

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. 4)

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.
CLIFFORD CHANCE 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)

JULY 5, 2000

(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 5 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

1,805,407

NUMBER OF
UNITS
BENEFICIALLY
OWNED BY
EACH
REPORTING
PERSON WITH

8. SHARED VOTING POWER

0

9. SOLE DISPOSITIVE POWER

1,805,407

10. SHARED DISPOSITIVE POWER

0

11. AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON

1,805,407

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

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

4.71%

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. 4, 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 ("Boehringer"), 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, Amendment No. 2, filed with the Commission on September 2, 1999, and Amendment No. 3 filed with the Commission on June 12, 2000.

ITEM 5. INTEREST IN THE SECURITIES OF THE ISSUER.

Item 5 is hereby amended to read in its entirety as follows:

(a) Beneficial Ownership: 1,805,407

Percentage Ownership: 4.71%

(b) Sole Voting Power: 1,805,407

Shared Voting Power: -0-

Sole Dispositive Power: 1,805,407

Shared Dispositive Power: -0-

(c) Recent Transactions: The following table sets forth sales of shares of Common Stock by Boehringer since June 5, 2000. Such sales were effected on the open market over the Nasdaq Stock Market by a broker.

| DATE | AMOUNT OF SHARES | APPROXIMATE PRICE PER SHARE (exclusive of commissions) |
|---------|---------------------|--|
| ----- | ----- | ----- |
| 6/6/00 | 40,000 | \$11.2500 |
| 6/8/00 | 5,800 | \$13.0000 |
| 6/13/00 | 200 | \$13.2500 |
| 6/14/00 | 1,500 | \$13.1250 |
| 6/19/00 | 20,000 | \$13.0000 |
| 6/20/00 | 20,000 | \$13.5000 |
| 6/21/00 | 20,000 | \$14.0622 |
| 6/22/00 | 9,000 | \$14.0000 |
| 6/26/00 | 20,000 | \$13.0187 |
| 6/28/00 | 20,000 | \$13.0078 |
| 6/29/00 | 20,000 | \$13.0000 |
| 6/30/00 | 20,000 | \$14.2500 |
| 7/3/00 | 8,200 | \$14.5625 |
| 7/5/00 | 20,000 | \$14.2538 |

(d) Right to Receive Dividends: Not Applicable

(e) Ownership below 5%: Boehringer ceased to be the beneficial owner of more than 5% of the outstanding Common Stock on June 22, 2000.

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: July 11, 2000

BOEHRINGER INGELHEIM INTERNATIONAL GmbH

By: /s/ Mueller
Name: Mr. Mueller
Title: Authorized Signatory

By: /s/ Schoeberl
Name: Dr. Schoeberl
Title: Authorized Signatory