

SECURITIES AND EXCHANGE COMMISSION  
WASHINGTON, D.C. 20549

SCHEDULE 13D

UNDER THE SECURITIES EXCHANGE ACT OF 1934

AMENDMENT NO. 1

ISIS PHARMACEUTICALS, INC.  
(NAME OF ISSUER)

COMMON STOCK, \$.001 PAR VALUE  
(TITLE OF CLASS OF SECURITIES)

464330 10 9  
(CUSIP NUMBER)

DR. CHRISTIAN HAUKE  
HANS-PETER MULLER  
BOEHRINGER INGELHEIM INTERNATIONAL GmbH  
POSTBOX 200  
D-55216 INGELHEIM AM RHEIN  
GERMANY  
011 49 61 32 77 2414  
(NAME, ADDRESS AND TELEPHONE NUMBER OF PERSON  
AUTHORIZED TO RECEIVE NOTICES AND COMMUNICATIONS)

DECEMBER 2, 1996  
(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 which is the subject of this Schedule 13D, and is filing this schedule because of Rule 13d-1(b)(3) or (4), check the following box [ ].

Check the following box if a fee is being paid with this statement [ ]. (A fee is not required only if the reporting person: (1) has a previous statement on file reporting beneficial ownership of more than five percent of the class of securities described in Item 1; and (2) has filed no amendment subsequent thereto reporting beneficial ownership of five percent or less of such class. (See Rule 13d-7.)

NOTE: Six copies of this statement, including all exhibits, should be filed with the Commission. See Rule 13d-1(a) for other parties to whom copies are to be sent.

(Continued on following pages)  
(Page 1 of 7 Pages)

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CUSIP NO. 464330 10 9  
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1 NAME OF REPORTING PERSONS  
S.S. OR I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS  
Boehringer Ingelheim International GmbH  
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2 CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP\*  
(a) [ ] (b) [X]  
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3 SEC USE ONLY  
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4 SOURCE OF FUNDS (See Instructions)  
OO  
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5 CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDING IS REQUIRED PURSUANT TO  
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6	CITIZENSHIP OR PLACE OF ORGANIZATION Germany		
	NUMBER OF SHARES	7	SOLE VOTING POWER 2,408,607
	BENEFICIALLY OWNED BY	8	SHARED VOTING POWER -0-
	REPORTING PERSON WITH	9	SOLE DISPOSITIVE POWER 2,408,607
		10	SHARED DISPOSITIVE POWER -0-
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON		2,408,607
12	CHECK BOX IF THE AGGREGATE AMOUNT IN ROW 11 EXCLUDES CERTAIN SHARES*		[ ]
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW 11		9.2%
14	TYPE OF REPORTING PERSON*		CO

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## ITEM 1. SECURITY AND ISSUER

This Amendment No. 1 (the "Amendment") to the Statement on Schedule 13D dated as of July 18, 1995 and filed with the Securities and Exchange Commission on July 27, 1995 relates to the ownership of shares of the Common Stock (the "Common Stock") of Isis Pharmaceuticals, Inc., a Delaware corporation (the "Issuer"). The principal executive offices of the Issuer are located at 2292 Faraday Avenue, Carlsbad, CA 92008.

This Amendment is being filed pursuant to Section 13(d)(2) of the Securities Exchange Act of 1934, as amended, and Rule 13D-2(a) thereunder to disclose the acquisition of an additional 408,607 shares of Common Stock (the "Additional Shares") pursuant to that certain Stock Purchase Agreement dated as of July 18, 1995 between the Issuer and Boehringer Ingelheim International GmbH (the "Stock Purchase Agreement").

## ITEM 2. IDENTITY AND BACKGROUND

This Amendment is filed by Boehringer Ingelheim International GmbH, a corporation organized under the laws of Germany ("Boehringer Ingelheim"). Boehringer Ingelheim is an international pharmaceutical company which has substantial experience, expertise, technology and intellectual property rights in and related to the development and commercialization of human and animal diagnostic products and therapeutic drugs. Its principal office is located at D-55216 Ingelheim/Rhein, Germany. The name, business address, present principal occupation or employment and citizenship of (a) each executive officer and director of Boehringer Ingelheim, (b) each person controlling Boehringer Ingelheim and (c) each executive officer and director of each person ultimately in control of Boehringer Ingelheim (collectively the "Control Persons") are set forth in Attachment A. There have been no criminal proceedings against Boehringer Ingelheim or any of the Control Persons during the last five years. Neither Boehringer Ingelheim nor any of the Control Persons have been a party to any civil proceeding resulting in a judgment, decree, or final order enjoining activities subject to, or finding a violation of Federal or state securities laws during the last five years.

## ITEM 3. SOURCE AND AMOUNT OF FUNDS OR OTHER CONSIDERATION

In July 1995, Boehringer Ingelheim obtained 2,000,000 shares of Common Stock of the Issuer (the "Initial Shares") by means of a private placement in consideration of cash in the amount of \$28,500,000 plus a license for certain

technology owned by Boehringer Ingelheim. The source of the cash portion of the purchase consideration was Boehringer Ingelheim's working capital.

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On December 2, 1996, Boehringer Ingelheim purchased the Additional Shares pursuant to the terms of the Stock Purchase Agreement in consideration of cash in the amount of \$10,000,000. The source of the cash consideration was Boehringer Ingelheim's working capital.

ITEM 4. PURPOSE OF THE TRANSACTION

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 or non-immune based inflammatory diseases. By purchasing the shares, Boehringer Ingelheim desires in part to assist the Issuer in financing its share of the costs of such collaborative research, development and commercialization.

Under the terms of the Stock Purchase Agreement, Boehringer Ingelheim is obligated to purchase, and the Issuer is obligated to sell, an indeterminate number of additional shares of the Issuer's Common Stock upon the achievement of certain milestones. In addition, the Stock Purchase Agreement provides that subject to certain exceptions Boehringer Ingelheim will not, directly or indirectly, (i) without the prior consent of a majority of the Board, acquire (or offer or agree to acquire) any Issuer Common Stock or Preferred Stock with equivalent voting rights, or options, convertible securities or other rights to acquire such stock (collectively "Voting Stock") if, as a result, Boehringer Ingelheim would beneficially own more than 20% of the then outstanding Voting Stock; (ii) directly or indirectly solicit proxies or consent or become a participant in a solicitation, or (iii) transfer to any third party, other than its affiliates or associates, officers, directors or employees, the right to vote any of the Issuer's Voting Stock except in connection with the transfer of ownership of the Voting Stock for fair value. These provisions terminate (i) if Boehringer Ingelheim owns less than 2% of the Voting Stock, (ii) if Boehringer Ingelheim makes a tender offer to purchase 100% of the then outstanding Voting Stock and such offer is accepted by the holders of more than 50% of the Voting Stock not owned directly or indirectly by Boehringer Ingelheim, (iii) if any person or group, excluding Boehringer Ingelheim, makes a bona fide offer to acquire Voting Stock of the Issuer which would, if successful, result in the bidder's beneficial ownership of at least 15% of the then outstanding Voting Stock, or (iv) upon the fifth anniversary of the date of the Stock Purchase Agreement. The Stock Purchase Agreement further grants to Boehringer Ingelheim the right to purchase its pro rata share of Voting Stock in certain financings by the Issuer in which Voting Stock is sold to investors for cash not in connection with any other financing transaction.

Pursuant to the terms of the Stock Purchase Agreement, Boehringer Ingelheim also is entitled to designate a representative reasonably satisfactory to the Issuer to be nominated for election to the Issuer's Board of Directors.

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ITEM 5. INTEREST IN SECURITIES OF THE ISSUER

(a)	Beneficial Ownership:	2,408,607
	Percentage Ownership:	9.2%
(b)	Sole Voting Power:	2,408,607
	Shared Voting Power:	-0-
	Sole Dispositive Power:	2,408,607
	Shared Dispositive Power:	-0-
(c)	Recent Transactions:	See items 3 and 4, above.
(d)	Right to Receive Dividends:	Not applicable
(e)	Ownership below 5%:	Not applicable

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

Boehringer Ingelheim has entered into a Stock Purchase Agreement with the Issuer, which grants Boehringer Ingelheim registration rights for the shares issued pursuant to the Stock Purchase Agreement (and any shares of Voting Stock issued as a dividend or other distribution with respect to, or in exchange or in replacement thereof).

See Item 4 for a description of the other rights granted to Boehringer Ingelheim pursuant to the Stock Purchase Agreement.

ITEM 7. MATERIAL TO BE FILED AS EXHIBITS

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

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

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SIGNATURE

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: December 2, 1996

BOEHRINGER INGELHEIM INTERNATIONAL GMBH  
ppa.

By: /S/ HANS-PETER MULLER

\_\_\_\_\_  
Name: Hans-Peter Muller

\_\_\_\_\_  
Its: Corporate Legal Department

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ATTACHMENT A

Executive Officers and Directors of Corporations  
or Other Persons in Control of Boehringer Ingelheim International GmbH

Name, Occupation  
and Citizenship

Business Address

-----  
Dr. Heribert Johann  
Manager, Finance  
German

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Boehringer Ingelheim GmbH  
D-55216 Ingelheim am Rhein  
Germany

Prof. Dr. h.c. Rolf Krebs  
Manager, Pharmaceuticals  
German

Boehringer Ingelheim GmbH  
D-55216 Ingelheim am Rhein  
Germany

Dr. Hans-Jurgen Leuchs  
Manager, Production  
German

Boehringer Ingelheim GmbH  
D-55216 Ingelheim am Rhein  
Germany

Dr. Claus Rohleder  
Manager, Personnel, Industrial

Boehringer Ingelheim GmbH  
D-55216 Ingelheim am Rhein

and Special Products  
German

Germany

Persons in Control of Boehringer Ingelheim International GmbH  
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Name and Citizenship  
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Business Address  
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C. H. Boehringer Sohn  
German

D-55216 Ingelheim am Rhein  
Germany