

**UNITED STATES
SECURITIES AND EXCHANGE
COMMISSION**

Washington, D.C. 20549

SCHEDULE 13D

Under the Securities Exchange Act of 1934
(Amendment No.)*

Isis Pharmaceuticals, Inc

(Name of Issuer)

Common Stock, par value \$0.001 per share

(Title of Class of Securities)

464330109

(CUSIP Number)

**Peter Wirth
Genzyme Corporation
500 Kendall Street
Cambridge, Massachusetts 02142
(617) 252-7500**

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

with copies to:

**Paul Kinsella
Ropes & Gray LLP
One International Place
Boston, Massachusetts 02110
(617) 951-7000**

January 7, 2008

(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 §§240.13d-1(e), 240.13d-1(f) or 240.13d-1(g), check the following box.

Note: Schedules filed in paper format shall include a signed original and five copies of the schedule, including all exhibits. See §240.13d-7 for other parties to whom copies are to be sent.

* The remainder of this cover page shall be filled out for a reporting person's initial filing on this form with respect to the subject class of securities, and for any subsequent amendment containing information which would alter disclosures provided in a prior cover page.

The information required on the remainder of this cover page shall not be deemed to be "filed" for the purpose of Section 18 of the Securities Exchange Act of 1934 ("Act") or otherwise subject to the liabilities of that section of the Act but shall be subject to all other provisions of the Act (however, see the Notes).

CUSIP No. 464330109

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1. Names of Reporting Persons.
Genzyme Corporation
I.R.S. Identification Nos. of above persons (entities only)
06-1047163

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2. Check the Appropriate Box if a Member of a Group (See Instructions)

(a)

(b)

3. SEC Use Only

4. Source of Funds (See Instructions)
WC

5. Check if Disclosure of Legal Proceedings Is Required Pursuant to Items 2(d) or 2(e)

6. Citizenship or Place of Organization
Massachusetts

7. Sole Voting Power
5,000,000 shares of Common Stock

Number of
Shares
Beneficially
Owned by
Each
Reporting
Person With

8. Shared Voting Power

9. Sole Dispositive Power
5,000,000 shares of Common Stock

10. Shared Dispositive Power

11. Aggregate Amount Beneficially Owned by Each Reporting Person
5,000,000 shares of Common Stock

12. Check if the Aggregate Amount in Row (11) Excludes Certain Shares (See Instructions)

13. Percent of Class Represented by Amount in Row (11)
5.7%

14. Type of Reporting Person (See Instructions)
CO

Item 1. Security and Issuer

This Schedule 13D relates to the Common Stock, \$0.001 par value per share (the “*Common Shares*”), of Isis Pharmaceuticals, Inc. (the “*Issuer*”), a Delaware corporation. The principal executive offices of the Issuer are located at 1896 Rutherford Road, Carlsbad, CA 92008.

Item 2. Identity and Background

Genzyme Corporation (“*Genzyme*”), a Massachusetts corporation, is a publicly-held, global biotechnology company focused on rare inherited disorders,

kidney disease, cancer, transplant and immune diseases, orthopaedics and diagnostic testing. Genzyme's principal place of business and principal office is located at 500 Kendall Street, Cambridge, Massachusetts 02142.

To the best of Genzyme's knowledge as of the date hereof, set forth in Schedule I to this Schedule 13D and incorporated herein by reference is the following information with respect to each director and executive officer of Genzyme:

- (1) name;
- (2) business address;
- (3) present principal occupation or employment and the name, principal business and address of any corporation or other organization in which such employment is conducted; and
- (4) citizenship.

During the last five years, neither Genzyme nor, to the best of Genzyme's knowledge, any of its directors or executive officers has been (1) convicted in a criminal proceeding (excluding traffic violations or similar misdemeanors) or (2) a party to a civil proceeding of a judicial or administrative body of competent jurisdiction and as a result of such proceeding has been or is subject to a judgment, decree or final order enjoining future violations of, or prohibiting or mandating activities subject to, federal or state securities laws or finding any violation with respect to such laws.

Item 3. Source and Amount of Funds or Other Consideration

On January 7, 2008 Genzyme and the Issuer entered into a Stock Purchase Agreement (the "*Stock Purchase Agreement*") pursuant to which the Issuer issued and sold to Genzyme 5,000,000 shares of Common Stock for an aggregate purchase price of \$150,000,000 representing a per share purchase price of \$30. The source of the funds for the purchase of the shares (the "*Purchase*") was the working capital of Genzyme.

As an inducement to enter into the Stock Purchase Agreement, and in consideration thereof, Genzyme and the Issuer entered into a License and Research Agreement (the "*License and Research Agreement*"), dated as of the date of the Stock Purchase Agreement (the "*Effective Date*"). Pursuant to the terms and conditions of the License and Research Agreement, the Issuer has granted Genzyme an exclusive worldwide license of mipomerson, which is currently in phase 3 clinical trials. In addition, under the License and Research Agreement, for a two-year period from the Effective Date Genzyme has been granted the option to exclusively license certain Issuer drugs that become development candidates in the Issuer's neuro-degenerative and rare disease programs. The terms of these licenses will be negotiated in good faith by Genzyme and the Issuer. Upon granting any such license, Genzyme will be solely responsible for the commercialization of any such licensed drug, including all funding, resourcing and decision-making, all

further clinical development, manufacturing, and regulatory approval. All research activities prior to the identification of the development candidate will be funded by the Issuer.

A copy of the Stock Purchase Agreement is attached as Exhibit 1 to this Schedule 13D. References to, and descriptions of, the Stock Purchase Agreement as set forth above in this Item 3 are qualified in their entirety by reference to the Stock Purchase Agreement included as Exhibit 1 to this Schedule 13D and incorporated herein in its entirety by this reference. The information set forth and/or incorporated by reference in Item 6 is hereby incorporated by reference into this Item 3.

Item 4. Purpose of Transaction

The information set forth and/or incorporated by reference in Item 3 is hereby incorporated by reference into this Item 4. The purpose of the Purchase described in Item 3 is for investment purposes and the Purchase was made in the ordinary course of business and was not made for the purpose of acquiring control of the Issuer. The purpose of entering into the License and Research Agreement is to share the risks and rewards associated with developing and commercializing certain Issuer drugs and was made in the ordinary course of business and was not made for the purpose of acquiring control of the Issuer. However, because of the exclusive licensing relationship, a material amount of assets of the Issuer could be deemed to be transferred to Genzyme.

Except to the extent the foregoing may be deemed a plan or proposal, Genzyme has no plans or proposals which relate to, or could result in, any of the matters referred to in paragraphs (a) through (j), inclusive, of the instructions to Item 4 of Schedule 13D. Genzyme may, at any time and from time to time, review or reconsider its position and/or change its purpose and/or formulate plans or proposals with respect thereto.

Item 5. Interest in Securities of the Issuer

- (a) – (c) The information contained in Items 3, 4 and 6 is hereby incorporated herein by reference. The following disclosure assumes that there are 87,317,938 Common Shares issued and outstanding as of the Effective Date, based on representations made in the Stock Purchase Agreement by the Issuer to Genzyme.

As of the Effective Date and taking into account the transactions described in Item 3, Genzyme beneficially owns and has sole power to vote and sole power of disposition over 5,000,000 Common Shares representing approximately 5.7% of the Common Shares outstanding.

The persons listed on Schedule I hereto, as the directors and executive officers of Genzyme, may be deemed to share voting and dispositive power with respect to 5,000,000 Common Shares currently held by Genzyme, representing approximately 5.7% of the Common Shares outstanding. The persons listed on Schedule I hereto, however, disclaim beneficial ownership of such Common Shares, and this statement shall not be construed as an admission that any person listed on Schedule I hereto is the beneficial owner for any purpose of the Common Shares covered by this Schedule 13D disclosure.

- (d) To the best of Genzyme's knowledge as of the date hereof, neither Genzyme nor any of its directors and executive officers named in Schedule I hereto has or knows any other person who has the right to receive or the power to direct the receipt of dividends from, or the proceeds from the sale of, any Common Shares beneficially owned by Genzyme.

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- (e) Not applicable.

Item 6. Contracts, Arrangements, Understandings or Relationships with Respect to Securities of the Issuer

The information set forth and/or incorporated by reference in Items 2 through 5 is hereby incorporated by reference into this Item 6.

As described in Item 3, on January 7, 2008, Genzyme entered into the Stock Purchase Agreement and the License and Research Agreement with the Issuer. The Stock Purchase Agreement contains customary representations and warranties and indemnification provisions. The Stock Purchase Agreement also requires the Issuer to file a registration statement with the Securities and Exchange Commission (the "SEC") covering the resale of the Registrable Securities (as defined in the Stock Purchase Agreement) within 30 days after the closing of the transactions contemplated by the Stock Purchase Agreement and to effect such registration within 90 days if such registration statement is not reviewed by the SEC or within 120 days if it is reviewed by the SEC. Pursuant to the Stockholders Agreement, Genzyme is also subject to certain standstill restrictions, including restrictions on acquiring Issuer securities, participating in any solicitation of proxies to vote Issuer securities, or publicly proposing any business combination or similar transaction with the Issuer. The standstill provisions continue in effect until the earlier of (a) the ten-year anniversary of the License and Research Agreement or (b) the date on which Genzyme holds less than 2% of the Issuer's outstanding common stock, unless a tender or exchange offer is commenced by a third party or a change of control of the Issuer is announced. Pursuant to the terms and conditions of the Stock Purchase Agreement, Genzyme also agreed not to sell the shares acquired until the earlier of (a) the four-year anniversary of the effective date of the License and Research Agreement, (b) the first commercial sale of a product under the License and Research Agreement, or (c) the termination or reversion of the product license granted to Genzyme under the License and Research Agreement. In addition, after the expiration of such holding period, Genzyme will not sell more than 500,000 of the Common Shares acquired in any thirty-day period.

Item 7. Material to Be Filed as Exhibits

<u>Exhibit No.</u>	<u>Description</u>
1	Stock Purchase Agreement, between Genzyme Corporation and Isis Pharmaceuticals, Inc., dated January 7, 2008.

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SIGNATURES

After reasonable inquiry and to the best of its knowledge and belief, the undersigned certifies that the information set forth in this Statement is true, complete and correct.

Dated: January 15, 2008

GENZYME CORPORATION

By: /s/ Peter Wirth
Name: Peter Wirth
Title: Chief Legal Officer & Executive Vice President, Legal & Corporate Development

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SCHEDULE 1

DIRECTORS AND EXECUTIVE OFFICERS OF GENZYME CORPORATION

Set forth below is the name, present principal occupation or employment and the name, principal business and address of any corporation or other organization in which such employment is conducted for each director and executive officer of Genzyme. Unless otherwise indicated, each individual is a citizen of the United States, and his or her business address is c/o Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142.

Directors

Henri A. Termeer
Chairman of the Board, President and Chief Executive Officer
Genzyme Corporation

Douglas A. Berthiaume
President and Chief Executive Officer
Waters Corporation (high technology manufacturer of high performance liquid chromatography instrumentation and consumables, and thermal analysis and

mass spectrometry products used for analysis and purification)
34 Maple Street
Milford, Massachusetts 01757

Gail Koziara Boudreaux
Executive Vice President
Health Care Service Corporation (health and life insurance company)
300 East Randolph Street
Chicago, Illinois 60601

Robert J. Carpenter
Chairman
Hydra Biosciences, Inc. (biopharmaceutical company developing novel drugs to treat pain, inflammation, cardiovascular and other diseases using its expertise in novel ion channels)
790 Memorial Drive
Cambridge, MA 02139

Charles L. Cooney
Professor of Chemical and Biochemical Engineering
Massachusetts Institute of Technology
Room 56-469B
77 Massachusetts Avenue
Cambridge, Massachusetts 02139

Victor J. Dzau
Chancellor for Health Affairs and President and Chief Executive Officer
Duke University Medical Center and Health System
106 Davidson Building
Durham, North Carolina 27710

Connie Mack III
Senior Policy Advisor and Co-Chairman of the Government Relations Practice Group
King & Spalding LLP
1700 Pennsylvania Avenue, NW, Suite 200
Washington, DC 20006

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Richard F. Syron
Chairman and Chief Executive Officer
Federal Home Loan Mortgage Corporation
8200 Jones Branch Drive
McLean, Virginia 22102

Executive Officers

Henri A. Termeer
Chairman of the Board, President and Chief Executive Officer
(See Above)

Earl M. Collier, Jr.
Executive Vice President, Cardiovascular and Oncology

Zoltan A. Csirma
Chief Human Resources Officer; Senior Vice President

Georges Gemayel, Ph.D.
Executive Vice President, Therapeutics

Richard A. Moscicki, M.D.
Chief Medical Officer; Senior Vice President, Clinical, Medical and Regulatory Affairs

Alan E. Smith, Ph.D.
Chief Scientific Officer; Senior Vice President, Research

Sandford D. Smith
Executive Vice President; President, International Group

Peter Wirth
Chief Legal Officer; Executive Vice President, Legal and Corporate Development; Secretary

Michael S. Wyzga
Chief Financial and Accounting Officer; Executive Vice President, Finance

