

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>BROWN RICHARD K</u> (Last) (First) (Middle) <u>C/O ISIS PHARMACEUTICALS, INC.</u> <u>1896 RUTHERFORD ROAD</u> (Street) <u>CARLSBAD CA 92008</u> (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) Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <u>Vice President</u> |
| | 3. Date of Earliest Transaction (Month/Day/Year) <u>02/27/2006</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 | | | |
| Common Stock | 02/27/2006 | 02/27/2006 | M | | 3,715 | A | \$6.81 | 6,063 | D | |
| Common Stock | 02/27/2006 | 02/27/2006 | s ⁽¹⁾ | | 500 ⁽¹⁾ | D | \$8.07 | 5,563 | D | |
| Common Stock | 02/27/2006 | 02/27/2006 | s ⁽¹⁾ | | 500 ⁽¹⁾ | D | \$8.08 | 5,063 | D | |
| Common Stock | 02/27/2006 | 02/27/2006 | s ⁽¹⁾ | | 1,015 ⁽¹⁾ | D | \$8.09 | 4,048 | D | |
| Common Stock | 02/27/2006 | 02/27/2006 | s ⁽¹⁾ | | 700 ⁽¹⁾ | D | \$8.1 | 3,348 | D | |
| Common Stock | 02/27/2006 | 02/27/2006 | s ⁽¹⁾ | | 1,000 ⁽¹⁾ | D | \$8.17 | 2,348 | D | |
| Common Stock | 02/28/2006 | 02/28/2006 | M | | 2,000 | A | \$6.81 | 4,348 | D | |
| Common Stock | 02/28/2006 | 02/28/2006 | s ⁽¹⁾ | | 2,000 ⁽¹⁾ | D | \$8.01 | 2,348 | D | |

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) | \$6.81 | 02/27/2006 | 02/27/2006 | M | | | 3,715 | 01/02/2005 ⁽²⁾ | 01/01/2014 | Common Stock | 3,715 | \$0 | 4,660 | D | |
| Employee Stock Option (right to buy) | \$6.81 | 02/28/2006 | 02/28/2006 | M | | | 2,000 | 01/02/2005 ⁽³⁾ | 01/01/2014 | Common Stock | 2,000 | \$0 | 2,660 | D | |

Explanation of Responses:

- The sale reported in this Form 4 was effected pursuant to a Rule 10b5-1 trading plan adopted by the reporting person on 2-16-06.
- Stock option under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vested and became exercisable on 1-2-05. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 4,500 shares per year. The option was exercisable as to 4,660 shares on 2-27-06.
- Stock option under the Isis Pharmaceuticals, Inc. 1989 Stock Option Plan. 25% of the shares subject to the option vested and became exercisable on 1-2-05. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 4,500 shares per year. The option was exercisable as to 2,660 shares on 2-28-06.

Remarks:

/s/B. Lynne Parshall, Attorney-in-Fact 03/01/2006

** 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.

