

SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

SCHEDULE 13D
(Rule 13d-101)

INFORMATION TO BE INCLUDED IN STATEMENTS FILED PURSUANT
TO RULE 13d-1(a) AND AMENDMENTS THERETO FILED PURSUANT TO
RULE 13d-2(a)

(AMENDMENT NO. 2)

ISIS PHARMACEUTICALS, INC.

(Name of Issuer)

COMMON STOCK, PAR VALUE \$0.001 PER SHARE

(Title of Class of Securities)

464330 10 9

(CUSIP Number)

HANS-PETER MUELLER
BOEHRINGER INGELHEIM INTERNATIONAL GmbH
BINGER STRASSE 173
D-55216 INGELHEIM AM RHEIN, GERMANY
011-49-61-32-77-2414
AND
KLAUS H. JANDER, ESQ.
ROGERS & WELLS LLP
200 PARK AVENUE
NEW YORK, NY 10166
(212) 878-8000

(Name, Address and Telephone Number of Person
Authorized to Receive Notices and Communications)

AUGUST 31, 1999

(Date of Event Which Requires Filing of This Statement)

If the filing person has previously filed a statement on
Schedule 13G to report the acquisition that is the subject of this
Schedule 13D, and is filing this schedule because of Rule 13d-1(e),
13d-1(f) or 13d-1(g), check the following box

Note. Schedules filed in paper format should include a signed
original and five copies of the schedule, including all exhibits. See
Rule 13d-7(b) for the other parties to whom copies are to be sent.

(Continued on following pages)

(Page 1 of 8 Pages)
(Exhibit begins at Page 6)

CUSIP No. 464330 10 9

13D

Page 2 of 8 Pages

1. NAMES OF REPORTING PERSONS
S.S. OR I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)

Boehringer Ingelheim International GmbH

2. CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP

(a)
(b)

3. SEC USE ONLY

4. SOURCES OF FUNDS

00

5. CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEM 2(d) OR 2(e)

6. CITIZENSHIP OR PLACE OF ORGANIZATION

Federal Republic of Germany

7. SOLE VOTING POWER

NUMBER OF
UNITS
BENEFICIALLY
OWNED BY
EACH
REPORTING
PERSON WITH

2,412,607

8. SHARED VOTING POWER

0

9. SOLE DISPOSITIVE POWER

2,412,607

10. SHARED DISPOSITIVE POWER

0

11. AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON

2,412,607

12. CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES

13. PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11)

8.8%

14. TYPE OF REPORTING PERSON

CO

SCHEDULE 13D
FILED PURSUANT TO RULE 13d-1
OF THE GENERAL RULES AND REGULATIONS UNDER
THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

This Amendment No. 2, which relates to shares of the common stock, par value \$0.001 per share (the "Common Stock") of Isis Pharmaceuticals, Inc. (the "Issuer") and is being filed by Boehringer Ingelheim International GmbH, supplements and amends the statement on Schedule 13D, originally filed with the Commission on July 28, 1995, as amended by Amendment No. 1, filed with the Commission on December 23, 1996.

ITEM 4. PURPOSE OF THE TRANSACTION.

The first paragraph of Item 4 is amended to read in its entirety as follows:

The Initial Shares and the Additional Shares were acquired in connection with a collaboration between the Issuer and Boehringer Ingelheim in the research, development and commercialization of potential products in the field of cellular adhesion for the treatment of immune and non-immune based inflammatory diseases. By purchasing the shares, Boehringer Ingelheim originally desired in part to assist the Issuer in financing its share of the costs of such collaborative research, development and commercialization. Boehringer Ingelheim and the Issuer have mutually agreed, effective as of August 31, 1999, that a portion of their research collaboration will continue to be funded by Boehringer Ingelheim only through December 31, 1999. Other than royalty payments that the Issuer and Boehringer Ingelheim will be obligated to pay one another and Isis's repayment of loans made by Boehringer Ingelheim, the development and commercialization aspects of the collaboration have ended.

Item 4 is further amended by the addition of the following:

On August 31, 1999 Boehringer and Ingelheim entered into an Amendment to the Stock Purchase Agreement (the "Amendment"), a copy of which is filed herewith as Exhibit B.

Pursuant to the Amendment, the provisions under the Stock Purchase Agreement obligating the Issuer to sell, and Boehringer Ingelheim to purchase, Additional Shares have been deleted. Under the Amendment, Boehringer Ingelheim's right to designate a director to the Issuer's board of directors will terminate upon the earliest to occur of May 1, 2000, the effectiveness of a change-of-control of the Issuer, or Boehringer Ingelheim's ceasing to hold at least 2,000,000 shares of Common Stock.

The above summary of the terms of the Amendment does not purport to be a complete summary of the Amendment and is qualified in its entirety by reference to Exhibit B.

In addition, Dr. Burkhard Blank, Boehringer Ingelheim's designee on the Issuer's board of directors, has informed Boehringer Ingelheim and the Issuer that he is resigning from the board. Boehringer Ingelheim has decided to relinquish its right to nominate a member of the Issuer's board.

ITEM 6. CONTRACTS, ARRANGEMENTS, UNDERSTANDINGS OR RELATIONSHIPS WITH RESPECT TO SECURITIES OF THE ISSUER.

Item 6 is amended by the addition of the following:

As stated above, on August 31, 1999 Boehringer and Ingelheim entered into the Amendment, which is described in Item 4.

ITEM 7. MATERIAL TO BE FILED AS EXHIBITS.

Exhibit A. Stock Purchase Agreement, dated July 18, 1995, between the Issuer and Boehringer Ingelheim.*

Exhibit B. Amendment to the Stock Purchase Agreement, dated August 31, 1999, between the Issuer and Boehringer Ingelheim.

*Filed as an exhibit to the Issuer's Current Report on Form 8-K on July 27, 1995, and incorporated herein by reference.

SIGNATURES

After reasonable inquiry and to the best of my knowledge and belief, I certify that the information set forth in this statement is true, complete and correct.

Dated: August 31, 1999

BOEHRINGER INGELHEIM INTERNATIONAL GmbH

By: /s/ Burkhard Blank

Name: Burkhard Blank
Title: Authorized Signatory

By: /s/ Hans-Peter Mueller

Name: Hans-Peter Mueller
Title: Authorized Signatory

EXHIBIT B

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: