

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* <b>CROOKE STANLEY T</b>  (Last) (First) (Middle)  <b>C/O ISIS PHARMACEUTICALS, INC.</b> <b>2855 GAZELLE COURT</b>  (Street) <b>CARLSBAD CA 92010</b>  (City) (State) (Zip)	2. Issuer Name and Ticker or Trading Symbol <b>ISIS PHARMACEUTICALS INC [ ISIS ]</b>	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) <b>Chairman, President and CEO</b>
	3. Date of Earliest Transaction (Month/Day/Year) <b>01/02/2014</b>	
	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	01/02/2014	01/02/2014	M <sup>(1)</sup>		25,000 <sup>(1)</sup>	A	\$14.47	26,661	D	
Common Stock	01/02/2014	01/02/2014	S <sup>(1)</sup>		25,000 <sup>(1)</sup>	D	\$39.253	1,661	D	
Common Stock	01/02/2014	01/02/2014	M <sup>(1)</sup>		4,000 <sup>(1)</sup>	A	\$14.47	5,661	D	
Common Stock	01/02/2014	01/02/2014	S <sup>(1)</sup>		4,000 <sup>(1)</sup>	D	\$4	1,661	D	
Common Stock	01/02/2014	01/02/2014	M <sup>(2)</sup>		2,500 <sup>(2)</sup>	A	\$14.47	2,674	I	By Wife
Common Stock	01/02/2014	01/02/2014	S <sup>(2)</sup>		2,500 <sup>(2)</sup>	D	\$39.253	174	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	Amount or Number of Shares				
Employee Stock Option (right to buy)	\$39.87	01/02/2014	01/02/2014	A		187,500		01/02/2015 <sup>(3)</sup>	01/01/2021	Common Stock	187,500	\$0	187,500	D	
Employee Stock Option (right to buy)	\$39.87	01/02/2014	01/02/2014	A		8,500		01/02/2015 <sup>(4)</sup>	01/01/2021	Common Stock	8,500	\$0	8,500	I	By Wife

Explanation of Responses:

- Acquired as a result of exercising a stock option pursuant to a Rule 10b5-1 Trading Plan. The purchase and sale reported on this Form 4 was effective pursuant to a Rule 10b5-1 Trading Plan adopted by the reporting person on 8/6/13.
- Acquired as a result of exercising a stock option pursuant to a Rule 10b5-1 Trading Plan. The purchase and sale reported on this Form 4 was effective pursuant to a Rule 10b5-1 Trading Plan adopted by the reporting person's wife on 8/6/13.
- Grant of 1/2/14 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan. 25% of the shares subject to the option vest and become exercisable on 1/2/15. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 46,875 shares per year. The option shall be fully vested and exercisable on 1/2/18. The option is exercisable as to 0 shares on 1/2/14.
- Grant of 1/2/14 to reporting person's wife of stock options under the Isis Pharmaceuticals, Inc. 2011 Equity Incentive Plan. 25% of the shares subject to the option vest and become exercisable on 1/2/15. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 2,125 shares per year. The option shall be fully vested and exercisable on 1/2/18. The option is exercisable as to 0 shares on 1/2/14.

Remarks:

/s/Stanley T. Crooke

01/02/2014

\*\* 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.

POWER OF ATTORNEY

Know all by these presents, that the undersigned hereby constitutes and appoints each of Stanley T. Crooke and B. Lynne Parshall, signing individually, the undersigned (1) execute for and on behalf of the undersigned, an officer, director or holder of 10% or more of a registered class of securities of Isis Pharmaceuticals, Inc. (2) do and perform any and all acts for and on behalf of the undersigned that may be necessary or desirable to complete and execute such Form 3, 4 or 5, complete and (3) take any other action of any nature whatsoever in connection with the foregoing which, in the opinion of such attorney-in-fact, may be of benefit, in the best interest of the undersigned. The undersigned hereby grants to each such attorney-in-fact full power and authority to do and perform any and every act and thing whatsoever requisite, necessary, and proper to carry out the powers and authority herein granted. This Power of Attorney shall remain in full force and effect until the earliest to occur of (a) the undersigned is no longer required to file Forms 3, 4 and 5 with the SEC.

IN WITNESS WHEREOF, the undersigned has caused this Power of Attorney to be executed as of this 9th day of September, 2002.

/s/Stanley T. Crooke