

## INITIAL STATEMENT OF BENEFICIAL OWNERSHIP OF SECURITIES

OMB APPROVAL

OMB Number: 3235-0104

Estimated average burden

hours per response: 0.5

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934  
or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person* <u>Treble Michael J</u>  (Last) (First) (Middle) <u>ISIS PHARMACEUTICALS, INC.</u> <u>2292 FARADAY AVENUE</u>  (Street) <u>SAN DIEGO CA 92008</u>  (City) (State) (Zip)	2. Date of Event Requiring Statement (Month/Day/Year) <u>12/14/2004</u>	3. Issuer Name and Ticker or Trading Symbol <u>ISIS PHARMACEUTICALS INC [ ISIS ]</u>	
		4. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <u>Vice President</u>	5. If Amendment, Date of Original Filed (Month/Day/Year)  6. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person

## Table I - Non-Derivative Securities Beneficially Owned

1. Title of Security (Instr. 4)	2. Amount of Securities Beneficially Owned (Instr. 4)	3. Ownership Form: Direct (D) or Indirect (I) (Instr. 5)	4. Nature of Indirect Beneficial Ownership (Instr. 5)
<u>No securities beneficially owned</u>	<u>0</u>	<u>D</u>	

Table II - Derivative Securities Beneficially Owned  
(e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 4)	2. Date Exercisable and Expiration Date (Month/Day/Year)		3. Title and Amount of Securities Underlying Derivative Security (Instr. 4)		4. Conversion or Exercise Price of Derivative Security	5. Ownership Form: Direct (D) or Indirect (I) (Instr. 5)	6. Nature of Indirect Beneficial Ownership (Instr. 5)
	Date Exercisable	Expiration Date	Title	Amount or Number of Shares			
<u>Employee Stock Option (right to buy)</u>	<u>12/06/2005<sup>(1)</sup></u>	<u>12/05/2011</u>	<u>Common Stock</u>	<u>90,000</u>	<u>5.95</u>	<u>D</u>	

## Explanation of Responses:

1. Grant of 12-6-04 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option will vest and become exercisable on 12-6-05. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 22,500 shares per year. The option is exercisable as to 0 shares on 12-6-04.

## Remarks:

Michael J. Treble12/21/2004

\*\* Signature of Reporting Person

Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

\* If the form is filed by more than one reporting person, see Instruction 5 (b)(v).

\*\* Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.