

| OMB APPROVAL                                 |           |
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**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

|  |   |   |
|--|---|---|
| 1. Name and Address of Reporting Person*<br><b>CROOKE STANLEY T</b><br><br>(Last) (First) (Middle)<br><b>C/O ISIS PHARMACEUTICALS, INC.</b><br><b>2855 GAZELLE COURT</b><br><br>(Street)<br><b>CARLSBAD CA 92010</b><br><br>(City) (State) (Zip) | 2. Issuer Name and Ticker or Trading Symbol<br><b>ISIS PHARMACEUTICALS INC [ ISIS ]</b> | 5. Relationship of Reporting Person(s) to Issuer (Check all applicable)<br><input checked="" type="checkbox"/> Director 10% Owner<br><input checked="" type="checkbox"/> Officer (give title below) Other (specify below)<br><b>Chairman, CEO and President</b> |
|  | 3. Date of Earliest Transaction (Month/Day/Year)<br><b>01/30/2013</b>                   |   |
|  | 4. If Amendment, Date of Original Filed (Month/Day/Year)                                | 6. Individual or Joint/Group Filing (Check Applicable Line)<br><input checked="" type="checkbox"/> Form filed by One Reporting Person<br>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 |   |  |   |

**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 |
| Restricted Stock Units                     | (1)  | 01/30/2013                           | 01/30/2013   | A                              |   | 22,190   |     | (2)  | (2)             | Common Stock  | 22,190                                     | \$0  | 22,190  | D  |       |
| Employee Stock Option (right to buy)       | \$14.69  | 01/30/2013                           | 01/30/2013   | A                              |   | 133,180  |     | 01/02/2014 <sup>(3)</sup>                                | 01/29/2020      | Common Stock  | 133,180                                    | \$0  | 133,180   | D  |       |

**Explanation of Responses:**

- Each restricted stock unit represents a contingent right to receive one share of Isis common stock, or its equivalent cash value.
- Grant of 1/30/2013 to reporting person of Restricted Stock Units under the Isis Pharmaceuticals, Inc., 2011 Equity Incentive Plan. Restricted Stock Units vest in four equal annual installments, the first installment vesting on January 15, 2014. Upon vesting, the restricted stock units will be paid out in whole shares of Isis common stock or cash as may be determined by the Company. The RSU shall be fully vested on January 15, 2017. The RSU is vested as to 0 shares on January 30, 2013.
- Grant of 1/30/2013 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 1/2/2014. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 33,295 shares per year. The option is exercisable as to 0 shares on 1/30/2013.

**Remarks:**

/s/Stanley T. Crooke

02/01/2013

\*\* 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.