

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

OMB APPROVAL	
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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

1. Name and Address of Reporting Person* <u>CROOKE STANLEY T</u> (Last) (First) (Middle) <u>C/O ISIS PHARMACEUTICALS, INC.</u> <u>1896 RUTHERFORD ROAD</u> (Street) <u>CARLSBAD CA 92008</u> (City) (State) (Zip)			2. Issuer Name and Ticker or Trading Symbol <u>ISIS PHARMACEUTICALS INC [ISIS]</u>			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) <p style="text-align: center;">Chairman, President, CEO</p>		
			3. Date of Earliest Transaction (Month/Day/Year) <u>12/30/2008</u>					
			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	12/30/2008	12/30/2008	M ⁽¹⁾		7,500 ⁽¹⁾	A	\$12.9375	7,500	D	
Common Stock	12/30/2008	12/30/2008	S ⁽²⁾		7,500 ⁽²⁾	D	\$13.3691	0	D	
Common Stock								875,391	I	By Trust

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)	\$12.9375	12/30/2008	12/30/2008	M			7,500	01/01/2003	12/31/2008	Common Stock	7,500	\$0	0	D	
Employee Stock Option (right to buy)	\$14.47	01/02/2009	01/02/2009	A			150,000	01/02/2010 ⁽³⁾	01/01/2016	Common Stock	150,000	\$0	150,000	D	
Employee Stock Option (right to buy)	\$14.47	01/02/2009	01/02/2009	A			7,000	01/02/2010 ⁽⁴⁾	01/01/2016	Common Stock	7,000	\$0	7,000	I	By wife

Explanation of Responses:

- Acquired as a result of exercising a stock option that was scheduled to expire on 12/31/08. The purchase reported on this Form 4 was effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on 2/15/08.
- The sale reported in this Form 4 was effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on 2/15/08.
- Grant of 1-2-09 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 1-2-10. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 37,500 shares per year. The option is exercisable as to 0 shares on 1-2-09.
- Grant of 1-2-09 to the reporting person's wife 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 1-2-10. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 1,750 shares per year. The option is exercisable as to 0 shares on 1-2-09.

Remarks:

/s/B. Lynne Parshall, Attorney-in-Fact 01/02/2009

** 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.