

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

| OMB APPROVAL | |
|--|-----------|
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| | | |
|---|---|--|
| 1. Name and Address of Reporting Person* <u>KLEIN JOSEPH III</u> (Last) (First) (Middle) C/O ISIS PHARMACEUTICALS, INC. 2855 GAZELLE COURT (Street) CARLSBAD CA 92010 (City) (State) (Zip) | 2. Issuer Name and Ticker or Trading Symbol <u>ISIS PHARMACEUTICALS INC [ISIS]</u> | 5. Relationship of Reporting Person(s) to Issuer (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner Officer (give title below) Other (specify below) |
| | 3. Date of Earliest Transaction (Month/Day/Year) 03/19/2013 | |
| | 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 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 | 03/19/2013 | 03/19/2013 | M ⁽¹⁾ | | 3,726 ⁽¹⁾ | A | \$5.93 | 3,826 | I | By Son |
| Common Stock | 03/19/2013 | 03/19/2013 | S ⁽¹⁾ | | 3,726 ⁽¹⁾ | D | \$18 | 100 | I | By Son |
| Common Stock | 03/19/2013 | 03/19/2013 | M ⁽¹⁾ | | 3,726 ⁽¹⁾ | A | \$5.93 | 3,726 | I | By Daughter |
| Common Stock | 03/19/2013 | 03/19/2013 | S ⁽¹⁾ | | 3,726 ⁽¹⁾ | D | \$18 | 0 | I | By Daughter |
| Common Stock | 03/19/2013 | 03/19/2013 | M ⁽¹⁾ | | 3,727 ⁽¹⁾ | A | \$5.93 | 3,727 | I | By Son |
| Common Stock | 03/19/2013 | 03/19/2013 | S ⁽¹⁾ | | 3,727 ⁽¹⁾ | D | \$18 | 0 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 3,750 ⁽¹⁾ | A | \$13.88 | 3,850 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 3,750 ⁽¹⁾ | D | \$18 | 100 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 4,166 ⁽¹⁾ | A | \$9.77 | 4,266 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 4,166 ⁽¹⁾ | D | \$18 | 100 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 2,500 ⁽¹⁾ | A | \$16.32 | 2,600 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 2,500 ⁽¹⁾ | D | \$18 | 100 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 1,250 ⁽¹⁾ | A | \$9.22 | 1,350 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 1,250 ⁽¹⁾ | D | \$18 | 100 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 173 ⁽¹⁾ | A | \$5.93 | 273 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 173 ⁽¹⁾ | D | \$18 | 100 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 3,750 ⁽¹⁾ | A | \$13.88 | 3,750 | I | By Daughter |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 3,750 ⁽¹⁾ | D | \$18 | 0 | I | By Daughter |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 4,167 ⁽¹⁾ | A | \$9.77 | 4,167 | I | By Daughter |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 4,167 ⁽¹⁾ | D | \$18 | 0 | I | By Daughter |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 2,500 ⁽¹⁾ | A | \$16.32 | 2,500 | I | By Daughter |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 2,500 ⁽¹⁾ | D | \$18 | 0 | I | By Daughter |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 1,250 ⁽¹⁾ | A | \$9.22 | 1,250 | I | By Daughter |

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 | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 1,250 ⁽¹⁾ | D | \$18 | 0 | I | By Daughter |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 174 ⁽¹⁾ | A | \$5.93 | 174 | I | By Daughter |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 174 ⁽¹⁾ | D | \$18 | 0 | I | By Daughter |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 3,750 ⁽¹⁾ | A | \$13.88 | 3,750 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 3,750 ⁽¹⁾ | D | \$18 | 0 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | M ⁽¹⁾ | | 4,167 ⁽¹⁾ | A | \$9.77 | 4,167 | I | By Son |
| Common Stock | 03/20/2013 | 03/20/2013 | S ⁽¹⁾ | | 4,167 ⁽¹⁾ | D | \$18 | 0 | I | By Son |

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 | | | | |
| Director Stock Option (right to buy) | \$5.93 | 03/19/2013 | 03/19/2013 | M | | 3,726 | | 07/03/2010 | 07/02/2016 | Common Stock | 3,726 | \$0 | 173 | I | By Son |
| Director Stock Option (right to buy) | \$5.93 | 03/19/2013 | 03/19/2013 | M | | 3,726 | | 07/03/2010 | 07/02/2016 | Common Stock | 3,726 | \$0 | 174 | I | By Daughter |
| Director Stock Option (right to buy) | \$5.93 | 03/19/2013 | 03/19/2013 | M | | 3,727 | | 07/03/2010 | 07/02/2016 | Common Stock | 3,727 | \$0 | 174 | I | By Son |
| Director Stock Option (right to buy) | \$13.88 | 03/20/2013 | 03/20/2013 | M | | 3,750 | | 07/01/2009 | 06/30/2018 | Common Stock | 3,750 | \$0 | 0 | I | By Son |
| Director Stock Option (right to buy) | \$9.77 | 03/20/2013 | 03/20/2013 | M | | 4,166 | | 07/02/2011 | 07/01/2017 | Common Stock | 4,166 | \$0 | 0 | I | By Son |
| Director Stock Option (right to buy) | \$16.32 | 03/20/2013 | 03/20/2013 | M | | 2,500 | | 07/01/2011 | 06/30/2019 | Common Stock | 2,500 | \$0 | 0 | I | By Son |
| Director Stock Option (right to buy) | \$9.22 | 03/20/2013 | 03/20/2013 | M | | 1,250 | | 07/01/2011 | 06/30/2020 | Common Stock | 1,250 | \$0 | 0 | I | By Son |
| Director Stock Option (right to buy) | \$5.93 | 03/20/2013 | 03/20/2013 | M | | 173 | | 07/03/2010 | 07/02/2016 | Common Stock | 173 | \$0 | 0 | I | By Son |
| Director Stock Option (right to buy) | \$13.88 | 03/20/2013 | 03/20/2013 | M | | 3,750 | | 07/01/2010 | 06/30/2018 | Common Stock | 3,750 | \$0 | 0 | I | By Daughter |
| Director Stock Option (right to buy) | \$9.77 | 03/20/2013 | 03/20/2013 | M | | 4,167 | | 07/02/2011 | 07/01/2017 | Common Stock | 4,167 | \$0 | 0 | I | By Daughter |

**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 | | | | |
| Director Stock Option (right to buy) | \$16.32 | 03/20/2013 | 03/20/2013 | M | | | 2,500 | 07/01/2011 | 06/30/2019 | Common Stock | 2,500 | \$0 | 0 | I | By Daughter |
| Director Stock Option (right to buy) | \$9.22 | 03/20/2013 | 03/20/2013 | M | | | 1,250 | 07/01/2011 | 06/30/2020 | Common Stock | 1,250 | \$0 | 0 | I | By Daughter |
| Director Stock Option (right to buy) | \$5.93 | 03/20/2013 | 03/20/2013 | M | | | 174 | 07/03/2010 | 07/02/2016 | Common Stock | 174 | \$0 | 0 | I | By Daughter |
| Director Stock Option (right to buy) | \$13.88 | 03/20/2013 | 03/20/2013 | M | | | 3,750 | 07/01/2011 | 06/30/2018 | Common Stock | 3,750 | \$0 | 0 | I | By Son |
| Director Stock Option (right to buy) | \$9.77 | 03/20/2013 | 03/20/2013 | M | | | 4,167 | 07/02/2011 | 07/01/2017 | Common Stock | 4,167 | \$0 | 0 | I | By Son |
| Director Stock Option (right to buy) | \$16.32 | 03/20/2013 | 03/20/2013 | M | | | 2,500 | 07/01/2011 | 06/30/2019 | Common Stock | 2,500 | \$0 | 0 | I | By Son |
| Director Stock Option (right to buy) | \$9.22 | 03/20/2013 | 03/20/2013 | M | | | 1,250 | 07/01/2011 | 06/30/2020 | Common Stock | 1,250 | \$0 | 0 | I | By Son |
| Director Stock Option (right to buy) | \$5.93 | 03/20/2013 | 03/20/2013 | M | | | 174 | 07/03/2010 | 07/02/2016 | Common Stock | 174 | \$0 | 0 | I | By Son |

Explanation of Responses:

1. 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 9/7/12.

Remarks:

Report 1 of 2

/s/B. Lynne Parshall, Attorney- 03/21/2013
in-Fact

** 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.