amgen, its Affiliates and Sublicensees to a non-Sublicensee Third Party which is not an Affiliate or Sublicensee of Amgen (unless such Affiliate or Sublicensee is the end user of such product, in which case the amount billed therefor will be deemed to be the amount that would be billed to a Third Party in an arm's-length transaction) for sales of such Product to such end users less the following items, as allocable to such Product (if not previously deducted from the amount invoiced): (i) trade discounts, rebates, credits or allowances, (ii) credits or allowances additionally granted upon returns, rejections or recalls (except where any such recall arises out of Amgen's or its Affiliate's or Sublicensee's gross negligence, willful misconduct or fraud), (iii) packing, freight, shipping and insurance charges, (iv) taxes, duties or other governmental tariffs (other than income taxes) and (v) government mandated rebates.

A-48. [***]

A-49. "PATENT RIGHTS" means (a) valid and enforceable United States patents, re-examinations, reissues, renewals, extensions and term restorations, and foreign counterparts thereof, and (b) pending applications for United States patents including, without limitation, provisional applications, continuations, continuations-in-part, divisional and substitute applications including, without limitation, inventors' certificates, and foreign counterparts thereof.

A-50. "PHASE II CLINICAL TRIALS" means those trials on sufficient numbers of patients that are designed to establish the safety and preliminary efficacy of a drug for its intended use, and to define warnings, precautions and

adverse reactions that are associated with the drug in the dosage range to be prescribed and that satisfy the requirements of 21 CFR 312.21(b) (or its successor regulation), or its foreign equivalent.

A-51. "PHASE IIA CLINICAL TRIALS" means that portion of Phase II Clinical Trials constituting a study of a candidate drug in the target patient population of a sufficient number (i.e., at least 100 subjects) and sufficient length of time whereby adequate safety data is provided and there is a clear indication of dosage effects with respect to efficacy as defined in the study protocol.

A-52. "PHASE III CLINICAL TRIALS" means those clinical trials on sufficient numbers of patients that, if the defined end-points are met, are designed (and agreed to by the FDA based upon existing data in the same patient population) as of the start of the trial to definitively establish that a drug is safe and efficacious for its intended use, and to define warnings, precautions and adverse reactions that are associated with the drug in the dosage range to be prescribed, and provide pivotal data supporting Regulatory Approval of such drug or label expansion of such drug and that satisfy the requirements of 21 CFR 321.21(c) (or its successor regulation), or its foreign equivalent.

A-53. "PRODUCT" means a pharmaceutical product containing (i) one or more Collaboration ASO Compounds and/or (ii) one or more Amgen ASO Compounds. For the purpose of any

royalty payments that may be due under Section 6.4(a), a single Product will comprise all formulations (e.g., topical formulations, oral formulations, parenteral formulations, sustained-release formulations) of the same ASO Compound defined in the preceding sentence.

A-54. "REGULATORY APPROVAL" means any and all approvals (including price and reimbursement approvals), licenses, registrations, or authorizations of the European Union or any country, federal, state or local regulatory agency, department, bureau or other government entity that is necessary for the manufacture, use, storage, import, transport and/or sale of a Product in such jurisdiction.

A-55. "REGULATORY FILINGS" shall mean, collectively, INDs, biologic license applications (BLAs), NDAs, establishment license applications (ELAs) and drug master files (DMFs), applications for designation of a Product(s) such as an "Orphan Product(s)" under the Orphan Drug Act, or any other similar filings (including any foreign equivalents), including any related correspondence and discussions as may be required or requested by the FDA or equivalent foreign governmental authority(ies), for the clinical testing, manufacture or sale of a Product in the Territory.

A-56. "RESEARCH MANAGEMENT COMMITTEE" or "RMC" means the committee formed pursuant to Section 2.1.

A-57. "RESEARCH PLAN" means the written plan for conducting the Collaboration, as amended from time to time by the RMC.

A-58. "ROYALTY TERM" means, in the case of any Product, and on a country-by-country basis, the period of time commencing on the First Commercial Sale of such Product and ending upon the later of (a) [***] years after the date of First Commercial Sale of such Product, or (b) the expiration of the last to expire of the Isis Patent Rights (excluding Patent Rights licensed under the [***] License and/or the [***] License) or Joint Patent Rights having one or more claims (which have not been declared invalid by a court of competent jurisdiction) which would, but for the licenses granted under this Agreement, be infringed by the selling of such Product in the country of sale by Amgen, its Affiliates or Sublicensees.

A-59. "SUBLICENSEE" means any Third Party to which Amgen or any of its Affiliates grants any right to make, have made, use sell, offer for sale, import, export or otherwise exploit or transfer physical possession of or title in a Product. Solely for purposes of compensation payable to Isis hereunder, a Third Party who is granted only the right to sell a Product (such as a wholesaler or distributor) or to use a Product (such as a customer receiving an implied license as a consequence of purchase) shall not be considered a Sublicensee.

A-60. "TERM" has the meaning provided in Section 12.1.

A-61. "THIRD PARTY" means any entity other than Amgen or Isis or an Affiliate of Amgen or Isis.

EXHIBIT B

RESEARCH PLAN

[***]

EXHIBIT C

AMGEN GENE TARGETS

[***]

EXHIBIT D

ISIS ASO COMPOUND PATENT RIGHTS

[***]

ISIS CORE TECHNOLOGY PATENT RIGHTS

[***]

ISIS MANUFACTURING PATENT RIGHTS

[***]

EXHIBIT E

EXAMPLE COMPETITION CALCULATION

[***]

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

[ISIS PHARMACEUTICALS LOGO]

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OLIGONUCLEOTIDE MANUFACTURING AND SUPPLY AGREEMENT

By and between

ISIS PHARMACEUTICALS, INC.

2292 Faraday Avenue, Carlsbad, CA 92008
- Hereinafter referred to as ISIS -

and

INTEGRATED DNA TECHNOLOGIES, INC.

1710 Commercial Park, Coralville, IA 52241
- Hereinafter referred to as IDT -

TABLE OF CONTENTS

RECITALS

WHEREAS, ISIS and its GeneTrove Division have a need for a reliable supply of quality-controlled oligonucleotides for use in its antisense functional genomics and target validation program; and

WHEREAS, IDT has the expertise and manufacturing capacity sufficient to supply ISIS quality controlled oligonucleotides at required volumes; and

WHEREAS, both IDT and ISIS are willing to collaborate in continuous efforts to refine IDT's oligonucleotides manufacturing, purification and quality controlled techniques to ensure that ISIS receives optimized oligonucleotides for use in its functional genomics program;

NOW THEREFORE, IDT and ISIS agree to the following Oligonucleotide Manufacturing and Supply Agreement according to the terms and conditions as stated herein.

ARTICLE 1: DEFINITIONS

For purposes of this Oligonucleotide Manufacturing and Supply Agreement, the following words, phrases, or terms shall have the meanings as herein defined:

1.0 "Agreement" shall mean this Oligonucleotide Manufacturing and Supply

Agreement, including Appendices A and B, as originally executed and as properly amended from time to time according to Article 10.

1.1 "Antisense Oligonucleotides" shall mean a polynucleotide, oligonucleotide or oligonucleotide analog, which hybridizes in a sequence specific manner under physiological conditions to RNA forming an RNA-DNA duplex, which duplex acts to modulate the production of a targeted gene product. An antisense oligonucleotide analog may include naturally occurring or non-natural heterocycles, sugar and/or backbone linkages, and may be a molecule in which the sugar may be absent, in which the backbone linkage may be phosphate based, amide based, or based on other chemistries and which may or may not include stem loop or structural units.

1.2 "Assigned Supply Period" shall mean the [***] year period immediately following the Effective Date.

1.3 "Assigned Systems" shall mean oligonucleotide synthesizers, purification and analytical instruments, and other supporting equipment assigned by IDT to support the manufacture and delivery of ISIS's requirements of Program Oligonucleotides.

1.4 "Business Day(s)" shall mean those days from Monday through Friday, which are not declared as national holidays in the United States, or as holidays routinely recognized by one or more of the Parties.

1.5 "Calendar Days" shall mean all days Sunday through Saturday, which appear on the calendar from January 1 through December 31.

1.6 "Customer Deposit" shall mean the credit for dedicated Program Oligonucleotide supply and Program Oligonucleotide purchases obtained by ISIS under this Agreement, which will be credited to the benefit of ISIS against Program Oligonucleotide purchases by ISIS at a rate of [***] of the monthly Program Oligonucleotide invoice described in section 4.8 herein.

1.7 "Dedicated Data Management System" shall mean the components of an integrated hardware and software system designed to support the isolated processing, tracking and storage of all information related to ISIS Program Oligonucleotide orders, with access limited to authorized personnel of IDT and/or ISIS.

1.8 "Effective Date" shall mean the execution date of the last signature on the signature page of this Agreement.

1.9 "IDT" shall mean Integrated DNA Technologies, Inc., and its affiliates, if any.

1.10 "IDT List Price" shall mean the then current IDT Catalog price for a specified product or service as displayed in IDT's World Wide Web On-line Catalog at (www.idtdna.com) or any successive Internet URL.

1.11 "Intellectual Property" shall mean and includes, but is not limited to, inventions (whether patentable or unpatentable), trade secrets, all present improvements thereto and future improvements thereto, and all United States, and foreign patents, patent applications, patent disclosures, and patentable inventions, together with all reissuances, continuations, continuations-in-part, divisionals, revisions, extensions and reexaminations thereof.

1.12 "ISIS" shall mean ISIS Pharmaceuticals, Inc., its and its divisions, including specifically GeneTrove-TM-.

1.13 "ISIS Supplied Reagent" shall mean those reagents to be supplied by ISIS to IDT that are necessary for the specific and limited purpose of enabling or optimizing IDT's manufacture and supply of MOE Oligonucleotides or Antisense Oligonucleotides to ISIS.

1.14 "MOE Oligonucleotides" shall mean oligonucleotides ordered from IDT by ISIS, which contain one or more of ISIS's proprietary 2'methoxy-ethoxy modifications (or any combination of an alkyl, alkoxy or thioalkoxy together with an ether, ester, amino or aminohydroxy substituent). With the exception of Appendix A and paragraph 4.2 herein, and at ISIS's

sole discretion, MOE Oligonucleotide may also mean any Antisense Oligonucleotide ordered by ISIS from IDT.

1.15 "Parties" shall refer collectively to ISIS and IDT, each individually referred to as a "Party".

1.16 "Primers" shall refer to unmodified oligonucleotides used to promote amplification of a targeted sequence.

1.17 "Probes" shall refer to dye-labeled or similarly modified oligonucleotides used to detect and/or quantify the presence of a targeted sequence in a sample.

1.18 "Program Oligonucleotide" means a MOE Oligonucleotide and/or a Quantification Oligonucleotide conforming to the specifications and criteria set forth in Appendix A (as amended from time to time) for supply and delivery to ISIS.

1.19 "Quantification Oligonucleotide" shall mean Primers and Probes, either ordered individually by ISIS, or as 96-well plate combinations referred to as "Primer-Probes Sets" as defined in Appendix A (as amended from time to time).

ARTICLE 2
OLIGONUCLEOTIDE SUPPLY PERIOD AND DEPOSIT

2.1 SUPPLY PERIOD. For the duration of the Assigned Supply Period, IDT will utilize the Assigned Systems to manufacture and sell Program Oligonucleotides ordered by ISIS according to the terms and conditions as described in this Agreement. This commitment by IDT includes the obligations of IDT to individually staff, train, and fully compensate, the personnel needed to operate the Assigned Systems for ISIS, and to otherwise fully manage the production and delivery of Program Oligonucleotides to ISIS.

2.2 SUPPLY DEPOSIT. ISIS shall advance IDT five million dollars ($5 million) to IDT within five (5) Business Days of the effective date of the Amended and Restated IDT-ISIS Licensing Agreement, in the form of Customer Deposit.

2.3 ASSIGNMENT OF MANUFACTURING CAPACITY. IDT will utilize the Customer Deposit to assign within its facility sufficient Program Oligonucleotide synthesis, processing and purification capacity to manufacture [***] MOE Oligonucleotides and [***]

Quantification Oligonucleotides per calendar year for ISIS over the term of this Agreement.

2.4 DEDICATED DATA MANAGEMENT SYSTEM. IDT will further utilize the Customer Deposit to design and implement the Dedicated Data Management System to accommodate the expected ordering parameters of Program Oligonucleotides and to specifically track the utilization of ISIS's Customer Deposit.

2.5 SALE OF PROGRAM OLIGONUCLEOTIDES. For the duration of the Assigned Supply Period, IDT will make and sell Program Oligonucleotides to ISIS in accordance with the pricing provisions contained in Article 3. IDT will invoice ISIS at the listed prices less [***] for each Program Oligonucleotide ordered by ISIS and shipped by IDT, and shall reduce ISIS's Customer Deposit by the corresponding [***] sum.

ARTICLE 3
PROGRAM OLIGONUCLEOTIDE SPECIFICATIONS COMMITTEE

3.1 COMMITTEE OBJECTIVE. In order to ensure the manufacture and supply to ISIS of optimized Program Oligonucleotides for the duration of this Agreement, IDT and ISIS will form a joint committee of their respective employees to develop, enforce and continuously refine specifications for the manufacture, supply, and receipt of MOE Oligonucleotides and/or Quantification Oligonucleotides (the "Program Oligonucleotide Specifications Committee").

3.2 COMMITTEE FORMATION AND MANAGEMENT. It is contemplated by the Parties that all decisions affecting or regarding Program Oligonucleotide specifications (Appendix A) will be the result of informed deliberation

and mutual consent of the Program Oligonucleotide Specifications Committee (POSC). Each Party shall appoint a Committee Co-Chair, who will have the joint authority, independent of the POSC, to make any decision regarding modifications to the Program Oligonucleotide specifications. The Co-Chairs will appoint additional individuals to serve on the POSC. The POSC will meet at least once monthly to review the performance of each Party under the Agreement, to forecast future supply requirements, and to resolve any Program Oligonucleotide supply, quality and/or invoicing issues. The POSC will instruct staff members to direct all related issues or concerns through the POSC and will distribute minutes of its meetings to the relevant members of their organizations. IDT hereby appoints Trey Martin and ISIS hereby appoints Henry Sasmor as the acting Committee Co-Chairs for each respective Party.

3.3 INITIAL OLIGO SPECIFICATION DEVELOPMENT. The specifications listed on Appendix A will serve as the Program Oligonucleotide Specifications until amended by POSC. Within ten (10) days of the Effective Date, the POSC will meet to initiate the controlled development of refined manufacturing specifications (including yield, purity, quality control tests and criteria, shipping standards, remake policies, etc.) for both MOE Oligonucleotides and Quantification Oligonucleotides.

3.4 SCOPE OF POSC AUTHORITY. The POSC (or the Co-Chairs acting jointly) has the authority to change the following with respect to Program Oligonucleotide specifications: synthesis scale; yield guarantees; chemical compositions; purity requirements; analytical or quality control tests and/or specifications; and all pricing changes directly related to such changes, provided that the resulting prices reflect, whenever possible, the fixed percentage discount rate of paragraph 4.3. All price changes require the signed written agreement of both Co-Chairs prior to their use in an invoice issued to ISIS pursuant to paragraph 4.8 hereunder. The POSC shall not have the authority to apply Customer Deposit to oligonucleotides or other products other than to Program Oligonucleotides.

ARTICLE 4
ORDERING, PRICING AND INVOICING

4.1 PROGRAM OLIGONUCLEOTIDE ORDERING. ISIS shall place all orders for Program Oligonucleotides over the Dedicated Data Management System, using the customer order entry software developed by IDT for ISIS pursuant to paragraph 2.5.

4.2 MOE OLIGONUCLEOTIDE PRICING. Subject to the provisions contained in paragraphs 2.4, 4.4, and 4.5 hereunder, the invoice price for MOE Oligonucleotides prior to the application of Customer Deposit will be:

(i) [***] for each MOE Oligonucleotide manufactured on the [***] scale that meets the MOE specifications;

(ii) [***] for each MOE Oligonucleotide manufactured on the [***] scale that meets the MOE specifications.

4.3 QUANTIFICATION OLIGONUCLEOTIDE PRICING/FIXED PERCENTAGE DISCOUNT. Subject to the provisions contained in paragraphs in 2.4, 4.4 and 4.5 hereunder, the invoice price for Quantification Oligonucleotides (and/or Antisense Oligonucleotide) prior to application of Customer Deposit shall be [***] of the IDT List Price for corresponding oligonucleotide Primers and/or Probes and the associated purification, analytical and/or set-up fees. This fixed percentage discount is also to be used by the POSC to guide its pricing decisions relevant to changes to MOE Oligonucleotide specifications, including specifically changes to purification, analytical, loading, shipping or handling specifications. Appendix B illustrates the application of this fixed percentage discount to Primer-Probe Sets and MOE Oligonucleotides using IDT List Prices.

4.4 EXTERNAL FACTORS & PRICE INCREASES. IDT warrants that it has performed adequate manufacturing cost-forecasting to ensure that IDT can supply Program Oligonucleotides in commercially viable fashion at the above quoted per base prices or at the established [***] discount. However, should unforeseeable events beyond the control of IDT cause the manufacturing costs of IDT to increase by [***] then IDT shall have the right to

increase the per [***] price to reflect the increased manufacturing cost. The term "unforeseeable events" as used in this paragraph includes, but is not limited to:

(i) new and substantial regulatory or legal restrictions imposed on the manufacture of oligonucleotides or related manufacturing processes;

(ii) substantial increase(s) in the cost of necessary oligonucleotide manufacturing amidites, reagents, solvents, or quality control components, necessary to manufacture Program Oligonucleotides;

Should IDT rely upon "unforeseeable events" beyond the control of IDT as a basis for a price increase, IDT shall immediately as is practical disclose in writing to ISIS through the POSC the cause of the price increase, and IDT's relevant manufacturing costs in sufficient detail to allow for confirmation of the costs by ISIS.

4.5 PRICE DECREASES/MOST FAVORED PRICING. If there are substantial decreases in the market cost of commercial amidites, reagents, solvents, or quality control components necessary to manufacture Program Oligonucleotides that result in [***] or greater reduction in the average cost [***] to IDT, then IDT shall reduce the [***] price charges to ISIS by the amount greater than the [***] cost per base threshold.

4.6 TURNAROUND. The specifications and requirements for delivery of manufacture of Program Oligonucleotides will be those specifications and turnaround requirements identified in Appendix A, as amended from time-to-time by the POSC.

4.7 SUPPLY FORECASTS/ISIS SUPPLIED REAGENT INVENTORY. On or before the [***] of each month during the Assigned Supply Period, ISIS will supply IDT with a forecast of its intended Program Oligonucleotide orders for the following month. IDT will advise ISIS within [***] Days of receipt of its ability to meet the forecast. IDT will specifically advise ISIS of its then current inventory of ISIS Supplied Reagents and of its need for additional ISIS Supplied Reagents to meet the forecast for the following month. It is the expectation of both Parties that IDT will:

(i) maintain on-site, a constant minimum [***] inventory of quality-controlled ISIS Supplied Reagents;

(ii) maintain available manufacturing capacity to meet any forecast that requires a monthly MOE Oligonucleotide supply of [***] MOE Oligonucleotides or less, and a monthly Quantification Oligonucleotide supply of [***] Primer-Probe Sets or less;

(iii) make reasonable efforts to meet forecasts that exceed those limits in (ii) above. In the event that an ISIS forecast is for volumes of Program Oligonucleotides, which volumes are [***] greater than the prior month, then IDT's ability to meet such a forecast may require a scale-up period.

4.8 INVOICING. During the Assigned Supply Period, IDT will invoice ISIS following the close of each month in accordance with 2.5 herein, for Program Oligonucleotides delivered that meet the specifications established by the POSC. Payment of the invoice by ISIS will be due within [***] Days from receipt of the invoice by ISIS, and payment will be made by electronic wire transfer into an account as designated by IDT. Should ISIS fail to pay the full invoice within [***] Days, IDT will have the right to suspend Program Oligonucleotide manufacturing until the invoice is paid in full.

4.9 MOST-FAVORED QUANTIFICATION OLIGONUCLEOTIDE PRICING. In addition to IDT's commitment to maintain a fixed [***] discount for Quantification Oligonucleotides and Antisense Oligonucleotides, IDT agrees not to extend more favorable pricing to third-parties with comparable orders for Antisense Oligonucleotides and/or Probes, whether ordered individually or as part of a Primer-Probe Set. For purposes of this

provision, "comparable orders" shall mean orders for oligonucleotides in equal or lesser volumes, on the same or substantially similar scale, with the same or substantially similar modifications, purification or purity requirements, analytical specifications, and loading requirements. This provision shall not apply to more favorable prices extended to third-parties by IDT for Primers ordered without corresponding orders for Probes, nor shall it apply to Probes, Primers, or Antisense Oligonucleotides when sold or transferred in any of the following non-limiting circumstances: as part of a bona-fide research collaboration; as a component of a kit; as part of a defined promotion; as a test-order; or as a remake.

4.10 CUSTOMER DEPOSIT DEPLETION. Unless IDT and ISIS agree in writing to extend the Agreement and the Assigned Supply Period, any unused portions of the Customer Deposit at the end of the Assigned Supply Period will be forfeited by ISIS and will become the exclusive property of IDT.

ARTICLE 5
INTELLECTUAL PROPERTY

5.1 INVENTIONS AND DISCOVERIES. The Parties do not anticipate but do acknowledge that Intellectual Property may be developed through the joint efforts of the Parties and their employees under this Agreement. If Intellectual Property is developed by an individual Party, or by or through the joint efforts of the Parties, the ownership of the Intellectual Property, whether joint or separate, will be determined by the relevant applicable United States patent laws. In the event that an invention or know-how is developed through the joint or collaborative efforts of the Parties and their employees, IDT and ISIS agree to instruct their respective employees to report the invention or the development in a thorough and prudent manner to the management of the respective Parties, and each Party and agrees to notify the other Party of the invention or the development as soon as commercially practical following internal reporting. The Parties thereafter agree to initiate good faith negotiations directed toward the completion of a separate written agreement directed to licensing and/or assignment of such Intellectual Property.

5.2 TRADENAMES AND TRADEMARKS. IDT acknowledges that GeneTrove-TM- and ISIS, among others, are trademarks and tradenames of ISIS, and that nothing in this Agreement is intended as a grant to IDT, express, implied, or otherwise, to use any trademark, tradename or trade dress of ISIS unless expressly agreed to in writing by ISIS.

5.3 PROGRAM OLIGONUCLEOTIDES AND OLIGONUCLEOTIDE MANUFACTURING METHODS. Notwithstanding the provisions of paragraph 5.1, ISIS shall be the sole owner of the Program Oligonucleotides, which are or contain the Confidential Information of ISIS and subject to the provisions of Article 7. Except with respect to patents and patent applications exclusively licensed to IDT in the field of antisense technology, IDT hereby assigns its entire worldwide right, title, and interest, if any, in any Program Oligonucleotide to ISIS, and IDT agrees to take all necessary action to effect any such transfer, and to cooperate with and assist ISIS, at ISIS's expense, in the pursuit, enforcement, and defense of any Intellectual Property rights in any Program Oligonucleotide. IDT shall be the sole owner of the oligonucleotide manufacturing and tracking methods developed by IDT prior to and/or during the term of this Agreement, including, but not limited to, IDT's proprietary technology in the following fields: oligo reagent preparation methods; oligo synthesis methods; oligo processing and automation protocols; oligo mass order entry software; oligo tracking software; and oligo quality control systems; excluding, however, the aforementioned IDT manufacturing and tracking methods pertaining specifically and/or exclusively to ISIS Supplied Reagents.

ARTICLE 6
REPRESENTATIONS AND WARRANTIES

6.1 REPRESENTATIONS AND WARRANTIES BY IDT:

IDT represents and warrants as follows:

(i) IDT is a corporation duly organized, validly existing and in corporate good standing under the laws of the State of Iowa;

(ii) IDT has the legal right, authority and power to enter into this Agreement;

(iii) IDT has taken all necessary action to authorize the execution, delivery and performance of this Agreement;

(iv) upon the execution and delivery of this Agreement, this Agreement shall constitute valid and binding obligations against IDT enforceable in accordance with its terms, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws affecting creditors' and contracting parties' rights generally;

(v) the performance of its obligations under this Agreement will not conflict with its charter documents or result in a breach of any agreements, contracts or other arrangements to which it is a Party;

(vi) IDT will not during the term of this Agreement enter into any agreements, contracts or other arrangements that would be inconsistent with its obligations under this Agreement;

(vii) IDT has obtained, or will obtain, all governmental permits, licenses, agreements, contracts, and other enabling documents to fully implement and fulfill its duties hereunder; and

(viii) IDT represents and warrants that all employees or others acting on its behalf pursuant to this Agreement are and shall be obligated under a binding written agreement to assign to IDT all inventions made or conceived by such employee or other person.

6.2 REPRESENTATIONS AND WARRANTIES BY ISIS:

ISIS represents and warrants as follows:

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

(ii) ISIS has the legal right, authority and power to enter into this Agreement;

(iii) ISIS has taken all necessary action to authorize the execution, delivery and performance of this Agreement;

(iv) upon the execution and delivery of this Agreement, this Agreement shall constitute valid and binding obligations against ISIS enforceable in accordance with its terms, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization, moratorium or similar laws affecting creditors' and contracting parties' rights generally;

(v) the performance of its obligations under this Agreement will not conflict with its charter documents or result in a breach of any agreements, contracts or other arrangements to which it is a Party;

(vi) to the best of ISIS's knowledge, IDT's manufacture of Program Oligonucleotides for use by ISIS does not constitute contributory infringement with respect to any issued patent of any third party that has issued prior to the effective date of this Agreement;

(vii) ISIS will not during the term of this Agreement enter into any agreements, contracts or other arrangements that would be inconsistent with its obligations under this Agreement; and,

(viii) ISIS represents and warrants that all employees or others acting on its behalf pursuant to this Agreement are and shall

be obligated under a binding written agreement to assign to ISIS all inventions made or conceived by such employee or other person.

6.3 LIMITED WARRANTY FOR PROGRAM OLIGONUCLEOTIDES. IDT warrants that Program Oligonucleotides will meet the specifications as determined in Appendix A, and as later amended by the POSC if applicable. This limited warranty represents ISIS's sole and exclusive remedy with respect to Program Oligonucleotides manufactured for and sold to ISIS or its Affiliates. IDT does not warrant, guarantee or make any representations above and beyond the criteria set forth in Appendix A (as amended from time to time) regarding the use of Program Oligonucleotides in functional genomics, target validation, or any other application, or with respect to the correctness, accuracy, reliability or otherwise of the results of any such use. ISIS ASSUMES THE ENTIRE RISK AS TO THE RESULTS OBTAINED FROM THE USE OF PROGRAM OLIGONUCLEOTIDES. ISIS FURTHER ACKNOWLEDGES THAT ISIS, AND NOT IDT, IS SOLELY RESPONSIBLE FOR ANY WARRANTY OR GUARANTEE MADE TO COLLABORATORS OF ISIS OR GENETROVE WITH RESPECT TO THE USE OF PROGRAM OLIGONUCLEOTIDES. THE FOREGOING WARRANTY IS EXCLUSIVE AND IS MADE IN LIEU AND TO THE EXCLUSION OF ANY OTHER WARRANTIES, WHETHER ORAL OR WRITTEN, EXPRESS OR IMPLIED, DIRECT OR INDIRECT, BY ESTOPPEL, OR BY EFFECT OF THE UNIFORM COMMERCIAL CODE, USAGE IN THE INDUSTRY OR THROUGH COURSE OF DEALINGS OF THE PARTIES, INCLUDING BUT NOT LIMITED TO THOSE CONCERNING MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.

6.4 NO CONSEQUENTIAL DAMAGES. NEITHER PARTY HERETO WILL BE LIABLE FOR SPECIAL, INCIDENTAL OR CONSEQUENTIAL DAMAGES ARISING OUT THE MANUFACTURE, SALE OR USE OF PROGRAM OLIGONUCLEOTIDES UNDER THIS AGREEMENT, OR ARISING OUT OF THE EXERCISE OF EITHER PARTY'S RIGHTS HEREUNDER, REGARDLESS OF ANY NOTICE OF SUCH DAMAGES.

ARTICLE 7
CONFIDENTIAL INFORMATION

7.1 CONFIDENTIAL INFORMATION. For the purpose of this Agreement, Confidential Information means all information, data, and material, labeled or otherwise designated or identified as confidential by ISIS or by IDT.

7.2 DESIGNATED CONFIDENTIAL INFORMATION OF ISIS. All information relating to Program Oligonucleotides including specifically target sequences (i.e., the sequence ordered and/or its complementary sequence or components thereof) ordered by ISIS during the course of this Agreement are hereby permanently designated as ISIS Confidential Information. ISIS agrees that it will, in writing, clearly identify as confidential, any and all additional information that it provides to IDT that it considers to be the Confidential Information of ISIS.

7.3 DESIGNATED CONFIDENTIAL INFORMATION OF IDT. Any and all data generated by IDT's validation or use of the Assigned Systems and/or the Dedicated Data Management System, except for the information described in 7.2 herein, are hereby designated as IDT's Confidential Information. IDT agrees that it will, in writing, clearly identify as confidential, any and all such information that it provides to ISIS that it considers to be the Confidential Information of IDT.

7.4 USE OF CONFIDENTIAL INFORMATION. Each Party may use the other Party's Confidential Information only for the purpose of performing each Party's duties and obligations under this Agreement.

7.5 OBLIGATIONS OF CONFIDENTIALITY. Except as expressly provided herein, ISIS and IDT, and their officers, employees, agents, consultants, and authorized representatives (a) shall hold in strict confidence all Confidential Information from the other Party or any of its officers, employees, agents or representatives and (b) shall not distribute, disclose or disseminate such Confidential Information to any third party without the prior written approval of the other Party (that is, the original disclosing Party), provided, however, that such approval will not be unreasonably withheld where the receiving Party reasonably believes that disclosure of the other Party's Confidential Information is reasonably necessary to obtain patents, authorization to conduct clinical trials, or regulatory approval.

7.6 OTHER INFORMATION. For purposes of this section, information will not be considered to be Confidential Information of a Party if the

information:

(i) was lawfully in the receiving Party's possession prior to disclosure under this Agreement and was not acquired directly or indirectly from the disclosing Party; or,

(ii) was, at the date of disclosure by the disclosing Party, public knowledge; or subsequently becomes public knowledge other than through the failure of the receiving Party to comply with its obligations of confidentiality under the terms of this Agreement; or,

(iii) was or is acquired by the receiving Party from any third party lawfully having possession of such information and who is not under an obligation of confidentiality to the disclosing Party; or,

(iv) was or becomes independently known by the receiving Party without utilizing information provided by the disclosing Party and wherein such independent knowledge is supported in contemporaneously written and dated documentation of the receiving Party; or,

(v) is required to be disclosed, retained, or maintained by either Party, by applicable law or regulation or under the rules of any regulatory or governmental authority, including specifically federal district courts; provided however that each Party shall immediately notify the other Party in writing of such required disclosure and must provide such notice at least thirty (30) days prior to the date when disclosure is proposed to take place, and provided that the Party or third party required to make disclosure shall use its best efforts to secure confidential treatment of any such information required to be disclosed.

7.7 ADDITIONAL REMEDIES. The Parties hereto understand and agree that remedies at law may be inadequate to protect against any breach of any of the provisions of this Article 7 by either Party or their employees, agents, officers or directors or any other person acting in concert with it or on its behalf. Accordingly, each Party shall be entitled to the granting of injunctive relief by a court of competent jurisdiction against any action that constitutes any such breach of this Article 7.

7.8 EXTENDED TERM. The provisions of this Article 7 shall survive any termination or expiration of this Agreement and continue in force for a period of [***] years.

ARTICLE 8
TERM AND TERMINATION

8.1 TERM. The term of this Agreement will be from the Effective Date and will continue for a period of eight (8) years from the Effective Date, unless earlier terminated by a Party or the Parties under one of the provisions of this Article 8.

8.2 BANKRUPTCY. This Agreement shall terminate upon written notice subject to paragraph 10. 4, by one Party to the other Party in the event the other Party shall become insolvent, asks its creditors for a moratorium, files a bankruptcy petition, or suffers appointment of a temporary or permanent receiver, trustee, or custodian, for all or a substantial portion of its assets. In the event of any termination pursuant to this provision, any unused Customer Deposit shall be immediately forfeited by ISIS, and shall become the exclusive property of IDT.

8.3 TERMINATION. Either Party may terminate this Agreement for default by the other Party in performing any of its material obligations under this Agreement by notifying the other Party in writing of such default and allowing the other Party [***] Days within which to cure such default, unless the default is the failure to pay money, in which case the defaulting Party shall have only [***] Days to cure such default after receiving written

notice of non-payment. If such default is not cured within [***] Days from receipt of such notice of default (or [***] Days in the case of non-payment of money owed), the non-defaulting Party may terminate this Agreement by written notice, subject to paragraph 10.4, to the defaulting Party.

8.4 ELECTIVE TERMINATION. ISIS may terminate this Agreement by providing IDT [***] days written notice if IDT materially fails to comply with any of the Program Oligonucleotide manufacturing or supply requirements set forth in Article 4 and in Appendix A, as amended from time to time. The Parties recognize and acknowledge that the production of Program Oligonucleotides conforming to the specifications is important to ISIS and is a material term of this Agreement, and further that time is of the essence with respect to ISIS's demand for Program Oligonucleotides. IDT's failure to materially produce and deliver Program Oligonucleotides to ISIS as set forth in Article 4 and in conformity with the specifications, is considered a material breach of this Agreement and must be cured to the satisfaction of ISIS within [***] Days of notice of the same to IDT by ISIS. Failure by IDT to cure such a breach within thirty [***] Days is grounds for ISIS's elective termination of this Agreement. In the event IDT refuses to supply Program Oligonucleotides to ISIS in accordance with Article 2 herein, and/or IDT refuses to cure a material breach of this Agreement, such acts shall constitute an elective termination by IDT, and in such events ISIS shall be entitled to a refund of its unused and outstanding Customer Deposit.

8.5 EFFECT OF EXPIRATION OR TERMINATION OF AGREEMENT. Within [***] days after expiration or termination (the date of termination will be the date upon which the [***] day notice period lapses) of this Agreement, each Party shall return to the other Party any and all Confidential Information (Article 7) provided by the other Party pursuant to this Agreement. ISIS shall have the right to obtain and use all Program Oligonucleotides for which ISIS has paid and that are in IDT's possession, or that are scheduled to be manufactured, at the time of termination. Except to the extent expressly provided to the contrary, the rights and obligations of the Parties pursuant to Articles 5,6,7 9, and 10, shall survive the expiration or termination of this Agreement. Any and all rights of IDT to payments accrued through expiration or termination as well as obligations of the Parties under firm orders for purchase and delivery of Program Oligonucleotides at the time of such expiration or termination shall remain in effect. IDT will have no obligation to sell and deliver Program Oligonucleotides to ISIS that have delivery dates more than thirty (30) Business Days after the date of termination, and in the case of termination under paragraphs 8.2 or 8.3, the terminating Party has discretion in electing whether firm orders will remain in effect. Upon expiration of this Agreement, or termination of this Agreement for reasons other than an IDT elective termination as defined in 8.4 herein, any unused Customer Deposit shall be forfeited by ISIS and will default to IDT. Upon termination of this Agreement under paragraphs 8.2, 8.3, or 8.4, or upon expiration of this Agreement under 8.1, IDT shall immediately transfer to ISIS possession of ISIS Supplied Reagents upon notice from ISIS of the final post-termination receipt of Program Oligonucleotides, if any.

ARTICLE 9
INDEMNIFICATION

9.1 INDEMNIFICATION. Each Party (the "Indemnifying Party") agrees to defend the other Party and such other Party's Affiliates and their respective directors, officers, employees and agents (the "Indemnified Parties") at the Indemnifying Party's cost and expense, and shall hold the Indemnified Parties harmless from and against any losses, costs, damages, fees or expenses arising out of any third party claim relating to (i) any breach by the Indemnifying Party of any of its representations, warranties or obligations pursuant to this Agreement, or (ii) product liability or liability stemming from allegations of contributory infringement resulting from use of a product made, sold or imported by or for the Indemnifying Party.

9.2 NOTICE/REPRESENTATION. In the event of any claim against the Indemnified Parties by any third party for which indemnification may be sought pursuant to this Agreement, the Indemnified Party shall promptly notify the Indemnifying Party in writing of the claim; provided that the failure to promptly notify the Indemnifying Party of such claim shall not result in the loss of rights of indemnification hereunder

except to the extent that the Indemnifying Party was materially prejudiced by such failure. The Indemnifying Party shall assume, at its sole expense, the defense of the claim and its settlement. The Indemnified Parties shall cooperate with the Indemnifying Party and may, at their option and expense, be represented in any such action or proceeding. The Indemnifying Party shall not be liable for any litigation costs or expenses incurred by the Indemnified Parties. In addition, the Indemnifying Party shall not be responsible for the indemnification of any Indemnified Party arising from any negligent or wrongful acts by such Indemnified Party, or as the result of any settlement or compromise by the Indemnified Parties without the Indemnifying Party's prior written consent. The Indemnifying Party may not settle or compromise any matter without the consent of the Indemnified Parties unless such settlement or compromise imposes no obligations on the Indemnified Parties and does not restrict the rights of the Indemnified Parties.

ARTICLE 10
GENERAL

10.1 GOVERNING LAW. This Agreement shall be construed and the respective rights of the Parties determined according to the laws of the State of New York (without regard to the conflict of law rules of any jurisdiction), except as regarding matters of intellectual property law, which shall be determined in accordance with the national intellectual property laws relevant of the intellectual property in question.

10.2 ASSIGNMENT. Neither IDT nor Isis may assign this Agreement in whole or in part without the consent of the other Party, except if such assignment occurs in connection with the sale or transfer of all or substantially all of the business or assets of the assigning Party to which the subject matters of this Agreement pertains.

10.3 ENTIRE AGREEMENT; AMENDMENTS. This Agreement, together with the Appendices incorporated herein, constitute the entire agreement between the Parties with respect to the subject matter hereof, and supersedes all previous arrangements with respect to the subject matter hereof, whether written or oral. Any amendment or modification to this Agreement shall be made in writing signed by both Parties.

10.4 NOTICES. Notices with respect to IDT shall be sent to:

Joseph A. Walder, M.D., Ph.D.
Attn: Legal Department
Integrated DNA Technologies, Inc.
1710 Commercial Park
Coralville, IA
52241-9802;

With a duplicate sent to:

Mark Campbell, J.D., COO
Corporate Vice President
Integrated DNA Technologies, Inc.
8930 Gross Point Road, Suite 700
Skokie, Illinois,
60077;

and with respect to ISIS:

B. Lynne Parshall, J.D.
Isis Pharmaceuticals, Inc.
Executive Vice President and CFO
2292 Faraday Avenue
Carlsbad, CA
92008

With a duplicate sent to:

President, GeneTrove Division
Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA
92008

Any Party may change its address by giving notice to the other Party in the manner herein provided. Any notice required or provided for by the terms of this Agreement shall be in writing and shall be (a) delivered personally, (b) sent by registered or certified mail, return receipt requested, postage prepaid, (c) sent via a reputable overnight courier service, or (d)

sent by facsimile transmission with an original to be followed the same day via a reputable overnight courier service, in each case properly addressed in accordance with the paragraph above. The effective date of notice shall be the actual date of receipt by the Party receiving the same.

10.6 FORCE MAJURE. No failure or omission by a Party in the performance of any of its obligations of this Agreement shall be deemed a breach of this Agreement or create any liability if the same shall arise from any cause or causes beyond the control of such Party, including, but not limited to, the following: acts of God; acts or omissions of any government; any rules, regulations or orders issued by any governmental authority or by any officer, department, agency or instrumentality thereof; fire; storm; flood; earthquake; accident; war; rebellion; insurrection; riot; terrorist activities; and invasion and provided that such failure or omission resulting from one of the above causes is cured as soon as is practicable after the occurrence of one or more of the above-mentioned causes.

10.7 DISCLOSURE OF PROVISIONS OF AGREEMENT.

Each Party agrees to hold as confidential the terms of this Agreement, except that:

(i) IDT may furnish a copy of this Agreement to the University of Iowa Research Foundation; and,

(ii) Each Party shall have the right to disclose the terms of this Agreement to investors and other third parties in connection with financing activities and to potential collaborators, provided that any such third party has entered into a written obligation with the disclosing Party to treat such information and materials as confidential and to not use the information materials for any purposes other than the evaluation of the potential investment or collaboration and that the disclosing Party shall enforce against the third party recipient of such information and materials, for and on behalf of the other Party, such written obligation; and,

(iii) Each Party may furnish a copy of this Agreement or disclose the terms of this if such is required to be disclosed by the receiving Party to comply with applicable laws, to defend, prosecute or preclude litigation, or to comply with governmental regulations, PROVIDED THAT the receiving Party provides prior written notice of such disclosure to the disclosing Party and takes reasonable and lawful actions to avoid and/or minimize the degree of such disclosure. At the request of the other Party, the disclosing Party shall use commercially reasonable efforts to enforce such obligations against such third parties.

(iv) Each Party may include this Agreement, in any report, statement or other document filed by such Party with the United States Securities and Exchange Commission (the "SEC"). In such event, the disclosing Party shall use reasonable efforts to obtain, to the extent permitted by law,

confidential treatment from the SEC of any trade secrets and commercial or financial information of a privileged or confidential nature, including without limitation all information on the Exhibits

hereto relating to patent applications of Isis or IDT, and shall notify the other Party as to such efforts and all related communications with the SEC; provided that notwithstanding the foregoing no Party shall submit a confidentiality request or include this Agreement without the prior review and approval of the confidentiality request by the other Party, which review and approval shall not be unreasonably withheld or delayed.

(v) The Parties will cooperate in the development of any public announcement announcements or similar publicity with respect to the execution of this Agreement. The content and timing of any such announcement or publicity shall be agreed upon between Parties in advance of such announcement.

10.8 INDEPENDENT CONTRACTORS. It is understood and agreed that the relationship between the Parties hereunder is that of independent contractors and that nothing in this Agreement shall be construed as authorization for either Party to act as agent for the other.

10.9 NO STRICT CONSTRUCTION. This Agreement has been prepared jointly and shall not be strictly construed against any Party.

10.10 HEADINGS. The captions or headings of the Sections or other subdivisions hereof are inserted only as a matter of convenience or for reference and shall have no effect on the meaning of the provisions hereof.

10.11 NO IMPLIED WAIVERS; RIGHTS CUMULATIVE. No failure on the part of either Party to exercise, and no delay in exercising, any right, power, remedy or privilege under this Agreement, or provided by statute or at law or in equity or otherwise, shall impair, prejudice or constitute a waiver of any such right, power, remedy or privilege or be construed as a waiver of any breach of this Agreement or as an acquiescence therein, nor shall any single or partial exercise of any such right, power, remedy or privilege preclude any other or further exercise thereof or the exercise of any other right, power, remedy or privilege.

10.12 SEVERABILITY. If any provision hereof should be held invalid, illegal or unenforceable in any respect in any jurisdiction, then, to the fullest extent permitted by law, (a) all other provisions hereof shall remain in full force and effect in such jurisdiction and shall be liberally construed in order to carry out the intentions of the Parties as nearly as may be possible and (b) such invalidity, illegality or unenforceability shall not affect the validity, legality or enforceability of such provision in any other jurisdiction.

10.13 CURRENCY. All references to prices and/or monies owed in this Agreement are to United States dollars.

10.14 EXECUTION IN COUNTERPARTS. This Agreement may be executed in counterparts, each of which counterparts, when so executed and delivered, shall be deemed to be an original, and all of which counterparts, taken together, shall constitute one and the same instrument.

REMAINDER OF THIS PAGE LEFT INTENTIONALLY BLANK
SIGNATURE PAGE TO IMMEDIATELY FOLLOW

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement by their duly authorized representatives.

ISIS PHARMACEUTICALS, INC.	INTEGRATED DNA TECHNOLOGIES, INC.
By: Richard K. Brown	By: Dr. Joseph A. Walder

Signature: /s/ Richard K. Brown	Signature: /s/ Dr. Joseph A. Walder
Title: President, GeneTrove Vice President, ISIS Pharmaceuticals	Title: President & CEO
Date: 12/04/01	Date: 12/04/01

APPENDIX A

PROGRAM OLIGONUCLEOTIDE SPECIFICATIONS AND OTHER CRITERIA

PROGRAM OLIGONUCLEOTIDE TYPE	PURITY BY MASS SPEC	ABSORBANCE	ADDITIONAL HPLC	RATIO	ANALYSIS/HANDLING
MOE OLIGOS [***]	To be determined*	To be determined	To be determined	To be determined	To be determined
[***]	To be determined	To be determined	To be determined	To be determined	To be determined
QUANTIFICATION OLIGOS	To be determined	To be determined	To be determined	To be determined	To be determined
Probes To be determined	To be determined	To be determined	To be determined	To be determined	To be determined
Primers To be determined	To be determined	To be determined	To be determined	To be determined	To be determined
"Primer Probe Sets" To be determined	To be determined	To be determined	To be determined	To be determined	To be determined

* POSC to determine test use and test specifications

APPENDIX B
APPLICATION OF 4.3 PRICING PROVISION

PROGRAM OLIGONUCLEOTIDE TYPE	SYNTHESIS SCALE
[***]	

* NON-CATALOG ITEM

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

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

[ISIS PHARMACEUTICALS LOGO]

AMENDED & RESTATED IDT-ISIS LICENSING AGREEMENT

By and between

ISIS PHARMACEUTICALS, INC.

2292 Faraday Avenue, Carlsbad, California 92008
Hereinafter referred to as "ISIS"

and

INTEGRATED DNA TECHNOLOGIES, INC
1710 Commercial Park, Coralville, Iowa 52241
Hereinafter referred to as ("IDT")

Dated as of

DECEMBER 4, 2001.

RECITALS

WHEREAS, ISIS and IDT entered into a Licensing Agreement dated as of March 12, 1999, (the "Original Agreement") which contains certain limitations in the licenses obtained by each Party; and,

WHEREAS, ISIS and IDT would mutually benefit from expanding and clarifying the scope of licenses obtained in the Original Agreement to include more broad sublicensing rights for ISIS, including rights in the fields of functional genomics, target validation, and antisense drug development, and to provide IDT with rights under ISIS's RNase H suite of patents for sales of oligonucleotides;

NOW, THEREFORE the parties hereby agree to replace and irrevocably supercede the Original Agreement with this Amended and Restated IDT-ISIS Licensing Agreement (hereinafter the "Restated Agreement") as follows:

ARTICLE I
INTERPRETATION & EFFECT

1.1 SUPERCEDING AGREEMENT. It is the intent of the Parties to irrevocably supercede the Original Agreement with this Restated Agreement. The rights and obligations of the parties are to be exclusively defined by the terms, conditions, rights, and obligations as expressed herein. All existing and future rights and obligations of the Parties, including specifically all post-termination rights and obligations, contained in the Original Agreement are hereby null and void. In the event any term of the Original Agreement is not specifically superceded, modified or replaced by a corresponding term of the Restated Agreement, it shall be construed as a deliberate omission by the Parties.

1.2 EFFECTIVE DATE; WAIVERS. In exchange for the good and valuable consideration received by each Party described herein, each Party hereby irrevocably waives all claims to royalties or related damages arising out of the performance or conduct of the other Party prior to the Restated Agreement Effective Date, as hereinunder defined. The execution of this Restated Agreement shall not be interpreted as requiring either the repayment of licensing fees paid by ISIS pursuant to the Original Agreement, nor shall it be interpreted as requiring refund of such payments by IDT.

ARTICLE 2
DEFINTIONS

The following terms when used in this Restated Agreement shall be given the meanings contained herein:

2.1 "Academic Market" shall mean end-users employed by and located at or in academic, university, government, and other 501(c)(3) registered not-for-profit organizations; provided however that specifically excluded from this definition shall be those end-users at such institutions whose research is directly funded by a for-profit corporation for the purpose of drug discovery, drug development, or target validation/gene functionalization wherein the funding corporation has a specific legal interest or right to the data and information of the funded research.

2.2 "Affiliates" shall mean any corporation, company, partnership, joint venture or other entity, which controls, is controlled or under common control with Isis or IDT as the case may be, and in the case of Isis shall also mean and include Pantheco, APS. For the purposes of this definition, control shall mean the direct or indirect ownership of at least fifty percent (50%) or, if less than fifty percent (50%), the maximum percentage as allowed by applicable law of (a) the stock shares entitled to vote for the election of directors; or (b) ownership interest.

2.3 "Antisense Drug Development Sublicenses" shall mean licenses/sublicenses under the Walder Patents to third parties to pursue all Medical Applications, which are not based on ISIS Licensed Products. Antisense Drug Development Sublicense holders shall have the limited right to issue sublicenses as a Product Sublicense under the Walder Patents to third-parties.

2.4 "Antisense Oligonucleotide" shall mean a polynucleotide, oligonucleotide, or oligonucleotide analog, which hybridizes in a sequence specific manner under physiological conditions to RNA forming an RNA-DNA duplex, which duplex acts to modulate the production of a targeted gene product. An antisense oligonucleotide analog may include naturally occurring or non-natural heterocycles, sugar and/or backbone linkages, and may be a molecule in which the sugar may be absent, in which the backbone linkage may be phosphate based, amide based, or based on other chemistries and which may or may not include stem loop or structural units.

2.5 "Competing Oligonucleotide Supplier" shall mean any entity having a license from ISIS or its Affiliates to manufacture and/or sell Antisense Oligonucleotides for use in Research Applications.

2.6 "Confidential Information" shall mean information disclosed pursuant to an obligation contained in this Restated Agreement, including, without limitation, proprietary information and materials (whether or not patentable) regarding a Party's technology, products, business information or objectives, which is designated as confidential in writing by the disclosing Party, whether by letter or by the use of an appropriate stamp or legend, prior to or at the time any such information is disclosed by the disclosing Party to the other Party.

2.7 "Fee for Service FGTV Licenses" shall mean sublicenses under the Walder Patents to commercial entities offering antisense functional genomics/target validation products or services, including but not limited to database subscriptions, to third-parties. Specifically

excluded from this definition shall be licenses under the Walder Patents to Competing Oligonucleotide Suppliers and other entities that sell oligonucleotides as an independent product (i.e, sales of oligonucleotides that are not related to the provision of a complementary functional genomic or target validation service to the third-party purchasing the oligonucleotides).

2.8 "IDT Licensed Commercial Product" shall mean and include any diagnostic, therapeutic, or prophylactic material, composition of matter, or method that either (a) is covered by a Valid Claims of any patent within the definition of the Walder Patents; or (b) the manufacture, use or sale of which would constitute, but for the license granted pursuant to this Restated Agreement, an infringement of any Valid Claim within the definition of the Walder Patents.

2.9 "In-House FGTV Licenses" shall mean licenses under the Walder patents to end-users at any for-profit commercial entity using Antisense Oligonucleotides to use antisense-based functional genomic/target validation products and services for that licensee's internal research and development.

2.10 "ISIS Academic Patents". Those patents defined, described or listed on Exhibit 1, as it may be expanded from time to time at ISIS's discretion. {Specifically INCLUDED in the definition of the "ISIS Academic Patents" are U.S. Patents [***] and the two allowed patent applications listed on Exhibit 1 herein, and all existing and future patent applications or patents that specifically claim the RNase H Mechanism of Action, which patents or applications ISIS can license or sublicense to IDT that IDT may require to make, use or sell Antisense Oligonucleotides for the Academic Market. Specifically EXCLUDED from the definition of "ISIS Academic Patents" shall be all patents or relevant patent claims related to clinical formulations and administration of oligonucleotides (including, without limitation, methods and reagents for the clinical delivery of oligonucleotides); gene-related patents, including without limitation patents to specific gene structures, gene targets and methods of treatment; 2' MOE technology, and any other patents and/or claims regarding chemistries not listed on Exhibit 1.}

2.11 "ISIS Licensed Product" an ISIS oligonucleotide drug or drug candidate molecule licensed to a third party for further development, commercialization, manufacture or distribution of the oligonucleotide drug or drug candidate molecule.

2.12 "Licensed Purchaser of RNase H Oligonucleotides " shall mean a third-party for-profit commercial entity that has obtained from ISIS a license to use RNase H Oligonucleotides.

2.13 "Medical Applications" shall mean diagnostic products, therapeutic and prophylactic drugs or vaccines, intended for the diagnosis, prevention, or treatment of disease in humans, animals or plants and all discovery, research, development, and commercialization efforts to support those uses, including without limitation, elucidation of gene function and target validation.

2.14 "Net Sales" shall mean the gross receipts received by ISIS or its Affiliates or sublicensees, as appropriate, for the sale of IDT Licensed Commercial Products by ISIS and its Affiliates or its sublicensees, as appropriate, less the following deductions:

(i) Prompt payment or other trade or quantity discounts actually allowed and taken in such amounts as are customary in the trade;

(ii) Commissions paid or allowed to distributors and agents who are independent third parties other than such parties who are solely performing detailing functions;

(iii) Amounts paid or credited by reason of timely rejection or returns;

(iv) Taxes (other than franchise or income taxes on the income of Isis actually paid or withheld;

(v) Allowances including any allowances for bad debt. Provided that upon the extinguishment of any such allowance, the extinguishment will be determined to be a receipt;

(vi) Transportation and delivery charges, including insurance premiums actually incurred;

Notwithstanding the foregoing, amounts received by ISIS or its Affiliates or sublicensees for the sale of IDT Licensed Commercial

Products among ISIS, its Affiliates or sublicensees whether for their internal use or for resale or other disposition will not be included in the computation of Net Sales hereunder. For purposes of this Restated Agreement a distributor will not be deemed a sublicensee and sales by ISIS, its Affiliates or sublicensees to a distributor will not be subject to royalties.

2.15 "Original Agreement" shall mean the Licensing Agreement executed by IDT and ISIS with an effective date of March 12, 1999 (attached hereto as Attachment 1).

2.16 "Product Sublicense" shall mean a sublicense under the Walder Patents to further develop, commercialize, manufacture or distribute an oligonucleotide drug or drug candidate molecule, which sublicense is granted by either: (a) ISIS under Article 3 of the Restated Agreement; or (b) an Antisense Drug Development Sublicense holder.

2.17 "Restated Agreement Effective Date" shall be the day of last dated signature of a signatory to this Restated Agreement.

2.18 "RNase H Mechanisms of Action" means methods of using RNase H enzymes to cleave a targeted RNA in cells.

2.19 RNase H Oligonucleotides" shall mean an Antisense Oligonucleotide that acts by the RNase H Mechanism of Action.

2.20 "Research Applications" shall mean all non-therapeutic uses of oligonucleotides including but not limited to all in vitro cell culture, tissue culture, laboratory animal, plant and microorganism studies.

2.21 "Walder Patents" shall mean and include [***] and all divisionals, reissues, and foreign counterparts derived from these patents and patent applications.

2.22 "Valid Claim" shall mean a claim of an issued patent that has not been ruled invalid or unenforceable by a court of competent jurisdiction in an unappealed or unappealable decision.

ARTICLE 3
IDT GRANT OF LICENSES TO ISIS

3.1 MEDICAL APPLICATIONS. IDT grants to Isis, a non-exclusive, royalty-bearing, worldwide license to make, have made, use, offer to sell, import, and sell IDT Licensed Commercial Products for all Medical Applications (the "Medical Applications License"). Isis may at its option extend the licenses granted hereunder to an Affiliate, in which event a sublicensing fee will not be required.

3.1.1 PRODUCT SUBLICENSES. ISIS may grant written sublicenses under this Medical Applications License to third parties to further develop, commercialize, manufacture or distribute an oligonucleotide drug or drug candidate molecule (a "Product Sublicense" and/or Product Sublicensee). Isis will inform IDT of the identity of any such Product Sublicensee and the nature of such sublicense within 60 days of execution of such sublicense and warrant to IDT that the grant of rights to any sublicensee will conform to the grant of rights hereunder. Any agreement granting a sublicense shall state that the sublicense is subject to the terms of this Restated Agreement. Isis shall have the same accounting and reporting responsibilities for the activities of any sublicensee, as if the activities were directly those of Isis.

3.2 FUNCTIONAL GENOMICS AND TARGET VALIDATION LICENSE. IDT grants to ISIS a fully paid-up, non-royalty bearing, worldwide, exclusive license (except with respect to IDT, and with respect to rights already granted to [***] (as described in section 3.2.1 hereunder) under the Walder Patents to make, have made, use, import, offer to sell, and sell all functional genomics and target validation products and services ("the FGTV License").

3.2.1 FEE-FOR-SERVICE FGTV SUBLICENSES. IDT grants to ISIS the exclusive right, even as to IDT, to issue Fee-for Service

FGTV Licenses under the Walder Patents to third parties. ISIS will have no royalty or other contingent payment obligations to IDT with respect to sublicenses granted under this provision. ISIS acknowledges that prior to the execution of this Restated Agreement, [***] has obtained a Fee for Service FGTV license from IDT, the scope and validity of which is not affected by the exclusive rights granted ISIS in 3.2.1, herein. IDT agrees that it shall not

amend or expand the [***] attached hereto as Exhibit 3, without the prior written approval of ISIS.

3.2.2 IN-HOUSE FGTV SUBLICENSES. IDT grants to ISIS the exclusive right even as to IDT to issue future In-House FGTV Licenses under the Walder Patents to third parties. ISIS will have no royalty or other contingent payment obligations to IDT with respect to sublicenses granted under this provision.

3.2.3 IDT RETAINED RIGHTS. IDT reserves all rights under the Walder Patents to make, use and sell oligonucleotides and other products and services.

3.3 ANTISENSE DRUG DEVELOPMENT SUBLICENSES. IDT grants to ISIS a term-limited exclusive license (even as to IDT) to issue Antisense Drug Development Sublicenses under the Walder patents to third-parties. ISIS's shall pay IDT a [***] initial license payment pursuant to Article 5 herein, within ten (10) days of the Restated Agreement Effective Date, to maintain the exclusivity of the license for a period of [***] years following the Restated Agreement Effective Date.

3.3.1 OPTION TO EXTEND EXCLUSIVITY. ISIS will have the option to extend the exclusivity of the license for the duration of the last to expire of the Walder Patents for an additional [***]payment, such payment to be made within thirty (30) days of the expiration of the initial [***] period, stated herein.

3.3.2 EFFECT OF LOST EXCLUSIVITY. Should ISIS not exercise the option in 3.3.1 ISIS's exclusive right to issue Antisense Drug Development Sublicenses will revert to a non-exclusive right, without further initial payment obligation to IDT. In that event, IDT shall have the right to issue Antisense Drug Development Sublicenses under the Walder Patents to third-parties. In this instance, notwithstanding the provisions of 3.2.2., IDT shall have the right to grant an In-House FGTV Licenses under the Walder Patents as a part of an Antisense Drug Development Sublicense.

3.3.3 SUBLICENSING PAYMENTS. For each Antisense Drug Development sublicense issued by ISIS under this provision, ISIS will pay IDT or will obligate the Antisense Drug Development Sublicense Holder to pay IDT, the initial sublicensing fees and Royalties as established in Appendix A, attached, and to comply with or fulfill all necessary reporting and accounting obligations as defined in this Restated Agreement. ISIS's initial license payments (specifically the [***] payment and the optional [***] payment) made under this provision will be creditable against initial sublicensing fees and royalty payments owed to IDT pursuant to the issuance of Antisense Drug Development Sublicenses.

3.3.4 PRIOR LICENSES. ISIS acknowledges that prior to this First Amendment, Hybridon Inc., and Epigenesis Pharmaceuticals, Inc., have each obtained an Antisense Drug Development Sublicense from IDT, the scope and validity of which is not affected by the exclusive rights granted ISIS in paragraph 3.3 herein. IDT agrees that it shall not amend or expand either of such licenses without ISIS's prior written approval.

3.4 NOTICE OBLIGATIONS. To minimize confusion with respect to the sublicensing activities of ISIS, or its sublicensees, ISIS agrees to the following:

3.4.1 NOTICES TO IDT OF SUBLICENSES. Isis shall provide IDT with written notice of any sublicense granted pursuant to this Restated Agreement within ten (10) days after the grant of such sublicense, such written notice specifying the name of the sublicensee, the date of the sublicense, and whether such sublicense is a Product Sublicense, a Fee-for-Service FGTV Sublicense, an In-House FGTV Sublicense, or an Antisense Drug Development Sublicense. With respect to Antisense Drug Development Sublicenses, ISIS will pay or cause the Antisense Drug Development Sublicense Holder to pay, the initial sublicensing fee to IDT within twenty (20) days of the execution of such sublicense.

3.4.2 NOTICE TO IDT OF LICENSED PURCHASERS. Along with notice of an In-House FGTV Sublicense required in 3.4.1, Isis shall provide to IDT, a complete list of Licensed Purchasers of RNase H Oligonucleotides upon the written request of IDT, such requests not to exceed two per calendar year.

3.4.3 [***]

ARTICLE 4
LICENSES TO IDT

4.1 IDT SALES TO THE ACADEMIC MARKET. ISIS grants to IDT a worldwide, fully paid-up, non-royalty bearing, non-exclusive license under the ISIS Academic Patents to make, have made, use, import, offer to sell, sell, and have sold oligonucleotides and other related research products to the Academic Market.

4.2 RESTRICTIONS ON SALES. Within thirty (30) days of the Restated Agreement Effective Date, and consistent with the provisions of section 3.2.1 herein, IDT agrees to suspend sales of any RNase H Oligonucleotides to third-parties except as may be required by IDT's existing obligations, for incorporation into antisense-based functional genomics/target validation products or incorporation into a commercial service, unless IDT receives the prior written authorization from ISIS.

4.3 THIRD-PARTY OBLIGATIONS. IDT acknowledges that ISIS may have certain financial and reporting obligations under licenses it has obtained from third parties to certain patents included in the definition of ISIS Academic Patents. IDT agrees to either pay all associated financial obligations (except upfront licensing fees) and fulfill all associated legal/reporting obligations that may be required of ISIS to a third-party for sales of products by IDT under the sublicense, or IDT shall refuse the sublicense under such patent(s) and it shall be deleted from the Academic Patents. ISIS shall promptly notify IDT of the precise nature of all such obligations so that IDT can make the required election(s).

4.4 ISIS RETAINED RIGHTS. Notwithstanding the licenses granted to IDT herein, Isis shall retain all rights, however characterized under all ISIS Academic Patents and the RNase H Suite of Patents, including without limitation, rights to use, have used, make, have made, import, have imported, offer to sell, sell, and have sold oligonucleotides and related technologies for any and all applications.

4.5 [***]

ARTICLE 5
CONSIDERATION

5.1 GUARANTEED PAYMENTS. Within five (5) days of the Restated Agreement Effective Date, ISIS will pay to IDT the sum of $3,500,000 structured as follows:

(i) $3 million in non-refundable licensing fees;
(ii) $500,000 for exclusive rights to issue Antisense Drug Development sublicenses under section 3.3 herein,

In addition, ISIS will pay IDT $350,000 in non-refundable licensing fees on or before each of the first four (4) anniversary dates of the Restated Agreement Effective Date (i.e. four anniversary payments totaling $1.4 million).

5.2 CONTINGENT ROYALTY PAYMENTS. In further consideration for the Medical Application License and the exclusive right to issue Antisense Drug Development Sublicenses granted herein, Isis agrees to pay IDT [***] of Net Sales from each IDT Licensed Commercial Product sold by Isis, or its Sublicensees, however characterized, beginning with the first sale to any unrelated third party, according to the terms and conditions of Article 6 herein.

5.3 CONTINGENT SUBLICENSING FEES. ISIS shall pay to IDT, or shall cause the sublicensee to pay to IDT, the initial licensing fees as defined in Appendix A for all Antisense Drug Development sublicenses issued by ISIS under this Restated Agreement.

ARTICLE 6
ACCOUNTING /PAYMENTS

6.1 QUARTERLY ESTIMATES. For each calendar year in which there are Net Sales of IDT Licensed Commercial Products ISIS shall prepare, or cause its Affiliates or sublicensees to prepare, deliver and pay to IDT a quarterly estimate of the royalty payments due to IDT under Section 5.1 herein, within sixty (60) days following the last day of the first, second, and third quarters of each calendar year of ISIS.

6.2 ANNUAL REPORT. Within ninety (90) days following the last day of each calendar year, ISIS, its Affiliates, or licensees, whichever is applicable, shall prepare and deliver an annual report of the total royalty payments due to IDT for the calendar year expired. The reporting party shall tender payment of the balance owed for the year, including all payments owed for the fourth quarter of the year expired, and any necessary adjustments

to the quarterly estimate payments previously paid. Each quarterly estimate or annual payment shall be accompanied by a statement of account which shall indicate the estimated or actual Net Sales, as the case may be, by the reporting party for the previous period and shall show the amount of royalties due IDT with sufficient detail to enable confirmation of the calculations by IDT.

6.3 PAYMENT CURRENCY. Except as otherwise directed, all amounts owing to IDT under this Restated Agreement shall be paid in U.S. dollars to IDT at the addresses provided or via wire transfer to a specified IDT account. All royalties owing with respect to Net Sales stated in currencies other than U.S. dollars shall be converted at the rate shown in the Wall Street Journal on the last day of the quarter for which the royalty is due, or shall be converted according to the terms governing conversion for an Isis sublicensee.

6.4 RECORDKEEPING. Isis, its Affiliates and its sublicensee(s) shall keep books and records sufficient to verify the accuracy and completeness of the accounting referred to above, including without limitation sales, accounts receivable, and invoice records relating to IDT Licensed Commercial Products. Such books and records shall be preserved for a period not less than five (5) years after they are created during and after the term of this Restated Agreement.

6.5 AUDITING/DEFICIENCIES. Isis, its Affiliates, and its sublicensee(s) shall take all steps necessary so that IDT may, within sixty days of its request, review and copy all the books and records at a single U.S. location to verify the accuracy of Isis and its sublicensee(s)'s accounting. Such review shall be made not more than once each calendar year, upon reasonable notice and during regular business hours, at the expense of IDT by a certified public accountant to whom there is no reasonable objection by either party. If a royalty payment deficiency for a calendar year is determined, the reporting party shall pay the royalty deficiency outstanding within thirty (30) days of receiving written notice thereof, and shall reimburse IDT for the cost of the inspection.

ARTICLE 7
WARRANTIES/INDEMNIFICATIONS.

7.1 NO CONSEQUENTIAL DAMAGES. Neither Party shall be liable to the other Party, its Affiliates, sublicensees, successors, or assigns for any loss of profits, loss of business, interruption of business, nor for indirect, special or consequential damages of any kind under this Restated Agreement.

7.2 WARRANTY OF AUTHORITY. The parties warrant each has the right to grant the licenses granted to the other party in this Restated Agreement. IDT warrants that it does not own or control any patents or patent applications with claims to antisense compounds and/or methods not already disclosed in the definition of the "Walder Patents".

7.3 WARRANTY DISCLAIMERS. Except as expressly set forth herein, IDT and Isis make no representations, extend no warranties of any kind, either express or implied, and assume no responsibilities whatsoever with respect to use, sale, or other disposition by the other

party, its Affiliates, sublicensees or their vendees or other transferees, of IDT Licensed Commercial Products. EXCEPT AS EXPRESSLY SET FORTH HEREIN, NOTHING IN THIS RESTATED AGREEMENT, NOR ANY PRIOR COMMUNICATION, SHALL BE CONSTRUED AS:

(i) A WARRANTY OR REPRESENTATION BY IDT OR ISIS AS TO THE VALIDITY OR SCOPE OF ANY OF THE PATENTS CONTAINED WITHIN THE DEFINITIONS OF THE WALDER PATENTS AND ISIS ACADEMIC PATENTS, RESPECTIVELY;

(ii) A WARRANTY OR REPRESENTATION THAT ANYTHING MADE, USED, SOLD OR OTHERWISE DISPOSED OF UNDER THE LICENSES GRANTED IN THIS RESTATED AGREEMENT WILL OR WILL NOT INFRINGE PATENTS OF THIRD PARTIES; OR

(iii) AN OBLIGATION TO FURNISH ANY KNOW-HOW NOT PROVIDED IN THE WALDER PATENTS OR THE ISIS ACADEMIC PATENTS OR ANY SERVICES OTHER THAN THOSE SPECIFIED IN THIS RESTATED AGREEMENT OR RELATED AGREEMENTS.

7.4 INDEMNIFICATION. Isis and IDT shall at all times during the term of this Restated Agreement and thereafter, indemnify, defend and hold each other, the University of Iowa Research Foundation/University of Iowa, and the authors and inventors of the Walder Patents and the Isis Academic Patents harmless against all claims and expenses, including legal expenses and reasonable attorneys fees, arising out of the death of or injury to any person or persons or out of any damage to property and against any other claim, proceeding, demand, expense and liability of any kind whatsoever resulting from the production, manufacture, sale, use, lease, consumption or advertisement of products or processes arising from any right or obligation of IDT or Isis, or their Affiliates, or any of its sublicensee(s) granted herein. Notwithstanding the above, IDT and Isis at all times reserves the right to retain counsel of its own to defend IDT's or Isis's interest.

ARTICLE 8
CONFIDENTIAL INFORMATION

8.1 CONFIDENTIALITY. Isis and IDT each agrees to treat as confidential and to use only in the conduct of its business, all Confidential Information disclosed to it by the other party.

8.2 NON-DISCLOSURE AND NON-USE. Isis and IDT each agrees not to disclose any of the Confidential Information received from the other party to any unauthorized third party and not to use any of the Confidential Information except to fulfill the terms of the Restated Agreement, for a period of five (5) years from the receipt of the Confidential Information.

8.3 RELEASE FROM RESTRICTIONS. All information which is characterized as Confidential Information shall cease to be confidential and the receiving party shall be released from their respective obligations under sections 8.1 and 8.2 herein, if such information (i) is legally known to or was in the possession of the receiving party at the time of the disclosure; (ii) legally is or has become part of the public domain through no act or omission of the receiving party; (iii) has been disclosed to the recipient by a third party

without restriction as to the use or disclosure of the information: (iv) is available to the general public as a result of a governmentally required release or disclosure.

ARTICLE 9.
TERM AND TERMINATION.

9.1 TERM. The term of this Restated Agreement shall extend until the last patent to expire included within the Walder Patents or Isis Academic Patents, whichever expires later.

9.2 TERMINATION FOR BREACH. In the event either party shall materially breach any of the terms, conditions and agreements contained in this Restated Agreement, then the alleging party may, at its election, notify the other party of the alleged breach giving the other party thirty (30) days written notice to cure the breach or begin good faith negotiations to resolve such alleged breach. If the alleged breach is not resolved to the satisfaction of the alleging party within thirty (30) days of the first giving of notice the alleging party may, at its option, bring arbitration proceedings under Article 12. In the event of a good faith dispute about monetary obligations, the notified party will pay any undisputed amounts to the alleging party and pay any disputed amounts into escrow pending resolution of such dispute, with payment to be made to the prevailing party. The licenses granted hereunder are not terminable except in the event of bankruptcy of a Licensee, subject to Sections 9.3 9.4, and 9.5, and the continuing rights of sublicensees.

9.3 ELECTIVE TERMINATION FOR BANKRUPTCY. In the event either Party shall become insolvent, bankrupt or subject to the provisions of the United States Bankruptcy Code, or makes any assignment for the benefit of creditors, or ceases to carry on business as a going concern, then the other Party shall have the right but not the obligation to terminate the licenses granted by the termination party in this Restated Agreement; provided however, that Isis hall have the right to grant to its sublicensee(s), the power to assume Isis's rights and obligations under its licenses, and correspondingly Isis, and its successor in interest, however organized, shall, to the extent permitted by law, maintain the licenses granted to IDT pursuant to this Restated Agreement.

9.3.1 BANKRUPTCY RIGHTS. In the event that this Restated Agreement is terminated by a Party hereto or its receiver or trustee under applicable bankruptcy laws due to such Party's bankruptcy, then all rights and licenses granted under or pursuant to this Restated Agreement by such Party to the other Party are, and will otherwise be deemed to be, for purposes of Section 365(n) of the Bankruptcy code and any similar law or regulation in any other country, licenses of rights to "intellectual property" as defined under section 101(35A) of the Bankruptcy Code. The Parties agree that all intellectual property rights licensed hereunder, including without limitation any patents or patent applications in any country of a Party covered by the license grants under this Restated Agreement, are part of the "intellectual property" as defined under Section 101(35A) of the Bankruptcy Code subject to the protections afforded the non-terminating Party under Section 365(n) of the Bankruptcy Code, and any similar law or regulation in any other country.

9.4 POST TERMINATION RIGHTS/OBLIGATIONS. Notwithstanding the foregoing, the following rights and obligations shall survive termination of this Restated Agreement to the degree necessary to permit their complete fulfillment or discharge:

9.4.1 IDT's right to receive or recover and ISIS's obligation to pay licensing or sublicensing fees or royalties accrued or accruable for payment at the time of any termination.

9.4.2 Licensee's obligation to maintain records and Licensor's right to receive final year accounting reports as provided in Section 3E.

9.4.3 Any cause of action or claim of Licensor, accrued or to accrue because of any breach or default by the Licensee;

9.4.4 The rights and obligations of both parties regarding confidentiality as defined in section 7 herein;

9.4.5 The warranty, indemnification and insurance provisions as set forth in Section 6C, 6D, and 6E.

9.4.6 The rights of ISIS, its Affiliates or sublicensees within [***] months following such date of termination, to sell or dispose of IDT Licensed Commercial Products completed or substantially completed on the date of termination and to complete orders, outstanding on such date of termination for such products.

9.4.7 The right of IDT or its Affiliates within [***] months following such date of termination, to sell or dispose of RNase H Oligonucleotides completed or substantially completed on the date of termination and to complete orders, outstanding on such date of termination for such products.

9.5 SUCCESSOR IN INTEREST TO IDT. Should IDT, or its assigns, become insolvent, bankrupt or subject to the provisions of the United States Bankruptcy Code or any other similar legislation of any jurisdiction, the right of the University of Iowa Research Foundation to assume IDT's interest in the Walder Patents shall not be abrogated in any way by any term or provision of this Agreement.

9.6 SURVIAL OF SUBLICENSES. Notwithstanding the termination of this Restated Agreement or any of the licenses or sublicenses granted hereunder, any sublicenses to the Walder Patents granted by ISIS or its Affiliates pursuant to Article 3 hereof prior to the termination of the Restated Agreement shall survive such termination. In such event, ISIS shall have the right to exercise all of the rights of IDT as the sublicensor under such sublicense, subject to its compliance with continuing obligations regarding surviving sublicenses as defined in section 9.4 herein.

ARTICLE 10
DISPUTE RESOLUTION

10.1 DISPUTES--ARBITRATION. The parties agree to attempt initially, to solve all claims, disputes, or controversies arising under, out of, or in connection with this Restated Agreement by conducting good faith negotiations. Except with respect to disputes as to the validity of patents, applications for injunctions, specific performance, or other equitable relief, any dispute arising out of or in connection with this Restated Agreement or any legal relationship associated therewith, that cannot be resolved amicably by the parties, shall be finally resolved by arbitration. The arbitration shall be conducted in accordance with the arbitration rules of the American Arbitration Association ("AAA") then in force, by one or more arbitrators appointed in accordance with said rules; provided, however, that arbitration proceedings may not be instituted until the party alleging breach of this Restated Agreement by the other party has given the other party not less than sixty (60) days notice to remedy any alleged breach and the other party has failed to do so. The place of arbitration shall be Cedar Rapids, Iowa, if Isis institutes the proceeding, and San Diego, California, if IDT institutes the proceeding. The award rendered shall be final and binding upon both parties. The judgment rendered shall include costs of arbitration, reasonable attorney's fees and reasonable costs for any expert and other witnesses. The arbitration may expressly consider the amounts paid pursuant to Sections 3B, 3C, and 3D, in considering any claims of any damages. Judgment upon the award may be entered in any court having jurisdiction, or application may be made to such court for judicial acceptance of the award and/or an order of enforcement. Disputes as to the validity and scope of patents shall be resolved by the courts of appropriate jurisdiction.

ARTICLE 11
MISCELLANEOUS

11.1 APPLICABLE LAW. This Restated Agreement shall be construed in accordance with the internal laws of the State of New York. If any provisions of this Agreement are or shall come into conflict with the laws or regulations of any jurisdiction or any governmental entity having jurisdiction over the parties or this Restated Agreement, those provisions shall be deemed automatically deleted, if such deletion is allowed by relevant law, and the remaining terms and conditions of this Restated Agreement shall remain in full force and effect. If such a deletion is not so allowed or if such a deletion leaves terms thereby made clearly illogical or inappropriate in effect, the parties agree to substitute new terms as similar in effect to the present terms of this Restated Agreement as may be allowed under the applicable laws and regulations. The parties hereto are independent contractors and not joint ventures or partners.

11.2 CONSTRUCTION/EFFECT. The parties acknowledge that this Restated Agreement has been the subject of full opportunity for negotiation and amendment and that the party who has taken the role of drafter shall not suffer any adverse construction of any terms or language of this Restated Agreement because of such role.

11.3 FORCE MAJEURE. A party hereto shall not be deemed in default with respect to the performance of or compliance with the terms, covenants, agreements conditions or provisos of this Agreement if the failure to perform or comply shall be due to any event of force majeure. "Force majeure" shall include natural disasters, acts of God, or any other event or cause beyond the control of the party claiming the benefit of this paragraph and which that party could not reasonably have protected itself against, provided however that lack of funds or credit shall not constitute an event of force majeure.

11.4 ASSIGNABILITY. This Restated Agreement may not be transferred or assigned by either party without the prior written consent of the other party, except that either Party may freely assign this Restated Agreement to (i) an Affiliate, if the assigning Party guarantees the full performance of its Affiliates' obligations hereunder, or (ii) an entity acquiring substantially all of Licensee's business to which the License relates. Any purported assignment in contravention of this section shall, at the option of the non-assigning party, be null and void and of no effect.

11.5 NOTICES. Any notice required to be given pursuant to the provisions of this Restated Agreement shall be in writing and shall be deemed to have been given at the earlier of the time when actually received as a consequence of any effective method of delivery, including but not limited to hand delivery, transmission by facsimile, or delivery by a professional courier service, or the time when sent by certified or registered mail addressed to the party. Any notice of change of address shall be effective only upon actual receipt, by the persons listed below or other formally authorized person(s) acting in their behalf.

With respect to IDT:

Joseph A. Walder, M.D., Ph.D.
Attn: Legal Department
Integrated DNA Technologies, Inc.
1710 Commercial Park
Coralville, IA 52241-9802;

With a duplicate sent to:

Mark Campbell, J.D., COO
Corporate Vice President
Integrated DNA Technologies, Inc.
8930 Gross Point Road, Suite 700
Skokie, Illinois, 60077

With respect to ISIS:

B. Lynne Parshall, J.D.
Isis Pharmaceuticals, Inc.
Executive Vice President and CFO

2292 Faraday Avenue
Carlsbad, CA 92008

With a duplicate sent to:

President of GeneTrove
Isis Pharmaceuticals, Inc.
2292 Faraday Avenue
Carlsbad, CA 92008

11.6 INTEGRATION. This Restated Agreement constitutes the full understanding between the parties with reference to the subject matter hereof, and no statements or agreements by or between the parties, whether orally or in writing, made prior to or at the signing hereof, shall vary or modify the written terms of this Restated Agreement. Neither party shall claim any amendment, modification, or release from any provisions of this Restated Agreement by mutual agreement, acknowledgement, or otherwise, unless such mutual agreement is in writing, signed by the other party, and specifically states that it is an amendment to this Restated Agreement.

11.7 BENEFITS. All terms and provisions of this Restated Agreement shall bind and inure to the benefit of the parties hereto, and upon their respective successors and assigns as those are permitted under the terms of this Restated Agreement.

11.8 AUTHORITY. The persons signing on behalf of IDT and Isis hereby warrant and represent that they have authority to execute this Restated Agreement on behalf of the party for whom they have signed.

REMAINDER OF THIS PAGE LEFT INTENTIONALLY BLANK
SIGNATURE PAGE TO IMMEDIATELY FOLLOW

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement by their duly authorized representatives.

ISIS PHARMACEUTICALS, INC.	INTEGRATED DNA TECHNOLOGIES, INC.
By: Richard. K. Brown	By: Dr. Joseph A. Walder
Signature: /s/ Richard. K. Brown	Signature: /s/ Dr. Joseph A. Walder
Title: President, GeneTrove Vice President, ISIS Pharmaceuticals	Title: President & CEO
Date: 12/04/01	Date: 12/04/01

Restated Agreement
Appendix A

LICENSE FEE AND ROYALTY SCHEDULES FOR
ANTISENSE DRUG DEVELOPMENT SUBLICENSES

[***]

EXHIBIT 1
ISIS ACADEMIC PATENTS

[***]

MASTER AGREEMENT

This Master Agreement is entered into and made effective as of October 30, 2001 (the "Effective Date"), between ISIS PHARMACEUTICALS, INC. of 2292 Faraday Avenue, Carlsbad, CA 92008, USA ("ISIS") and ANTISENSE THERAPEUTICS LTD., ACN 095 060 745 of Level 1, 10 Wallace Avenue, Toorak, Victoria 3142, AUSTRALIA ("ATL").

The purpose of this Master Agreement is to confirm that ISIS will enter into a Collaboration and License Agreement, a Stock Purchase Agreement, and a Clinical Supply Agreement (in the forms attached hereto; collectively, the "Agreements") with ATL if certain conditions are met, as further described herein. The Agreements will become effective (other than the Stock Purchase Agreement) if the following 5 conditions (the "Conditions Precedent") are met not later than 28 March 2002 (the "Completion Date"). The Stock Purchase Agreement will become effective immediately conditions 1 and 3 are met, provided they are met not later than the Completion Date. The Collaboration and License Agreement and the Clinical Supply Agreement will become effective immediately conditions 1,2,3,4 and 5 are met, provided they are met not later than the Completion Date.

1. ATL has successfully completed an Initial Public Offering ("IPO") on the Australian Market in which it has raised a minimum of $8,000,000 (AU) during that IPO.

2. The Australian Stock Exchange Limited ACN 008 624 691 ("ASX") approves an ASX Listing of ATL and ATL satisfies all conditions attaching to such approval, in each case on or before 26 March 2002. As used herein, "ASX Listing" means admission of ATL to the ASX Official List and quotation by the ASX of shares in ATL. (All capitalized terms used but not otherwise defined herein have the meanings set forth in the Stock Purchase Agreement attached hereto.)

3. ATL is capitalised by various shareholders prior to the ASX Listing of ATL on the basis set out below:

ENTITY	NUMBER OF ATL SHARES
Polychip	54.375 million
Syngene	54.375 million
Murdoch Interests	11.250 million
Total	120 million

4. After the ASX Listing of ATL, but prior to 28 March 2002, ATL will:

   (a) be capitalised as to approximately 190 million to 215 million ATL Shares; and

   (b) have granted between 105 million Options and 117.5 million Options.

   ATL Shares will be offered to the public for a subscription price of 20 Australian cents per ATL Share, with a free Option attaching to each ATL Share at the rate of 1 Option for every 2 ATL Shares issued.

5. After the ASX Listing of ATL, the ATL Shares issued and Options granted by ATL will be as follows:

PARTY	NUMBER OF ATL SHARES	NUMBER OF OPTIONS
Polychip	54.375	

million Syngene 54.375 million Murdoch Interests 11.250 million Isis* 30 million 20 million Public Subscribers 40 to 65 million 20 to 32.5 million Circadian Shareholders** 42 million Syngene Shareholders** 23 million TOTAL*** 190 TO 215 MILLION 105 TO 117.5 MILLION***

*To be issued and granted to Isis pursuant to the Stock Purchase Agreement.

**The number of Options to be granted to Circadian Shareholders and Syngene Shareholders respectively are approximate only, based on the issued capital of each of Circadian and Syngene as at the Record Date. It is intended that those shareholders will be issued Options on the basis of 1 Option for every share held by the shareholders in Circadian and Syngene (as the case may be) on payment to ATL of 1 cent per Option. The Isis and Public Options will be free.

***This total will be increased by any options granted pursuant to the share option scheme described in clause 3.2(e) of the Stock Purchase Agreement.

On or before the Completion Date and otherwise in compliance with the Stock Purchase Agreement, Isis will do all of the following:

(a) provide to ATL a Restriction Agreement duly signed by Isis and any controller of Isis (as defined by the ASX Listing Rules) in accordance with clause 5 of the Stock Purchase Agreement;

(b) provide to ATL all such other documents as are required pursuant to the terms of the Restriction Agreement;

(c) provide to ATL an application for the Subscription Shares to be subscribed for by Isis pursuant to clause 3.1 of the Stock Purchase Agreement;

(d) provide to ATL an application for Options to be granted to Isis pursuant to clause 3.1 of the Stock Purchase Agreement.

On or before the Completion Date and otherwise in compliance with the Stock Purchase Agreement, ATL will, subject to compliance by Isis with the provisions of the previous paragraph herein, issue to Isis the Subscription Shares and the Options to be granted pursuant to clause 3.1 of the Stock Purchase Agreement.

If the Conditions Precedent set forth in clauses 1-5 above are not met by 28 March 2002, the Agreements (other than the Stock Purchase Agreement) will not become effective and Isis will be under no further obligation to enter into the remaining Agreements with ATL.

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

ANTISENSE THERAPEUTICS, LIMITED ISIS PHARMACEUTICALS, INC.

By: /s/ C. Belyea	By: /s/ B. Lynne Parshall
Name: C. Belyea	Name: B. Lynne Parshall
Title: CEO	Title: Executive Vice President and Chief Financial Officer

Exhibits:

Stock Purchase Agreement
Collaboration and License Agreement
Clinical Supply Agreement

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

COLLABORATION AND LICENSE AGREEMENT

This Collaboration and License Agreement (the "Agreement") between ISIS PHARMACEUTICALS, INC. of 2292 Faraday Avenue, Carlsbad, CA 92008, USA ("ISIS") and ANTISENSE THERAPEUTICS LTD., ACN 095 060 745 of Level 1, 10 Wallace Avenue, Toorak, Victoria 3142, AUSTRALIA ("ATL") is entered into and made effective in accordance with the provisions of the agreement entitled "Master Agreement" between ATL and ISIS, dated October 30, 2001. The effective date of this Collaboration and License Agreement will be the date upon which all of the conditions in the Master Agreement have been met (the "Effective Date"). If the Effective Date has not occurred by March 28, 2002, this Agreement will be null and void and will not become effective.

INTRODUCTION AND OVERVIEW

ISIS possesses proprietary technology and expertise related to antisense drug discovery and the development of antisense including target validation and gene functionalization.

ATL is interested in using antisense for developing and discovering antisense drugs.

ATL and ISIS desire to collaborate to enable ATL to develop and commercialize antisense drugs, on the terms and conditions set forth herein. In essence, ISIS and ATL are jointly creating a new company focused on the discovery and development of antisense therapeutic drugs.

In support of the foregoing, ISIS will license ISIS 107248 to ATL, as the first Collaboration Compound hereunder, for development and commercialization and will work together with ATL to discover antisense drugs to additional gene targets and grant ATL licenses to intellectual property related to ISIS' antisense technology necessary to develop and commercialize such drugs. In addition, ISIS will manufacture active pharmaceutical ingredient ("API") for use in preclinical and clinical studies during the collaboration term. ATL will be responsible for all of its other manufacturing needs, including the manufacture of Product. ISIS will provide contract and consulting services for ATL for preclinical studies and will provide various other services in support of activities hereunder.

In consideration for the licenses and other services provided by ISIS, ATL will grant ISIS pre-IPO common shares in ATL pursuant to the related Stock Purchase Agreement and will reimburse ISIS on a cash basis for contract service work performed by ISIS during the term of the collaboration. ATL will be responsible for developing, marketing, selling, and distributing all Products that arise from the collaboration and will pay ISIS certain royalty payments on sales of such Products.

In connection with the collaborative and development activities described herein, the parties will also enter into the related Clinical Supply Agreement pursuant to which ISIS will supply ATL with API.

Therefore, in consideration of the foregoing premises and the mutual covenants herein contained, the parties hereby agree as follows.

AGREEMENT

ARTICLE 1

DEFINITIONS

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

ARTICLE 2

DRUG DEVELOPMENT PROGRAM

2.1 GENERAL.

Under the Drug Development Program, ATL will develop and commercialize antisense drugs arising out of the Collaborative Research Program conducted hereunder as well as ISIS 107248, a Collaboration Compound discovered by ISIS. In general, ATL will be responsible for all development and commercialization activities for Collaboration Compounds. ISIS will initially perform preclinical activities (IND-supporting toxicology) for ISIS 107248, but it is the intent of the parties that ATL will assume responsibility for all preclinical and IND-enabling activities with respect to subsequent Collaboration Compounds, as more specifically provided in this Agreement. Other than certain consulting services to be provided by ISIS to ATL hereunder at no charge, ATL will be responsible for all costs of development and commercialization of Collaboration Compounds including, without limitation, the reimbursement of ISIS' expenses as provided herein. Because ISIS 107248 is a Collaboration Compound discovered by ISIS and licensed to ATL hereunder, ISIS will be heavily involved in the development plans for ISIS 107248. With regard to future Collaboration Compounds, it is the parties' intent that, subject to meeting the Development Milestones, ATL will proceed with considerably more autonomy.

2.2 ISIS 107248 DEVELOPMENT PLAN.

(a) The plan for the development of ISIS 107248, including the roles and responsibilities of the parties, is contained in Exhibit 2.2 (the "ISIS 107248 Development Plan"). ATL will use commercially reasonable efforts to develop ISIS 107248 to maximize its commercial value. ISIS will use commercially reasonable efforts to assist ATL pursuant to the Development Plan. Each party will conduct its portion of the ISIS 107248 Development Plan 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. Each party will proceed diligently with its projects set out in the ISIS 107248 Development

Plan using commercially reasonable efforts to provide sufficient time, effort, equipment, facilities and skilled personnel.

(b) The target that is modulated by ISIS 107248 is CD49d, which is a Research Target hereunder and is listed in Exhibit 3.4.

(c) ISIS 107248 DEVELOPMENT MILESTONES. ATL commits to reach the following milestones in the development of ISIS 107248.

(i) MILESTONES:

(A) File IND (or analogous AU application) not later than December 31, 2002;

(B) Initiate Phase I studies not later than the first quarter of 2003;

(C) Initiate Phase IIa studies not later than December 31, 2004;

(D) Initiate Phase III studies not later than December 31, 2007;

(E) File an NDA not later than 18 months after the successful completion of a pivotal trial; and

(F) Use commercially reasonable efforts to bring ISIS 107248 Product to market and maximize the commercial value of such Product worldwide.

(ii) Pursuant to the provisions of this Agreement and the Joint Development Plan, ISIS will conduct certain IND-enabling studies and will use commercially reasonable efforts to complete such studies prior to [***]. In addition, ISIS will supply API ordered by ATL pursuant to the Clinical Supply Agreement.

(iii) If ATL will not be able to meet the milestone set forth in (i)(A) above due to a delay on the part of ISIS in completing the studies referenced in (ii) or if ISIS is unable to meet its obligations to supply API ordered by ATL pursuant to the Clinical Supply Agreement, the [***].

(iv) Except as provided otherwise in (v) below, if ATL fails to meet any of the ISIS 107248 Development Milestones, the License to Research applicable to ISIS 107248 will immediately terminate.

(v) If a Development Milestone is not met, but ATL has proceeded in good faith and the Development Milestone was missed for circumstances beyond ATL's control, [***]. If the JDC cannot agree on this issue, the matter will be referred to the designated officers of ATL and ISIS for resolution, consistent with the provisions of Section 16.6(a).

2.3 ADDITIONAL DEVELOPMENT ACTIVITIES.

(a) GENERAL.

(i) As provided herein, during the term of this Agreement, ATL will advance additional Collaboration Compounds through the various stages of an Active Program hereunder, i.e., from the research phase through preclinical and IND-enabling studies to human clinical studies and commercialization. To maintain any Collaboration Compound in Active Development status, ATL must meet the Development Milestones for each such Collaboration Compound.

(ii) The terms under which ISIS and ATL will collaborate to develop such additional Collaboration Compounds will be in accordance with the terms set forth herein. Within [***] days of ATL's providing written notice to ISIS that ATL has initiated IND enabling studies on a Collaboration Compound, ATL will prepare a mutually-agreed-upon Development Plan for that Collaboration Compound, with ISIS' assistance, consistent with the terms of this Agreement.

(b) IND-ENABLING STUDIES. While it is the intent of the parties that ATL will assume responsibility for all preclinical and IND-enabling activities with respect to Collaboration Compounds other than ISIS 107248, ISIS will be available to assist with the management of, or provide consulting support for, IND-enabling toxicology studies on up to [***] Collaboration Compounds following ISIS 107248, if requested to do so by ATL. Should ATL request ISIS' assistance in this regard, the parties will agree on terms pertaining to ISIS' participation, which terms will be included in the Development Plan referenced in (a). With the possible exception of ISIS 107248 and an IGF-1R Collaboration Compound, ISIS will not be requested to participate in the conducting, management or support of IND-enabling toxicology studies for more than one Collaboration Compound at a time.

2.4 ANNUAL REPORTS.

ATL will provide ISIS with an annual written report describing all activities performed by the parties and the results achieved during the relevant year with respect to each Collaboration Compound in Active Development hereunder including, without limitation, ISIS 107248. Each such report will include details regarding the stage of development a Collaboration Compound has reached within an Active Program including, without limitation, what Development Milestones have been achieved. To the extent that it is feasible to do so, ATL will also include the projected goals and Development Milestones it anticipates achieving during the coming year with respect to such Collaboration Compound in each such report.

2.5 COMMERCIALIZATION.

(a) ATL will use commercially reasonable efforts to bring Products into commercial use as quickly as is reasonably possible, in a manner designed to maximize the commercial potential of such Products worldwide. Prior to the launch of any Product, ATL will prepare a global integrated Product plan outlining the key aspects of market launch and commercialization (the "Integrated Product Plan" or "IPP"). Each IPP will be updated annually in accordance with ATL's internal planning and budgeting process. ATL will provide ISIS a copy of the final draft of each IPP (original and updates) for each Major

Market.

(b) Each IPP will also include appropriate milestones and the dates upon which such milestones must be met by ATL. If ATL prepares and manages or carries out the IPP, ATL will use commercially reasonable efforts to Manufacture, market, promote, distribute, and sell the Product on a worldwide basis. ATL will provide resources and expend funds in connection with such activities in a manner and to an extent comparable to the efforts of similar companies that manufacture, market, and sell pharmaceutical products of similar commercial potential at a similar stage of the product life cycle.

(c) If a Sublicensee of ATL bears primary responsibility for preparing, managing and carrying out the IPP, the sublicense agreement will require that such Sublicensee will use commercially reasonable efforts to Manufacture, market, promote, distribute, and sell the Product on a worldwide basis and will require that the Sublicensee provide resources and expend funds in connection with such activities in a manner and to an extent comparable to the efforts of similar companies that manufacture, market, and sell pharmaceutical products of similar commercial potential at a similar stage of the product life cycle. In addition, the IPP to be carried out by such Sublicensee will include appropriate milestones and the dates upon which such milestones must be met, as approved by ISIS in advance, which approval will not unreasonably be withheld.

(d) Consistent with Section 4.3 below, if ATL elects to meet any of its responsibilities and obligations under this Section via sublicense agreements, ATL will ensure that such agreements are subject to and will be consistent with the terms and conditions of this Agreement including, without limitation, the provisions of this Section.

(e) If ATL or a Sublicensee of ATL anticipates any difficulty in meeting its commercialization obligations under this Section including, without limitation, the milestones set forth in the IPP, ATL or its Sublicensee will provide ISIS with prompt notice thereof, in order that the parties may endeavor to work out an appropriate and acceptable resolution prior to pursuing other remedies hereunder.

ARTICLE 3

COLLABORATIVE RESEARCH PROGRAM

3.1 GENERAL; COLLABORATION TERM.

(a) ATL and ISIS will work together under the Collaborative Research Program described herein and as further detailed in the Collaborative Research Plan, as described in Section 3.2, to discover and develop antisense therapeutics. The parties will collaborate to assess Research Targets that may be important in the prevention or treatment of a disease or condition, consistent with Sections 3.2 - 3.5. ISIS will discover and design antisense oligonucleotides to modulate the Research Targets as provided in Section 3.7 and will

provide them to ATL; also, if contracted by ATL, will evaluate the antisense oligonucleotides in various functional assays. ATL will perform IN VITRO and IN VIVO studies utilizing the antisense oligonucleotides provided by ISIS. ISIS may perform additional studies, at ATL's request and expense, with the antisense oligonucleotides as part of a GeneTrove Investigation to better understand a particular Research Target's role in a specific biological pathway, as further described in Section 3.8. It is the intent of the parties that Collaboration Compounds will be identified during the Collaboration Term and that pursuant to Active Programs hereunder, such Collaboration Compounds will progress through research and preclinical development, meeting the relevant Development Milestones (see Exhibit 1, Section 1.2) and will each become the focus of a Development Plan hereunder.

(b) The Collaboration Term will begin on the Effective Date and will continue for 5 years unless earlier terminated due to termination of the Agreement under Sections 12.2 or 12.3, or unless terminated or extended upon mutual agreement of the parties.

3.2 JOINT RESEARCH COMMITTEE.

(a) Within [***] days of the Effective Date, the parties will create a Joint Research Committee of 4 people to facilitate the research collaboration called for herein. The JRC will consist of 2 representatives nominated by each party. Each party will designate a representative as a project leader to serve as the principal contact person for that party. The parties may agree to add additional members to the JRC, as long as equal representation is maintained. [***].

(b) During the Collaboration Term, the JRC will be the primary vehicle for interaction between the parties with respect to the collaborative research conducted hereunder. The JRC will be responsible for preparing an annual budget and plan for the collaborative research activities to be conducted during each year of the Collaborative Research Program (the "Collaborative Research Plan") and for managing that program. The JRC will be responsible for updating the Collaborative Research Plan as needed and will also be responsible for determining the order in which Research Targets are prioritized for Gene Walks.

(c) The JRC will meet as needed during the Collaboration Term. Meetings will be via teleconference or videoconference, or as the parties may otherwise agree. The JRC will review the progress of the activities carried out under the Collaborative Research Program and will consider and decide on proposed modifications to the strategy and goals of that program. The frequency, dates and times of all meetings will be mutually agreed upon by the parties. At its first meeting the JRC will determine such procedures as it will reasonably require to conduct its business.

3.3 RESEARCH TARGETS: GENERAL.

As noted above, ATL and ISIS will collaborate to assess Research Targets that may be important in the prevention or treatment of a disease or condition.

3.4 RESEARCH TARGETS: DESIGNATION.

(a) The collaborative research hereunder will be focused on specific gene targets thought to be attractive for the development of antisense drugs. ATL will choose targets in accordance with the provisions of this Section 3.4 as the basis for its antisense drug discovery efforts. ATL commits to use commercially reasonable efforts to conduct research and drug discovery activities with respect to each Research Target to maximize its commercial value.

(b) Exhibit 3.4 hereto contains a list of the initial targets that are the object of Licenses to Research (the "Research Targets"), as well as the nucleic acid sequences for the corresponding human genes and a brief record of any studies performed on those targets by ISIS. Research Targets listed on Exhibit 3.4 that are Dermatology Targets are listed in Section B, and all other Research Targets are listed in Section A of Exhibit 3.4. During the Collaboration Term, targets may be added to and removed from Exhibit 3.4 in accordance with the terms of this Section and Section 3.5.

3.5 RESEARCH TARGETS: SELECTION, REMOVAL, REPLACEMENT AND APPROVAL PROCESS.

(a) As noted above, on the Effective Date, Exhibit 3.4 will list the initial Research Targets agreed upon by the parties. ATL warrants and represents that if it has not provided ISIS with the nucleic acid sequences for the corresponding human genes for any of the Research Targets listed in Exhibit 3.4 by the Effective Date, it will do so promptly thereafter. Consistent with the terms of this Agreement, ISIS will have no obligation to conduct any activities with respect to such Research Targets until the required materials, information and/or payments (if applicable) have been submitted to ISIS by ATL. The addition of new Research Targets to the list in Exhibit 3.4 is at ISIS' sole discretion.

(b) If ATL wishes to designate a new Research Target, it will provide ISIS with written notice of the target it wishes to add to the list set forth in Exhibit 3.4. Such written notice will include the gene name, the NCBI accession number or nucleic acid sequence, and one or

more mammalian cell lines that express the Research Target. ISIS will not, and is not required to, accept a proposed Research Target without such information. In addition, ATL will inform ISIS of whether or not to the best of ATL's knowledge the proposed target is in the public domain or is proprietary to a Third Party.

(i) ATL will not propose a target for consideration as a possible Research Target if to its knowledge ATL is not able to provide ISIS with rights to use such target sufficient to enable ISIS to carry out its activities in support of the Collaborative Research Program as contemplated by the parties hereunder.

(ii) If ATL proposes a target that is encumbered by Third Party restrictions, [***].

(iii) If a target proposed by ATL is subject to an ISIS drug discovery and development program or a contractual obligation of ISIS to a Third Party with respect to that target, then the proposed target will not be approved as a Research Target hereunder.

(c) Within [***] days after receipt of the ATL notice under subsection (b), ISIS will notify ATL, in writing, of its decision either to approve or to reject a proposed target.

(i) If a proposed target is not approved as a Research Target, the notice provided by ISIS will advise ATL of the reason(s) the target was not approved, and ATL will be invited to submit a different proposed target for consideration.

(ii) If a proposed target is approved as a Research Target, ISIS' notice to ATL will indicate this and will also indicate whether or not the new Research Target is a Dermatology Target. ISIS will add the Research Target to the list in Exhibit 3.4 (as well as the nucleic acid sequence of the gene) and will provide ATL with an amended copy of Exhibit 3.4. If ISIS has performed animal or other preclinical studies on any antisense molecule that modulates the newly-added Research Target, or has established efficacy, ISIS will add that information to Exhibit 3.4 and will provide ATL with a copy of the amended exhibit.

(iii) Upon receipt of written notice from ISIS that a proposed target has been approved as a Research Target and added to Exhibit 3.4, ATL will begin Active Development of such Research Target, consistent with the terms of this Agreement.

(d) After the Effective Date, Research Targets may be removed from the list in Exhibit 3.4 as follows.

(i) If ATL wishes to remove a Research Target from the approved list in Exhibit 3.4, it will provide ISIS with prompt written notice of its election to do so. Upon ISIS' receipt of such notice, it will remove the Research Target from the list.

(ii) Upon receipt of notice at any time during the term of this Agreement that a Research Target is no longer in Active Development, ISIS will remove the target from the list set forth in Exhibit 3.4 and will provide ATL with prompt written notice of same.

(iii) The License to Research or License to Exploit applicable to any Research Target removed pursuant to (i) or (ii) herein (each an "Abandoned Research Target") will immediately terminate, consistent with the provisions of Sections 4.1 or 4.2, as applicable. Notwithstanding the foregoing, an Abandoned Research Target may still bear royalty or other payment obligations, as described in Sections 5.1 - 5.3 herein.

(iv) Once a target has been removed from the list of Research Targets, Exhibit 3.4 will be amended to delete such target and a copy of amended Exhibit 3.4 will be sent to ATL by ISIS.

(v) Upon termination of a License to Research or a License to Exploit for any reason, a Research Target will be automatically removed from Exhibit 3.4 and will thereafter be considered an Abandoned Research Target.

(e) At no time during the term of this Agreement or the Collaboration Term will there be any more than [***] designated Research Targets. As of the Effective Date, ATL may nominate up to [***] Research Targets; after the Effective Date, ATL may not substitute more than [***] Research Targets in any year during the Collaboration Term.

3.6 GENEWALKS; GENETROVE INVESTIGATIONS.

(a) GENERAL OVERVIEW. ISIS will perform Gene Walks on all of the Research Targets designated in Exhibit 3.4, with the exception of CD49d, as a Collaboration Compound for that Research Target has already been identified by ISIS (i.e., ISIS 107248). The Gene Walks are expected to provide ATL with at least one optimized antisense oligonucleotide designed to modulate the respective Research Target together with control oligonucleotides. Upon ATL's request, ISIS will then evaluate those antisense oligonucleotides selected for further study by ATL in functional assays. ATL will utilize the antisense oligonucleotides further in IN VITRO and IN VIVO studies. A GeneTrove Investigation, which ATL may request after a Gene Walk for the relevant Research Target has been performed, includes the use of the antisense oligonucleotides that are obtained as a direct result of the Gene Walk in primary cellular phenotypic assays currently conducted by ISIS, as further described below and in Exhibit 3.8. The ownership and use of all materials, including Antisense Inhibitors, and of all data and information generated as a result of a Gene Walk, a GeneTrove Investigation, or otherwise provided to ATL by ISIS pursuant to this Agreement, is governed by the provisions of Article 6.

(b) PROJECT COORDINATORS. ATL and ISIS will each select one employee to serve as the Project Coordinator for that party, with respect to Gene Walks and GeneTrove Investigations. The Project Coordinators will facilitate the selection, prioritization, removal and replacement of Research Targets. The Project Coordinators will each have appropriate technical credentials, knowledge and ongoing familiarity with the foregoing activities. The Project Coordinators will meet on an as-needed basis via teleconference or videoconference, at times mutually agreed upon by the parties. Decisions of the Project Coordinators will be unanimous. If the Project Coordinators cannot agree on an issue, the issue will be submitted to the JRC for resolution.

3.7 GENE WALKS.

(a) ISIS agrees to perform up to [***] Gene Walks on Research Targets for ATL during the Collaboration Term [***]. Gene Walks performed on genes of different species are considered separate Gene Walks; for example, a Gene Walk performed on a mouse gene and one performed on its human equivalent counts as two Gene Walks. ATL may request that ISIS perform an additional [***] Gene Walks on Research Targets during the Collaboration Term, at a cost to ATL of [***] each. If ISIS agrees to perform additional Gene Walks, ATL will compensate ISIS for the cost of each such additional Gene Walk [***].

(b) Irrespective of the timing of ATL's requests for Gene Walks - that is, whether or not ATL uses its allocation of [***] Gene Walks within the first [***] years of the Collaboration Term, and regardless of when ATL elects to use its allocation of [***] Gene Walks at [***] apiece - ISIS will not be required to perform more than [***] Gene Walks per year for ATL during the first [***] years of the Collaboration Term and will not be required to perform more than [***] Gene Walks per year for ATL during the remaining [***] years of the Collaboration Term. Gene Walks, a sample Gene Walk schedule for the Collaboration Term, and the related activities of the parties are further described in Exhibit 3.7.

(c) A Gene Walk is automatically requested when a Research Target is added to the list in Exhibit 3.4. Therefore, as of the Effective Date, ATL will be deemed to have requested a Gene Walk for each Research Target listed in Exhibit 3.4, except for CD49d. Within [***] days of the Effective Date, ATL will provide ISIS with written notice of the order in which it wishes the Research Targets to be scheduled for Gene Walks. As new Research Targets are added to Exhibit 3.4, they will be added to the end of the list of targets on which Gene Walks are to be performed.

(d) After each successful Gene Walk, ISIS will provide up to [***] Antisense Inhibitors and a control oligonucleotide to ATL for use in confirming studies in quantities not to exceed 2 (mu)mole per Research Target. ATL may request quantities for use in preclinical pharmacology studies at the price of [***] per order for amounts up to [***] of the particular Antisense Inhibitor ordered. [***]

3.8 GENETROVE INVESTIGATIONS.

(a) ATL may request that ISIS perform up to [***] GeneTrove Investigations per year during the Collaboration Term on Research Targets at a cost to ATL of [***] per GeneTrove Investigation. GeneTrove Investigations and the related activities of the parties are further set forth in Exhibit 3.8.

(b) ATL may request that ISIS perform additional GeneTrove Investigations. If ISIS agrees, at its sole discretion, to perform additional GeneTrove Investigations, ATL will compensate ISIS for each such additional GeneTrove Investigation in accordance with comparable rates charged by ISIS' GeneTrove division to other GeneTrove customers.

(c) To request a GeneTrove Investigation under subsection (a) or (b) herein, ATL will submit a written request to ISIS, which request will indicate the identity of the Research Target on which ATL requests that a GeneTrove Investigation be performed. ATL will provide ISIS with any additional information reasonably requested by ISIS to enable ISIS to conduct such GeneTrove Investigation.

(d) Except as provided otherwise herein, the data and information generated by the GeneTrove Investigations pursuant to the collaboration hereunder will be considered confidential and will be subject to the provisions of Article 6.

(e) ATL agrees that ISIS may enter data and information from ISIS' conduct of each GeneTrove Investigation for ATL hereunder into its proprietary human gene function database(s), [***].

3.9 OTHER COLLABORATIVE RESEARCH PROGRAM-RELATED ACTIVITIES.

(a) ACCESS TO CONSULTING SUPPORT AND TRAINING.

(i) During the Collaboration Term, ISIS will provide ATL with reasonable amounts of preclinical and research advice [***] (phone consultation or visit at ISIS only) in support of any Active Program hereunder that involves a Collaboration Compound made using ISIS Standard Chemistry for which a License to Research exists.

(ii) During the first [***] years of the Collaboration Term, upon ATL's request and at times mutually agreed upon by the parties, ISIS will allow [***] visiting scientists from ATL to work in the ISIS laboratories to be trained in [***], during normal business hours and upon reasonable prior notice, subject to any restrictions imposed by ISIS in order to protect the confidentiality of programs, activities and information unrelated to any ongoing Active Program hereunder. The visiting scientists may visit and receive training at ISIS for up to [***]. ATL will pay all expenses (e.g. salary, travel, lodging, meals, transportation, etc.) incurred by its visiting scientists while receiving training from ISIS personnel. No ISIS personnel will be required to visit ATL's facilities.

(iii) ISIS acknowledges that ATL may desire to train its academic collaborators. If ATL wishes to substitute an academic collaborator for an ATL employee with respect to the training referenced in (a) above, ATL will provide ISIS with a specific written request to do so in advance, for ISIS' approval, which approval will not unreasonably be withheld. Any such academic collaborator, once approved by ISIS, must enter into a confidentiality agreement with ISIS before any training can be initiated.

(iv) If ATL requests additional amounts or types of consulting support or training and if ISIS agrees to provide such training, the parties

will negotiate appropriate terms including, without limitation, the scope, timing, duration and cost of such training, in good faith.

ARTICLE 4

LICENSE GRANTS AND OTHER RIGHTS

4.0 LICENSE TERM. As used herein, "License Term" means the term beginning on the Effective Date and ending on the date on which all obligations to pay royalties hereunder have expired.

4.1 LICENSES TO RESEARCH. A License to Research is a license to perform research and development activities relating to a Research Target until the filing of an NDA or non-US equivalent on a Product that modulates such Research Target.

(a) LICENSE GRANT.

(i) For each Research Target, ISIS will grant to ATL and its Affiliates when ATL takes a License to Research, an exclusive, worldwide license under the ISIS Core Technology Patent Rights, the ISIS Formulation Patent Rights, the Manufacturing Patent Rights, the Research Target Patent Rights and the Third Party Patent Rights solely to conduct research and clinical development for all therapeutic and cosmetic applications for Collaboration Compounds that modulate such Research Target. For Collaboration Compounds that modulate Dermatology Targets, the license is limited to topical dermatological indications only. These rights will only be sublicensable as explicitly provided in Section 4.3. The license grant described hereunder will commence automatically on grant of the License to Research and will terminate upon termination of the corresponding License to Research.

(ii) For each Research Target, ISIS will grant to ATL and its Affiliates when ATL takes a License to Research, a nonexclusive, worldwide license under the Research Target Patent Rights, the ISIS C5-Propyne Patent Rights, and the ISIS Formulation Patent Rights solely to conduct research and clinical development for all therapeutic and cosmetic applications for Research Target Compounds that modulate such Research Target. For Research Target Compounds that modulate Dermatology Targets, the license is limited to topical dermatological indications only. These rights will only be sublicensable as explicitly provided in Section 4.3. The license granted hereunder will commence automatically on grant of the License to Research and will not terminate upon termination of the corresponding License to Research.

(b) As of the Effective Date, ISIS grants to ATL a License to Research with respect to each Research Target listed in Exhibit 3.4. ATL will receive additional Licenses to Research with respect to Research Targets when added to Exhibit 3.4. Licenses to Research may only be obtained during the Collaboration Term. No License to Research will be granted to ATL on any Research Target after the Collaboration Term ends.

(c) [***]

(d) ATL may terminate a License to Research with respect to a Research Target for any reason, at any time during the term of this Agreement, by providing ISIS with written notice that the Research Target is being removed from Exhibit 3.4.

(e) With the exception of the License to Research applicable to ISIS 107248, which is governed by the provisions of subsections (f) and (g) below, if a Research Target is no longer part of an Active Program, ISIS may terminate the License to Research applicable to that Research Target at any time during the term of this Agreement upon written notice to ATL.

(f) As provided in Section 2.2(c), ISIS may terminate the License to Research applicable to ISIS 107248 at any time during the term of this Agreement upon written notice to ATL, if the milestones or other conditions set forth in Section 2.2(c) are not timely met.

(g) Once ATL has elected and obtained 5 Licenses to Exploit pursuant to Section 4.2, all remaining Licenses to Research will immediately terminate, and all rights to the remaining Research Targets licensed to ATL will revert to ISIS; provided, however, that the licenses granted pursuant to Section 4.1(a)(ii) will remain in effect.

(h) ISIS will provide ATL with a semiannual report summarizing the status of Research Target Patent Rights subject to a License to Research hereunder and will include updates to any Exhibits that are affected.

4.2 LICENSES TO EXPLOIT. A License to Exploit is a license to perform research, development and commercialization activities on Products that modulate a Research Target.

(a) ISIS grants ATL the option to convert any active License to Research hereunder into a License to Exploit, as set out below. Notwithstanding the foregoing, ATL may convert not more than 5 Licenses to Research into Licenses to Exploit, and each License to Exploit must be requested by ATL prior to the filing of an NDA (or non-US equivalent) for the relevant Research Target. The option to convert Licenses to Research to Licenses to Exploit expires [***] after the end of the Collaboration Term.

(b) If ATL elects to convert a License to Research into a License to Exploit, ATL will provide ISIS with written notice effecting the exercise of the option, which will identify the particular Research Target to which the License to Research applies and will include written verification that all applicable milestones and obligations of ATL with respect to that Research Target have been timely met. Upon ISIS' receipt of such written notice, ISIS will have [***] days to object if it believes that ATL has not timely met all applicable milestones and obligations with respect to that Research Target. At the end of such [***]-day period, the License to Exploit will be granted with respect to the relevant Research Target if ISIS has not objected. [***].

(c) LICENSE GRANT.

(i) For each Research Target for which a License to Exploit is granted ISIS will grant to ATL an exclusive, worldwide license under the ISIS Core Technology Patent Rights, the ISIS Formulation Patent Rights, the Manufacturing Patent Rights, the Research Target Patent Rights and the Third Party Patent Rights solely to make, have made, use, develop, offer for sale and sell Collaboration Compound Products that modulate such Research Target for all therapeutic and cosmetic applications. For Collaboration Compound Products that modulate Dermatology Targets, the license is limited to topical dermatological indications only. These rights will only be sublicensable as explicitly provided in Section 4.3. This license will commence automatically on grant of the corresponding License to Exploit and will terminate upon termination of the corresponding License to Exploit.

(ii) For each Research Target for which a License to Exploit is granted ISIS will grant to ATL a nonexclusive worldwide license under the Research Target Patent Rights, the ISIS C5-Propyne Patent Rights, and the ISIS Formulation Patent Rights solely to make, have made, use, develop, offer for sale and sell Research Target Compound Products for all therapeutic and cosmetic applications. For Research Target Compound Products that modulate Dermatology Targets, the license is limited to topical dermatological indications only. These rights will only be sublicensable as explicitly provided in Section 4.3. This license will commence automatically on grant of the corresponding License to Exploit and will not terminate upon termination of the corresponding License to Exploit.

(d) No substitutions may be made on Licenses to Exploit. Once a License to Exploit has been taken with respect to a Research Target, a different Research Target may not be substituted thereunder.

(e) ATL may terminate a License to Exploit with respect to a Research Target, for any reason, at any time during the term of this Agreement, by providing ISIS with written notice.

(f) The party bearing primary responsibility for the prosecution,

maintenance and defense of any Research Target Patent Rights pursuant to Article 8 herein will provide the other party hereto with a semiannual report summarizing the status of Research Target Patent Rights subject to a License to Exploit hereunder for which such party is responsible and will include updates to any Exhibits listing rights in any Patents licensed hereunder that are affected, if appropriate.

4.3 SUBLICENSES UNDER ISIS PATENT RIGHTS AND THIRD PARTY PATENT RIGHTS.

(a) Any sublicense granted by ATL and its Affiliates under this Agreement is subject to and will be consistent with the terms and conditions of this Agreement and with the terms of the agreements pursuant to which ISIS obtained its rights in Third Party Patent Rights. The grant of any such sublicense hereunder will not relieve ATL or its Affiliates of its obligations under this Agreement. ATL will promptly provide ISIS with copies of all sublicenses granted by ATL or its Affiliates, as well as Sublicensee contact information.

(b) Subject to the terms and conditions of this Agreement and during the License Term, ATL and its Affiliates will have the right to grant sublicenses (each an "ATL Sublicense") under the licenses from ISIS set forth in Sections 4.1 and 4.2 to Third Parties as follows.

(i) ATL and its Affiliates may grant an ATL Sublicense to a Third Party collaborator under the Research Target Patent Rights solely for the purpose of enabling such Third Party to collaborate with ATL on bona fide research, development and commercialization work on a Research Target Compound and, after such collaborative work, to make, have made, use, offer for sale and sell a Product containing such Research Target Compound.

(ii) ATL and its Affiliates may grant an ATL Sublicense to a Third Party collaborator

under the ISIS Core Technology Patent Rights, the ISIS Formulation Patent Rights, the Manufacturing Patent Rights, the Research Target Patent Rights and the Third Party Patent Rights solely for the purpose of making, developing or using a Collaboration Compound or making, having made, using, developing, offering for sale or selling a Collaboration Compound Product.

(iii) In the event of a material default by any Sublicensee under an ATL Sublicense, ATL will inform ISIS and take commercially reasonable efforts to cause the Sublicensee to cure the default or will terminate the ATL Sublicense. ATL will specifically state that ISIS is a third party beneficiary in any ATL Sublicense(s) hereunder.

4.4 MAXIMUM NUMBER OF LICENSES.

Not more than [***] Licenses to Research or Licenses to Exploit may be in existence at any time during the term of this Agreement. Each such license is to a discrete Research Target.

4.5 RIGHT OF FIRST REFUSAL.

(a) During the term of this Agreement, if ATL is approached by a Third Party regarding, or elects to offer to a Third Party, the opportunity to collaborate on the development of a compound that modulates a Research Target other than IGF-1R, ATL will provide written notice of same to ISIS. Such notice will include information identical to that presented by ATL to a Third Party including, at a minimum, (i) information possessed and disclosable by ATL that supports the development of such a compound and is reasonably necessary for ISIS to assess the commercial potential of such compound; and (ii) a proposal that ATL would be prepared to accept. Within [***] days of receipt of such notice, ISIS will provide written notice to ATL indicating whether it is interested in negotiating with ATL to obtain the rights to develop and commercialize such compound with ATL.

(b) If ISIS fails to respond to ATL's notification within [***] days or indicates that it is not interested in developing and commercializing such compound with ATL, ATL will thereafter be free to enter into discussions with one or more Third Parties regarding the development and commercialization of such compound.

(c) If ISIS timely indicates its interest in obtaining such rights to develop and commercialize such compound with ATL, the parties will negotiate in good faith the terms of a separate development and commercialization agreement, which terms will be commercially reasonable, including without limitation license fees, milestone payments, and royalties, during the period up to [***] days following receipt of ISIS' notice. If the parties are unable to execute such an agreement within such time period, despite good faith negotiations by each party, ATL will thereafter be free to develop and commercialize such compound with one or more Third Parties, provided that the terms offered to such Third Party include financial terms that are no more favorable than those offered to ISIS.

4.6 RIGHTS RETAINED BY ISIS.

ISIS will retain the right to practice under all patent rights licensed to ATL hereunder as necessary to carry out ISIS' obligations under this Agreement and the Clinical Supply Agreement, and for any purpose other than to make, have made, use, import, offer for sale and sell Collaboration Compound Products, except as provided otherwise herein. ATL will not practice any of the patent rights licensed to ATL hereunder other than as expressly licensed in this Article 4.

4.7 ACCESS TO ADDITIONAL TECHNOLOGY.

(a) If, after the Effective Date and during the Collaboration Term, ISIS comes to own, or acquires a license with the right to grant sublicenses thereunder, any new or additional ISIS Core Technology Patent Rights or Manufacturing Patent Rights, and ATL desires access to such rights, any licenses or sublicenses from ISIS to ATL under such Patents pursuant to Sections 4.1 and 4.2 are conditioned on ATL's agreement (i) to pay, on a flow-through basis, any royalties, milestones or other financial obligations owed to ISIS' licensor arising from a license or sublicense grant to ATL and the practice under such license or sublicense by ATL, its Affiliates or Sublicensees; and (ii) to abide by all terms of the agreement under which a Third Party license is granted to ISIS.

(b) If, after the Effective Date and during the Collaboration Term, a change in the manufacturing process as a result of a change in the master batch records for ISIS 107248 requires access of ATL to Manufacturing Patent Rights that were not practiced in the manufacture of the ISIS 107248 API prior to such change, and if ISIS has obtained ownership or control of such Manufacturing Patent Rights by way of a license from or via collaboration with a Third Party, then any license or sublicense granted to ATL under such Manufacturing Patent Rights is conditioned on the prior agreement to be negotiated in good faith by the parties regarding (i) the assumption by ATL of all financial obligations owed to such Third Party arising from the grant of a license or sublicense to ATL and the practice under such license or sublicense by ATL, its Affiliates or Sublicensees; (ii) the payment to ISIS of an equitable portion of acquisition costs incurred by ISIS; and (iii) an agreement by ATL to abide by all terms of the agreement under which such Manufacturing Patent Rights were acquired, if applicable.

4.8 EFFECT OF TERMINATION OF LICENSES TO RESEARCH AND LICENSES TO EXPLOIT.

(a) Upon termination of any License to Research or License to Exploit hereunder, ATL will assign and transfer to ISIS, to the extent ATL is not prohibited from doing so, all rights it owns or controls and any data and information relating to any Collaboration Compound or Collaboration Compound Product relating to the relevant Research Target obtained or generated by ATL during the term of the Agreement. [***].

(b) If a License to Research or License to Exploit pertaining to a Research Target other than ISIS 107248 is terminated for any reason, promptly upon any such termination, the parties will

prepare a transition plan to ensure the seamless transition of any

clinical studies and distribution and sales activities relating to any Antisense Inhibitor, Collaboration Compound, and/or Collaboration Compound Product from ATL to ISIS. In addition, ATL will provide ISIS with any and all data relating to such Antisense Inhibitor, Collaboration Compound, Product using ISIS Standard Chemistry and/or to any ISIS Patent Rights relating to any Research Target that are in ATL's possession or control.

(c) Upon termination of the License to Research or License to Exploit applicable to ISIS 107248, ATL will promptly return to ISIS all information and materials relating to ISIS 107248 provided to ATL by ISIS or independently generated by ATL, its Affiliates, Sublicensees or contractors and all quantities of ISIS 107248 API provided by ISIS under the Clinical Supply Agreement that have not been used.

(d) Upon termination of any License to Research or License to Exploit applicable to a Collaboration Compound or Collaboration Compound Product, ATL will promptly return to ISIS all quantities of API provided by ISIS under the Clinical Supply Agreement that have not been used. In addition, ATL will promptly provide to ISIS all information and materials relating to such Collaboration Compound or Collaboration Compound Product provided to ATL by ISIS. ATL will also promptly provide to ISIS all information and materials relating to such Collaboration Compound or Collaboration Compound Product independently generated by ATL, its Affiliates, Sublicensees or contractors. With respect to information and materials relating to such Collaboration Compound or Collaboration Compound Product that were independently generated by ATL, its Affiliates, Sublicensees or contractors, ISIS will compensate ATL as follows:

(1) [***].

(2) [***].

ARTICLE 5

ROYALTIES AND PAYMENTS

5.1 MINIMUM ROYALTIES PAYABLE TO ISIS BY ATL ON SALES OF PRODUCTS BY ATL OR ITS AFFILIATES.

Subject to the terms and conditions of, and during the term of, this Agreement, ATL will pay to ISIS royalties on sales of Products by ATL or its Affiliates, according to the terms set forth below.

(a) The minimum royalty payable to ISIS by ATL for sales of any Product by ATL or its Affiliates containing ISIS 107248 is [***] of Net Sales for as long as there are issued and unexpired claims within the patent rights applicable to such Product and [***] of Net Sales thereafter for the life of such Product.

(b) [***].

(c) Except as otherwise provided above, the minimum royalty payable to ISIS for sales of any Product by ATL or its Affiliates comprising a compound that modulates a Research Target or Abandoned Research Target for which ISIS has not established efficacy in an animal model or has not conducted preclinical toxicology studies is [***] of Net Sales. Such minimum royalty is due and payable for the life of the Product.

(d) Except as otherwise provided above, the minimum royalty payable to ISIS by ATL for sales of any Product by ATL or its Affiliates for which ISIS has established efficacy in an animal model or has conducted preclinical toxicity studies will be negotiated in good faith by the parties on a case-by-case basis, but will not be less than [***] of Net Sales.

(e) For Products under (a) or (c), in addition to any minimum royalties due under (a) or (c), the royalty payable to ISIS by ATL for sales of any Product by ATL or its Affiliates, the manufacture, use, sale, or importation of which would, but for the licenses granted hereunder, infringe an issued and unexpired claim under the ISIS Formulation Patent Rights is [***] of Net Sales for Products containing compounds that modulate a Research Target. Such minimum royalty is due and payable for the term of issued and unexpired claims within the patent rights applicable to such Product.

(f) The minimum royalties payable as described in Sections 5.1 (a)-(e) are in addition to any royalties payable to ISIS for Third Party Patent Rights as set forth in Section 5.3 below.

5.2 SUBLICENSE INCOME PAYABLE TO ISIS BY ATL OR ITS AFFILIATES ON PRODUCTS SOLD BY SUBLICENSEE(S).

Subject to the terms and conditions of, and during the term of, this Agreement, ATL or its Affiliates will pay to ISIS certain shares of Sublicense Income received by ATL or its Affiliates, according to the terms set forth hereinbelow.

(a) The share of Sublicense Income payable to ISIS by ATL or its Affiliates on Sublicensee sales of a Collaboration Compound Product containing ISIS 107248 is [***] of all Sublicense Income for the term of issued and unexpired claims within the patent rights applicable to such Product and [***] of all Sublicense Income thereafter for the life of such Product.

(b) [***].

(c) Except for Products containing ISIS 107248 or a compound that modulates IGF-1R, ATL will pay ISIS a [***] royalty on Net Sales of any Product by Sublicensee and [***] of Sublicense Income exclusive of royalties. Such amounts are due and payable for the life of the Product.

(d) In addition to amounts payable under (a) or (c), ATL will pay ISIS [***] of Sublicense Income for sales of Products by Sublicensees containing compounds that modulate a Research

Target other than IGF-1R and that that would, but for the licenses granted hereunder, infringe the ISIS Formulation Patent Rights. Such amounts are due and payable for the term of issued and unexpired claims within the ISIS Formulation Patent Rights.

(e) Except as otherwise provided above, the share of Sublicense Income payable to ISIS by ATL or its Affiliates for the license of rights to and/or sale of a Product for which ISIS has established efficacy in an animal model or has conducted preclinical studies will be negotiated in good faith by the parties, but will not be less than [***] of the Sublicense Income.

5.3 ROYALTIES PAYABLE TO ISIS FOR THIRD PARTY PATENT RIGHTS.

(a) In addition to the royalties and other payments set forth in Sections 5.1 and 5.2, the following royalties (percentages of Net Sales) are payable to ISIS by ATL for sales of Products including Products that modulate IGF-1R, whether sold by ATL, its Affiliates, or Sublicensees, the manufacture, use, sale, or import of which would, but for the licenses granted hereunder, infringe an issued and unexpired claim of the following patent rights on a Product by Product basis:

[***]

(b) [***].

(c) [***]

5.4 ROYALTY CAP.

(a) Should the royalty payable by ATL to ISIS pursuant to Sections 5.1 and 5.3 with respect to sales of a Product comprising a CD49d-modulating compound, including ISIS 107248, exceed [***] of Net Sales, the total royalty ATL must pay ISIS for such Product will be [***] of Net Sales.

(b) Should the royalty payable by ATL to ISIS pursuant to Sections 5.1 and 5.3 with respect to sales of a Product other than a Product comprising a CD49d-modulating compound, exceed [***] of Net Sales, the total royalty ATL must pay ISIS for such Product will be [***] of Net Sales.

(c) The foregoing royalty caps apply only to the royalty rates set forth in Sections 5.1 and 5.3 and thus do not apply to any new technology or patent rights acquired or accessed by ISIS after the Effective Date, as described in Sections 4.7 and 8.4 or to the royalties owed pursuant to Section 5.2.

5.5 EXAMPLES.

(a) EXAMPLE OF CALCULATION OF ROYALTY RATE FOR SALES OF PRODUCTS COMPRISING ISIS 107248 BY ATL OR ITS AFFILIATES:

The royalty payable to ISIS for sales of Product by ATL or its Affiliates (as a percentage of Net Sales) comprising non-topically-administered formulations of ISIS 107248 is calculated as follows (assuming all relevant patent rights are issued and unexpired):

[***]

(b) EXAMPLE OF ROYALTIES AND SUBLICENSE INCOME PAYABLE TO ISIS BY ATL OR ITS AFFILIATES ON SALES OF PRODUCTS COMPRISING ISIS 107248 BY SUBLICENSEES:

[***]

5.6 PAYMENT OF ROYALTIES AND INCOME; REPORTS.

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

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

(a) PAYMENTS. All payments to ISIS under this Agreement will be made in United States Dollars by bank wire transfer in next day available funds to such bank account in the United States designated in writing by ISIS from time to time. All amounts payable to ISIS hereunder are noncreditable and nonrefundable.

(b) LATE PAYMENTS; COLLECTIONS. In the event that any payment, including royalty, milestone or research payments, due hereunder is not made when due, the payment will bear interest from the date due at the lesser of (i) [***] per month, compounded monthly, or (ii) the highest rate permitted by law; provided, however, that in no event will such rate exceed the maximum legal annual interest rate. If ATL disputes the amount of an invoice presented by ISIS within [***] days of receipt of such invoice, the late fees will only apply to the correct amount as later determined or agreed. The payment of such interest will not limit a party from exercising any other rights it may have as a consequence of the lateness of any payment. In addition, ATL agrees to pay all costs of collection, including reasonable attorneys' fees, incurred by ISIS in enforcing the payment obligations of ATL after a due date has passed under this Agreement.

5.8 AUDITS REQUESTED BY ISIS.

(a) Upon the written request of ISIS, and not more than once in each calendar year, ATL will permit ISIS' independent certified public accountant to have access during normal business hours to such of the records of ATL as may be reasonably necessary to verify the accuracy of the royalty reports hereunder for the current year and the preceding 2 years prior to the date of such request. The accounting firm will disclose to ISIS only whether the royalty reports are correct or incorrect, the specific details concerning any discrepancies, and the corrected amount of Net Sales and Sublicense Income. No other information will be provided to ISIS.

(b) At the request of ISIS, ATL will direct its Affiliates to permit audits of the Affiliates' records in accordance with the provisions of subsection (a) above. Further, ATL will include in each sublicense granted by it pursuant to this Agreement a provision

requiring the Sublicensee to submit reports to ATL, to keep and maintain records of sales made pursuant to such sublicense and to grant access to such records by ISIS' independent accounting firm, to the same extent required of ATL hereunder. ISIS' independent accounting firm will also be granted access to such reports in ATL's possession as part of the audit referenced in subsection (a) above.

(c) If such accounting firm concludes that additional royalties were owed during such period, ATL will pay the additional royalties within [***] days of the date ISIS delivers to ATL such accounting firm's written report. The fees charged by such accounting firm will be paid by ISIS unless the additional royalties, milestones or other payments owed by ATL exceed [***] of the royalties, milestones or other payments paid for the time period subject to the audit, in which case ATL will pay the reasonable fees and expenses charged by the accounting firm.

(d) ISIS will treat all financial information subject to review under this Section 5.8 or under any sublicense agreement in accordance with the confidentiality provisions of Article 9, and will cause its accounting firm to enter into an acceptable confidentiality agreement with ATL and its Sublicensees obligating such firm to retain all such financial information in confidence pursuant to such confidentiality agreement.

5.9 AUDITS REQUESTED BY ATL.

(a) Upon the written request of ATL, and not more than once in each calendar year, ISIS will permit ATL's independent certified public accountant to have access during normal business hours to such of the records of ISIS as may be reasonably necessary to verify the accuracy of the invoices submitted to ATL hereunder for the 12 months preceding the date of such request. The accounting firm will disclose to ATL only whether the invoiced amounts are correct or incorrect, the specific details concerning the basis for the invoiced amounts, and the corrected amount, if applicable. No other information will be provided to ATL.

(b) If such accounting firm concludes that any amounts invoiced were in error during such period and ATL is entitled to a refund of such amounts, ISIS will refund to ATL the amounts overcharged within [***] days of the date ATL delivers to ISIS such accounting firm's written report. The fees charged by such accounting firm will be paid by ATL unless the additional refunded amounts owed by ISIS exceed [***] of the total amount for which ATL was invoiced during the time period subject to the audit, in which case ISIS will pay the reasonable fees and expenses charged by the accounting firm.

(c) ATL will treat all financial information subject to review under this Section 5.9 in accordance with the confidentiality provisions of Article 9 and will cause its accounting firm to enter into an acceptable confidentiality agreement with ISIS obligating such firm to retain all such financial information in confidence pursuant to such confidentiality agreement.

5.10 TAXES.

If laws, rules or regulations require withholding of income taxes or other taxes imposed upon payments set forth in this Article 5, ATL will make such withholding payments as required and subtract such withholding payments from the payments set forth in this Article 5. ATL will submit appropriate proof of payment of the withholding taxes to ISIS within a reasonable period of time.

ARTICLE 6

USE OF MATERIALS, DATA AND INFORMATION

6.1 Unless provided otherwise herein, all Antisense Inhibitors and any related research materials delivered to ATL under this Agreement will be used only in furtherance of a Development Program or Collaborative Research Program, will not be used or delivered to or for the benefit of any Third Party without the prior written consent of ISIS, and will not be used in research or testing involving human subjects. The Antisense Inhibitors and any related research materials supplied under this Agreement must be used with prudence and appropriate caution in any experimental work, since not all of their characteristics may be known. ATL agrees to comply with all

applicable laws, rules and regulations in connection with its use of Antisense Inhibitors and related research materials provided hereunder.

6.2 All Antisense Inhibitors and related research materials provided to ATL hereunder are proprietary to ISIS. Any unused quantities of Antisense Inhibitors and research materials will be returned to ISIS by ATL, upon ISIS' request, at ISIS' expense.

6.3 ATL may use data and information generated pursuant to a Gene Walk or GeneTrove Investigation, or otherwise provided to ATL by ISIS hereunder, for internal drug discovery purposes only, consistent with the terms of this Agreement. Except as provided otherwise herein, all data and information provided to ATL by ISIS pursuant to this

Agreement is confidential and proprietary to ISIS and will not be disclosed to Third Parties, consistent with the provisions of Article 9 herein. ISIS acknowledges that ATL may wish to provide such data and/or information to a Third Party in connection with ATL's bona fide development, commercialization or partnering activities under this Agreement; ISIS will not unreasonably withhold its consent to such a transfer of data and information, provided that the receiving party is advised of the confidentiality provisions hereunder and agrees to be bound thereby. Notwithstanding the foregoing, ISIS reserves the absolute right to withhold consent if ATL wishes to transfer such data or information to an antisense company or other competitor of ISIS.

6.4 Consistent with the foregoing provisions, if ATL conducts studies comparing ISIS Standard Chemistry with the chemistry of a Third Party, all data and information incorporating or relating to ISIS Standard Chemistry that result from such studies is confidential and proprietary to ISIS and will not be disclosed to Third Parties, consistent with the provisions of Article 9 herein.

ARTICLE 7

FUNDING PROVISIONS

7.1 FUNDING FOR DEVELOPMENT ACTIVITIES.

(a) As of the Effective Date, ATL will pay for all activities described in the ISIS 107248 Development Plan or any other Development Plan hereunder, or as approved by the JDC and performed by ISIS in the course of any Development Program on a time and materials basis. Labor will be [***]. Materials and out of pocket expenses incurred by ISIS will be [***].

(b) ISIS will submit an invoice for such expenditures to ATL after each Calendar Quarter, and ATL will submit payment to ISIS within [***] days from the date of invoice, consistent with the provisions of Section 5.7.

7.2 FUNDING FOR COLLABORATIVE RESEARCH PROGRAM ACTIVITIES.

(a) Except as specifically provided otherwise herein, as of the Effective Date, ATL will pay for all activities performed by ISIS in the course of the Collaborative Research Program hereunder on a time and materials basis. Labor will be [***]. Materials and out of pocket expenses incurred by ISIS will be [***].

(b) ATL will pay for additional Gene Walks, for GeneTrove Investigations, and for additional quantities of Antisense Inhibitors as specified in Sections 3.7 and 3.8 herein.

(c) ISIS will submit an invoice for such expenditures to ATL after each Calendar Quarter, and ATL will submit payment to ISIS within [***] days from the date of invoice, consistent with the provisions of Section 5.7.

7.3 FUNDING FOR OTHER ATL ACTIVITIES.

ATL will also pay for any other activities ATL deems necessary to research, develop or commercialize a Collaboration Compound or Product, or which are otherwise required for ATL to fulfill its obligations hereunder, on a time and materials basis. Labor will be [***]. Materials and out of pocket expenses incurred by ISIS will be [***].

ARTICLE 8

INTELLECTUAL PROPERTY

8.1 OWNERSHIP OF INVENTIONS.

(a) Neither party hereto will be deemed by this Agreement to have been granted any license or other rights to the other party's rights in any inventions, technology, discoveries, or other proprietary property (collectively, "Inventions") existing as of the Effective Date of this Agreement, except as expressly provided herein.

(b) Except as provided otherwise herein, each party will solely own all Inventions that are made (as determined by U.S. rules of inventorship) solely by employees of or Consultants to that party pursuant to the Collaborative Research Program or any Development Program under this Agreement. Such an Invention will be an "ISIS Invention" or an "ATL Invention," as the case may be, and Patents claiming such Inventions will be "ISIS Patents" or "ATL Patents," respectively.

(c) ISIS agrees to assign to ATL its rights in any ISIS Inventions or Joint Inventions claiming Antisense Inhibitors that modulate IGF-1R and methods of using same, provided that a License to Research or License to Exploit for IGF-1R exists. If ATL does not convert the License to Research for IGF-1R into a License to Exploit IGF-1R, or if the License to Research or License to Exploit applicable to IGF-1R is terminated for any reason, ATL will assign back to ISIS the latter's rights in any such ISIS Inventions and Joint Inventions, as well as ISIS' rights in any Patents filed on such Inventions. Notwithstanding the foregoing, if such assignment of rights back to ISIS would interfere with ATL's ability to practice any ATL Inventions or ATL Patent Rights pertaining to IGF-1R, ISIS agrees to sublicense, in favor of ATL, only that portion of any such Invention or Patent, and only for that time period, as is required for ATL to practice an ATL Invention or ATL Patent that would otherwise infringe the ISIS Invention or ISIS Patent, on a nonexclusive, mutually agreeable basis that is consistent with the royalties set out in this Agreement, provided that ISIS is not otherwise precluded from doing so.

(d) Except as provided otherwise herein, ISIS and ATL will jointly hold title to all Inventions, whether or not patentable, that are made (as determined by the U.S. rules of inventorship) jointly by employees of or Consultants to ISIS and ATL pursuant to the Collaborative

Research Program or any Development Program under this Agreement, as well as to Patents filed thereon. Such Inventions will be "Joint Inventions," and Patents claiming such Joint Inventions will be "Joint Patents." ISIS and ATL will promptly provide each other with notice whenever a Joint Invention is made. The parties agree and acknowledge that, except insofar as this Agreement provides otherwise, the default rights conferred on joint owners under US patent law, including the right of each party to independently practice, license and use a Joint Patent, will apply in relation to the Joint Patents throughout the world as though US patent law applied worldwide.

(e) The parties understand that if ATL or a Third Party collaborator of ATL provides a proprietary gene sequence or utility not known to ISIS, the discovery of inhibitors of that sequence may be a Joint Invention. Similarly, the parties understand that the discovery of a method of treating human disease by inhibiting a particular gene product, where ISIS' Antisense Inhibitor data is used to support the claims of the Patent, may be a Joint Invention.

(f) The parties agree, upon reasonable request, to execute any documents reasonably necessary to effect and perfect each other's ownership of any Invention.

(g) [***].

8.2 FILING, PROSECUTION, MAINTENANCE, ENFORCEMENT AND DEFENSE OF PATENTS OWNED OR CONTROLLED BY ISIS AND OF CERTAIN JOINT PATENTS.

(a) Except as provided otherwise herein, ISIS will have the sole and

exclusive right to file, prosecute, maintain, enforce and defend any Research Target Patent Rights and any ISIS Patents or Joint Patents filed on Inventions claiming an Antisense Inhibitor to a Research Target or a method of treatment using an antisense molecule that modulates a Research Target subject to a License to Research or License to Exploit hereunder, regardless of inventorship. ISIS will consider ATL's input with respect to the prosecution, maintenance, enforcement and defense of any such Patents. ISIS will also consider any supporting information provided by ATL that relates to the Research Target and its uses, as well as any supporting IN VIVO or IN VITRO efficacy data generated from experiments performed by ATL or its collaborators. As used herein, Patent prosecution includes, without limitation, the handling of interference proceedings, oppositions, reexaminations and reissues.

(b) In the event ATL proposes the filing of a Joint Patent pursuant to subsection (a) and ISIS does not wish to file and prosecute such Joint Patent, ATL will have the right to file, prosecute, maintain, enforce and defend such Joint Patent. ATL will consider ISIS' input with respect to the prosecution, maintenance, enforcement and defense of any such Joint Patents.

(c) ISIS will also have the sole and exclusive right, in its sole discretion, to file, prosecute, maintain, enforce and defend any Patents within the ISIS Core Technology Patent Rights, the Manufacturing Patent Rights, and the ISIS Formulation Patent Rights.

(d) ISIS will pay for its own labor costs incurred in the filing, prosecution, maintenance, enforcement and defense of any Patents for which ISIS is responsible hereunder.

(e) ATL will reimburse ISIS for reasonable materials and out of pocket expenses incurred in connection with the activities recited in subsections (a), (c) and (d). As used herein, materials and out-of-pocket expenses means costs, other than ISIS' labor costs, [***]. ISIS will invoice ATL on a quarterly basis and ATL will submit payment to ISIS consistent with the provisions of Article 7 herein.

(f) Should ATL elect not to pay expenses relating to Patent protection in a particular country, ATL will provide ISIS with written notice of same, and ATL's payment obligations with respect to that country will cease once ISIS has received such notice, provided that all noncancelable costs and expenses incurred by ISIS prior to such date will nevertheless be reimbursed by ATL. Immediately upon ISIS' receipt of such written notice from ATL, the applicable License to Research or License to Exploit will be terminated with respect to such country.

(g) With respect to any ISIS Patent Rights exclusively licensed to ATL under a License to Exploit, ISIS will promptly advise ATL if ISIS becomes aware of any suspected or actual infringement of such ISIS Patent Rights by any person. Similarly, ATL will promptly advise ISIS if ATL becomes aware of any suspected or actual infringement of such ISIS Patent Rights by any person.

(h) If ISIS fails to initiate proceedings against any actual or suspected infringement of the ISIS Patent Rights exclusively licensed to ATL hereunder or to defend any claim of infringement against the parties pertaining to such rights within [***] days of receipt of a notice from ATL asking ISIS to do so, ATL will be entitled to initiate those proceedings at ATL's expense.

(i) Except as provided otherwise herein, ISIS will endeavor to take all action necessary to ensure that the ISIS Patent Rights that are or become subject to a License to Research or License to Exploit are maintained and diligently prosecuted.

8.3 FILING, PROSECUTION, MAINTENANCE, ENFORCEMENT AND DEFENSE OF PATENTS OWNED OR CONTROLLED BY ATL.

(a) Except as provided otherwise herein, ATL will have the sole and exclusive right and responsibility, in its sole discretion, to file, prosecute, maintain, enforce and defend any Patents filed on Inventions made solely by ATL (i.e., ATL Patents). ATL will provide ISIS with a semiannual report summarizing the status of any such ATL Patents. ATL hereby grants ISIS a worldwide, royalty-free, sublicensable, perpetual, nonexclusive license to practice under

ATL's rights to any such ATL Patent to carry out the activities contemplated by this Agreement and to make, have made, use, import, offer for sale and sell products other than a Product.

(b) If a License to Exploit is granted to ATL with respect to a Research Target or Collaboration Compound hereunder, ISIS will promptly thereafter transfer to ATL the sole and exclusive right to prosecute, maintain, enforce and defend any Patents owned, controlled or to which ISIS has prosecution rights that are within the Research Target Patent Rights. ATL will consider ISIS' input with respect to the prosecution, maintenance, enforcement and defense of any such Patents. If ATL decides to discontinue the prosecution, maintenance, enforcement or defense of any such Patent entirely or in a particular country, it will inform ISIS thereof with sufficient time for ISIS to assume those responsibilities with respect to such Patent and will thereafter transfer the relevant Patent files to ISIS or its designee.

8.4 INFRINGEMENT OF THIRD PARTY PATENTS.

If either party receives notice that a Product infringes a Third Party Patent, and the parties hereto agree to settle with and pay royalties to such Third Party, the additional royalty burden will be allocated as follows.

(a) If the alleged infringement is due to ATL's practice of ISIS Core Technology Patent Rights, Manufacturing Patent Rights, or ISIS 107248 Patent Rights, [***].

(b) If the alleged infringement is due to ATL's practice of any other Patent Rights licensed hereunder, [***].

8.5 PATENT COORDINATORS.

(a) Within 30 days of the Effective Date, the parties will each select a Patent Coordinator ("PC") to facilitate and coordinate the preparation, filing, prosecution and maintenance of Patents pursuant to this Agreement. The parties may agree to name additional Patent Coordinators, as long as equal representation is maintained.

(b) During the Collaboration Term, the PCs will be the primary contacts for interaction between the parties with respect to the activities referenced in (a).

(c) The PCs will meet as needed during the Collaboration Term. Meetings will be via teleconference or videoconference, or as the parties may otherwise agree. The frequency, dates and times of all meetings will be mutually agreed upon by the parties. At their first meeting, the PCs will determine such procedures as they will reasonably require to conduct their activities.

(d) The parties further agree that to facilitate the activities described in this Section, ATL's Patent Coordinator may, upon prior written notice to ISIS' Patent Coordinator and at such times as are mutually agreed upon by the Patent Coordinators, obtain access to and make copies of Patent file documents that are relevant to filing, prosecution, maintenance, enforcement and defense of Patents licensed to ATL hereunder. Any and all such documents will be maintained by ATL in confidence, pursuant to the provisions of Article 9 below.

ARTICLE 9

CONFIDENTIALITY

9.1 NONDISCLOSURE OBLIGATION.

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

9.2 PERMITTED DISCLOSURES.

Except as otherwise provided herein, a party may disclose Confidential Information received from the other party:

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

(b) to Affiliates, Sublicensees, agents, consultants, and/or other Third Parties for the development, manufacturing and/or marketing of the Product (or for such parties to determine their interest in performing such activities) in accordance with this Agreement on the condition that such Affiliates and Third Parties agree to be bound by the confidentiality obligations contained in this Agreement, provided the term of confidentiality for such Affiliates and Third Parties will be no less than 7 years; or

(c) if such disclosure is required by law 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.

ARTICLE 10

PUBLICATION AND PUBLICITY

10.1 PUBLICATION.

(a) The parties agree that it is customary in the industry to publish results obtained from clinical trials and other studies of a Collaboration Compound or Product, and that each party may publish such information obtained by such party in the performance of the Development Program, subject to the provisions of this Section.

(b) Except as provided otherwise herein, the parties will be entitled to publish or present on the results of any Development Program hereunder including, without limitation, the ISIS 107248 Development Program, and any Collaboration Compound or Product, provided that the party seeking to publish will deliver to the other party for its review a copy of any

proposed publication or an abstract of any oral presentation of clinical results at scientific meetings involving ISIS 107248, any Collaboration Compound or Product hereunder, or the Proprietary Information of the other party, at least 30 days prior to submission of scientific publications or abstracts of oral presentations. The reviewing party will have the absolute right to request that any of its Proprietary Information be deleted from such publication or presentation, and the disclosing party will comply with that request. If the disclosing party does not receive any feedback from the reviewing party within that 30-day period, the disclosing party will be free to proceed with the publication or presentation, with the following limitations:

(i) ISIS will be permitted to publish on matters relating to ISIS 107248, a Collaboration Compound or Product containing ISIS 107248, or any other Collaboration Compound or Product developed by ATL hereunder during the term of this Agreement only upon the prior written approval of ATL, which may be reasonably withheld by ATL.

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

10.2 PUBLICITY.

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

(b) Except as otherwise provided herein or required by law, neither party will originate any publication, news release or other public announcement, written or oral, whether in the public press, or stockholders' reports, or otherwise, relating to this Agreement, and neither party will use the name, trademark, trade name, logo or likeness of the other party or its employees in any publicity, news release or disclosure relating to this Agreement, or its subject

matter, without the prior express written permission of the other party.

(c) ATL will inform ISIS of any press releases relating to a Product permitted hereunder or required to be made by law in advance of general release to the public.

ARTICLE 11

INDEMNIFICATION

11.1 INDEMNIFICATION BY ATL.

ATL will indemnify, defend and hold ISIS and its agents, employees, officers and directors (the "ISIS Indemnitees") harmless from and against any and all liability, damage, loss, cost or

expense (including reasonable attorneys' fees) arising out of Third Party claims or suits related to (a) ATL's performance of its obligations under this Agreement; (b) breach by ATL of its representations and warranties set forth in Article 13; (c) patent infringement allegations or claims asserted by a Third Party against ISIS arising out of ISIS' performance of activities for ATL pursuant to this Agreement; or (d) ATL's choice of Research Targets pursuant to Section 3.4 or 3.5; PROVIDED, HOWEVER, that ATL's obligations pursuant to this Section 11.1 will not apply to the extent such claims or suits result from the gross negligence or willful misconduct of any of the ISIS Indemnitees. Notwithstanding the foregoing, ATL will have no obligation to indemnify the ISIS Indemnitees with respect to claims arising out of breach by ISIS of its representations and warranties set forth in Section 13.1.

11.2 INDEMNIFICATION BY ISIS.

ISIS will indemnify, defend and hold ATL and its Affiliates and each of their respective agents, employees, officers and directors (the "ATL Indemnitees") harmless from and against any and all liability, damage, loss, cost or expense (including reasonable attorney's fees) arising out of Third Party claims or suits related to (a) ISIS' performance of its obligations under this Agreement; or (b) breach by ISIS of its representations and warranties set forth in Article 13; PROVIDED HOWEVER, that ISIS' obligations pursuant to this Section 11.2 will not apply to the extent that such claims or suits result from the gross negligence or willful misconduct of any of the ATL Indemnitees. Notwithstanding the foregoing, ISIS will have no obligation to indemnify the ATL Indemnitees with respect to claims arising out of a breach by ATL of its representations and warranties set forth in Sections 3.5(b)(i) and 13.1.

11.3 NOTIFICATION OF CLAIMS; CONDITIONS TO INDEMNIFICATION OBLIGATIONS.

As a condition to a party's right to receive indemnification under this Article 11, it will (i) promptly notify the other party as soon as it becomes aware of a claim or action for which indemnification may be sought pursuant hereto, (ii) cooperate with the indemnifying party in the defense of such claim or suit, and (iii) permit the indemnifying party to control the defense of such claim or suit, including without limitation the right to select defense counsel. In no event, however, may the indemnifying party compromise or settle any claim or suit in a manner which admits fault or negligence on the part of the indemnified party without the prior written consent of the indemnified party. The indemnifying party will have no liability under this Article 11 with respect to claims or suits settled or compromised without its prior written consent.

ARTICLE 12

TERM AND TERMINATION OF AGREEMENT

12.1 TERM AND TERMINATION OF AGREEMENT.

This Agreement will be effective as of the Effective Date and unless terminated earlier pursuant to Sections 12.2 or 12.3 below, the term of this Agreement will continue in effect until expiration of

the License Term.

12.2 TERMINATION UPON FUNDAMENTAL BREACH.

This Agreement may be terminated upon written notice by either party to the other at any time during the term of this Agreement if the other party is in fundamental breach of its obligations hereunder (i.e., a breach which goes to the heart of the Agreement) and has not cured such breach within 90 days after written notice requesting cure of the breach; providing, however, that in the event of a good faith dispute with respect to the existence of such a fundamental breach, the 90-day cure period will be stayed until such time as the dispute is resolved pursuant to Section 16.6 hereof. Material breaches that are not fundamental give rise solely to a right of damages but not a right to terminate the Agreement.

12.3 TERMINATION UPON BANKRUPTCY; RIGHTS IN BANKRUPTCY.

All rights and licenses granted under or pursuant to this Agreement by ISIS or ATL are, and will otherwise be deemed to be, for purposes of Section 365(n) of the U.S. Bankruptcy Code, licenses of right to "intellectual property" as defined under Section 101 of the U.S. Bankruptcy Code. The parties agree that the parties, as licensees of such rights under this Agreement, will retain and may fully exercise all of their rights and elections under the U.S. Bankruptcy Code. The parties further agree that, in the event of the commencement of a bankruptcy proceeding-by or against either party under the U.S. Bankruptcy Code, the party hereto which is not a party to such proceeding will be entitled to a complete duplicate of (or complete access to, as appropriate) any such intellectual property and all embodiments of such intellectual property, and same, if not already in their possession, will be promptly delivered to them (i) upon any such commencement of a bankruptcy proceeding upon their written request therefor, unless the party subject to such proceeding elects to continue to perform all of its obligations under this Agreement, or (ii) if not delivered under (i) above, following the rejection of this Agreement by or on behalf of the party subject to such proceeding upon written request therefor by the non-subject party.

12.4 ACCRUED RIGHTS AND SURVIVING OBLIGATIONS.

Expiration or termination of the Agreement will not relieve the parties of any obligation accruing prior to such expiration or termination. Sections 4.8, 12.4 and 16.7, and Articles 5-9, 11 and 13-15 will survive expiration or termination of the Agreement. Provisions concerning reporting requirements will continue in effect in accordance with any applicable timetables set forth herein. Any expiration or early termination of this Agreement will be without prejudice to the rights of either party against the other accrued or accruing under this Agreement prior to termination, including the obligation to pay royalties for Product sold prior to such termination.

ARTICLE 13

REPRESENTATIONS AND WARRANTIES; DISCLAIMER

13.1 REPRESENTATIONS AND WARRANTIES OF THE PARTIES.

Each party represents and warrants to the other party that, as of the date of this Agreement:

(a) Such party is duly organized and validly existing under the laws of the state of its incorporation and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

(b) Such party has taken all corporate action necessary to authorize the execution and delivery of this Agreement and the performance its obligations under this Agreement;

(c) This Agreement is a legal and valid obligation of such party, binding upon such party and enforceable against such party in accordance with the terms of this Agreement The execution, delivery and performance of this Agreement by such party does not conflict with any agreement, instrument or understanding, oral or written, to which such party is a party or by which such party may be bound, and does not violate any law or regulation of any court, governmental body or administrative or other agency having authority over such party. All consents, approvals and authorizations from all

governmental authorities or other Third Parties required to be obtained by such party in connection with this Agreement have been obtained;

(d) Such party has the full and exclusive right, power and authority to enter into this Agreement, to perform the Development Program, the Collaborative Research Program and to grant the licenses granted hereunder;

(e) There are no agreements between such party and any Third Parties which would preclude or otherwise limit such party's ability to conduct its tasks and obligations under the Development Plan, the Collaborative Research Program or otherwise fulfill its obligations under this Agreement; and

(f) All individuals who will perform any activities on such party's behalf in connection with the Development Program and/or the Collaborative Research Program have assigned to such party or its Affiliates the whole of their rights in any intellectual property conceived or reduced to practice by them as a result of either program.

13.2 REPRESENTATIONS AND WARRANTIES BY ATL.

ATL warrants and represents that to the best of its knowledge, none of the Research Targets listed on Exhibit 3.4 as of the Effective Date are encumbered by any Third Party rights including, without limitation, intellectual property rights, that would interfere with ISIS' ability to carry out the activities contemplated by the parties hereunder. ATL further warrants and represents that, to the best of its knowledge as of the Effective Date, if ISIS makes an Antisense Inhibitor to any of the Research Targets, it will not constitute an infringement of any Third Party rights and that ATL will indemnify ISIS, as set forth in Section 11.1 herein, should a subsequent determination be made that Third Party rights were infringed.

13.3 REPRESENTATIONS AND WARRANTIES BY ISIS.

ISIS warrants and represents that to the best of its knowledge, the practice of the technology claimed in the ISIS Core Technology Patent Rights and the Manufacturing Patent Rights will not infringe any Third Party patents.

13.4 DISCLAIMERS.

THE ANTISENSE INHIBITORS BEING PROVIDED TO ATL HEREUNDER ARE PROVIDED "AS IS" AND WITHOUT ANY REPRESENTATION OR WARRANTY, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION ANY IMPLIED WARRANTY OF MERCHANTABILITY OR OF FITNESS FOR ANY PARTICULAR PURPOSE OR ANY WARRANTY THAT THE USE OF THE MATERIALS WILL NOT INFRINGE OR VIOLATE ANY PATENT OR OTHER PROPRIETARY RIGHTS OF ANY THIRD PARTY.

THE PARTIES EXPRESSLY DISCLAIM ALL WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, OR NON-INFRINGEMENT OF THIRD PARTY RIGHTS, UNLESS OTHERWISE EXPRESSLY PROVIDED IN THIS AGREEMENT.

ARTICLE 14

NOTICE

14.1 NOTICE.

All notices which are required or permitted hereunder will 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.: +1 (760) 931-9639

with a copy to: Attention: General Counsel
Fax No.: +1 (760) 603-3820

if to ATL, to: Antisense Therapeutics, Limited
ACN 095 060 745 of Level 1
10 Wallace Avenue, Toorak
Victoria 3142, AUSTRALIA
Attention: CEO
Fax No.: +61 (3) 9826 4399

with a copy to: Attention: General Counsel
Fax No.: +61 (3) 9826 4399

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

ARTICLE 15

RECORDS

15.1 RECORDS.

Each party will maintain records, in sufficient detail and in good scientific manner, which will fully and properly reflect all work done and results achieved in the performance of its responsibilities under each Development Plan hereunder including, without limitation, the ISIS 107248 Development Plan. Each party will have the right, during normal business hours and upon reasonable prior notice, to inspect and copy those records of the other party referred to herein that are necessary or useful to the inspecting party for the purposes of making any required filings with Regulatory Authorities in order to obtain manufacturing approvals and/or Marketing Approvals. Each party will maintain such records and the information disclosed therein in confidence in accordance with Article 9.

ARTICLE 16

MISCELLANEOUS PROVISIONS

16.1 RELATIONSHIP OF THE PARTIES.

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

16.2 SUCCESSORS AND ASSIGNS.

Neither this Agreement nor any interest hereunder may be assigned or otherwise transferred, nor, except as expressly provided hereunder, may any right or obligations hereunder be assigned or transferred by either party without the prior written consent of the other party; provided, however, that either party may, without such consent, assign the Agreement and its rights and obligations hereunder to an Affiliate or in connection with the transfer or sale of all or substantially all of its assets, or in the event of its merger or consolidation or change in control or similar transaction. Any permitted assignee will assume all obligations of its assignor under the Agreement, except that no intellectual property of any Third Party acquirer of ATL or ISIS will be included in the licenses granted hereunder. This Agreement will be binding upon the successors and permitted assigns of the parties. Any attempted assignment not in accordance with this Section 16.2 will be void.

16.3 ENTIRE AGREEMENT; AMENDMENTS.

This Agreement, the Stock Agreement and the Clinical Supply Agreement contain the entire understanding of the parties with respect to the license, development and commercialization of antisense APIs hereunder. 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.

16.4 FORCE MAJEURE.

Neither party will be held liable or responsible to the other party nor be deemed to have defaulted under or breached the Agreement for failure or delay in fulfilling or performing any term of the Agreement when such failure or delay is caused by or results from causes beyond the reasonable control of the affected party including, without limitation, embargoes, acts of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, or acts of God. The affected party will notify the other party of such force majeure circumstances as soon as reasonably practical and will make every reasonable effort to mitigate the effects of such force majeure circumstances.

16.5 APPLICABLE LAW

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

16.6 DISPUTE RESOLUTION

(a) The parties recognize that disputes may from time to time arise between the parties during the term of this Agreement. In the event of such a dispute, either party, by written notice to the other party, may have such dispute referred to the parties' respective executive officers designated below or their successors, for attempted resolution by good faith negotiations within 30 days after such notice is received. Said designated officers are as follows:

For ISIS:	Executive Vice President
For ATL:	CEO

(b) In the event the designated executive officers are not able to resolve such dispute after such 30-day period, each party may pursue its rights and remedies in law or equity in any court of competent jurisdiction.

16.7 NO CONSEQUENTIAL DAMAGES

IN NO EVENT WILL EITHER PARTY OR ANY OF ITS RESPECTIVE AFFILIATES BE LIABLE TO THE OTHER PARTY OR ANY OF ITS AFFILIATES FOR SPECIAL, INDIRECT, INCIDENTAL OR CONSEQUENTIAL DAMAGES, WHETHER IN CONTRACT, WARRANTY, TORT, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE, INCLUDING, BUT NOT LIMITED TO, LOSS OF PROFITS OR REVENUE, OR CLAIMS OF CUSTOMERS OF ANY OF THEM OR OTHER THIRD PARTIES FOR SUCH OR OTHER DAMAGES.

16.8 CAPTIONS

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.

16.9 WAIVER

The waiver by either party hereto of any right hereunder, or the failure to perform, or a breach by the other party will not be deemed a waiver of any other right hereunder or of any other breach or failure by said other party whether of a similar nature or otherwise.

16.10 COMPLIANCE WITH LAW

Nothing in this Agreement will be deemed to permit a party to export, re-export or otherwise transfer any Licensed Product sold under this Agreement without compliance with applicable laws.

16.11 SEVERABILITY.

In the event any one or more of the provisions contained in this Agreement should be held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein will not in any way be affected or impaired thereby, unless the absence of the invalidated provision(s) adversely affect the substantive rights of the parties. The parties will in such an instance use their best efforts to replace the invalid, illegal or unenforceable provision(s) with valid, legal and enforceable provision(s) which, insofar as practical, maintains the balance of the rights

and obligations of the parties under this Agreement.

16.12 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 will be construed against the drafting party will not apply.

16.13 COUNTERPARTS.

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

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

ANTISENSE THERAPEUTICS, LIMITED	ISIS PHARMACEUTICALS, INC.
By: /s/ C. Belyea	By: /s/ B. Lynne Parshall
Name: C. Belyea	Name: B. Lynne Parshall
Title: CEO	Title: Executive Vice President and CFO

EXHIBIT 1

DEFINITIONS

1.1 "ABANDONED RESEARCH TARGET" has the meaning set forth in Section 3.5(d) herein.

1.2 "ACTIVE PROGRAM" in relation to a Collaboration Compound or Product means an ongoing program for optimizing, developing and commercializing such Collaboration Compound or Product, including preclinical studies, human clinical studies, development activities aimed at obtaining registration for marketing, and marketing and selling activities, wherein such program includes the following specific "DEVELOPMENT MILESTONES" that must be met in order for the Collaboration Compound or Product to achieve and maintain "ACTIVE DEVELOPMENT" status:

(a) initiation of phenotypic or functional assays by ATL within 12 months of ATL's receipt of reasonably sufficient quantities of the Antisense Inhibitors directed to a Research Target and corresponding control oligonucleotides;

(b) initiation of IND-enabling toxicology studies by ATL within 18 months of ATL's receipt of an Antisense Inhibitor directed to a Research Target;

(c) filing of an IND not later than 6 months after the completion of IND-enabling studies;

(d) initiation of Phase I studies not later than 6 months after the filing of the IND;

(e) initiation of Phase IIa studies not later than 24 months after the initiation of Phase I studies;

(f) initiation of Phase III studies not later than 3 years after the initiation of Phase IIa studies;

(g) filing of an NDA not later than 18 months after the successful completion of a pivotal trial; and

(h) the use of commercially reasonable efforts by ATL to bring each Product to market and to maximize the commercial value of each such Product worldwide.

If ATL will not be able to meet a Development Milestone set forth above for circumstances beyond ATL's control but has proceeded in good faith in its development efforts, ATL will be granted a 12-month extension on any of the milestones identified in above, provided that ATL [***].

A compound that is in "Active Development" is one that is in an Active Program, as defined above.

1.3 "AFFILIATE" with respect to either party means any person, organization, corporation or other business entity (collectively, "Person") controlling, controlled by, or under common control with such party. For purposes of this definition, "control" refers to the

possession, directly or indirectly, of the power to direct the management or policies of a Person, whether through the ownership of voting securities, by contract or otherwise, of a Person.

1.4 "ANTISENSE INHIBITOR" means an oligonucleotide or analog thereof that inhibits protein synthesis at the nucleic acid level by specifically binding to the sequence of a selected messenger or viral ribonucleic acid (RNA) by base-pairing, thus causing a selective inhibition of gene expression.

1.5 "ANTISENSE TECHNOLOGY" means the selective modulation of protein synthesis at the nucleic acid level caused by the binding of an oligonucleotide or an analog thereof to a complementary sequence.

1.6 "ATL INVENTION" has the meaning set forth in Section 8.1(b).

1.7 "ATL PATENT" has the meaning set forth in Section 8.1(b).

1.8 "ATL SUBLICENSE" has the meaning set forth in Section 4.3(b).

1.9 "AUSTRALIAN APPROVAL" means approval of a Product for marketing in Australia by the Therapeutic Goods Administration ("TGA"), without the requirement for price having been approved. If a Product can be sold in Australia without TGA approval, Australian Approval will be deemed to have been obtained on the first sale of a Product in Australia.

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

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

1.12 "COLLABORATION" has the meaning set forth in Section 2.1.

1.13 "COLLABORATION COMPOUND" means an Antisense Inhibitor of a Research Target that is discovered or developed by ISIS that (i) incorporates Antisense Technology; (ii) incorporates ISIS Standard Chemistry; (iii) is subject to a License to Research or License to Exploit hereunder; and (iv) is in Active Development, consistent with Section 1.2 herein.

1.14 "COLLABORATION COMPOUND PRODUCT" means a product containing a Collaboration Compound.

1.15 "COLLABORATION TERM" means the term of the Collaborative Research Program as set forth in Section 3.1.

1.16 "COLLABORATIVE RESEARCH PLAN" has the meaning set forth in Section 3.1, as further detailed in Exhibit 3.1.

1.17 "COLLABORATIVE RESEARCH PROGRAM" means the research program described in Article 3, as modified from time to time by the parties (e.g., via the JRC).

1.18 "CONFIDENTIAL INFORMATION" means information which is (a) of a confidential and proprietary nature; (b) designated by either party as

Confidential Information or Proprietary Information; and (c) not readily available to that party's competitors and which, if known by a competitor of that party, might lessen any competitive advantage of that party or give such competitor a competitive advantage. Confidential Information which is disclosed in oral, written, graphic, electronic or any other form by one party to the other party that is clearly marked as "confidential" or "proprietary." Oral information must be reduced to writing and designated as "confidential" within 30 days of disclosure.

For the purposes of this Agreement, "Confidential Information" includes, without limitation, (a) information that is proprietary or confidential or which is treated by that party as confidential and which relates either directly or indirectly to the business of that party regardless of the form in which that information is constituted, and which is not lawfully in the public domain; and (b) any confidential information in relation to Patents, technology, know-how, or any improvements owned or controlled by a party hereto.

"Confidential Information" will not include any information that the receiving party can establish by written records:

(i) was known by it prior to the receipt of Confidential Information from the disclosing party;

(ii) was disclosed to the receiving party by a Third Party having the right to do so;

(iii) was, or subsequently became, in the public domain through no fault of the receiving party, its officers, directors, employees or agents;

(iv) was concurrently or subsequently developed by personnel of the receiving party without having had access to the disclosing party's Confidential Information;

(v) was disclosed with the prior written consent of the disclosing party; or

(vi) was disclosed by the receiving party pursuant to any judicial or governmental request, requirement or order, so long as the receiving party provides the disclosing party with sufficient prior notice in order to allow the disclosing party to contest such request, requirement or order.

1.19 "CONSULTANT" means an individual who is not an employee of either party hereto, but who has been engaged by a party hereto in order to perform certain activities, wherein

that individual has an obligation to assign to the engaging party, at the time an Invention is made, all rights that individual may have in such Invention.

1.20 "DERMATOLOGY TARGETS" means those Research Targets designated as Dermatology Targets, as listed in Section A of Exhibit 3.4.

1.21 "DEVELOPMENT MILESTONES" means the Development Milestones set forth in Section 1.2 hereinabove.

1.22 "DEVELOPMENT PLAN" means the plan for the development of any Antisense Inhibitor or Collaboration Compound hereunder.

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

1.24 "GENETROVE," when used to refer to an organization, corporation or other business entity, means the functional genomics division of ISIS.

1.25 "GENETROVE INVESTIGATION" or "GENE FUNCTIONALIZATION ASSAY" has the meaning set forth in Section 3.8, as further described in Exhibit 3.8.

1.26 "GENE WALK" has the meaning set forth in Section 3.7, as further described

in Exhibit 3.7.

1.27 [***].

1.28 [***].

1.29 "IND" means an Investigational New Drug Application or similar application or submission for approval to conduct human clinical investigations filed with or submitted to a Regulatory Authority or hospital ethics committee in conformity with applicable Regulatory Authority regulations.

1.30 "IND-ENABLING STUDIES" means, at a minimum, the pharmacokinetic and toxicology studies required to meet the safety regulations for filing an IND, as well as any additional studies required by a Regulatory Authority or hospital ethics committee as a prerequisite to filing an IND.

1.31 "INTEGRATED PRODUCT PLAN" or "IPP" means a plan for the development, commercialization and marketing of a Collaboration Compound hereunder. The IPP will

include Product charter, strategic intent, a market analysis (event maps - demographics, market dynamics), label need and wants (based on the applicable Development Plan), Product life overview, geographic overview, and financial overview. In addition, a global marketing plan will be developed and incorporated into the IPP which includes analysis of market (disease overview, Product profile, archetype, patient segmentation), strategic ends (strategic intent, product positioning, brand character, core messages, critical success factors, marketing objectives) strategic means (global Product, place, price, promotion, launch, market research programs), operational plan (implementation plan, marketing activities) and budget for the execution of the plan. Each IPP will also include appropriate milestones and the dates upon which such milestones must be met by ATL, as agreed upon by the parties hereto.

1.32 "INVENTION" has the meaning set forth in Section 8.1 herein.

1.33 "ISIS 107248" means the oligonucleotide that targets human CD49d disclosed and claimed (as SEQ ID NO 81) in U.S. Patent No. 6,258,790.

1.34 "ISIS 107248 DEVELOPMENT PLAN" means the plan for the development of ISIS 107248 hereunder as set forth in Exhibit 2.2, as amended by the JDC from time to time.

1.35 "ISIS 107248 PATENT RIGHTS" means the Patents owned by ISIS as of the Effective Date or during the Collaboration Term that claim antisense oligonucleotides that modulate human CD49d, methods of making such oligonucleotides for therapeutic use, or methods of using such oligonucleotides for therapeutic applications. The ISIS 107248 Patent Rights are the Patents listed in Exhibit 1.35.

1.36 "ISIS C5-PROPYNE PATENT RIGHTS" means all Patents owned by ISIS as of the Effective Date or during the Collaboration Term that claim any of the 5-(1-propynyl) pyrimidine phosphoramidite compounds listed in Exhibit 1.37.

1.37 "ISIS CORE TECHNOLOGY PATENT RIGHTS" means the Patents owned by ISIS as of the Effective Date or during the Collaboration Term that claim ISIS Standard Chemistry, the cellular mechanisms of action by which phosphorothioate antisense oligonucleotides exert their effect, or to methods of treatment using such oligonucleotides. ISIS Core Technology Patent Rights also include the ISIS C-5 Propyne Patent Rights. The ISIS Core Technology Patent Rights are the Patents listed in Exhibit 1.37.

1.38 "ISIS FORMULATION PATENT RIGHTS" means the Patents owned by ISIS as of the Effective Date or during the Collaboration Term that claim topical formulations incorporating antisense oligonucleotides made using ISIS Standard Chemistry, methods of making formulations containing such oligonucleotides for topical administration, or methods of treatment using such topical formulations. The ISIS Formulation Patent Rights are the Patents listed in Exhibit 1.38.

1.39 "ISIS FTE RATE" means [***].

1.40 "ISIS INVENTION" has the meaning set forth in Section 8.1(b).

1.41 "ISIS NET ROYALTY" means the [***].

1.42 "ISIS PATENT" has the meaning set forth in Section 8.1(b).

1.43 "ISIS PATENT RIGHTS" means all rights in Patents owned by ISIS that are within the ISIS Core Technology Patent Rights, the Manufacturing Patent Rights, the ISIS Formulation Patent Rights, or the Research Target Patent Rights.

1.44 "ISIS STANDARD CHEMISTRY" means the technology, whether or not subject to a Patent, that is owned, acquired or controlled by ISIS as of the Effective Date or during the Collaboration Term that claims or covers 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-[methoxyethyl] (MOE) modified sugar units with natural and methyl substituted heterocycle bases ("MOE Gapmer Technology"). ISIS Standard Chemistry also includes the technology owned, acquired or controlled by ISIS as of the Effective Date that claims or covers the cellular mechanisms of action by which MOE Gapmer Technology antisense oligonucleotides exert their effect. ISIS Standard Chemistry does not include any target gene-specific technology.

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

1.46 "LICENSE TO EXPLOIT" has the meaning set forth in Section 4.2.

1.47 "LICENSE TO RESEARCH" has the meaning set forth in Section 4.1.

1.48 "LICENSE TERM" has the meaning set forth in Section 4.0.

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

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

1.51 "MANUFACTURING PATENT RIGHTS" means the Patents owned by ISIS as of the Effective Date or during the Collaboration Term that claim the Manufacturing Technology. The

Manufacturing Patent Rights as of the Effective Date are the Patents listed in Exhibit 1.51.

1.52 "MANUFACTURING PROCESS" means the process steps set forth in master batch records for ISIS 107248 in the version existing as of the Effective Date, including reasonable minor variants and extensions of process steps thereof.

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

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

1.55 "NDA" means New Drug Application or similar application or submission for approval to market and sell a new pharmaceutical product filed with or submitted to a Regulatory Authority in conformity with applicable Regulatory Authority regulations.

1.56 "NET SALES" means, with respect to a Product, the gross amount invoiced by ATL or ISIS, as appropriate, or by their Affiliates or sublicensees,

to unrelated Third Parties for the Product, less:

(a) Trade, quantity and cash discounts allowed;

(b) Commissions, discounts, refunds, rebates, chargebacks, retroactive price adjustments, and any other allowances which effectively reduce the net selling price;

(c) Credits for actual Product returns;

(d) Any tax imposed on the production, sale, delivery or use of the Product, including, without limitation, sales, use, excise or value added taxes;

(e) Allowance for distribution expenses at levels customary in the industry; and

(f) Any other similar and customary deductions.

"NET SALES" excludes:

(i) The transfer of reasonable and customary quantities of free samples of Product(s) and the transfer of Product(s) as clinical trial materials, other than for subsequent resale;
(ii) Sales or transfers of Product(s) among ATL and its Affiliates, unless the receiving party is the consumer or user of the Product; and

(iii) Use by ATL or its Affiliates or sublicensees of Product for any use connected with the securing of regulatory approval or validating of a manufacturing process or the obtaining of other necessary Marketing Approvals for Product (unless such Product is subsequently sold).

1.57 [***].

1.58 "PATENT" or "PATENTS" means (a) patent applications (including provisional applications and applications for certificates of invention); (b) any patents issuing from such patent applications (including certificates of invention); (c) all patents and patent applications worldwide based on, corresponding to, or claiming the priority date(s) of any of the foregoing; (d) any reissues, substitutions, confirmations, registrations, validations, re-examinations, additions, continuations, continued prosecution applications, continuations-in-part, requests for continued examination, or divisions of or to any of the foregoing; and (e) term extension or other governmental action which provide exclusive rights to a Product beyond the original patent expiration date.

1.59 "PRODUCT" means a Collaboration Compound Product or a Research Target Compound Product.

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

1.61 "RESEARCH TARGET" means a gene product - usually, a protein - that may be modulated by another molecule, such as an antisense drug. Modulation of a Research Target may be accomplished in a variety of ways including, without limitation, the modulation of the synthesis, function or degradation of a Research Target, or the expression of the corresponding gene.

1.62 "RESEARCH TARGET COMPOUND" means a compound that modulates a Research Target or Abandoned Research Target that was discovered by ATL alone or as part of a bona fide drug discovery collaboration with a Third Party in which ATL played a significant role.

1.63 "RESEARCH TARGET COMPOUND PRODUCT" means a product containing a Research Target Compound.

1.64 "RESEARCH TARGET PATENT RIGHTS" means the Patents owned by ISIS as of the Effective Date or during the Collaboration Term that claim antisense

oligonucleotides that modulate a Research Target, methods of making such oligonucleotides, or methods of treatment using such oligonucleotides. The Research Target Patent Rights thus include the ISIS 107248 Patent Rights. The Research Target Patent Rights are the Patents listed in Exhibit 1.64, which will be amended from time to time as new Patents are added.

1.65 "SUBLICENSEE" means any Third Party (including a distributor) to which ATL or any of its Affiliates grants any right to make, use, market, or import and sell a Product. A Third Party who is granted only the right to import and sell a Product (such as a wholesaler) will not be considered a Sublicensee.

1.66 "SUBLICENSE INCOME" means all consideration paid to ATL from Sublicensees pursuant to a sublicense by ATL or an Affiliate of ATL including, without limitation, up-front license fees, milestones, and royalties.. If non-monetary consideration is received from Sublicensees by ATL or its Affiliates, then a commercially reasonable monetary value will be assigned for purposes of calculating Sublicense Income.

1.67 "TECHNOLOGY" means inventions (whether or not patentable), know-how, trade secrets, research tools, materials, and technical information, including but not limited to information in the form of research data, databases, experimental procedures, designs, formulas, and process information.

1.68 "THIRD PARTY" means any party other than ISIS or ATL and their respective Affiliates.

1.69 "THIRD PARTY INTELLECTUAL PROPERTY" means any intellectual property owned by a Third Party.

1.70 "THIRD PARTY PATENT RIGHTS" means the [***].

1.71 [***].

EXHIBIT 1.27

[***]

EXHIBIT 1.28

[***]

EXHIBIT 1.35

ISIS 107248 PATENT RIGHTS

- - U.S. Patent No. 5,968,826, issued October 19, 1999, entitled "Antisense Modulation of Integrin Alpha 4 Expression."

- - U.S. Patent No. 6,258,790, issued July 10, 2001, entitled "Antisense Modulation of Integrin Alpha 4 Expression."

EXHIBIT 1.37

ISIS CORE TECHNOLOGY PATENT RIGHTS

[***]

EXHIBIT 1.38

ISIS FORMULATION PATENT RIGHTS

[***]

EXHIBIT 1.51

MANUFACTURING PATENT RIGHTS

[***]

EXHIBIT 1.57

[***]

EXHIBIT 1.64

RESEARCH TARGET PATENT RIGHTS

[***]

EXHIBIT 1.71

[***]

EXHIBIT 2.2

ISIS 107248 DEVELOPMENT PLAN

[***]

EXHIBIT 3.4
RESEARCH TARGETS
[***]

EXHIBIT 3.7

GENE WALKS

[***]

EXHIBIT 3.8

GENETROVE INVESTIGATIONS:
GENE FUNCTIONALIZATION ASSAYS

[***]

CONFIDENTAIL TREATMENT REQUESTED UNDER
17 C.F.R. SECTIONS 200.80(b)4 AND 240.24B-2

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

CLINICAL SUPPLY AGREEMENT

This Clinical Supply Agreement ("Agreement") between ISIS PHARMACEUTICALS, INC. of 2292 Faraday Avenue, Carlsbad, CA 92008, USA ("ISIS") and ANTISENSE THERAPEUTICS LTD., ACN 095 060 745 of Level 1, 10 Wallace Avenue, Toorak, Victoria 3142, AUSTRALIA ("ATL") is entered into and made effective in accordance with the provisions of the agreement entitled "Master Agreement" between ATL and ISIS, dated October 30 2001. The effective date of this Clinical Supply Agreement will be the date upon which all of the conditions in the Master Agreement have been met (the "Effective Date"). If the Effective Date has not occurred by March 28, 2002, this Agreement will be null and void and will not become effective.

INTRODUCTION AND OVERVIEW

ISIS and ATL will collaborate in the discovery and development of Products pursuant to the related Collaboration and License Agreement. When ATL submits an order to ISIS for a Collaboration Compound which ATL is committed to use in IND-enabling studies, ISIS will manufacture active pharmaceutical ingredient ("API") for each such Collaboration Compound ordered, using ISIS Standard Chemistry, for use by ATL in IND-enabling toxicology studies and subsequent clinical studies, during the term of this Agreement.

During the term of this Agreement, the parties will also work together to facilitate the transfer of antisense drug manufacturing technology to ATL or its Contractors. As of the Effective Date, ISIS will supply ATL with API, and ATL will be responsible for the formulation, filling, finishing, labeling and packaging of all Products, including stability studies. By the time the term of this Agreement ends, however, it is the parties' intent that ATL will be solely responsible for manufacturing its requirements of API and Product.

Therefore, in consideration of the foregoing premises and the mutual covenants herein contained, the parties hereby agree as follows.

ARTICLE 1

DEFINITIONS

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

ARTICLE 2

MANUFACTURE AND SUPPLY OF API AND ISIS 107248 PRODUCT

2.1 RESPONSIBILITIES OF ATL AND ISIS

ISIS will provide API for Collaboration Compounds to ATL for use consistent with this Agreement and the Collaboration and License Agreement, and ISIS will also perform API stability studies on all API provided by ISIS. Except as provided in Section 2.3, ATL will be responsible for the formulation, filling, finishing, labeling and packaging of all Products, including stability studies.

2.2 FORMULATION, FILL AND FINISH OF PRODUCT

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

2.3 PURCHASE, FORMULATION AND CERTIFICATION OF ISIS 107248 PRODUCT FOR IND-ENABLING STUDIES

(a) Within 30 days of the Effective Date, ATL will purchase from ISIS the [***] grams of ISIS 107248 API that ISIS has in its inventory and will pay ISIS for that API in the amount of [***], consistent with the provisions of Article 7. ISIS will hold such API for ATL's account in order to formulate and certify such ISIS 107248 API in January 2002, as further described herein.

(b) Pursuant to ATL's request, and at ATL's expense, ISIS will formulate and certify the ISIS 107248 API referenced in (a) above. ATL and/or an ATL Contractor other than ISIS will participate in the formulation and certification process, at ATL's expense, to facilitate the Technology Transfer, as further described in Section 6.2.

(c) As ISIS will be performing the formulation and certification of the ISIS 107248 API and the release of Clinical Product for ATL as a Contractor, ATL is responsible for certain losses prior to Delivery, consistent with the provisions of Section 5.2.

2.4 FORMULATION AND RELEASE OF ISIS 107248 CLINICAL PRODUCT FOR HUMAN STUDIES

ATL will bear sole responsibility for the formulation, fill, finish and release of ISIS 107248 Clinical Product for use in human studies pursuant to the Collaboration and License Agreement. ATL will use commercially reasonable efforts to promptly establish,

by itself or through a Third Party manufacturer, the manufacturing process for formulating, filling, finishing, and releasing ISIS 107248 Clinical Product.

ARTICLE 3

ORDERS AND LIMITATION OF SUPPLY

3.1 PRODUCTION AND DELIVERY PLANS AND ORDERS

(a) With the exception of 2001, not later than July 1 of each year in which this Agreement is in effect, up to and including July 1, 2005, ATL will provide ISIS with a written API order estimate indicating the amount of API ATL will require during the subsequent Calendar Year, which estimate will indicate the quantity and identity of each Collaboration Compound for which API is requested. ISIS has agreed, pursuant to the Collaboration and License Agreement, to supply API for up to [***] different Collaboration Compounds in active development by ATL each year from 2002-2006. The total quantity of such API to be supplied by ISIS in any Calendar Year during the term of this Agreement will not exceed [***], and the minimum order of API for each Collaboration Compound must be at least [***] kg. Each estimate and order submitted by ATL will indicate which Collaboration Compound API(s) is/are being ordered and the quantity of each such API ordered.

(b) At the time ATL provides each API order estimate for Calendar Years 2003 through 2006, ATL representatives will meet with ISIS representatives to discuss and agree upon a production and delivery plan for the next Calendar Year (the "Production and Delivery Plan"). Each year's agreed-upon Production and Delivery Plan will specify the quantity and identity of each Collaboration Compound for which ISIS will supply API to ATL during the subsequent Calendar Year, taking into account all relevant factors including, without limitation, ISIS' obligations to other parties. Each such Production and Delivery Plan will be deemed a firm purchase order of ATL for the quantity of API for each Collaboration Compound specified therein, and a firm commitment of ISIS to Manufacture and supply such quantities of API to ATL. Each lot of API Manufactured and supplied to ATL by ISIS after the Effective Date and during the term of this Agreement will be for use in IND-enabling studies and human clinical studies.

(c) [***]

(d) The Production and Delivery Plan for Calendar Year 2002 is attached as

Exhibit 3.1 hereto and is considered ATL's firm purchase order of API for Calendar Year 2002.

(e) The Production and Delivery Plan will further specify one or more dates upon which Delivery of the API to be supplied by ISIS will occur during the relevant Calendar Year. ISIS will use commercially reasonable efforts to Deliver the API to ATL according to the agreed-upon Delivery schedule set forth in the Production and Delivery Plan. The Production and Delivery Plan will provide for Delivery of API promptly after completion

of Manufacture and release. The date on which the parties agree upon a Production and Delivery Plan for the following Calendar Year will be referred to herein as the "API Order Date."

(f) ISIS will perform a mutually agreed upon stability program for API Manufactured by ISIS at ATL's expense. ISIS will invoice ATL for such activities and for materials and expenses incurred in accordance therewith, as further described in Article 7.

3.2 LIMITATIONS OF SUPPLY

(a) In the event that ISIS anticipates, at any time during the term of this Agreement, that it will be unable to supply in whole or in part the quantities of API set forth in an agreed-upon Production and Delivery Plan for any reason, including without limitation force majeure, ISIS will notify ATL in writing as soon as possible of such shortfall. ISIS will also notify ATL of the underlying reason for the shortfall, proposed remedial measures, the date such inability to supply the full order of API is expected to end, and a proposed amount of API to be Delivered to ATL. [***] The proposed amount of API to be made available to ATL hereunder will be no less than [***] of the amount of raw materials or other resources required for the Manufacture of API, taking into consideration the amount of such raw materials or other resources required by (i) ATL under this Agreement and (ii) ISIS and its other programs.

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

ARTICLE 4

QUALITY STANDARDS

4.1 QUALITY STANDARDS

(a) With respect to API Manufactured by ISIS after the Effective Date, ISIS will Manufacture such API in accordance with the API Specification in effect at the start of Manufacture, US cGMP, and other applicable rules and regulations of all Regulatory Authorities and other regulatory agencies with jurisdiction over the manufacture, use or sale of the API, as then in effect. If cGMP for the U.S. and its foreign equivalent differ, ATL will specify in writing which cGMP will apply to each batch of Collaboration Compound API ordered from ISIS by ATL. ISIS will be responsible for Manufacturing issues related to API safety and regulatory compliance. Each party will promptly notify the other party of any relevant new instructions or specifications required by a Regulatory Authority, and of other applicable and regulations of which that party becomes aware. The parties will confer with each other with respect to the best means to comply with

such requirement and will allocate any costs of implementing such changes on an equitable basis.

(b) ISIS will perform quality control testing as is specified (i) in the API Specification; and (ii) as required by a Regulatory Authority and by the mutual written consent of the parties, on each lot of API supplied for use

in Product, prior to shipment of such API.

(c) As ATL develops Collaboration Compounds pursuant to the Collaboration and License Agreement, modified or expanded API Specifications appropriate to the stage of development may be required. Such API Specifications will be consistent with the API Specifications of other ISIS antisense compounds at a similar stage of development.

(d) New API Specifications will be prepared and processed as follows.

(i) Not later than [***] days prior to its submission of an API order estimate for a new Collaboration Compound to ISIS, ATL will provide ISIS with written notice of its intent to order API for which API Specifications have not yet been prepared.

(ii) Upon receipt of such written notice, ISIS will initiate any required development work and subsequently prepare an API Specification for each new Collaboration Compound that ATL intends to order, which will be consistent with the API Specifications of other ISIS antisense compounds at a similar stage of development.

(iii) Once a new API Specification has been prepared by ISIS, it will be added to this Agreement as an Exhibit thereto, and ATL will be provided with a copy, in advance of Delivery of the API.

4.2 CERTIFICATE OF ANALYSIS

(a) ISIS will provide a Certificate of Analysis to ATL or its designated Contractor with each lot of API supplied hereunder. Consistent with Section 3.1(b), each lot of API supplied to ATL by ISIS after the Effective Date and during the term of this Agreement will be for use in IND-enabling studies and human clinical studies. The foregoing provisions do not, however, apply to the ISIS 107248 Product for IND-enabling studies, which Product ISIS will formulate and certify, consistent with the provisions of Section 2.3. Each Certificate of Analysis will contain the results of the analysis of API as required in the API Specification, and will certify with respect to each shipment and lot (identified by lot number): (i) the quantity of the shipment, (ii) that the API delivered was Manufactured in accordance with the API Specification and in conformance with the applicable cGMP. The Certificate of Analysis will contain any information in addition to that required herein as may be required by the Regulatory Authority of the country of destination of API or Product; provided, however, that ATL provides to ISIS, in a timely manner, sufficient documentation and information necessary or useful to enable ISIS to conform with such requirements. ISIS will provide the results of such analysis to ATL, along with any supporting data.

(b) ATL will be under no obligation to accept any Delivered lot of API without an accompanying Certificate of Analysis that conforms to subsection (a) above. ISIS will also make available for ATL's review ISIS' Manufacturing records for the API, including its master and production batch records, for the purposes of assuring product quality and compliance with agreed-upon Manufacturing procedures.

4.3 CHANGES TO MANUFACTURING PROCESS

(a) If ISIS proposes a material change to the Manufacturing Process, ISIS will notify ATL in writing and will provide information to ATL regarding the change at a level sufficient to allow ATL to understand any impact of such change on the Manufacturing Process.

(b) The parties will obtain the prior Regulatory Approval(s), and any other approvals required to be obtained, before any changes are implemented.

4.4 COMPLIANCE WITH LAWS

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

ARTICLE 5

SUPPLY PRICE; DELIVERY; PAYMENT TERMS

5.1 SUPPLY PRICE

(a) The API Supply Price will apply to all quantities of API supplied to ATL hereunder.

(b) Within [***] days of each API Order Date, ISIS will invoice ATL for [***] of the projected API Supply Price of API to be Manufactured during the relevant Calendar Year pursuant to the Production and Delivery Plan. ATL will pay each invoice within [***] days after receipt. Payment terms are set forth in Section 5.5 below.

(c) For each Calendar Quarter, ISIS will invoice ATL for the actual API Supply Price of API Delivered to ATL during such Calendar Quarter, minus the amount already paid by ATL pursuant to subsection (b) above. Such invoice will reflect an adjustment equal to the amount by which the actual API Supply Price is greater than or less than the projected API Supply Price for API Delivered to ATL during such Calendar Quarter. ATL will pay each invoice within [***] days after receipt. Payment terms are set forth in Section 5.5 below.

5.2 DELIVERY

(a) ISIS will deliver API and ISIS 107248 Product for IND-enabling studies to a carrier designated by ATL FCA ISIS' Facility (Incoterms 2000). The shipping and packaging specifications will be agreed upon by the parties.

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

5.3 ACCEPTANCE AND CLAIMS; MATERIALS REVIEW BOARD

(a) If ATL claims that any sample of API did not meet the warranty specified in Section 10.1, ATL will notify ISIS in writing within 30 days of such Delivery, and a joint Materials Review Board formed under subsection (b) below will review the test data generated by ATL and ISIS under QA approved procedures mutually agreed upon by the parties within 30 days after ATL's notice to ISIS.

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

(c) If the members of the MRB are thereafter unable to agree as to whether the API met the warranty specified in Section 10.1, the parties will cooperate and have the test data reviewed by an independent third party selected by ATL and approved by ISIS, which approval will not be unreasonably withheld. If the independent third party reviewer cannot determine whether the Delivered API in dispute met the warranty of Section 10.1, a sample of the batch of the Delivered API in dispute retained by ISIS will be analyzed in accordance with the API Specifications, under QA approved procedures, by an independent testing laboratory of recognized repute selected by ATL and approved by ISIS, which approval will not be unreasonably withheld. Unless provided otherwise herein, the results of such laboratory testing will be final and binding on the parties on the issue of compliance of the API with such warranty.

(d) If the API is determined to meet the warranty set forth in Section 10.1, ATL will bear the cost of any third party review and/or independent laboratory testing performed pursuant to subsection (c) above and will pay for the API in accordance with the terms of this Agreement. If the API is determined not to meet the warranty set forth in Section 10.1, ISIS will bear the cost of any third party review and/or independent laboratory testing performed pursuant to subsection (c) above.

(e) If ISIS agrees, or if it is determined pursuant to subsection (c) above, that API did not conform to the warranty set forth in Section 10.1, ISIS will use commercially reasonable efforts to Manufacture and Deliver a replacement batch of API to ATL for the batch of

API that did not conform to such warranty, and ATL will pay ISIS for any such replacement batch of API, including without limitation, all costs and expenses associated with such Manufacture, consistent with the provisions of Section 5.1 herein. The API Supply Cost for the Manufacture of the batch of API that did not conform to such warranty will be shared by ATL and ISIS as follows: ISIS will be responsible for the [***] for such batch of API; and ATL will be responsible for the [***] for such batch of API. Replacement of API will be ATL's sole and exclusive remedy for breach of the warranty set forth in Section 10.1.

(f) Any Delivered API which ISIS agrees did not meet, or which was determined not to have met, the Section 10.1 warranty that is in ATL's control will, at ISIS' option, either be returned to ISIS or will be destroyed pursuant to ISIS' instructions and with ATL's approval, which approval will not be unreasonably withheld, at ISIS' expense.

(g) Failure by ATL to notify ISIS within [***] after Delivery of API which does not meet the warranty under Section 10.1 will be a waiver of the remedies available to ATL under this Section 5.3.

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

5.4 TERMS OF SALE

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

5.5 PAYMENT TERMS

(a) PAYMENTS. All payments to ISIS under this Agreement will be made in United States Dollars by bank wire transfer in next day available funds to such bank account in the United States designated in writing by ISIS from time to time. All amounts payable to ISIS hereunder are noncreditable and nonrefundable, unless specifically provided otherwise herein.

(b) LATE PAYMENTS; COLLECTIONS. In the event that any payment, including royalty, milestone or research payments, due hereunder is not made when due, the payment will bear interest from the date due at the lesser of (i) [***] per month, compounded monthly, or (ii) the highest rate permitted by law; provided, however, that in no event will such rate exceed the maximum legal annual interest rate. The payment of such interest will not

limit a party from exercising any other rights it may have as a consequence of the lateness of any payment. [***]

ARTICLE 6

TECHNOLOGY TRANSFER

6.1 TECHNOLOGY TRANSFER COMMITTEE

(a) The Release Technology Transfer (as defined in Section 6.2) and the API Technology Transfer (as defined in Section 6.3) will be

coordinated and implemented under the supervision of a joint committee (the "Technology Transfer Committee" or "TTC") comprised of 2 employees appointed by each of the parties. ATL may appoint a Contractor instead of an employee, provided that any Contractor appointed by ATL is approved by ISIS, which approval will not unreasonably be withheld. ATL warrants that any Contractor appointed by ATL will be bound by all applicable terms of this Agreement and by the confidentiality provisions of the Collaboration and License Agreement, which are incorporated herein and made part of this Agreement by reference. Members of the Technology Transfer Committee will each have appropriate technical credentials, experience and knowledge; the TTC will be co-chaired by an ATL representative and an ISIS representative. The advice of additional employees of either party (or Contractors, in the case of ATL) may by mutual consent of the parties be obtained.

(b) Decisions of the TTC will be made by unanimous decision of the two-co-chairs; provided however, in the event that the co-chairs do not, after good faith efforts, reach agreement on an issue, the resolution and/or course of conduct in issue will be determined in good faith by the Oversight Committee, as provided in Section 16.6.

(c) Throughout the entire Technology Transfer Term, the TTC will meet as needed, but no less often than every 2 months, either in person or by teleconference, videoconference or by other mutually acceptable means, as necessary to implement effectively and efficiently the Release Technology Transfer Plan and the API Technology Transfer Plan.

6.2 TECHNOLOGY TRANSFER FOR CLINICAL PRODUCT RELEASE

(a) Promptly after the Effective Date, the Technology Transfer Committee will establish a plan (the "Release Technology Transfer Plan") for the transfer to ATL or a Contractor designated by ATL of the Release Technology for ISIS 107248 and the Release Technology for other Collaboration Compounds, as specified in the Release Technology Transfer Plan (the "Release Technology Transfer"). Before any Release Technology is transferred to any Contractor of ATL, such Contractor must be approved by ISIS, which approval will not unreasonably be withheld. The goal of the Release Technology Transfer Plan is to effect the Release Technology Transfer within the first year that this

Agreement is in effect to enable ATL to carry out its obligation to conduct release testing for all Products, including without limitation Clinical Products.

(b) The Release Technology Transfer applicable to ISIS 107248 will begin promptly after the Effective Date, in conjunction with the formulation and certification of ISIS 107248 Product for IND-enabling studies scheduled for [***]. ATL will appoint employees or ISIS-approved Contractors to participate with ISIS in the formulation and certification of ISIS 107248 Product for IND-enabling studies at the site at which the formulation and certification activities will take place. It is anticipated by the parties that the Release Technology Transfer applicable to ISIS 107248 Clinical Product will take place during the [***] this Agreement is in effect, in order to enable ATL to carry out its obligations hereunder.

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

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

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

(f) ATL and its Contractors will use commercially reasonable efforts, pursuant to the Technology Transfer Plan described above, to implement the Release Technology to be transferred by ISIS pursuant to this Section 6.2 and to make available all necessary personnel and other resources to enable such transfer without delay.

6.3 TECHNOLOGY TRANSFER PLAN FOR MANUFACTURE OF API

(a) Within [***] of the Effective Date, the Technology Transfer Committee will establish a plan (the "API Technology Transfer Plan") for the transfer of the Manufacturing Process and the Manufacturing Technology for the Manufacture of API from ISIS to ATL and/or its Contractors (the "API Technology Transfer"). The goal of the API Technology Transfer Plan is to enable ATL to apply the Manufacturing Technology, implement the Manufacturing Process and Manufacture API as soon as practicable thereafter and in no event later than December 31, 2006.

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

accomplish the API Technology Transfer; (iii) a description of the training and support to be provided by ISIS to ATL during the API Technology Transfer; (iv) a budget and resource plan; and (v) the time period during which ISIS will perform the API Technology Transfer.

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

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

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

6.4 TRAINING AND SUPPORT

The training and support to be provided by ISIS to ATL and its ISIS-approved Contractors in connection with the Release Technology Transfer and the API Technology Transfer (the "Technology Transfer") will include without limitation training and support in a mutually acceptable facility in all of the methods necessary to practice the Release Technology and the Manufacturing Technology, as detailed in the Release Technology Transfer Plan and the API Technology Transfer Plan. In addition, a reasonable number of employees or ISIS-approved Contractors of ATL will be entitled to visit ISIS facilities including, without limitation, pilot and commercial scale facilities and testing laboratories to observe relevant processes in operation.

ARTICLE 7

FUNDING PROVISIONS

7.1 FUNDING FOR VARIOUS ACTIVITIES AND MATERIALS HEREUNDER

(a) ATL will compensate ISIS for the following:

(i) ATL's purchase of the ISIS 107248 API referenced in Section 2.3(a);

(ii) the formulation and certification of ISIS 107248 Product for IND-enabling studies;

(iii) ISIS' performance of a mutually agreed upon stability program for API Manufactured by ISIS, as set forth in Section 3.1(f);

(iv) all future API supplied to ATL by ISIS, consistent with Section 5.1 herein;

(v) all ISIS' activities relating to the Release Technology Transfer and/or the API Technology Transfer pursuant to Article 6, [***];

(vi) preparation of CMC Reports and regulatory filings pursuant to Section 9.1; and

(vii) analytical method development and stability program activities pursuant to Section 9.2.

(b) ATL will submit payment to ISIS for the materials and activities referenced in subsections (a)(i) and (iv) above at the times indicated in the Sections specifically referenced therein. Unless otherwise indicated herein, ISIS will invoice ATL on a quarterly basis for all activities performed and for materials and expenses incurred in accordance with the activities enumerated herein, including those listed in subsections (a)(ii), (iii), and (v) - (vii) above. [***]. ATL will pay each invoice within [***] days after receipt. The terms set forth in Section 5.5 will apply to all payments made hereunder and include, without limitation, the payment of interest on late payments.

ARTICLE 8

RECORDS AND AUDITS

8.1 QUALITY STANDARDS

ISIS will keep complete, accurate and authentic accounts, notes, data and records of all of ISIS' work performed under this Agreement, including, but not limited to, complete and adequate records pertaining to the methods and facilities used for the Manufacture in accordance with master production records, batch production records, product history documents (e.g., master formulae, validation packages, specifications, batch-specific deviation reports, COAs) Standard Operating Procedures ("SOPs"), as well as the applicable regulations, including in the United States, so that API may be used in the production of a substance to be used in humans. ISIS will maintain these records for 2 years after expiration of the Product that incorporates the particular API. ATL will notify ISIS in writing of the expiration of Products that incorporate specific API and if ATL changes the expiration date on any Product. SOPs will be maintained for 5 years after the document is superseded or deleted. Upon expiration of the retaining periods for the respective records as provided in this Section and in case ISIS wishes to cease retention of such records, ISIS will notify ATL so that ATL may, at its cost, retain such records.

8.2 API SUPPLY PRICE; RECORD KEEPING AND AUDIT

(a) ISIS will keep accurate records in sufficient detail to enable the API Supply Price to be verified. Upon written request of ATL and not more than once in each Calendar Year, ISIS will permit ATL's independent certified public accountant (or equivalent) to have

access during normal business hours to such records of ISIS as may be reasonably necessary to verify the accuracy of the invoices for API Supply Price submitted to ATL hereunder for the preceding Calendar Year. Once specific records have been audited under this Section 8.2, no further audit of such records may be made. The accounting firm will disclose to ATL only whether the invoiced amounts are correct or incorrect, the specific details concerning the basis for the invoiced amounts, and the corrected amount, if applicable. No other information will be provided to ATL.

(b) If such accounting firm concludes that any amounts invoiced were in error during such period and ATL is entitled to a refund of such

amounts, ISIS will refund to ATL the amounts overcharged within [***] days of the date ATL delivers to ISIS such accounting firm's written report. The fees charged by such accounting firm will be paid by ATL unless the additional refunded amounts owed by ISIS exceed [***] of the total amount for which ATL was invoiced during the time period subject to the audit, in which case ISIS will pay the reasonable fees and expenses charged by the accounting firm.

(c) ATL and its accounting firm will treat all financial information subject to review under this Section 8.2 in accordance with the confidentiality provisions of Article 9 of the Collaboration and License Agreement, which provisions are incorporated herein and made part of this Agreement by reference, and will cause its accounting firm to enter into an acceptable confidentiality agreement with ISIS obligating such firm to retain all such financial information in confidence pursuant to such confidentiality agreement.

8.3 TECHNOLOGY TRANSFER RECORDS

ISIS will maintain records, in sufficient detail and in good scientific manner appropriate for patent, regulatory and manufacturing purposes, which will fully and properly reflect all of the work done and the progress achieved in the performance of the Release Technology Transfer and the API Technology Transfer (the "Records"). The Records at all times will be available to the Technology Transfer Committee and ATL will have the right, during normal business hours and upon reasonable notice, to inspect and copy all such Records. ATL also will have the right to arrange for its employees and/or Contractors to visit ISIS at its offices and laboratories and other facilities during normal business hours on reasonable notice concerning or in furtherance of the Release Technology Transfer or the API Technology Transfer and/or to discuss the progress of the Release Technology Transfer or the API Technology Transfer and its results in detail with the technical personnel and consultants of ISIS.

ARTICLE 9

OTHER SUPPORTING ACTIVITIES

9.1 CMC ACTIVITIES

As of the Effective Date and during the first [***] years this Agreement is in effect, ISIS will support ATL's efforts to timely file an IND application for each Collaboration Compound with respect to the CMC activities described in Exhibit 9.1 for Collaboration Compounds for which ISIS supplied API.

9.2 ANALYTICAL METHOD DEVELOPMENT AND STABILITY PROGRAM ACTIVITIES

As of the Effective Date, ISIS will undertake various development efforts, such as analytical methods development for raw materials, API, API stability programs, and process development in connection with MOE gapmers and other second generation oligonucleotides made using ISIS Standard Chemistry, which additional activities support the activities of ISIS and ATL with regard to ISIS 107248 and other Collaboration Compounds under the Collaboration and License Agreement.

ARTICLE 10

PRODUCT WARRANTY

10.1 API SPECIFICATIONS; CGMPS; APPLICABLE LAWS

Subject to Section 10.2 below, ISIS warrants that the API will, at the time of Delivery, be Manufactured in accordance with and meet (a) the API Specification; (b) cGMP; and (c) the Legal Requirements.

10.2 FOREIGN MANUFACTURING REQUIREMENTS

If the cGMP or the Legal Requirements applicable to the Manufacture of API for use in the U.S. (the "U.S. Manufacturing Requirements") are different from those applicable outside to the Manufacture of API for use in countries other than the U.S. (the "Foreign Manufacturing Requirements"),

the warranty of Section 10.1 will include such Foreign Manufacturing Requirements only if ATL has informed ISIS thereof in writing as provided in Sections 4.1 and 4.4 and if the parties have adapted the Manufacturing Process, if necessary, as provided in Section 4.3.

ARTICLE 11

QUALITY SYSTEMS

11.1 MATTERS RELATING TO THE FACILITY

(a) ISIS will Manufacture API supplied by ISIS hereunder at the Facility, which ISIS represents and warrants has been and will be approved by Agencies which have inspected or will inspect the Facility for the manufacture of API. ISIS will perform release testing of API at the Facility and/or the facility of subcontractors approved by ISIS.

(b) ISIS will arrange for one or more qualified technical specialists from ATL or one or more qualified Contractors of ATL approved by ISIS (which approval will not unreasonably be withheld), upon reasonable prior notice and during normal business hours, to conduct inspections of the Facility. Observations and conclusions of ATL's audits or inspections will be issued to and promptly discussed with ISIS and such corrective action as ATL determines to be reasonably required will be promptly implemented by ISIS. ISIS will maintain complete and accurate records of all reasonably relevant information relating to the performance by ISIS of its obligations hereunder. ISIS will permit ATL or its ISIS-approved Contractors to review, during the inspection at the Facility, relevant cGMP documentation. The total number of inspections under this Section per CalendarYear will not exceed two.

11.2 TESTING

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

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

(c) After Technology Transfer with respect to analytical testing is complete in accordance with the terms contained herein and in the Collaboration and License Agreement, ATL may perform, at a designated quality control laboratory of recognized repute selected by ATL and approved by ISIS, which approval will not be unreasonably withheld, such quality control tests of API as specified in the API Specification and advise ISIS of any failure of such API to meet the API Specification.

11.3 INFORMATION RELATING TO MANUFACTURING CONDITIONS

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

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

regarding the API or Product.

11.4 AGENCY INSPECTIONS

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

11.5 STORAGE AND DELIVERY

ISIS will store and Deliver API in accordance with the applicable API Specification and cGMP.

ARTICLE 12

REGULATORY MATTERS

12.1 ISIS will prepare and promptly provide necessary and useful information, including without limitation Manufacturing information, as is needed to support filings of Registrations by ATL, its Contractors, sublicensees or distributors of Product. In addition, ISIS will participate as required in resolving regulatory concerns. ISIS will be responsible for maintaining current technical information needed to support such submissions of Registrations, and accordingly will promptly provide ATL with advance notification of all changes in such technical information required to be filed as amendment(s) to CMC. All such activities will be at ATL's expense, which will be agreed to in advance by the parties.

12.2 The mutual goal of ISIS and ATL will be to maintain an integrated approach to the content and timing of all submissions of Registrations made by ATL in an effort to obtain and maintain regulatory approvals of a Product. To ensure this mutual goal is met, with respect to issues pertaining to API or to a Product, ISIS will provide to ATL the right to review and reference all authorizations, certificates, methodologies and specifications in the possession or under the control of ISIS relating to the pharmaceutical/technical

development and Manufacture or any component thereof to the extent needed for ATL's filings of Registrations.

ARTICLE 13

INDEMNIFICATION AND INSURANCE

13.1 INDEMNIFICATION

(a) ISIS will defend, indemnify and hold harmless ATL, its Affiliates and their respective directors, officers, employees and agents, and their respective successors and permitted assigns, from any and all claims, actions, causes of action, liabilities, losses, damages, costs or expenses, including reasonable attorney's fees, which arise out of or relate to claims that may be brought or instituted against them by Third Parties to the extent based upon or arising out of (i) the failure by ISIS to meet the warranties set forth in Article 10; (ii) a material breach by ISIS of its obligations set forth in this Agreement; or (iii) gross negligence or willful misconduct of ISIS, its officers, employees and agents in the performance of its obligations hereunder.

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

Agreement; or (ii) gross negligence or willful misconduct of ATL, its officers, employees and agents in the performance of its obligations hereunder.

13.2 CLAIMS

If a claim is made against a party entitled to indemnification under this Article 13, and if that party intends to seek indemnification with respect thereto under this Article 13, the party seeking indemnification (the "Indemnitee") will promptly notify the indemnifying party (the "Indemnifying Party") of such claim. The Indemnifying Party will defend, negotiate and settle such claim, and the Indemnitee will cooperate with the Indemnifying Party in connection therewith. The Indemnitee may participate in the defense of any claim with counsel of its own choice and at its own expense. Neither party will settle or compromise any such claim without the other party's prior written consent, which consent will not be unreasonably withheld. The indemnity agreement in this Article 13 will not apply to amounts paid in settlement of any claim if such settlement is effected without the consent of the Indemnifying Party, which consent will not be unreasonably withheld. Failure of the Indemnitee to deliver notice to the Indemnifying Party within a reasonable time after becoming aware of a claim will not relieve the Indemnifying Party

of any liability to the Indemnitee pursuant to this Article 13, except to the extent such delay prejudices the Indemnifying Party's ability to defend such claim.

13.3 INSURANCE

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

ARTICLE 14

TERM AND TERMINATION

14.1 TERM

This Agreement will be effective as of the Effective Date, and unless sooner terminated as provided herein, will continue in effect until December 31, 2006, unless extended by mutual agreement of the parties.

14.2 TERMINATION BY EITHER PARTY

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

(a) if the other party is in breach of its material obligations hereunder and has not cured such breach within 90 days after written notice requesting cure of the breach has been given; provided, however, in the event of a good faith dispute with respect to the existence of a material breach, the 90-day cure period will be tolled until such time as the dispute is resolved pursuant to Section 16.6; or

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

14.3 TERMINATION OF COLLABORATION AND LICENSE AGREEMENT

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

14.4 PAYMENT OF OUTSTANDING DEBTS

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

14.5 EFFECT OF TERMINATION OR EXPIRATION

(a) If this Agreement is terminated by ATL pursuant to Section 14.2(a), all orders will be automatically cancelled and ISIS will terminate the Manufacture of API as soon as practicable. ATL will have the option but not the obligation to (i) purchase all quantities of API stored at ISIS by paying the price of API, as applicable, as provided in Section 5.1, and (ii) undertake the Manufacture of API or seek a Third Party to do such Manufacture. If ATL undertakes to Manufacture or have Manufactured API, then ISIS will continue the transfer of technology pursuant to Article 6 on an expedited basis, at ATL's expense.

(b) If this Agreement is terminated by ATL pursuant to Section 14.2(b), ATL (i) will purchase all quantities of API stored at ISIS by paying the price of API, as applicable, as provided in Section 5.1, and (ii) will have the right to undertake the Manufacture of API or seek a Third Party to do such Manufacture.

(c) If this Agreement is terminated by ISIS pursuant to Section 14.2(a), ISIS will have the option but not the obligation to supply under all outstanding quantities set forth in the Production and Delivery Plan at the API Supply Price. If ISIS elects to so supply, ATL's payment obligations relating thereto including, without limitation, those set forth in Section 5.1 will continue to apply until all outstanding obligations of ATL to ISIS are fulfilled.

(d) If this Agreement is terminated pursuant to Section 14.3, all outstanding quantities of API set forth in the Production and Delivery Plan will be automatically cancelled and ISIS will terminate the Manufacture of API as soon as practicable. In addition, ATL will be responsible for all other Manufacturing costs associated with API pursuant to Section 5.1 at the time of termination. Notwithstanding the foregoing, ISIS will use its best efforts to mitigate any costs payable by ATL under this Section 14.5(d).

(e) If this Agreement expires pursuant to Section 14.1, ATL will purchase all API ordered by ATL during the term of this Agreement. ISIS will Deliver such API in accordance with Section 5.2.

ARTICLE 15

DAMAGE LIMITATIONS

NOTWITHSTANDING ANYTHING TO THE CONTRARY CONTAINED HEREIN, IN NO EVENT WILL EITHER PARTY HERETO, OR ITS DIRECTORS, OFFICERS,

EMPLOYEES, AGENTS OR AFFILIATES BE LIABLE TO THE OTHER PARTY OR SUCH OTHER PARTY'S DIRECTORS, OFFICERS, EMPLOYEES, AGENTS, AFFILIATES OR SUBLICENSEES FOR ANY INDIRECT, CONSEQUENTIAL, INCIDENTAL OR SPECIAL DAMAGES, COSTS OR EXPENSES (INCLUDING, BUT NOT LIMITED TO, LOST PROFITS, LOST REVENUES AND/OR LOST SAVINGS) SUFFERED OR INCURRED BY THE OTHER PARTY, WHETHER BASED UPON A CLAIM OR ACTION OF CONTRACT, WARRANTY, NEGLIGENCE, STRICT LIABILITY OR OTHERWISE, ARISING FROM THIS AGREEMENT.

ARTICLE 16

MISCELLANEOUS

16.1 FORCE MAJEURE

Neither party will be held liable or responsible to the other party nor be deemed to have defaulted under or breached the Agreement for failure or delay in fulfilling or performing any term of the Agreement when such failure or delay is caused by or results from causes beyond the reasonable

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

16.2 ASSIGNMENT

This Agreement will inure to the benefit of and be binding upon each party, its successors and assigns. The Agreement may not be assigned or otherwise transferred, nor, except as expressly provided hereunder, may any right or obligations hereunder be assigned or transferred by either party without the prior written consent of the other party; provided, however, that either party may, without such consent, assign the Agreement and its rights and obligations hereunder to an Affiliate or in connection with the transfer or sale of all or substantially all of its assets, or in the event of its merger or consolidation or change in control or similar transaction. Any permitted assignee will assume all obligations of its assignor under the Agreement. Any attempted assignment not in accordance with this Section 16.2 will be void.

16.3 SEVERABILITY

In the event any one or more of the provisions contained in this Agreement should be held invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein will not in any way be affected or impaired thereby, unless the absence of the invalidated provision(s) adversely affect the substantive rights of the parties. The parties will in such an instance use their

best efforts to replace the invalid, illegal or unenforceable provision(s) with valid, legal and enforceable provision(s) which, insofar as practical, implement the purposes of this Agreement.

16.4 NOTICES

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

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

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

if to ATL, to: ANTISENSE THERAPEUTICS, LTD.
ACN 095 060 745 of Level 1
10 Wallace Avenue
Toorak, Victoria 3142
AUSTRALIA
Attention: CEO
Fax No.: +61 3 9826 4399
E-Mail:_____

with a copy to: Attention: Research Director
Fax No.: +61 3 9826 4399
E-Mail:_____

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

courier and on the third business day following the date of mailing if sent by mail.

16.5 GOVERNING LAW

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

16.6 DISPUTE RESOLUTION; OVERSIGHT COMMITTEE

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

For ISIS: Executive Vice President

For ATL: CEO

16.7 REMEDIES

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

16.8 ENTIRE AGREEMENT

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

16.9 HEADINGS

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

16.10 INDEPENDENT CONTRACTORS

It is expressly agreed that ISIS and ATL will be independent contractors and that the relationship between the two parties will not constitute a partnership, joint venture or

agency. Neither ISIS nor ATL will have the authority to make any statements, representations or commitments of any kind, or to take any action, which will be binding on the other, without the prior consent of the other party.

16.11 WAIVER

The waiver by either party hereto of any right hereunder, or the failure to perform, or a breach by the other party will not be deemed a waiver of any other right hereunder or of any other breach or failure by said other party whether of a similar nature or otherwise.

16.12 COUNTERPARTS

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

16.13 WAIVER OF RULE OF CONSTRUCTION

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

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

ANTISENSE THERAPEUTICS, LIMITED	ISIS PHARMACEUTICALS, INC.
By: /s/ C. Belyea	By: /s/ B. Lynne Parshall
Name: C. Belyea	Name: B. Lynne Parshall
Title: CEO	Title: Executive Vice President and CFO

EXHIBIT 1

DEFINITIONS

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

1.2 "AGENCY" means the U.S. Food and Drug Administration. In the event ATL provides written notice to ISIS that ATL intends to conduct Development Program activities outside of the United States, the term "Agency" will mean with respect to such activities outside the United States the Regulatory Authority (as defined below) of the country specified in such notice involved in granting any approvals relating to such Development Program activities.

1.3 "API" means a drug substance made using ISIS Standard Chemistry, before formulation, filling and finishing and containing a Collaboration Compound developed pursuant to the Collaboration and License Agreement.

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

1.5 "API SPECIFICATION" means the specification applicable to each API, which may variously comprise a product description, methods, tests and acceptance criteria, or test limits on API, as appropriate to the stage of development. API Specifications may be amended from time to time by ISIS. API Specifications will change from time to time as compounds advance through development and as analytical methods evolve. Thus, the API Specification for an early stage compound may consist only of a product description. The API Specification for each API Manufactured hereunder will be attached as an exhibit hereto; such exhibits will be amended from time to time as appropriate.

1.6 "API SUPPLY COST" means the cost of Manufacture of API described in Exhibit 5.2.

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

1.8 "API TECHNOLOGY TRANSFER" has the meaning set forth in Section 6.3 herein.

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

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

1.11 "CGMP" means the current good manufacturing practices described in Q7A ICH Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients and 21 CFR Parts 210 ET SEQ. as applicable to the Manufacture of API in the U.S., as are in effect on the Effective Date or as may subsequently be modified or supplemented. In the event ATL provides written notice to ISIS that ATL intends to conduct the Development Program activities in countries outside of the United States, the term "cGMP" will also include corresponding good manufacturing practices in such countries, provided that to the extent any conflict exists between cGMP applicable in the U.S. and in such countries, the cGMP of the U.S. will apply, unless the parties agree otherwise as provided in Sections 4.1, 4.4 and 10.2.

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

1.13 "CMC ACTIVITIES" means the activities listed Exhibit 9.1 hereto.

1.14 "COLLABORATION COMPOUND" has the meaning set forth in Exhibit 1 of the Collaboration and License Agreement.

1.15 "COLLABORATION AND LICENSE AGREEMENT" means the agreement for the collaborative research, development and commercialization of ISIS 107248 and other antisense drugs entered into by ISIS and ATL on even date herewith.

1.16 "CONTRACTOR" means ISIS or a Third Party to whom ATL or any of its Affiliates grants any right or obligation to manufacture, fill, finish, and/or release a Product, or to carry out any other obligations of ATL under this Agreement. Except as provided otherwise herein, each such Contractor must be approved by ISIS, which approval will not unreasonably be withheld.

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

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

1.19 "ISIS 107248" means the oligonucleotide that targets human CD49d disclosed and claimed (as SEQ ID NO 81) in U.S. Patent No. 6,258,790.

1.20 "ISIS FTE RATE" means the compensatory rate to be paid per FTE at ISIS for all activities under this Agreement. As used herein, "FTE" means [***].

1.21 "ISIS STANDARD CHEMISTRY" has the meaning set forth in Exhibit 1 of the Collaboration and License Agreement.

1.22 "LEGAL REQUIREMENTS" has the meaning set forth in Section 4.4 herein.

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

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

1.24 "MANUFACTURING PROCESS" means the process steps set forth in master batch records for any API Manufactured for ATL hereunder during the term of this Agreement, including reasonable minor variants and extensions of process steps thereof.

1.25 "OVERSIGHT COMMITTEE" has the meaning set forth in Section 16.6 herein.

1.26 "PRODUCT" means a formulated and finished pharmaceutical product containing API, including a Clinical Product and including formulated and finished product for use in toxicology studies.

1.27 "PRODUCTION AND DELIVERY PLAN" has the meaning set forth in Section 3.1(b) herein.

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

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

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

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

1.32 "RELEASE TECHNOLOGY" means any and all scientific and technical data and information including without limitation formulas, methods, techniques, protocols, and processes controlled by ISIS as of the Effective Date regarding API release and Clinical Product release and any improvements therein during the term of this Agreement.

1.33 "RELEASE TECHNOLOGY TRANSFER" has the meaning set forth in Section 6.2 herein.

1.34 "TECHNOLOGY TRANSFER COMMITTEE" has the meaning set forth in Section 6.1 herein.

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

1.36 "THIRD PARTY" means any party other than ISIS or ATL and their respective Affiliates.

EXHIBIT 3.1

PRODUCTION AND DELIVERY PLAN FOR CALENDAR YEAR 2002

[***]

EXHIBIT 5.2

CALCULATION OF API SUPPLY COST

1) [***]

EXHIBIT 9.1

CMC ACTIVITIES

[***]

ISIS PHARMACEUTICALS INC

ANTISENSE THERAPEUTICS LTD

STOCK PURCHASE AGREEMENT

MINTER ELLISON
Lawyers
Rialto Towers
525 Collins Street
MELBOURNE VIC 3000

DX 204 Melbourne
Telephone (03) 8608 2000
Facsimile (03) 8608 1000

JJS

STOCK PURCHASE AGREEMENT

This Stock Purchase Agreement (the "Agreement") between ISIS PHARMACEUTICALS, INC. of 2292 Faraday Avenue, Carlsbad, CA 92008, USA ("ISIS") and ANTISENSE THERAPEUTICS LTD., ACN 095 060 745 of Level 1, 10 Wallace Avenue, Toorak, Victoria 3142, AUSTRALIA ("ATL") is entered into and made effective in accordance with the provisions of the agreement entitled "Master Agreement" between ATL and ISIS, dated October 30, 2001. The effective date of this Stock Purchase Agreement will be the date upon which conditions 1 and 3 in the Master Agreement have been met (the "Effective Date"). If the Effective Date has not occurred by March 28, 2002, this Agreement will be null and void and will not become effective.

RECITALS

A. The parties intend to enter into a Collaboration and Licence Agreement dated 30 October 2001 ('COLLABORATION AND LICENCE AGREEMENT').

B. Under that Agreement Isis will licence intellectual property to ATL on the terms and conditions of the Collaboration and Licence Agreement.

C. ATL has agreed to issue and grant to Isis, and Isis has agreed to subscribe for, shares and options in the capital of ATL on the terms and conditions of this Stock Purchase Agreement.

AGREEMENT

1. DEFINITIONS

In this agreement, unless the contrary intention appears:

'ASX' means Australian Stock Exchange Limited ACN 008 624 691.

'ASX LISTING' means admission of ATL to the ASX Official List and quotation by the ASX of shares in ATL.

'ASX LISTING RULES' means the listing rules of the ASX as amended from time to time.

'ATL SHARES' means fully paid ordinary shares in ATL.

'BUSINESS DAY' means the day in which banks (as defined under the Banking Act 1959 (Cth)) are open for general banking business in Victoria, Australia excluding Saturdays and Sundays.

'CIRCADIAN' means Circadian Technologies Limited ACN 006 340 567 of Level 1, 10 Wallace Avenue, Toorak, Victoria 3142, Australia.

'COMPLETION' means completion of the subscription for, and issue of, the ATL Shares in accordance with clause 6.

'COMPLETION DATE' means the date 2 Business Days after the ASX has approved of the ASX Listing of ATL and ATL has satisfied all conditions attaching to such approval, or such other date as the parties may agree in writing.

'MURDOCH INSTITUTE' means the Murdoch Childrens Research Institute of Parkville, Victoria, Australia.

'MURDOCH INTERESTS' means the Murdoch Institute or other party nominated by the Murdoch Institute.

'OPTION' means an option to acquire by way of issue 1 ATL Share on the following terms:

(a) the exercise price for each option is 20 Australian cents per share;

(b) the exercise period will be the period commencing on the date of grant of the option and ending on 30 November 2006;

(c) such other terms as are set out in schedule 1 or as otherwise required by ASX.

'RECORD DATE' means a date proximate to the date of ASX listing to be determined in accordance with ASX requirements.

'RESTRICTION AGREEMENT' means the restriction agreement set out in Appendix 9A to the ASX Listing Rules as applies at Completion, the form of which (as at 3 September 2001) is set out in schedule 2.

'POLYCHIP' means Polychip Pharmaceuticals Pty Ltd ACN 006 455 456 of Level 1, 10 Wallace Avenue, Toorak, Victoria, 3142, Australia, a wholly owned subsidiary of Circadian.

'SUBSCRIPTION SHARES' means 30 million fully paid ordinary shares in ATL.

'SYNGENE' means Syngene Ltd ACN 006 161 753 of Level 1, 10 Wallace Avenue, Toorak, Victoria, 3142, Australia, a company in which Polychip has a minority shareholding.

2. CONDITION

2.1 CONDITION

The provisions of clauses 3, 4 and 6 have no effect and the issue of the ATL Shares, and grant of the Options by ATL to Isis as contemplated by clause 3 of this agreement shall not occur, unless and until the following condition is satisfied (the 'Condition'):

> ASX approves an ASX Listing of ATL and ATL satisfies all conditions attaching to such approval (other than the issue of shares and grant of options to Isis, as contemplated by clause 3), in each case on or before 26 March 2002 or such later date as the parties may agree in writing.

2.2 WAIVER OF CONDITION

The Condition may not be waived except by a waiver in writing signed by each party and will be effective only to the extent specifically set out in that waiver.

2.3 CONDUCT OF THE PARTIES

Each party must use its reasonable efforts within its own capacity to ensure that the Condition is satisfied.

2.4 FAILURE OF CONDITION

(a) Either party may terminate this agreement by giving notice in

writing to the other party at any time before Completion if the Condition is not satisfied, or waived by each party, before 5.00 pm on the Business Day immediately before the date set out in the Condition or such later date as may be agreed in writing by the parties.

3. ISSUE OF SHARES AND GRANT OF OPTIONS

3.1 AGREEMENT TO ISSUE SHARES AND GRANT OPTIONS

On and subject to the terms and conditions of this agreement:

(a) Isis agrees to subscribe for, and ATL agrees to issue to Isis, the Subscription Shares; and

(b) ATL agrees to grant to Isis 20 million Options.

3.2 ACKNOWLEDGMENT

The parties acknowledge that:

(a) ATL will be capitalised by various shareholders prior to the ASX Listing of ATL on the basis set out below:

ENTITY	NUMBER OF ATL SHARES -
Polychip	54.375 million
Syngene	54.375 million
Murdoch Interests	11.250 million
Total	120 million

(b) It is anticipated that, after the ASX Listing of ATL, ATL will:

(i) be capitalised as to approximately 190 million to 215 million ATL Shares; and

(ii) have granted between 105 million Options and 117.5 million Options.

(c) It is intended that ATL Shares will be offered to the public for a subscription price of 20 Australian cents per ATL Share, with a free Option attaching to each ATL Share at the rate of 1 Option for every 2 ATL Shares issued.

(d) It is intended that, after the ASX Listing of ATL, the ATL Shares issued and Options granted by ATL will be as follows:

PARTY	NUMBER OF ATL SHARES	NUMBER OF OPTIONS
Polychip	54.375 million	
Syngene	54.375 million	
Murdoch Interests	11.250 million	

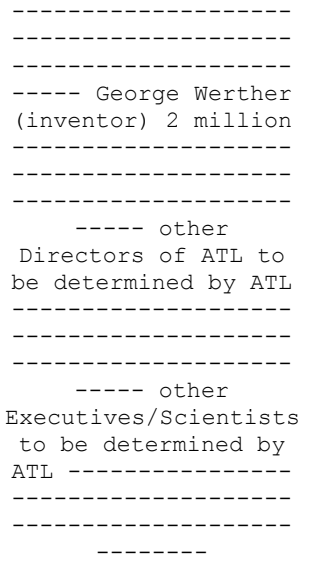
Isis	30 million	20 million
Public Subscribers	40 to 65 million	20 to 32.5 million
Circadian Shareholders*		42 million
Syngene Shareholders*		23 million
TOTAL**	190 TO 215 MILLION	105 TO 117.5 MILLION**

*The number of Options to be granted to Circadian Shareholders and Syngene Shareholders respectively are approximate only, based on the issued capital of each of Circadian and Syngene as at the Record Date. It is intended that those shareholders will be issued Options on the basis of 1 Option for every share held by the shareholders in Circadian and Syngene (as the case may be) on payment to ATL of 1 cent per Option. The Isis and Public Options will be free.

**This total will be increased by any options granted pursuant to the share option scheme described in clause 3.2(e).

(e) ATL intends putting in place a share option scheme in which senior originators inventors, employees and directors will participate. These options will have the same terms and conditions as the Options to be granted to the public under the prospectus, except it is intended there will be additional vesting conditions which will provide for gradual vesting for up to 5 years, restrictions on transfer and conditions on continued employment or involvement in ATL's projects. It is currently intended that the following entitlements will be granted under that scheme:

INDIVIDUAL	NUMBER OF OPTIONS
Stanley Crooke (Non-executive Director)	2 million
Chris Belyea (Managing Director and Originator)	2 million
George Tachas (Research Director (non-Board position), inventor and Originator)	1.5 million
Christopher Wraight (inventor)	2 million



4. CONSIDERATION

The parties acknowledge and agree that the consideration to be provided by Isis to ATL for the Subscription Shares and Options to be granted under clause 3 is the grant of the licences and provisions of the other services provided by Isis pursuant to the Collaboration and Licence Agreement.

5. ASX RESTRICTION AGREEMENT

5.1 The parties acknowledge that the ATL Shares and Options to be held by Polychip, Syngene, Murdoch Interests and Isis are likely to be regarded by the ASX as restricted securities for the purposes of the Chapter 9 of the ASX Listing Rules, to be placed in

escrow for a period of 2 years. Isis must sign a Restriction Agreement (and Isis must procure any controller (as that term is defined in the ASX Listing Rules) to sign a Restriction Agreement) in the form required by ASX and forward such documents (together with any other documents required under that agreement) to ATL within 2 Business Days of being requested in writing by ATL to do so for the purposes of facilitating the proposed ASX Listing of ATL.

6. COMPLETION

6.1 TIME AND PLACE

Completion will take place on the Completion Date at the office of Minter Ellison, Lawyers at Level 23, Rialto Towers, 525 Collins Street, Melbourne, Victoria, Australia or another place agreed by the parties.

6.2 SIMULTANEOUS ACTIONS AT COMPLETION

All actions at Completion will be treated as taking place simultaneously and no delivery will be regarded as having been made until all deliveries due to be made by Completion have been made.

6.3 OBLIGATIONS OF ISIS

At or before Completion, Isis must do all of the things listed below:

(a) provide to ATL a Restriction Agreement duly signed by Isis and any controller of Isis (as defined by the ASX Listing Rules) in accordance with clause 5;

(b) provide to ATL all such other documents as are required pursuant to the terms of the Restriction Agreement;

(c) provide to ATL an application for the ATL Shares to be subscribed for by Isis pursuant to clause 3.1;

(d) provide to ATL an application for Options to be granted to

Isis pursuant to clause 3.1.

6.4 OBLIGATIONS OF ATL

At Completion, ATL must, subject to compliance by Isis with the provisions of clause 6.3, issue to Isis the Subscription Shares and the Options to be granted pursuant to clause 3.1.

6.5 WAIVER

If any of the obligations set out in clauses 6.3 and 6.4 above are not complied with in any respect on the date set for Completion, the other party may in its absolute discretion:

(a) waiver compliance with that provision;

(b) defer Completion to a date not more than 5 Business Days after the date set for Completion;

(c) proceed to Completion as far as its practicable (without prejudice to any of its rights under this agreement); or

(d) terminate this agreement by notice in writing to the other party.

6.6 ACCRUED RIGHTS

Termination of this agreement does not affect any accrued rights or remedies of a party.

7. ASSIGNMENT

A party may not assign any of its rights under this agreement without the consent of the other parties.

8. WAIVER

8.1 WAIVER

A provision of or right under this agreement may not be waived except by a waiver in writing signed by the party granting the waiver, and will be effective only to the extent specifically set out in that waiver.

8.2 RIGHTS EXERCISABLE

The failure of a party at any time to require performance of any obligation under this agreement is not a waiver of that party's right:

(a) to insist on performance of, or claim damages for breach of, that obligation unless that party acknowledges in writing that the failure is a waiver; and

(b) at any other time to require performance of that or any other obligation under this agreement.

9. NOTICES

9.1 SERVICE OF NOTICES

A party giving or serving notice or notifying under this agreement must do so in writing:

(a) directed to the recipient's address specified in this clause, as varied by any notice; and

(b) hand delivered or sent by prepaid post or facsimile to that address.

The parties' addresses and facsimile numbers are:

Isis Pharmaceuticals, Inc
2292 Faraday Avenue
Carlsbad, CA 92008
United States of America
Facsimile No: +1 760 931 9639

Antisense Therapeutics Ltd
Level 1, 10 Wallace Avenue
Toorak, Victoria 3000
Australia
Facsimile No: +61 3 9824 0083

9.2 DEEMED RECEIPT

A notice given in accordance with clause 9.1 is taken to be received:

(a) if hand delivered, on delivery;

(b) if sent by prepaid post, two Business Days after the date of posting; or

(c) if sent by facsimile, when the sender's facsimile system generates a message confirming successful transmission of the total number of pages of the notice unless, within one Business Day after the transmission, the recipient informs the sender that it has not received the entire notice.

9.3 EXECUTION

A notice given in accordance with clause 9.1 is sufficiently signed for or on behalf of a party if:

(a) in the case of a company, it is signed by a director, secretary or other officer of the company; or

(b) in the case of an individual, it is signed by that party.

9.4 OTHER MODES OF SERVICE PERMITTED

The provisions of this clause 9 are in addition to any other mode of service permitted by law.

10. GOVERNING LAW AND JURISDICTION

This agreement is governed by the law applicable in Victoria, Australia and each party irrevocably and unconditionally submits to the non-exclusive jurisdiction of the courts of Victoria, Australia.

11. GENERAL

11.1 DURATION OF PROVISIONS

On completion of the transactions contemplated in this agreement, the provisions of this agreement will not merge and, to the extent any provision has not been fulfilled, will remain in force.

11.2 FURTHER ACTION

Each party must use reasonable efforts to do all things necessary or desirable to give full effect to this agreement.

11.3 COUNTERPARTS

This agreement may be executed in any number of counterparts.

11.4 ALTERATIONS

This agreement may be altered only in writing signed by each party.

11.5 COSTS

Each party must bear its own costs of negotiating, preparing and executing this agreement.

11.6 ATTORNEYS

Where this agreement is executed on behalf of a party by an attorney, that attorney by executing declares and warrants that the attorney has been duly appointed and has no notice of the revocation of the power of attorney under the authority of which the attorney executes the agreement on behalf of that party.

11.7 INTERPRETATION

In this agreement, unless the contrary intention appears:

(a) headings are for ease of reference only and do not affect the meaning of this agreement;

(b) the singular includes the plural and vice versa and words importing a gender include other genders;

(c) other grammatical forms of defined words or expressions have corresponding meanings;

(d) a reference to a clause, paragraph, schedule, annexure or attachment is a reference to a clause or paragraph of or schedule, annexure or attachment to this agreement and a reference to this agreement includes its schedules, annexures and attachments;

(e) a reference to a document or agreement, including this agreement, includes a reference to that document or agreement as novated, altered or replaced from time to time;

(f) a reference to `A$', `$A', `dollar' or `$' is a reference to Australian currency;

(g) a reference to a specific time for the performance of an obligation is a reference to that time in Melbourne, Australia even if the obligation is to be performed elsewhere;

(h) a reference to a party includes a reference to the party's executors, administrators, successors, substitutes and assigns;

(i) words and expressions importing natural persons include partnerships, bodies corporate, associations, governments and governmental and local authorities and agencies, and vice versa;

(j) a reference to any legislation or statutory instrument or regulation is construed in accordance with the ACTS INTERPRETATION ACT 1901 (Cth) or the equivalent State legislation, as applicable;

(k) a reference to writing includes typewriting, printing, lithography, photography and any other method of representing or reproducing words, figures or symbols in a permanent and visible form;

(l) if a day for payment under this agreement falls on a day which is not a Business Day, payment is due on the next Business Day;

(m) if a provision of this agreement binds two or more parties (including any representation, warranty or indemnity given, made or undertaken by two or more parties), that provision binds (and that representation, warranty or indemnity is given, made or undertaken by) those parties jointly and severally; and

(n) if a party comprises two or more persons, the provisions of this agreement binding that party bind those persons jointly and severally.

EXECUTED as an agreement.

ANTISENSE THERAPEUTICS, LIMITED ISIS PHARMACEUTICALS, INC.

By: /s/ C. Belyea	By: /s/ B. Lynne Parshall
Name: C. BELYEA	Name: B. LYNNE PARSHALL
Title: CEO	Title: EXECUTIVE VICE PRESIDENT AND CHIEF FINANCIAL OFFICER

SCHEDULE 1 - TERMS AND CONDITIONS OF OPTIONS

Each option ('OPTION') shall entitle the holder of the Option ('OPTION HOLDER') to acquire by way of issue one fully paid ordinary share ('SHARE') in Antisense Therapeutics Limited ('COMPANY') on the terms and conditions set out below:

1. Each Option is exercisable at any time after the date of grant to a date up to and including 30 November 2006.

2. If the Option is not exercised on or prior to the expiry of the Option Period, the Option shall lapse.

3. The Options may be exercised wholly or in part by giving notice in writing ('NOTICE OF EXERCISE') to the Board at any time during the Option Period.

4. Options shall only be exercisable in multiples of 100. Within 10 business days of the exercise of the Option the Company shall apply for the shares to be admitted for quotation on the Official List of Australian Stock Exchange Limited.

5. The exercise price for each Option is $0.20 per share ('EXERCISE PRICE') and is payable immediately on exercise.

6. On receipt by the Company of the Notice of Exercise and payment of the relevant Exercise Price, the Company must, within 14 days, issue to the Option Holder the number of Shares in respect of which the Option is exercised and despatch the relevant share certificate or other appropriate acknowledgment as soon as reasonably practicable thereafter.

7. Shares issued on the exercise of any Options will rank equally in all respects with the then existing issued ordinary fully paid shares in the Company and will be subject to the provisions of the Constitution of the Company.

8. An Option does not confer rights to participate in new issues of securities of the Company, unless the Option Holder has first exercised the Option.

9. Adjustments to the number of shares over which Options exist and/or the Exercise Price will be made to take account of changes to the capital structure of the Company by way of pro rata bonus and cash issues as follows:

   (a) Pro-Rata Cash issues

   Where a pro-rata issue is made (except a bonus issue) to the holders of underlying securities, the Exercise Price of an option may be reduced according to the following formula:

$$O' = O - \frac{E[P-(S+D)]}{N+1}$$

   where:
   O' = the new exercise price of the option.
   O = the old exercise price of the option.
   E = the number of underlying securities into which one option is Exercisable.
   P = the average Market Price per security (weighted by reference to volume) of the underlying securities immediately prior to the time of determining entitlements to participate in the issue.

S = the Subscription price for a security under the pro rata issue.
D = the Dividend due but not yet paid on the existing underlying securities (except those to be issued under the pro rata issue).
N = the Number of securities with rights or entitlements that must be held to receive a right to one new security.

(b) Pro-Rata Bonus Issues

If there is a bonus issue to the holders of the underlying securities, on the exercise of any options, the number of shares received will include the number of bonus shares that would have been issued if the options had been exercised prior to the date established to determine entitlements to participate in the bonus issue. The Exercise Price will not change.

(c) For the purposes of the definition of 'P' in paragraph (a), 'Market Price' in relation to a security means the arm's length value of the security as specified in a written report given to the Company by a person who is registered as a company auditor under a law in force in a State or a Territory and who is not a director, secretary or employee of the Company.

10. In the event of any reorganisation (including consolidation, sub-division, reduction or return) of the issued capital of the Company, the rights of the Option Holder including the number of options or the Exercise Price or both shall be reorganised (as appropriate):

(a) in the event of a consolidation of the share capital of the Company, the number of options will be consolidated in the same ratio as the ordinary share capital of the Company and the Exercise Price will be amended in inverse proportion to that ratio;

(b) in the event of a subdivision of the share capital of the Company, the number of options will be subdivided in the same ratio as the ordinary share capital of the Company and the Exercise Price will be amended in inverse proportion to that ratio;

(c) in the event of a return of the share capital of the Company, the number of options will remain the same and the Exercise Price will be reduced by the same amount as the amount returned in relation to each ordinary share;

(d) in the event of a reduction of the share capital of the Company by a cancellation of paid up capital that is lost or not represented by available assets where no securities are cancelled the number of options and the Exercise Price of each option will remain unaltered;

(e) in the event of a pro rata cancellation of shares in the Company, the number of options will be reduced in the same ratio as the ordinary share capital of the Company and the Exercise Price of each option will be amended in inverse proportion to that ratio; and

(f) in the event of any other reorganisation of the issued capital of the Company, the number of options or the Exercise Price or both will be reorganised (as appropriate) in a manner which will not result in any benefits being conferred on Option Holders which are not conferred on shareholders.

11. Notices may be given by the Company to the Option Holder in the manner prescribed by the Constitution of the Company for the giving of notices to the Shareholders of the Company and the relevant provisions of the Constitution of the Company will apply with all necessary modification to notices to be given to the Option Holder.

12. The Option Holder will be sent all reports and accounts required to be laid before Shareholders in general meeting and all notices of general meeting of Shareholders, but he will not have any right to attend or vote at these meetings.

SCHEDULE 2 - RESTRICTION AGREEMENT

APPENDIX 9A

RESTRICTION AGREEMENT

Introduced 1/7/96. Origin: Appendix 11. Amended 1/7/98.

We, the persons in:

- - Item 1 of the schedule ("entity");

- - Item 2 of the schedule ("holder");

- - Item 3 of the schedule ("controller"),

agree as follows.

INTRODUCTION

A. The entity wants to be listed and has issued restricted securities. The holder will hold the restricted securities as set out in this agreement on the basis that the entity will take the steps necessary to be admitted to the +official list of ASX.

B. We have provided ASX with all the information necessary to properly form an opinion about who is a +controller of the holder and who is required to execute this agreement.

C. We enter this agreement for the purpose of complying with chapter 9 of the listing rules.

AGREEMENT

Escrow restrictions

1. During the escrow period, the holder will not do any of the following.

(a) +Dispose of, or agree or offer to +dispose of, the restricted securities.

(b) Create, or agree or offer to create, any security interest in the restricted securities.

(c) Do, or omit to do, any act if the act or omission would have the effect of transferring effective ownership or control of the restricted securities.

2. During the escrow period, a controller will not do any of the following.

(a) +Dispose of, or agree or offer to +dispose of, the controller interests.

(b) Create, or agree or offer to create, any security interest in the controller interests.

(c) Do, or omit to do, any act if the act or omission would have the effect of transferring effective ownership or control of the controller interests.

3. We will comply with chapter 9 of the listing rules. If any of us is not a listed entity, we will comply as if we were a listed entity. Each of us will take any steps we are able to take that are necessary

to enable any of the others to comply.

4. The holder will deposit the certificates for the restricted securities with a bank or +recognised trustee for the escrow period.

Warranties

5. If only the holder and the entity are parties to this agreement, one of the following applies.

   (a) The holder is an individual.

   (b) The holder has no +controller.

   (c) The holder has the +controllers set out in item 3 with the interests identified in item 6, and each +controller comes within an exception set out in rule 9.1.4.

   The holder gives this warranty.

6. If the holder, the entity and any +controller are parties to this agreement, the holder has the +controllers set out in item 3 with the controller interests identified in item 6, and any +controller who is not a party to this agreement comes within an exception set out in rule 9.1.4. The holder and each +controller give this warranty.

7. If item 7 of the schedule is completed, the full particulars of security interests which have been created, or are agreed or offered to be created, in the restricted securities are set out. A release of the security interests is attached. Apart from this, before the escrow period begins, the holder has not done, or omitted to do, any act which would breach clause 1 if done or omitted during the escrow period. The holder gives this warranty.

8. If item 8 of the schedule is completed, the full particulars of security interests which have been created, or are agreed or offered to be created, in the controller interests are set out. A release of the security interests is attached. Apart from this, before the escrow period begins, the +controller has not done, or omitted to do, any act which would breach clause 2 if done or omitted during the escrow period. Each +controller gives this warranty.

9. A breach of any of these warranties is a breach of this agreement.

Consequences of breaching this agreement

10. If it appears to the entity that the holder or a +controller may breach this agreement, the entity must take the steps necessary to prevent the breach, or to enforce the agreement.

11. If the holder or a +controller breach this agreement, each of the following applies.

   (a) The entity must take the steps necessary to enforce the agreement, or to rectify the breach.

   (b) The entity must refuse to acknowledge, deal with, accept or register any sale, assignment, transfer or +conversion of any of the restricted securities. This is in addition to other rights and remedies of the entity.

   (c) The holder of the restricted securities ceases to be entitled to any dividends, distributions or voting rights while the breach continues.

Amendment

12. This agreement will not be changed or waived without ASX's written consent.

Jurisdiction

13. The laws of the State of the home branch of the entity apply to this agreement. We submit to the jurisdiction of the courts of that State.

Definitions and interpretation

In this agreement:

ASX means Australian Stock Exchange Limited.

CONTROLLER INTERESTS means the +securities, substantial economic interest or other interests in the restricted securities and each intermediate entity through which that interest occurs, full particulars of which are set out in item 6 of the schedule.

ESCROW PERIOD means the period set out in item 4 of the schedule.

RESTRICTED SECURITIES means the +securities set out in item 5 of the schedule and any +securities attaching to or arising out of those +securities that are restricted securities because of the definition of restricted securities in the listing rules.

The singular includes the plural and vice versa.

A reference to a party includes its successors, personal representatives and transferees.

Words and expressions defined in the listing rules of ASX, and not in this agreement, have the meanings given to them in the listing rules.

Every warranty or agreement (expressed or implied) in which more than one person joins, binds them individually and any combination of them as a group.

Schedule

1. Entity's name and address:

2. Holder's name and address:

3. Each +controllers' name and address:

4. Escrow period (the date from which the initial restricted securities are escrowed):

5. Particulars of restricted securities:

6. Particulars of controller interests:

7. Particulars of security interests over restricted securities:

8. Particulars of security interests over controller interests:

Dated:
[Proper execution as a deed]

AMGEN AND ISIS PHARMACEUTICALS TO COLLABORATE ON ANTISENSE DRUG DISCOVERY

THOUSAND OAKS and CARLSBAD, CA -- December 13 -- Amgen (NASDAQ: AMGN) and Isis Pharmaceuticals, Inc. (NASDAQ: ISIP) announced today that the companies have entered into a three-year collaboration to discover new antisense drugs. The therapeutic area of research and financial terms of the transaction were not disclosed.

Amgen and Isis will collaborate on antisense drugs utilizing Isis' proprietary second-generation chemistry, called 2'-O-methoxyethyl, to inhibit several gene targets. Antisense technology is a novel drug discovery method. Antisense drugs work at the genetic level to interrupt the process by which disease-causing proteins are produced.

Amgen has the right to develop and commercialize antisense drugs resulting from the collaboration. If drugs from the collaboration are successful, Isis will receive milestone payments upon key clinical and commercial achievements, as well as royalties on sales.

"We are intrigued with the possibility that through this collaboration with Isis, a leader in antisense technology, we may be able to provide important medicines for unmet medical needs," said Roger Perlmutter, Amgen's Executive Vice President for Research and Development.

"We are very pleased to initiate this collaboration with Amgen, a highly-regarded, innovative leader in the industry. This relationship extends the potential of antisense drugs and represents an additional effort to bring new antisense drugs to the market," said Stanley T. Crooke, M.D., Ph.D., Chairman and CEO of Isis. "Amgen is our third new drug discovery collaborator this year. We are pleased with the pharmaceutical and biotechnology industry's increasing recognition of antisense technology.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene-Registered Trademark- (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 products in its development pipeline, with two in Phase III clinical trials and seven in Phase II human clinical trials. ISIS 3521, an inhibitor of PKC-alpha, is in Phase III trials for non-small cell lung cancer and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in Phase III human clinical trials for Crohn's disease. Isis has a broad and proprietary patent estate of nearly 900 issued and allowed patents worldwide. Isis' GeneTrove-TM- division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services and access to an extensive gene function database. Ibis Therapeutics-TM- is a division focused on the discovery of small molecule drugs that bind to RNA.

Amgen is a global biotechnology company that discovers, develops, manufactures and markets important human therapeutics based on advances in cellular and molecular biology.

This news release contains forward-looking statements that involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including Amgen's most recent Form 10-Q. Amgen conducts research in the biotechnology/pharmaceutical field where movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate will be successful and become a commercial product.

Furthermore, Amgen's research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. In addition, sales of Amgen's products are affected by reimbursement policies imposed by third party payors, including governments, private insurance plans and managed care providers. These government regulations and reimbursement policies may affect the development, usage and pricing of products.

In addition, while Amgen routinely obtains patents for products and technology, the protection offered by patents and patent applications may be challenged, invalidated or circumvented by competitors.

Because forward-looking statements involve risks and uncertainties, actual results may differ materially from current results expected by Amgen. Amgen is providing this information as of December 13, 2001 and expressly disclaims any duty to update information contained in this press release.

This press release also contains forward-looking statements concerning Isis Pharmaceuticals and the potential of antisense drugs and Isis' current and future relationship with Amgen. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and financing such activities. Actual results could differ materially from those projected in this release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in the Isis Quarterly Report on Form 10-Q, for the period ended September 30, 2001, which is on file with the U.S. Securities and Exchange Commission, copies of which are available from Isis.

ISIS PHARMACEUTICALS AND CIRCADIAN TECHNOLOGIES FORM ANTISENSE THERAPEUTICS LIMITED

NEW AUSTRALIAN COMPANY FURTHERS ISIS' STRATEGY TO BROADEN APPLICATION OF ANTISENSE TECHNOLOGY

Carlsbad, CA, USA and Melbourne, Australia, December 19, 2001 - Isis Pharmaceuticals, Inc. (NASDAQ: ISIP) and Circadian Technologies Limited (ASX: CIR), a leading Australian biotechnology commercialization firm, announced today the companies have collaborated to create Antisense Therapeutics Limited (ATL). Isis and Circadian have established this new Australian-based biotechnology company to focus on the discovery and development of antisense drugs. ATL will further the application of Isis' antisense technology platform in new markets. ATL was listed on the Australian Stock Exchange (ASX) today under the symbol ANP, successfully completing its initial public offering.

As part of establishing ATL in the antisense field, Isis has licensed to ATL ISIS 107248, an antisense inhibitor to CD 49d, a sub-unit of VLA-4 (Very Late Antigen-4). Treatment by inhibition of VLA-4 has been demonstrated to have positive effects in animal models of a number of inflammatory diseases such as multiple sclerosis. Isis will complete the required preclinical studies for ISIS 107248 and will manufacture drug for human clinical trials at ATL's expense. ATL will undertake future clinical development and commercialization of the compound.

Isis and ATL will also participate in a five-year antisense drug discovery and development collaboration, which includes ATL's use of GeneTrove's-TM- gene functionalization services for a limited number of targets. ATL will pay Isis for access to the company's antisense expertise and for research and manufacturing services conducted during the collaboration. In addition, ATL will pay to Isis royalties on antisense drugs discovered and developed within the partnership. Isis owns approximately 14 percent of ATL equity and holds options for additional shares. Isis' Chairman and CEO Stanley T. Crooke, M.D., Ph.D., is a member of ATL's Board of Directors.

"In partnership with Circadian, we are very pleased to have formed a new company focused solely on exploiting antisense technology as a drug discovery and development platform. Our goals from the outset have been to lead the industry into antisense technology and encourage its use broadly. ATL is another example of our execution of these goals, on a global level," said Stanley T. Crooke, M.D., Ph.D., Isis' Chairman and Chief Executive Officer. "At Isis, we currently discover more potential drug candidates than we can afford to develop. ATL represents a strategic move to broaden the reach of antisense drugs, while minimizing financial obligations for us and our shareholders."

To build its business, ATL will engage in antisense drug discovery and development collaborations with academic research institutions throughout Australia, including the prestigious Murdoch Childrens Research Institute based in Melbourne. Murdoch Childrens Research Institute will contribute key specific intellectual property and expertise to ATL's antisense research efforts. In the future, ATL plans to work with additional corporate partners.

"Antisense is a revolutionary drug discovery platform that has progressed significantly over the last decade and is now prime for broad application. We look forward to working with Isis, the undisputed leader in antisense, as our key technology partner. We have created a powerful team and business plan to expand the investigation and development of this important platform technology into new therapeutics for patients in need," said Chris Belyea, ATL's founding Chief Executive Officer.

ATL's IPO raised A$13 million (Australian dollars), or US$6.5 million. Circadian directly and indirectly holds 36 percent of ATL issued capital.

"In recent years we have worked successfully to establish several listed Australian biotechnology companies and we are delighted to be involved in this collaboration with Isis who we regard as the pioneer of antisense technology," said Leon Serry, Circadian's Chief Executive Officer.

Circadian Technologies Limited was listed on the ASX in 1985. Circadian provides management and funding for the development and commercialization of Australian pharmaceutical research to the stage of either licensing or listing on the ASX. The company holds equity positions in Metabolic Pharmaceuticals Limited (developing a new obesity drug - ASX: MBP), Optiscan Imaging Limited (developing new diagnostic imaging equipment -ASX: OIL), and U.S.-based Axon Instruments, Inc. (genomics and high throughput screening equipment - ASX: AXN). For these

companies, Circadian provided funding and assistance in their listings on the ASX. Circadian is also now the largest shareholder in AMRAD Corporation Limited (with three drugs in Phase II trials - ASX: AML). Circadian's current unlisted R&D portfolio includes a novel platform technology for identification of potential cancer markers and an extensive patent portfolio in in situ hybridization techniques.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene-Registered Trademark- (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 products in its development pipeline with two in Phase III and seven in Phase II human clinical trials. ISIS 3521, an inhibitor of PKC-alpha, is in Phase III trials for non-small cell lung cancer and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is also in Phase III trials for Crohn's disease. Isis has a broad patent estate as the owner or exclusive licensee of nearly 900 issued patents worldwide. Isis' GeneTrove division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services and access to an extensive gene function database. Ibis Therapeutics-TM- is a division focused on the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at www.isip.com.

This press release contains forward-looking statements concerning the potential of Isis Pharmaceuticals, antisense technology as a drug discovery and development platform and a tool for functional genomics, the prospects of ISIS 107248 as a treatment for multiple sclerosis and Isis' relationship with ATL and Circadian Technologies. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and financing such activities. Actual results could differ materially from those projected in this release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail in the Company's Quarterly Report on Form 10Q, for the period ended September 30, 2001, which is on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

Vitravene-Registered Trademark- is a trademark of Novartis AG. GeneTrove-TM- and Ibis Therapeutics-TM- are trademarks of Isis Pharmaceuticals, Inc.

ISIS PHARMACEUTICALS ESTABLISHES NEW SUPPLY AGREEMENT AND BROADENS LICENSE TO KEY ANTISENSE INTELLECTUAL PROPERTY

Carlsbad, CA and Coraville, IA December 27, 2001 -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIP) announced today it has established a long-term research-scale antisense inhibitor supply agreement with Integrated DNA Technologies, Inc. (IDT). IDT is a leading supplier of antisense inhibitors used in research. Additionally, Isis has further solidified its intellectual property leadership position in antisense technology by broadening its license to certain antisense patents.

In the long-term supply agreement Isis has initiated with IDT, IDT will manufacture research-scale antisense inhibitors and research reagents to Isis specifications. The agreement enables Isis to meet increasing demand for functional genomics services that its GeneTrove division provides to a growing number of major pharmaceutical and biotechnology customers. Isis will pay IDT $5 million toward Isis' future purchase of antisense inhibitors from IDT. The transaction provides IDT with financing for the company's operations expansion.

Consistent with Isis' goal of broad control of intellectual property associated with antisense technology, Isis has expanded its existing licensing agreement with IDT on certain patents, which are useful in functional genomics and in making certain antisense drugs. The expanded license allows Isis to exclusively sublicense this intellectual property for functional genomics purposes. The agreement also eliminates milestone payments and significantly reduces royalty rates associated with commercialized second-generation antisense drugs. Isis will pay IDT $4.9 million for the broadened intellectual property license.

Isis' intellectual property estate is comprised of nearly 900 issued patents that Isis owns or exclusively licenses, covering RNA-based drug discovery and development. The company's functional genomics suite of patents is made up of approximately 50 patents and applications. This functional genomics suite of patents broadly covers the use of RNA/DNA oligonucleotides, or antisense inhibitors, in gene functionalization and target validation, including: chemistries; antisense inhibitor designs called "motifs;" methods of use of antisense inhibitors; and mechanisms of action by which antisense inhibitors inactivate an RNA target.

"Our GeneTrove division has enjoyed tremendous success this year, adding Celera, Lilly and Chiron to its roster of collaborators. The supply agreement we've initiated augments our capacity to support these programs and continue to build our GeneTrove business," said B. Lynne Parshall, Isis Executive Vice President and Chief Financial Officer. "Importantly, this transaction enhances Isis' intellectual property licensing program and supports our control over second-generation antisense drugs, which we believe offer broad potential to treat a wide range of diseases. It also improves the economics of the second-generation drugs we develop."

"IDT is pleased to enter into this licensing agreement with an established partner like Isis, and to continue to be a principle supplier of antisense inhibitors and research reagents for Isis' research and development programs, and to Isis' growing list of licensees and collaborators," said Joseph A. Walder, M.D., Ph.D., President and CEO of IDT. "Importantly for IDT, this transaction fortifies our financial position and facilitates our growth to meet market demand in the ever-expanding global life sciences market."

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene-Registered Trademark- (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 products in its development pipeline with two in Phase III and seven in Phase II human clinical trials. ISIS 3521, an inhibitor of PKC-alpha, is in Phase III trials for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is also in Phase III trials for Crohn's disease. Isis has a broad patent estate as the owner or exclusive licensee of nearly 900 issued patents worldwide. Isis' GeneTrove-TM- division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services and access to an extensive gene function database. Ibis Therapeutics-TM- is a division focused on the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at www.isip.com.

Integrated DNA Technologies, Inc., an Iowa-based biotechnology company, was founded in 1987 by Dr. Joseph A. Walder. Dr. Walder has continued with the company and is presently Corporate President and CEO. The company initially worked as a research facility in the antisense area, and continues research programs in nucleic acids and

related chemistries. The company has patented technology, which it has licensed to other companies as well as patents pending. Since 1992 the company has produced chemical/biological items used by researchers in the biotechnology industry focusing on short segment DNA. With over 300 employees, including a national and international sales force, IDT services over 16,000 customers in fifty countries around the globe. IDT is a recognized world leader in advancing biotechnology research as both a supplier of oligonucleotides and an innovator of new technology.

Integrated DNA Technologies' production facility is located in Coralville, Iowa near the University of Iowa, which has one of the largest medical complexes and medical teaching facilities in the country. The region is one of the fastest growing high tech corridors in the United States. The company also has a corporate office in the Chicago area. Integrated DNA Technologies, Inc. is dedicated to being the world's leader in innovation and precision in nucleic acid synthesis. Additional information about IDT may be found on its web site at www.idtdna.com.

This press release contains forward-looking statements concerning Isis Pharmaceuticals and the potential of the company's intellectual property position and Isis' current and future relationship with IDT. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and financing such activities. Actual results could differ materially from those projected in this release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' research and development programs are described in additional detail on Quarterly Report on Form 10-Q for the period ended September 30, 2001 which is on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.