

Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

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**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934, Section 17(a) of the Public Utility Holding Company Act of 1935 or Section 30(h) of the Investment Company Act of 1940

Filed By Romeo & Dye's Instant Form 4 Filer  
www.section16.net

1. Name and Address of Reporting Person* <b>Bennett C. Frank</b> (Last) (First) (Middle) <b>2292 Faraday Avenue</b> (Street) <b>Carlsbad, CA 92008</b> (City) (State) (Zip)			2. Issuer Name and Ticker or Trading Symbol <b>Isis Pharmaceuticals, Inc. (ISIS)</b>			6. Relationship of Reporting Person(s) to Issuer (Check all applicable) <input type="checkbox"/> Director <input type="checkbox"/> 10% Owner <input checked="" type="checkbox"/> Officer (give title below) <input type="checkbox"/> Other (specify below) <b>Vice President</b>		
3. I.R.S. Identification Number of Reporting Person, if an entity (voluntary)			4. Statement for Month/Day/Year <b>1/2/03</b>			7. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person <input type="checkbox"/> Form filed by More than One Reporting Person		
<b>Table I — Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned</b>								

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 & 5)			5. Amount of Securities Beneficially Owned Following Reported Transactions(s) (Instr. 3 & 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
<b>Common Stock</b>	<b>1/1/03</b>	<b>1/2/03</b>	<b>J</b>	<b>V</b>	<b>369</b> <sup>(1)</sup>	<b>A</b>	<b>\$5.6015</b>	<b>813</b>	<b>D</b>	

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 4(b)(v).

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**FORM 4 (continued)**

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)		5. Number of Derivative Securities Acquired (A) or Disposed of (D) (Instr. 3, 4 & 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Underlying Securities (Instr. 3 & 4)	8. Price of Derivative Security (Instr. 5)	9. Number of Derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form of Derivative Security: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date					
<b>Employee Stock Option (right to buy)</b>	<b>\$6.84</b>	<b>1-2-03</b>	<b>1-2-03</b>	<b>A</b>		<b>11,500</b>		<b>(2)</b>	<b>1-1-13</b>	<b>Common Stock</b>	<b>11,500</b>	<b>11,500</b>	<b>D</b>	

Explanation of Responses:

(1) Reporting 369 shares acquired under the Isis Pharmaceuticals, Inc. 2000 Employee Stock Purchase Plan on January 1, 2003.

(2) 25% of the shares subject to the option will vest and become exercisable on 1-2-04. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 2,875 shares per year. The option is exercisable as to 0 shares on 1-2-03.

By: /s/ **C. Frank Bennett**  
**B. Lynne Parshall**  
\*\*Signature of Reporting Person

**1-3-03**  
Date

\*\*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.

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