

**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>2855 GAZELLE COURT</u>  (Street) <u>CARLSBAD CA 92010</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) <u>Chairman and CEO</u>
	3. Date of Earliest Transaction (Month/Day/Year) <u>07/01/2014</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	07/01/2014	07/01/2014	M <sup>(1)</sup>		15,500 <sup>(1)</sup>	A	\$14.47	22,441	D	
Common Stock	07/01/2014	07/01/2014	S <sup>(1)</sup>		15,500 <sup>(2)</sup>	D	\$35.578	6,941	D	
Common Stock	07/01/2014	07/01/2014	M <sup>(3)</sup>		200 <sup>(3)</sup>	A	\$14.47	827	I	By Wife
Common Stock	07/01/2014	07/01/2014	S <sup>(3)</sup>		200 <sup>(3)</sup>	D	\$35.55	627	I	By Wife
Common Stock	07/01/2014	07/01/2014	M <sup>(3)</sup>		1,800 <sup>(3)</sup>	A	\$11.27	2,427	I	By Wife
Common Stock	07/01/2014	07/01/2014	S <sup>(3)</sup>		1,800 <sup>(3)</sup>	D	\$35.55	627	I	By Wife
Common Stock								725,391	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
Employee Stock Option (right to buy)	\$14.47	07/01/2014	07/01/2014	M		15,500		01/02/2013 <sup>(4)</sup>	01/02/2016	Common Stock	15,500	\$0	66,500	D	
Employee Stock Option (right to buy)	\$14.47	07/01/2014	07/01/2014	M		200		01/02/2013	01/02/2016	Common Stock	200	\$0	0	I	By Wife
Employee Stock Option (right to buy)	\$11.27	07/01/2014	07/01/2014	M		1,800		01/04/2014 <sup>(5)</sup>	01/03/2017	Common Stock	1,800	\$0	4,800	I	By Wife

**Explanation of Responses:**

- Acquired as a result of exercising a stock option pursuant to Rule 10b5-1 Trading Plan. The purchase and sale reported on this Form 4 was effective pursuant to Rule 10b5-1 Trading Plan adopted by the reporting person on 8/6/13.
- The price reported in Column 4 is a weighted average price. These shares were sold in multiple transactions at prices ranging from \$35.51 to \$35.65, inclusive. The reporting person undertakes to provide to Isis Pharmaceuticals, Inc., any security holder of Isis Pharmaceuticals, Inc. or the staff of the Securities and Exchange Commission, upon request, full information regarding the number of shares sold at each separate price within the ranges set forth in footnote (2) on this Form 4.
- Acquired as a result of exercising a stock option pursuant to Rule 10b5-1 Trading Plan. The purchase and sale reported on this Form 4 was effective pursuant to Rule 10b5-1 Trading Plan adopted by the reporting person's wife on 8/6/13.
- Grant of 1/2/2009 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vested and became exercisable on 1/2/2010. 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. Following this transaction, the option was exercisable as to 66,500 on 7/1/14.
- Grant of 1/4/10 to reporting person's wife of stock options under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vested and became exercisable on 1/4/11. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 1,650 shares per year. Following this transaction, the option was exercisable as to 4,800 on 7/1/2014.

**Remarks:**

/s/B. Lynne Parshall, attorney- 07/02/2014  
in-fact

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.

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