

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

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

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

OMB APPROVAL	
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1. Name and Address of Reporting Person* CROOKE STANLEY T (Last) (First) (Middle) C/O ISIS PHARMACEUTICALS, INC. 1896 RUTHERFORD ROAD (Street) CARLSBAD CA 92008 (City) (State) (Zip)	2. Issuer Name and Ticker or Trading Symbol ISIS PHARMACEUTICALS INC [ISIS]	5. Relationship of Reporting Person(s) to Issuer (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) Chairman, President, CEO
	3. Date of Earliest Transaction (Month/Day/Year) 12/26/2007	
	4. 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 <input type="checkbox"/> Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned

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 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 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			
Common Stock	12/26/2007	12/26/2007	M ⁽¹⁾		24,000 ⁽¹⁾	A	\$12.3125	896,241	D	
Common Stock	12/26/2007	12/26/2007	S ⁽²⁾		24,000 ⁽²⁾	D	\$16.5258	872,241	D	
Common Stock	12/27/2007	12/27/2007	M ⁽³⁾		2,100 ⁽³⁾	A	\$12.3125	3,150	I	By wife
Common Stock	12/27/2007	12/27/2007	M ⁽¹⁾		6,000 ⁽¹⁾	A	\$12.3125	878,241	D	
Common Stock	12/27/2007	12/27/2007	S ⁽²⁾		6,000 ⁽²⁾	D	\$16.321	872,241	D	
Common Stock	12/28/2007	12/28/2007	M ⁽¹⁾		20,000 ⁽¹⁾	A	\$12.3125	892,241	D	
Common Stock	12/28/2007	12/28/2007	S ⁽²⁾		20,000 ⁽²⁾	D	\$16.2215	872,241	D	

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 and 5)		6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)		8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)
				Code	V	(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Employee Stock Option (right to buy)	\$12.3125	12/26/2007	12/26/2007	M			24,000	01/01/2002	12/31/2007	Common Stock	24,000	\$0	18,000	D	
Employee Stock Option (right to buy)	\$12.3125	12/27/2007	12/27/2007	M			2,100	01/01/2002	12/31/2007	Common Stock	2,100	\$0	0	I	By wife
Employee Stock Option (right to buy)	\$12.3125	12/27/2007	12/27/2007	M			6,000	01/01/2002	12/31/2007	Common Stock	6,000	\$0	2,000	D	
Employee Stock Option (right to buy)	\$12.3125	12/28/2007	12/28/2007	M			2,000	01/01/2002	12/31/2007	Common Stock	2,000	\$0	0	D	
Employee Stock Option (right to buy)	\$12.3125	12/28/2007	12/28/2007	M			18,000	01/01/2002	12/31/2007	Common Stock	18,000	\$0	0	D	

Explanation of Responses:

- The purchase reported on this Form 4 was effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on 10/5/05. The stock option was expiring on 12-31-07.
- The sale reported on this Form 4 was effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on 10/5/05. The stock option was expiring on 12-31-07.
- Stock option exercise and hold by reporting person's wife. The stock option was expiring on 12-31-07.

Remarks:

/s/Stanley T. Crooke

12/28/2007

** 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 4 (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.