

| 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>COO, President</b> |
|   | 3. Date of Earliest Transaction (Month/Day/Year)<br><b>01/02/2013</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><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 |   |  |   |

**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)       | \$10.82  | 01/02/2013                           | 01/02/2013   | A                              |   | 10,000   |     | (1)  | 01/01/2020      | Common Stock  | 10,000                                     | \$0  | 10,000  | I  | By Wife |

**Explanation of Responses:**

1. Grant of 1/2/13 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 vest and become exercisable on 1/2/14. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 2,500 shares per year. The option is exercisable as to 0 on 1/2/13.

**Remarks:**

/s/Stanley T. Crooke 01/03/2013  
 \*\* 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.