

| OMB APPROVAL                                 |           |
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| OMB Number:                                  | 3235-0287 |
| Estimated average burden hours per response: | 0.5       |

**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

|  |  |   |
|--|--|---|
| <b>1. Name and Address of Reporting Person *</b><br><u>MUTO FREDERICK T</u><br><br>(Last) (First) (Middle)<br><u>C/O ISIS PHARMACEUTICALS, INC.</u><br><u>2855 GAZELLE COURT</u><br><br>(Street)<br><u>CARLSBAD CA 92010</u><br><br>(City) (State) (Zip) | <b>2. Issuer Name and Ticker or Trading Symbol</b><br><u>ISIS PHARMACEUTICALS INC [ ISIS ]</u> | <b>5. Relationship of Reporting Person(s) to Issuer</b><br>(Check all applicable)<br><input checked="" type="checkbox"/> Director 10% Owner<br><br>Officer (give title below) Other (specify below) |
|  | <b>3. Date of Earliest Transaction (Month/Day/Year)</b><br><u>06/01/2015</u>                   |   |
|  | <b>4. If Amendment, Date of Original Filed (Month/Day/Year)</b>                                |   |
| <b>6. Individual or Joint/Group Filing (Check Applicable Line)</b><br><input checked="" type="checkbox"/> Form filed by One Reporting Person<br><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    |   |  |   |
| Common Stock                    | 06/01/2015                           | 06/01/2015   | M <sup>(1)</sup>               |   | 10,000 <sup>(1)</sup>   | A          | \$3.95   | 11,095  | D  |   |
| Common Stock                    | 06/01/2015                           | 06/01/2015   | S <sup>(1)</sup>               |   | 10,000 <sup>(1)</sup>   | D          | \$66.911 | 1,095   | D  |   |
| Common Stock                    |                                      |  |                                |   |   |            |          | 1,500   | I  | By Cooley Godward Kronish LLP Sal Def & PSP U/A DTD 2/1/74 Pension Plan |

**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 |
| Non-Employee Director stock option (right to buy) | \$3.95   | 06/01/2015                           | 06/01/2015   | M                              |   |  | 10,000 | 07/01/2009   | 06/30/2015      | Common Stock  | 10,000                                     | \$0  | 0   | D  |       |

**Explanation of Responses:**

1. Acquired as a result of exercising a stock option that was scheduled to expire on 6/30/2015. 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 5/5/2013.

**Remarks:**

/s/B. Lynne Parshall, attorney-in-fact 06/03/2015

\*\* 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.