

| 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><u>REED JOHN C</u><br><br>(Last) (First) (Middle)<br><u>C/O ISIS PHARMACEUTICALS, INC.</u><br><u>1896 RUTHERFORD ROAD</u><br><br>(Street)<br><u>CARLSBAD CA 92008</u><br><br>(City) (State) (Zip) | 2. Issuer Name and Ticker or Trading Symbol<br><u>ISIS PHARMACEUTICALS INC [ ISIS ]</u> | 5. Relationship of Reporting Person(s) to Issuer (Check all applicable)<br><input checked="" type="checkbox"/> Director 10% Owner<br><br>Officer (give title below) Other (specify below) |
|   | 3. Date of Earliest Transaction (Month/Day/Year)<br><u>07/01/2008</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 |   |  |   |

**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 |
| Director Stock Option (right to buy)       | \$13.88  | 07/01/2008                           | 07/01/2008   | A                              |   | 15,000   |     | 07/01/2009 <sup>(1)</sup>                                | 06/30/2018      | Common Stock  | 15,000                                     | \$0  | 15,000  | D  |       |

**Explanation of Responses:**

1. Grant of 7-1-08 to reporting person of stock options under the Isis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan. The option vests and becomes exercisable in four equal annual installments, with the first installment vesting on 7-1-09. The option shall be fully vested and exercisable on 7-1-12. The option is exercisable as to 0 shares on 7-1-08.

**Remarks:**

/s/B. Lynne Parshall, Attorney-in-Fact 07/01/2008

\*\* 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.