



OMB APPROVAL
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UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
Washington, D.C. 20549

SCHEDULE 13G

Under the Securities Exchange Act of 1934  
(Amendment No. 1)\*

Isis Pharmaceuticals, Inc.

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(Name of Issuer)

Common Stock

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(Title of Class of Securities)

464330-1-09

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(CUSIP Number)

December 20, 2004

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(Date of Event Which Requires Filing of this Statement)

Check the appropriate box to designate the rule pursuant to which this Schedule is filed:

- Rule 13d-1 (b)
- Rule 13d-1 (c)
- Rule 13d-1 (d)

\*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 the disclosures provided in a prior cover page.

The information required in 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 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).

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1. Name of Reporting Person: I.R.S. Identification Nos. of above persons (entities only):  
Eli Lilly and Company 35-0470950

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2. Check the Appropriate Box if a Member of a Group:  
(a)   
(b)

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3. SEC Use Only: Indiana

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4. Citizenship or Place of Organization:  
Indiana

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5. Sole Voting Power:  
3,541,875

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Number of  
Shares  
Beneficially  
Owned by  
Each  
Reporting  
Person With

6. Shared Voting Power:  
624,791

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7. Sole Dispositive Power:  
3,541,875

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8. Shared Dispositive Power:  
624,791

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9. Aggregate Amount Beneficially Owned by Each Reporting Person:  
4,166,167

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10. Check if the Aggregate Amount in Row (9) Excludes Certain Shares:

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11. Percent of Class Represented by Amount in Row (9):  
7.3%

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12. Type of Reporting Person:  
CO

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- Item 1(a). Name of Issuer:  
Isis Pharmaceuticals, Inc.
- Item 1(b). Address of Issuer's Principal Executive Offices:  
2292 Faraday Avenue  
Carlsbad, CA 92008
- Item 2(a). Name of Person Filing:  
Eli Lilly and Company
- Item 2(b). Address of Principal Business Office or, if None, Residence:  
Lilly Corporate Center  
Indianapolis, IN 46285
- Item 2(c). Citizenship:  
Indiana
- Item 2(d). Title of Class of Securities:  
Common Stock
- Item 2(e). CUSIP Number:  
464330-1-09
- Item 3. If this statement is filed pursuant to Rule 13d-1(b), or 13d-2(b) or (c), check whether the person filing is a:  
(a)-(j) Not applicable  
If this statement is filed pursuant to Rule 13d-1(c), check this box.

Item 4.	Ownership.	
	(a) Amount Beneficially Owned:	
		4,166,167
	(b) Percent of Class:	
		7.3%
	(c) Number of shares as to which the person has:	
	Sole voting power	3,541,875
	Shared voting power	624,791
	Sole dispositive power	3,541,875
	Shared dispositive power	624,791

Item 5. Ownership of Five Percent or Less of a Class.  
Not applicable

Item 6. Ownership of More Than Five Percent on Behalf of Another Person.  
Not applicable

Item 7. Identification and Classification of the Subsidiary which Acquired the Security Being Reported on by the Parent Holding Company.  
Not applicable

Item 8. Identification and Classification of Members of the Group.  
Not applicable

Item 9. Notice of Dissolution of Group.  
Not applicable

Item 10. Certifications.

By signing below, I certify that, to the best of my knowledge and belief, the securities referred to above were not acquired and are not held for the purpose of or with the effect of changing or influencing control of the issuer of the securities and were not acquired and are not held in connection with or as a participant in any transaction having that purpose or effect.

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.

**ELI LILLY AND COMPANY**

By: /s/ Charles E. Golden  
Charles E. Golden  
Executive Vice President and  
Chief Financial Officer

Date: February 11, 2005

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