

**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 * <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) <p style="text-align: center;"><b>Chairman and CEO</b></p>
	3. Date of Earliest Transaction (Month/Day/Year) <u>10/21/2015</u>	
4. If Amendment, Date of Original Filed (Month/Day/Year)		

**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	10/21/2015	10/21/2015	M <sup>(1)</sup>		15,000 <sup>(1)</sup>	A	\$11.27	29,642	D	
Common Stock	10/21/2015	10/21/2015	S <sup>(1)</sup>		15,000 <sup>(1)</sup>	D	\$43 <sup>(2)</sup>	14,642	D	
Common Stock	10/21/2015	10/21/2015	M <sup>(3)</sup>		1,000 <sup>(3)</sup>	A	\$11.27	2,297	I	By wife
Common Stock	10/21/2015	10/21/2015	S <sup>(3)</sup>		1,000 <sup>(3)</sup>	D	\$43	1,297	I	By wife
Common Stock	10/21/2015	10/21/2015	M <sup>(3)</sup>		500 <sup>(3)</sup>	A	\$9.22	1,797	I	By wife
Common Stock	10/21/2015	10/21/2015	S <sup>(3)</sup>		500 <sup>(3)</sup>	D	\$43	1,297	I	By wife
Common Stock	10/23/2015	10/23/2015	M <sup>(1)</sup>		4,163 <sup>(1)</sup>	A	\$11.27	18,805	D	
Common Stock	10/23/2015	10/23/2015	S <sup>(1)</sup>		4,163 <sup>(1)</sup>	D	\$43.9	14,642	D	
Common Stock	10/23/2015	10/23/2015	M <sup>(1)</sup>		15,837 <sup>(1)</sup>	A	\$10.29	30,479	D	
Common Stock	10/23/2015	10/23/2015	S <sup>(1)</sup>		15,837 <sup>(1)</sup>	D	\$44.175 <sup>(4)</sup>	14,642	D	
Common Stock	10/23/2015	10/23/2015	M <sup>(1)</sup>		5,000 <sup>(1)</sup>	A	\$10.29	19,642	D	
Common Stock	10/23/2015	10/23/2015	S <sup>(1)</sup>		5,000 <sup>(1)</sup>	D	\$45.3	14,642	D	
Common Stock	10/23/2015	10/23/2015	M <sup>(3)</sup>		2,000 <sup>(3)</sup>	A	\$9.22	3,297	I	By wife
Common Stock	10/23/2015	10/23/2015	S <sup>(3)</sup>		2,000 <sup>(3)</sup>	D	\$44.175 <sup>(4)</sup>	1,297	I	By wife
Common Stock	10/23/2015	10/23/2015	M <sup>(3)</sup>		500 <sup>(3)</sup>	A	\$9.22	1,797	I	By wife
Common Stock	10/23/2015	10/23/2015	S <sup>(3)</sup>		500 <sup>(3)</sup>	D	\$45.3	1,297	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)	\$11.27	10/21/2015	10/21/2015	M			15,000	01/04/2014	01/03/2017	Common Stock	15,000	\$0	4,163	D	
Employee Stock Option (right to buy)	\$11.27	10/21/2015	10/21/2015	M			1,000	01/04/2014	01/03/2017	Common Stock	1,000	\$0	0	I	By wife

**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)	\$9.22	10/21/2015	10/21/2015	M			500	07/19/2014	07/18/2017	Common Stock	500	\$0	4,500	I	By wife
Employee Stock Option (right to buy)	\$11.27	10/23/2015	10/23/2015	M			4,163	01/04/2014	01/03/2017	Common Stock	4,163	\$0	0	D	
Employee Stock Option (right to buy)	\$10.29	10/23/2015	10/23/2015	M			20,837	01/03/2015	01/02/2018	Common Stock	20,837	\$0	101,259	D	
Employee Stock Option (right to buy)	\$9.22	10/23/2015	10/23/2015	M			2,500	07/19/2014	07/18/2017	Common Stock	2,500	\$0	2,000	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 9/21/2015.
- The price reported in Column 4 is a weighted average price. These shares were sold in multiple transactions at prices ranging from \$42.60 to \$43.40, 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 9/21/2015.
- The price reported in Column 4 is a weighted average price. These shares were sold in multiple transactions at prices ranging from \$43.90 to \$44.70, 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 (4) on this Form 4.

**Remarks:**

/s/B. Lynne Parshall, attorney-in-fact      10/23/2015

\*\* 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.**