

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 8-K

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

Date of Report (Date of earliest event reported): AUGUST 31, 1999

ISIS PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

DELAWARE
(State or other jurisdiction of incorporation)

0-19125
(Commission File No.)

33-0336973
(IRS Employer Identification No.)

2292 FARADAY AVENUE
CARLSBAD, CALIFORNIA 92008
(Address of principal executive offices and zip code)

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

ITEM 5. OTHER EVENTS.

On July 18, 1995, Isis Pharmaceuticals, Inc. ("Isis") and Boehringer Ingelheim International, GmbH ("BI") formed a collaboration to combine the clinical development and research programs of both companies in the field of cell adhesion. Effective August 31, 1999 Isis has reacquired control of the ISIS 2302 drug compound in order to redirect the commercialization of this product.

In connection with the collaboration, Isis and BI entered into a Stock Purchase Agreement effective July 18, 1995. The Stock Purchase Agreement has been amended effective August 31, 1999 in accordance with the attached Exhibit 10.2.

ITEM 7. FINANCIAL STATEMENTS AND EXHIBITS.

- (a) Financial Statements of Businesses Acquired. Not applicable.
- (b) Pro Forma Financial Information. Not applicable.
- (c) Exhibits

Exhibit 10.1* Agreement dated August 31, 1999 between
Boehringer Ingelheim International GmbH and Isis
Pharmaceuticals, Inc.

Exhibit 10.2 Amendment to the Stock Purchase Agreement dated
August 31, 1999

*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, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

ISIS PHARMACEUTICALS, INC.

Dated: September 2, 1999

By: /S/ B. LYNNE PARSHALL

B. Lynne Parshall
Executive Vice President

*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.

AGREEMENT

This AGREEMENT, dated as of August 31, 1999 (the "Effective Date"), by and between BOEHRINGER INGELHEIM INTERNATIONAL GmbH ("BI"), a company organized and existing under the laws of the Federal Republic of Germany, with its principal place of business at D-55216 Ingelheim/Rhein, Federal Republic of Germany, and ISIS PHARMACEUTICALS, INC. ("Isis"), a Delaware corporation with its principal place of business at 2292 Faraday Drive, Carlsbad, California 92008, U.S.A.,

W I T N E S S E T H :

WHEREAS, pursuant to the Collaborative Agreement, dated as of July 18, 1995, BI and Isis previously entered into collaborative research, development and commercial relationship in the Field; and

WHEREAS, BI and Isis have mutually agreed to terminate the Collaborative Agreement and to set forth in this Agreement, which shall supercede the Collaborative Agreement as of the Effective Date, their mutual agreement with respect to collaborative research in the Field

WHEREAS, BI and Isis have mutually agreed to continue their collaboration with respect to research under the Research Plan through December 31, 1999, and to discontinue their collaboration with respect to development, in each case, as provided herein,

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

ARTICLE 1.

DEFINITIONS

For purposes of this Agreement, the capitalized terms defined in this Agreement shall have the meanings specified in Appendix A attached hereto.

ARTICLE 2.

SCOPE AND STRUCTURE OF COLLABORATION

2.1 Termination of Collaborative Agreement. Pursuant to the Collaborative Agreement, BI and Isis established a collaboration for the purpose of identifying, developing and commercializing products in the Field. The Parties hereby acknowledge and mutually agree that as of the Effective Date the Collaborative Agreement shall be terminated. The Parties further hereby agree that as of the Effective Date this Agreement shall supercede the Collaborative Agreement and no agreement with respect to the subject matter hereof shall exist between the Parties other than the agreements expressly set forth herein. The Parties further agree that they will continue their collaboration with respect to research under the Research Plan and discontinue their collaboration with respect to development, in each case, as provided herein.

2.2 ISIS 2302.

(a) The Parties hereby acknowledge and agree that BI has abandoned its participation in the further development and commercialization of ISIS 2302 in any and all formulations and indications of every kind whatsoever. BI acknowledges and agrees that Isis has full responsibility and authority to develop and commercialize ISIS 2302.

(b) As of the Effective Date, Isis shall pay BI a royalty, on a country-by-country basis, on Net Sales of any formulation or indication of ISIS 2302 occurring on or after the Effective Date as follows:

(i) With respect to all sales of any [***] of ISIS 2302 for [***], such royalty rate shall be [***] of Net Sales;

(ii) With respect to all sales of any [***] other than for [***], such royalty rate shall be [***] of Net Sales;

(iii) With respect to sales of any [***] of ISIS 2302 for the indications of [***], such royalty rate shall be [***] of Net Sales; and

(iv) With respect to all sales of ISIS 2302 not specified in clause (i), (ii) or (iii) above, such royalty rate shall be [***] of Net Sales.

(c) The obligations to pay royalties under this Section 2.2 shall continue, on a country-by-country basis, until the later of (i) the [***], or (ii) [***] anniversary of the Effective Date.

2.3 Additional Compounds. The Parties further agree that, as of the Effective Date, they shall have the respective rights and obligations set forth in this Section 2.3 with respect to the Additional Compounds.

(a) BI shall have the sole right to develop, commercialize, sell and license any of the compounds known as [***] or any compound from out of the [***] series that had been synthesized as of the Effective Date. If BI commercializes any of the compounds known as [***] or any compound from out of the [***] series that had been synthesized as of the Effective Date, either by itself or through a Third Party, BI shall pay Isis a royalty, on a country-by-country basis, of [***] on any and all Net Sales of [***] or any compound from out of the [***] series that had been synthesized as of the Effective Date, as the case may be. Isis hereby represents that during the term of the Collaborative Agreement it did not discover any small-molecule compounds in the Field with the exception of Isis's small molecule combinatorial libraries.

(b) Isis shall have the sole right to develop, commercialize, sell and license any of the compounds known as [***]. If Isis commercializes the compounds known as [***], either by itself or through a Third Party, Isis shall pay BI a royalty, on a country-by-country basis, of [***] on any and all Net Sales of [***], as the case may be. BI hereby represents that during the term of the Collaborative Agreement it did not discover any Antisense Molecules in the Field.

(c) Each Party shall have the right, in its sole discretion, to in- and out-license and establish collaborations with Third Parties within the Field without the approval of, and without any obligation to, the other Party.

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(d) The obligations to pay royalties under Section 2.3(a) and Section 2.3(b), respectively, shall continue, on a country-by-country basis, until the later of (i) the [***], or (ii) the [***] anniversary of the Effective Date.

2.4 Both Parties shall have the right to practice the Joint [***] Patent(s); provided, however, that:

(i) Isis shall have the sole right to develop, commercialize and sell Antisense Molecules covered by any issued Joint [***] Patent(s), and Isis shall pay BI a royalty, on a country-by-country basis, of [***] of any and all Net Sales of such Antisense Molecules or compounds containing such Antisense Molecules;

(ii) BI shall have the sole right to develop, commercialize and sell small-molecule compounds covered by any issued Joint [***] Patent(s), and BI shall pay Isis a royalty, on a country-by-country basis, of [***] of any and all Net Sales of such small-molecule compounds or compounds containing such small-molecule compounds; and

(iii) Either Party may develop, commercialize and sell any compound that is not (a) an Antisense Molecule or (b) a small-molecule compound, covered by an issued Joint [***] Patent(s), so long as such Party has the intellectual property right to develop, commercialize or sell such compound, and such Party shall pay the other Party a royalty, on a country-by-country basis, of [***] of any and all Net Sales of such compound.

(b) The obligations to pay royalties under Section 2.4 shall continue, on a country-by-country basis, until the later of (i) the [***], or (ii) [***] anniversary of the Effective Date.

2.5 [***].

(a) As of the Effective Date, BI shall pay Isis a royalty, on a country-by-country basis, of [***] on Net Sales of the [***] in the indications of [***] occurring on or after the Effective Date.

(b) As of the Effective Date, BI shall pay Isis a royalty, on a country-by-country basis, of [***] on Net Sales of any formulation or indication of [***] occurring on or after the Effective Date.

(c) Isis acknowledges and agrees that BI has full responsibility and authority to develop and commercialize [***].

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(d) The obligations to pay royalties under this Section 2.5 shall continue, on a country-by-country basis, until the later of (i) the [***], as the case may be, or (ii) [***] anniversary of the Effective Date.

2.6 Other Compounds. Any given compound in the Field, including without limitation, compounds which have been part of the ongoing screening and optimization of (i) Antisense Molecules and small-molecule compounds by Isis and (ii) small-molecule compounds by BI, throughout the term of the Collaborative Agreement, other than ISIS 2302, [***], the Additional Compounds, and Antisense Molecules, small-molecule compounds and other compounds covered by an issued Joint [***] Patent may be commercialized and/or sold by the Party having the intellectual property right to develop, commercialize or sell such compound without any obligation whatsoever to the other Party under this Agreement.

ARTICLE 3.

RESEARCH PLAN

3.1 Research Plan. The Parties hereby agree to cooperate in carrying out the Research Plan during the Research Period, as described in this Article 3.

3.2 Research Agreement. During the Research Period, BI and Isis hereby agree to work cooperatively to fulfill the Research Plan.

3.3 Research Period. The Research Plan shall be undertaken by the Parties during the Research Period.

3.4 Research Management Committee. An RMC composed of four (4) representatives from each Party shall be appointed upon signing of this Agreement. The RMC shall be responsible for managing day-to-day work necessary to perform the Research Plan during the Research Period.

3.5 Research Expenses. BI shall make the payments with respect to the funding of the Research Plan in the amounts and at the times described in this Section 3.5:

(a) 1999 research expenses for Isis shall be [***].

(b) Other research expenses relating to the [***] and other expenses approved by the RMC for Isis shall be [***].

(c) 1999 research expenses for BI shall be [***].

(d) With respect to the expenses described in paragraphs (a), (b) and (c) above, BI shall pay Isis [***] on the 45th day after December 31, 1999. Other than the payment expressly set forth in this Section 3.5(d), there shall be no other costs or expenses of any kind with respect to the Research Plan attributable to or payable by BI. Isis shall not be responsible for any research expenses relating to [***] that have not already been paid as of the Effective Date.

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ARTICLE 4.

COLLABORATIVE COSTS

- 4.1 Collaborative Costs for 1998. Notwithstanding the termination of the Collaborative Agreement, the Parties hereby acknowledge and agree that all costs associated with the Collaborative Agreement incurred for calendar year 1998 shall be attributed and paid as provided in this Section 4.1.
- (a) Such 1998 collaborative costs in the amount of [***] shall be attributed to Isis.
- (b) Such 1998 collaborative costs in the amount of [***] shall be attributed to BI.
- (c) With respect to such 1998 collaborative costs, BI hereby agrees to make a cash payment to Isis in the amount of [***] by wire transfer in immediately available funds within ten (10) business days of the Effective Date. Except as expressly provided in this Section 4.1(c), there shall be no other research or development costs associated with the Collaborative Agreement payable by either Party to the other Party for calendar year 1998.
- 4.2 ISIS 2302 Development Costs in 1999. Notwithstanding the termination of the Collaborative Agreement, the Parties hereby acknowledge and agree that costs with respect to the development of ISIS 2302 in calendar year 1999 shall be attributed and paid as provided in this Section 4.2. Except as expressly provided in this Section 4.2, there shall be no other costs payable by either Party to the other Party for development costs related to ISIS 2302 in calendar year 1999. With respect to such development costs, BI hereby agrees to make a cash payment to Isis in the amount of [***] within ten (10) business days of the Effective Date and a cash payment to Isis in the amount of [***] on December 31, 1999, in each case, by wire transfer in immediately available funds.
- 4.3 Future Development Costs of ISIS 2302. There shall be no other costs or expenses of any kind with respect to the development of ISIS 2302 attributable to or payable by BI after December 31, 1999.
- 4.4 Other Costs. Except as expressly set forth in this Agreement, there shall be no other costs or expenses of any kind with respect to the research or development of any compound or product attributable to or payable by either Party.

ARTICLE 5.

REPAYMENT OF ADVANCES

- 5.1 Credit Facility under the Collaborative Agreement. The Parties hereby acknowledge and agree that BI has made Advances to Isis pursuant to Article 7 of the Collaborative Agreement (each, an "Outstanding Obligation"), in the aggregate amount of \$22,576,405, as follows:

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DATE OF ADVANCE -----	AMOUNT OF OUTSTANDING OBLIGATION -----	CREDIT MATURITY DATE ----	INTEREST RATE ----
October 15, 1996	\$8,300,000	October 15, 2003	8.46%
December 30, 1996	\$7,900,000	December 30, 2003	8.36%
June 30, 1997	\$6,376,405	June 30, 2004	8.45%

5.2 Repayment of Outstanding Obligations; No Further Advances. Isis shall repay the principal amount of each Outstanding Obligation to BI in full prior to the respective Credit Maturity Date of each Outstanding Obligation. The Parties expressly acknowledge and agree that BI and its Affiliates have no obligation whatsoever under the Collaborative Agreement or hereunder to make any additional Advances to Isis.

5.3 Interest Rate on Outstanding Obligations. Isis shall pay BI interest on the unpaid principal amount of each Outstanding Obligation at the respective interest rate specified in the column captioned "Interest Rate" in the chart set forth in Section 5.1. Interest shall be due and payable by Isis to BI two (2) times in each calendar year, on May 31st and November 30th, or the first business day thereafter, if any such date shall occur on a non-business day.

5.4 Prepayment of Principal.

(a) Optional Prepayment. Isis may prepay the outstanding principal balance of any Outstanding Obligation, in whole or in part, at any time without penalty or premium; provided, however, that the accrued interest on such prepaid amounts of Outstanding Obligations shall be included in the prepayment of principal on the date of such prepayment.

(b) Mandatory Prepayment. Notwithstanding anything to the contrary set forth in this Agreement, for as long as any Outstanding Obligation is outstanding:

(i) for each fiscal year in which commercial sales of [***] or any compound from out of the [***] series that had been synthesized as of the Effective Date, or any small-molecule compounds covered by the Joint [***] Patent(s) occur, Isis shall prepay the outstanding principal amount of the Outstanding Obligations in an amount calculated for such year equal to [***] of the total royalties received by Isis on such commercial sales during such year as determined based upon the audited year-end financial statements for such year;

(ii) prior to January 1, 2002, for each fiscal year in which commercial sales of ISIS 2302 occur, Isis shall prepay the outstanding principal amount of the Outstanding Obligations in an amount calculated for such year equal to [***] of the net royalties (total royalties received by Isis less the royalty paid by Isis to BI) on such commercial sales during such year as determined based upon the audited year-end financial statements for such year; and

(iii) after January 1, 2002, for each fiscal year in which commercial sales of ISIS 2302 occur, Isis shall prepay the outstanding principal amount of the Outstanding Obligations in an amount calculated for such year equal to [***] of the net royalties (total royalties received by Isis less the royalty paid by Isis to BI) on such commercial sales during such year, as determined based upon the audited year-end financial statements for such year.

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Each mandatory prepayment under this Section 5.4(b) shall be payable within 30 calendar days after completion of Isis' consolidated annual audited year-end financial statements for such year.

5.5 Method of Payment.

(a) All interest on each Outstanding Obligation shall be paid in cash and in U.S. dollars on the dates described in Section 5.3.

(b) All optional prepayments on Outstanding Obligations pursuant to Section 5.4(a) shall be paid in cash in U.S. dollars.

(c) All mandatory prepayments on Outstanding Obligations pursuant to Section 5.4(b) shall be made in cash in U.S. dollars.

(d) All regular repayments of principal on Outstanding Obligations shall be made on the applicable Credit Maturity Date in cash in U.S. dollars and/or, at the option of Isis, in shares of Isis Common Stock, par value U.S.\$0.001 par share, at a price per share equal to [***] of the average Fair Market Value (as such term is defined in the Stock Purchase Agreement) over the [***] trading days preceding the Credit Maturity Date.

(e) Bank Wire. All payments made to BI in immediately available cash funds hereunder shall be addressed and wired to:

Boehringer Ingelheim International GmbH
Corporate Department Pharma Controlling
Citibank AG, Frankfurt/Main, F.R. Germany
Bank Account: 120/3497/004

ARTICLE 6.

RECORDS, REPORTS AND INFORMATION EXCHANGE

- 6.1 Record Keeping. Isis and BI shall each maintain records in sufficient detail and in good scientific and commercial manner appropriate for regulatory, patent, know how, trade secret, other intellectual property and commercial purposes, including but not limited to the calculation of Net Sales, and as shall properly reflect all work done, results achieved and costs expended in the performance of each Party's respective obligations hereunder and under the Collaborative Agreement. Isis and BI shall each provide the other Party the right to inspect and make copies (at such other Party's expense) of all such records to the extent reasonably required for the performance of its obligations and the exercise of its rights under this Agreement.
- 6.2 Technology and Information Transfer. The Parties shall exchange all Isis Background Intellectual Property, BI Intellectual Property and Program Intellectual Property, and shall provide reasonable technical assistance and training to the other, as shall be necessary to carry out the Research Plan. All information transferred, provided or exchanged under this Section 6.2 shall be subject to the confidentiality requirements set forth in Article 9 and may be used and disclosed only to carry out the Research Plan hereunder.
- 6.3 Exchange Rate; Records of Net Sales. All payments with respect to royalties under this Agreement shall be payable [***]. All royalty payments to Isis shall be calculated in U.S. dollars on the last business day of each quarter or such pro rata share thereof as is then applicable, using the applicable exchange

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rates for such date published in the Wall Street Journal. All royalty payments to BI shall be calculated in Deutsche Mark or Euros, at the written request of BI prior to the date of calculation, on the last business day of each quarter or such pro rata share thereof as is then applicable, using the applicable exchange rates for such date published in the Wall Street Journal. Both parties shall keep complete and accurate records (including Net Sales information on a country-by-country basis) in sufficient detail to enable the amounts payable to be determined.

- 6.4 Right to Audit. Upon written request, each Party shall have the right to have an independent audit of Net Sales by the other Party and its Affiliates performed once after each calendar year on an aggregated country-by-country basis and on a country-by-country basis for Major Market Countries. As used in this Agreement, "Major Market Countries" shall mean the United States, Germany, France, Italy, Japan and the United Kingdom. Internal auditors or independent public accountants selected by each Party and acceptable to the other shall conduct such verification at the respective Party's expense and during regular business hours. With respect to Net Sales by a Party's licensees (including sub-licensees), the other Party shall have the right to request an audit of the Net Sales by such licensees and/or sub-licensees, at such requesting Party's expense, once after each calendar year on an aggregated country-by-country basis and on a country-by-country basis for Major Market Countries, in which case the Party receiving such request to audit shall promptly cause an audit to be undertaken of Net Sales made by its licensees and/or sub-licensees and promptly deliver the results of such audit to the Party requesting same. Any discrepancies of 5% or less shall not be considered material.

ARTICLE 7.

INTELLECTUAL PROPERTY RIGHTS

- 7.1 Ownership of Background Intellectual Property. The rights to BI Background Intellectual Property and Isis Background Intellectual Property shall remain the property of the respective Party which owned such rights at the date of execution of this Agreement. Each Party hereby acknowledges and agrees that it shall have no rights to the other Party's Background Intellectual Property other than the licensed rights specifically granted herein.
- 7.2 Ownership of Joint Intellectual Property. The rights to all Program Intellectual Property that are discovered, made or conceived during and as a result of the Research Plan solely by employees of one Party or by others acting on behalf of the same Party shall be owned by that Party. The rights to all Program Intellectual Property that is discovered, made or conceived during and as a result of the Research Plan jointly by employees of BI and Isis or others acting on their behalf shall be jointly owned by BI and Isis. Each Party shall disclose to the other Party the making, conception or reduction to practice of Program Intellectual Property by employees or others acting on behalf of such Party. Inventorship shall be determined in accordance with common international practice.
- 7.3 Joint [***] Intellectual Property. The Parties acknowledge and agree that the only joint intellectual property resulting from the Research Program (as such term is defined in the Collaborative Agreement) was the Joint [***] Patent(s) (as such term is defined herein). The Parties' agreement with respect to royalties relating to the Joint [***] Patent(s) are set forth in Section 2.4. The Parties' agreements with respect to the filing and prosecution of the Joint [***] Patent(s) and other matters are set forth in Article 13.

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ARTICLE 8.

GRANT OF LICENSES

- 8.1 Grant of License by BI to Isis. BI hereby agrees to grant and grants to Isis a worldwide, royalty-free license to the BI Background Intellectual Property and the Program Intellectual Property, owned or controlled by BI solely for the purpose of allowing Isis to carry out the Research Plan, as provided herein. Such license shall terminate upon the termination of the Research Period.
- 8.2 Grant of License by Isis to BI. Isis hereby agrees to grant and grants to BI a worldwide, royalty-free license to the Isis Background Intellectual Property and the Program Intellectual Property, owned or controlled by Isis solely for the purpose of allowing BI to carry out the Research Plan, as provided herein. Such license shall terminate upon the termination of the Research Period.
- 8.3 Characteristics of Licenses. The licenses granted under Sections 8.1 and 8.2 shall be exclusive for the purposes for which they are granted, except as to the Party granting the license, which shall retain all rights necessary to conduct the activities contemplated by this Agreement and to use the intellectual property freely. Notwithstanding the above, the Parties shall have the right to grant sublicenses to Affiliates.
- 8.4 Non-Use of Intellectual Property. Each of BI and Isis hereby covenants and agrees that it shall not, nor shall it cause its Affiliates to, use directly or indirectly any Isis Background Intellectual Property (in the case of BI) or BI Background Intellectual Property (in the case of Isis) or Program Intellectual Property (in both cases) for any purpose other than to conduct activities under this Agreement during the Research Period.

ARTICLE 9.

CONFIDENTIALITY

- 9.1 Confidentiality. Each Party hereto shall maintain in confidence all Confidential Information disclosed by the other Party hereto. Neither Party shall use, disclose or grant use of such Confidential Information except as expressly authorized by this Agreement and/or without the prior written consent of the other Party. To the extent that disclosure is authorized by this Agreement, the disclosing Party shall obtain prior agreement from its employees, agents, consultants or clinical investigators and designated permitted sublicensees to whom disclosure is to be made to hold in confidence and not make use of such Confidential Information for any purpose other than those permitted by this Agreement. Each Party shall use at least the same standard of care as it uses to protect its own trade secrets or proprietary information to ensure that such employees, agents, consultants and clinical investigators do not disclose or make any unauthorized use of such Confidential Information. Each Party shall promptly notify the other upon discovery of any unauthorized use or disclosure of the Confidential Information.
- 9.2 Authorized Disclosure. Each Party may disclose the Confidential Information to the extent such disclosure is reasonably necessary in filing or prosecuting patent applications, prosecuting or defending litigation or complying with applicable governmental regulations, or achieving the purposes of this Agreement; provided that, if such Party is required to make any such disclosure of the Confidential Information, it shall to the extent practicable give reasonable advance notice to the other Party of such disclosure requirement and, except to the extent inappropriate in the case of patent applications, shall use reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed.

ARTICLE 10.

TERM; TERMINATION

- 10.1 Term. This Agreement shall commence as of the Effective Date and, unless sooner terminated, as provided hereunder, shall continue in effect until such date as no royalties shall be payable to any Party hereunder.
- 10.2 Termination for Breach. In the event either Party breaches a material obligation under this Agreement, and such breach is not cured within 90 days of written notice thereof, the non-breaching Party shall not have the right to terminate this Agreement, but shall have the right only to pursue an action for damages, arising as a result of such breach pursuant to Article 15, and this Agreement shall continue in full force and effect, including all licenses and funding obligations hereunder.
- 10.3 Accrued Rights, Surviving Obligations. Termination, relinquishment or expiration of this Agreement or any part thereof for any reason shall be without prejudice to any rights that shall have accrued to the benefit of either Party prior to such termination, relinquishment or expiration, including damages arising from any breach hereunder. Such termination, relinquishment or expiration shall not relieve either Party from obligations that are expressly indicated to survive termination or expiration of this Agreement.
- 10.4 Survival. Section 2.2, Section 2.3, Section 2.4, Section 2.5, Section 3.4, Article 4, Article 5, Section 6.4, Article 7, Article 9, Article 13, Article 14 and Article 15 shall survive the termination of this Agreement.

ARTICLE 11.

REPRESENTATIONS AND WARRANTIES

Each Party hereby represents and warrants to the other that:

- 11.1 Corporate Power. Such Party is duly organized and validly existing under the laws of the jurisdiction of its incorporation and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof.
- 11.2 Due Authorization. Such Party is duly authorized to execute and deliver this Agreement and to perform its obligations hereunder.
- 11.3 Binding Agreement. This Agreement is a legal and valid obligation binding upon it and enforceable in accordance with its terms. 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 it is a Party or by which it may be bound, nor violate any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over it.
- 11.4 No Conflict. Such Party has not granted any licenses or rights to any other person which would restrict or conflict with or prevent such Party from granting the rights granted to the other Party pursuant to this Agreement.

ARTICLE 12.

PUBLICATIONS

12.1 Publications

(a) During the term of this Agreement, Isis and BI each acknowledge the other Party's interest in publishing certain of its results to obtain recognition within the scientific community and to advance the state of scientific knowledge. Accordingly, each Party shall have the right to publish such results pertaining to its own products or intellectual property without the prior review or consent of the other Party; provided, however, that each Party hereby agrees to exercise good scientific practice with respect to any publications involving joint authorship and, in the case of joint authorship, to provide the other Party with notice and a copy of such proposed publication sixty (60) days prior to such publication.

(b) Notwithstanding paragraph (a) of this Section 12.1, with respect to CS-11, an integrated clinical trial report shall be prepared in accordance with the study protocol. BI and Isis shall each have the right to review the final manuscript at least four (4) weeks prior to submission for publication.

ARTICLE 13.

PATENTS

13.1 Filing, Prosecution and Maintenance of the Joint [***] Patent(s). With respect to the Joint [***] Patent(s), Isis shall have the right, but not the obligation, to file, prosecute and maintain the Joint [***] Patent(s) and to pay the costs and expenses related thereto. If, however, Isis fails to file, prosecute or maintain the Joint [***] Patent(s) within a reasonable amount of time, then BI shall have the right, but not the obligation, to file, prosecute and maintain the Joint [***] Patent(s) and to pay the costs and expenses related thereto. Each of the Parties hereto shall consult with the other Party as to the filing, prosecution and maintenance of the Joint [***] Patent(s), shall furnish to the other Party copies of documents relevant to any filing, prosecution or maintenance sufficiently prior to filing such document or making any payment due thereunder to allow for review and comment by the other Party, and shall seriously consider all such comments.

13.2 Filings. With respect to any patent applications filed or to be filed with respect to any intellectual property conceived, created or developed either under the Collaborative Agreement or during and as part of the Research Plan, (a) BI shall be responsible for filing and prosecuting such application on such intellectual property owned solely by BI (each, a "BI Application or Patent") and paying the costs and expenses related thereto and (b) Isis shall be responsible for filing and prosecuting such application on such intellectual property owned solely by Isis (each, an "Isis Application and Patent") and paying the costs and expenses related thereto. Except as provided in Section 13.1, with respect to any such intellectual property jointly owned by BI and Isis (each, a "Joint Application or Patent"), (X) for any Joint Application or Patent relating or pertaining to small molecules, BI shall be responsible for filing such Joint Application or Patent and paying the costs and expenses related thereto; (Y) for any Joint Application and Patent relating or pertaining to Antisense Molecules or Ibis technology, Isis shall be responsible for filing and prosecuting such Joint Application or Patent and paying the costs and expenses related thereto; and (Z) for any Joint Application or Patent relating or pertaining to both small molecules, on the one hand, and Antisense Molecules or Ibis technology, on the other, or to none of small molecules,

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Antisense Molecules or Ibis technology, the Parties shall negotiate on a case-by-case basis which Party shall be responsible for filing and prosecuting such application and paying the costs and expenses related thereto.

- 13.3 Filing, Prosecution and Maintenance. The Party selected for filing a given Joint Application or Patent pursuant to Section 13.2 shall have the right, but not the obligation, to file, prosecute and maintain such Joint Application or Patent and to pay the costs and expenses related thereto. If, however, such Party fails to file, prosecute or maintain a given Joint Application or Patent within a reasonable amount of time, the other non-filing Party shall have the right, but not the obligation, to file, prosecute and maintain such Joint Application or Patent and to pay the costs and expenses related thereto. Each of the Parties hereto shall consult with the other Party as to the filing, prosecution and maintenance of each Joint Application or Patent, shall furnish to the other Party copies of documents relevant to any filing, prosecution or maintenance sufficiently prior to filing such document or making any payment due thereunder to allow for review and comment by the other Party, and shall seriously consider all such comments.

ARTICLE 14.

INDEMNIFICATION

- 14.1 Indemnification for Products. Unless otherwise provided herein, each Party agrees to indemnify and hold the other Party harmless, from and against all Third Party claims, demands, liabilities, damages and expenses (including attorney's fee) arising out of such Party's, its Affiliates or agents, research, development, manufacture, use, handling, storage, commercialization or sale of ISIS 2302 or any Additional Compound, but only to the extent such claims, demands and the like result from the negligence of the indemnifying Party, its Affiliates or agents and not to result from the negligence of the Party seeking to be indemnified. The Party providing the indemnity shall have the right to conduct the defense. Notwithstanding the foregoing, neither Party shall be responsible for any Third Party claims, demands, liabilities, damages and expenses (including attorney's fees) which may arise out of the use by the other Party of any information and data received by the other Party from it, its Affiliates and/or its licensees or sublicensees. In the event either Party receives notice of a claim with respect to ISIS 2302 or any Additional Compound, such Party shall inform the other as soon as reasonably practicable and the Parties shall confer in good faith as to how best to handle the claim in an efficient and equitable manner.

ARTICLE 15.

DISPUTE RESOLUTION; GOVERNING LAW

- 15.1 Dispute Resolution. In case of any possible disputes arising out of or relating or pertaining to the Collaborative Agreement and/or this Agreement, the Parties shall use their reasonable best efforts to try to settle those disputes amicably and, if unsuccessful, shall submit the matter for review under the Rules of Conciliation and Arbitration of the International Chamber of Commerce by one or more arbitrators appointed in accordance with said Rules. If resolution of such disputes satisfactory to both Parties cannot be reached in this manner, then either Party shall have the right to bring an action to resolve such dispute before a court of jurisdiction where the Party being sued maintains its principal executive offices.
- 15.2 Governing Law. This Agreement shall be governed and construed in accordance with the laws of the State of New York.

ARTICLE 16.

MISCELLANEOUS

- 16.1 Taxes. In the event a Party paying a royalty hereunder is required to withhold taxes imposed upon the Party receiving a royalty by virtue of the statutes, laws, codes or governmental regulations of a given country in which products subject to such royalties are sold, then such payments shall be made by the royalty-paying Party on behalf of the other Party by deducting them from the royalty payment due such other Party and remitting such taxes to the proper authorities on a timely basis; and the royalty payments provided for under this Agreement shall be adjusted appropriately, provided that the royalty-paying Party supplies the other Party with official documentation and/or tax receipts on such withholdings supporting such taxes and such payments as may be required by such other Party for its tax records.
- 16.2 Export. In order to comply with the United States Export Administration Act of 1979, as amended from time to time (the "Export Act"), each Party hereby certifies that no technology or information licensed from the other, and no product thereof, shall be made available or re-exported, directly or indirectly, to any areas outside the United States except in compliance with all applicable laws and regulations of the Bureau of Export Administration in accordance with the Export Act. BI shall give Isis such written assurance against re-export as required by the Export Act.
- 16.3 Force Majeure. Neither Party shall be held liable or responsible to the other Party nor be deemed to have defaulted under or breached this Agreement for failure or delay in fulfilling or performing any term of this Agreement when such failure or delay is caused by or results from causes beyond the reasonable control of the affected Party, including but not limited to fire, floods, embargoes, war, act of war (whether war be declared or not), insurrections, riots, civil commotions, strikes, lockouts or other labor disturbances, acts of God or acts, omissions or delays in acting by any governmental authority or the other Party; provided, however, it is understood that this Section 16.3 is intended only to suspend and not discharge a Party's obligations under this Agreement and that when the causes of the failure or delay are removed or alleviated, the affected Party shall resume performance of its obligations hereunder.
- 16.4 Assignment. This Agreement may not be assigned or otherwise transferred nor, except as expressly provided hereunder, may any right or obligations hereunder be assigned or transferred, by either Party without the written consent of the other Party; provided, however, that either Isis or BI may, without such consent, assign this Agreement and its rights and obligations thereunder to a wholly-owned subsidiary. Isis and BI may elect to assign this Agreement (a) in connection with the transfer or sale of all or substantially all of its business to which this Research Plan is related, if such assets include substantially all of the assets relating to its performance of its respective obligations hereunder, or (b) in the event of its merger or consolidation with another company at any time during the term of this Agreement. Each Party shall promptly inform the other of the identity and location of any permitted assignee. Any purported assignment in violation of the preceding sentence shall be void. Any permitted assignee shall assume all obligations of its assignor under this Agreement.
- 16.5 Severability. In case any provision contained in this Agreement shall be held to be invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein shall not in any way be affected or impaired thereby.

16.6 Notices. All notices, requests, consents and other communications hereunder shall be in writing, shall be delivered personally, by facsimile transmission or mailed by first-class registered or certified airmail or by internationally recognized overnight express courier, postage prepaid, and shall be deemed given upon personal delivery, upon confirmation of receipt of such facsimile transmission or on the 10th day following such mailing and shall be addressed as follows:

if to Isis, to:

Isis Pharmaceuticals, Inc.
2292 Faraday Drive
Carlsbad, California 92008
Attn.: Ms. B. Lynne Parshall
Executive Vice President

or to such other person at such other address as Isis shall designate to BI in writing; and

if to BI, to:

Boehringer Ingelheim International GmbH
Postbox 200
D 55216 Ingelheim/Rhein
Federal Republic of Germany
Attn.: Corporate Division Pharma Business Development
Telephone: 49 61 32 77 2430
Telecopy: 49 61 32 77 3926

with copy to

Boehringer Ingelheim International GmbH
Postbox 200
D 55216 Ingelheim/Rhein
Federal Republic of Germany
Attn.: Head of Corporate Legal Department
Telephone: 49 61 32 77 2106
Telecopy: 49 61 32 77 4080

or to such other person(s) at such other address(es) as BI shall designate to Isis in writing.

16.7 Entire Agreement. This Agreement constitutes the full and entire understanding and agreement among the Parties with regard to the subjects hereof and no Party shall be liable or bound to any other Party in any manner by any representations, warranties, covenants, or agreements except as specifically set forth herein or therein. Nothing in this Agreement, expressed or implied, is intended to confer upon any Party, other than the Parties hereto and their respective successors and assigns, any rights, remedies, obligations, or liabilities under or by reason of this Agreement, except as expressly provided herein.

16.8 Amendment and Waiver. Any term of this Agreement may be waived or amended in a writing agreed to by Isis and BI.

16.9 Headings. The headings of the various sections of this Agreement have been inserted for convenience of reference only and shall not be deemed to be part of this Agreement.

- 16.10 Independent Contractors. It is expressly agreed that Isis and BI shall be independent contractors and that the relationship between the two Parties shall not constitute a partnership or agency of any kind. Neither Isis nor BI shall have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on the other, without the prior written authorization of the Party to do so.
- 16.11 Waiver. This waiver by either Party hereto of any right hereunder or the failure to perform or of a breach by the other Party shall not be deemed a waiver of any other right hereunder or of any other breach or failure by said other Party whether of a similar nature or otherwise.
- 16.12 English language. The official text of this Agreement or any notices given or accounts or statements required shall be in English.
- 16.13 Public Announcements. Isis and BI shall consult with each other before issuing any press release or otherwise making any public statements or disclosures with respect to the transactions contemplated by this Agreement or by that certain Amendment to the Stock Purchase Agreement, dated as of August 31, 1999, by and between Isis and BI, and shall not issue any such press release or make any such public statement or disclosure prior to such consultation, except as may be required by applicable law.

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

ISIS PHARMACEUTICALS, INC.

By: _____
Name:
Title:

BOEHRINGER INGELHEIM INTERNATIONAL GmbH

By: _____
Name:
Title:

By: _____
Name:
Title:

APPENDIX A

DEFINITIONS

- - "Additional Compounds" shall mean, collectively, the compounds known as [***] and any compound from out of the [***] series that had been synthesized as of the Effective Date, the compounds known as [***].
- - "Advance" shall have the meaning set forth in Article 7 of the Collaborative Agreement.
- - "Affiliate" shall mean any corporation or other entity which controls, is controlled by, or is under common control with a Party to this Agreement. A corporation or other entity shall be regarded as in control of another corporation or entity if it owns or directly or indirectly controls more than fifty percent (50%) of the voting stock or other ownership interest of the other corporation or entity, or if it possesses, directly or indirectly, the power to direct or cause the direction of the management and policies of the corporation or other entity or the power to elect or appoint fifty percent (50%) or more of the members of the governing body of the corporation or other entity.
- - "Agreement" shall mean this Agreement, dated as of August 31, 1999, by and between BI and Isis, including all appendices, exhibits and schedules attached hereto.
- - "Antisense Molecule" shall mean [***]. An "oligonucleotide" may include [***].
- - "Bankruptcy" shall have the meaning set forth in the Stock Purchase Agreement.
- - "BI Background Intellectual Property" shall mean all issued patents and patent applications owned or controlled by BI or any of its Affiliates, together with any reissues, reexamination certificates, divisions, continuations or continuations-in-part and extensions (patent term restoration, supplementary protection certificate, etc.) thereof and know-how necessary or useful to carry out the Research Plan.
- - "Change in Control" shall have the meaning set forth in the Stock Purchase Agreement.
- - "Collaborative Agreement" shall mean that certain Collaborative Agreement, dated as of July 18, 1995, between Boehringer Ingelheim International GmbH and its Affiliates and Isis and the appendices, exhibits and schedules thereto, as amended.
- - "Confidential Information" means any confidential information, trade secrets, know how and any other information relating to any research project, work in process, future development, scientific engineering, manufacturing, marketing, business plan, financial or personnel matter relating to either Party, whether under the Collaborative Agreement or this Agreement, such Party's present or future products, sales suppliers, customers, employees, investors or business, whether in oral, written, graphic or electronic form. Confidential Information shall not include:

*CONFIDENTIAL TREATMENT REQUESTED

(a) information already known to the receiving Party, other than under an obligation of confidentiality, at the time of disclosure by the other Party;

(b) information generally available to the public or otherwise part of the public domain at the time of its disclosure to the other Party,

(c) information that became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the receiving Party in breach of this Agreement;

(d) information disclosed to the receiving Party, other than under an obligation of confidentiality, by a Third Party who had no obligation to the other Party not to disclose such information to others.

The Parties agree that the material financial terms of this Agreement shall also be considered Confidential Information of both Parties. The ownership and control of all Confidential Information relating or pertaining to Antisense Molecules shall be deemed to have been transferred to Isis hereunder and the ownership and control of all Confidential Information relating or pertaining to small molecules shall be deemed to have been transferred to BI hereunder in a manner consistent with the treatment of Additional Compounds pursuant to Section 2.3.

- - "Credit Maturity Date" means, as to each Advance, the date seven (7) years after the date upon which such Advance was made pursuant to the Collaborative Agreement.
- - "Field" shall mean the identification, optimization and development of molecules which interfere with the normal process of leucocyte adhesion to cellular and extracellular substrates to be used in the treatment of immune and non-immune based inflammatory diseases. Specifically included within the Field are (a) Antisense Molecules which directly inhibit the expression of ICAMs, VCAM-1, PECAM-1, selectins and (beta)2 integrins, (b) compounds which modulate the interaction of leucocyte integrins, with their respective binding ligands and the interaction of selectins with their binding structures, (c) non-antisense compounds which modulate the expression of ICAMs, VCAM-1, PECAM-1, selectins and leucocyte integrins by interfering with an intracellular process, and (d) compounds which inhibit the shedding of selectins, ICAMs, VCAM-1, and PECAM-1 from the cell surface.
- - "Isis Background Intellectual Property" shall mean all issued patents and patent applications owned or controlled by Isis or any of its Affiliates, together with any reissues, reexamination certificates, divisions, continuations or continuations-in-part and extensions (patent term restoration, supplementary protection certificate, etc.) thereof and know-how necessary or useful to carry out the Research Plan.
- - "Joint [***] Patent(s)" shall mean all joint issued patents and joint patent applications, together with any reissues, reexamination certificates, divisions, continuations or continuations-in-part and extensions (patent term restoration, supplementary protection certificate, etc.) thereof relating to antagonism of [***] activity covered by the Collaborative Agreement.
- - "Net Sales" shall mean the gross invoiced price charged by BI or Isis (as appropriate) or its respective Affiliates or licensees (including sub-licensees), as the case may be, for a given product to an independent Third Party less the following customary deductions:

*CONFIDENTIAL TREATMENT REQUESTED

- (i) trade and quantity discounts actually granted;
- (ii) credits for returns or allowances;
- (iii) the amount of any sales tax or other taxes assessed directly on the sale of such product which is not refunded;
- (iv) charge back payments or rebates granted to managed health care organizations or federal, state and local governments, their agencies, purchasers and reimbursers.

In the case of sales of a given product by a Party's licensee or sub-licensee under an agreement in the ordinary course of a Party's business containing terms customary for the pharmaceuticals industry, if net sales are calculated under such agreement differently than Net Sales are calculated hereunder, "Net Sales" hereunder shall be deemed to be calculated in the manner calculated under the applicable agreement, provided that such calculation of net sales shall be reasonably consistent with this definition of "Net Sales." Each Party shall be obligated to notify the other Party on a timely basis of the method of calculation of net sales under all such agreements with licensees or sub-licensees.

- - "Party" shall mean BI or Isis and "Parties" shall mean BI and Isis collectively.
- - "Program Intellectual Property" shall mean all patents and patent applications together with any reissues, reexamination certificates, divisions, continuations or continuations-in-part and extensions (patent term restoration, supplementary protection certificate, etc.) thereof and know-how conceived, created or developed by either Party, solely or jointly, during and as part of the Research Plan.
- - "Research Management Committee" (RMC) shall mean the joint committee composed of an equal number of representatives of BI and Isis responsible for overseeing the Research Plan as described in Section 3.4 of this Agreement.
- - "Research Period" shall mean the time period commencing on the Effective Date and ending on December 31, 1999.
- - "Research Plan" shall mean a description of the activities as defined by the RMC to be performed by BI and Isis during the Research Period of the Research Plan, consisting of the design and performance of experiments for the purpose of evaluating the Ibis technology and functional genomics using antisense technology.
- - "Stock Purchase Agreement" shall mean that certain Stock Purchase Agreement, dated July 18, 1995, between Isis and BI.
- - "Third Party" shall mean any entity other than Isis and BI and their respective Affiliates and licensees (which shall include sub-licensees).

AMENDMENT TO THE STOCK PURCHASE AGREEMENT

This AMENDMENT TO THE STOCK PURCHASE AGREEMENT (this "Amendment"), made this 31st day of August, 1999, by and between Isis Pharmaceuticals, Inc., a Delaware corporation ("Isis"), and Boehringer Ingelheim International GmbH, a German corporation ("Boehringer"),

W I T N E S S E T H :

WHEREAS, Isis and BI entered into that certain stock purchase agreement, dated as of July 18, 1995 (the "Stock Purchase Agreement");

WHEREAS, Paragraph 11.5 of the Stock Purchase Agreement provides that any term thereof may be amended in a writing agreed to by Isis and Boehringer; and

WHEREAS, Isis and Boehringer have agreed to amend the Stock Purchase Agreement as provided herein,

NOW, THEREFORE, in consideration of the mutual agreements and covenants set forth herein, and for other good and valuable consideration, the parties hereby agree that the Stock Purchase Agreement shall be amended as of the date hereof as follows:

Section 1. Sub-paragraphs (b), (c) and (d) of Paragraph 3.1 and the final paragraph of Paragraph 3.1 of the Stock Purchase Agreement (Agreement to Sell and Purchase the Additional Shares) shall be deleted in their entirety.

Section 2. Paragraph 3.2 of the Stock Purchase Agreement (Delivery of Additional Shares at a Subsequent Closing; Purchase price) shall be deleted in its entirety.

Section 3. The first sentence of Paragraph 10 of the Stock Purchase Agreement (Termination) shall be amended to read in its entirety as follows:

This Agreement shall terminate upon (i) any Change in Control of Isis, (ii) the Bankruptcy of Isis or (iii) the termination of the New Agreement pursuant to Article 10 thereof.

Section 4. Sub-paragraph (e) of Paragraph 8.1 (Board Representation) is amended in its entirety to read as follows:

- (e) Paragraph 8.1 shall terminate upon the earliest to occur of:
 - (i) May 1, 2000;
 - (ii) The effectiveness of any Change in Control; or
 - (iii) Boehringer ceases to hold at least 2,000,000 shares of

Common Stock (appropriately adjusted for stock splits, stock dividends, recapitalization and the like). If Paragraph 8.1 terminates, the BI Designate shall resign from the Board.

Section 5. In Exhibit A, the definition of "Additional Shares shall be amended to read in its entirety as follows:

"ADDITIONAL SHARES" shall mean the shares issued to Boehringer Ingelheim under Paragraph 3.1 of the Agreement prior to the effective date of the Amendment.

Section 6. Exhibit A shall be amended by the addition of the following definitions:

"AMENDMENT" shall mean that certain Amendment to the Stock Purchase Agreement, dated August 31, 1999, by and between Isis and Boehringer.

"NEW AGREEMENT" shall mean that certain Agreement, dated as of August 31, 1999, by and between Boehringer and Isis.

Section 7. This Amendment shall be governed by and construed in accordance with the laws of the State of Delaware and the federal law of the United States of America.

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

ISIS PHARMACEUTICALS, INC.

By: _____
Name:
Title:

BOEHRINGER INGELHEIM INTERNATIONAL GMBH

By: _____
Name:
Title:

By: _____
Name:
Title: