FORM 4

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washin

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

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| gton, D.C. 20549 | OMB APPROVAL |
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| | OMB Number: | 3235-0287 |
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| ı | hours por rosponso: | 0.5 |

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

| 2. Issuer Name and Ticker or Trading Symbol ISIS PHARMACEUTICALS INC [ISIS] PHARMACEUTICALS INC [ISIS] (Last) (First) (Middle) C/O ISIS PHARMACEUTICALS, INC. 1896 RUTHERFORD ROAD CARLSBAD CA 92008 Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially (Month/Day/Year) Page (Month/Day/Year) 2. Transaction A Securities Acquired (A) or light and point (Instr. 4) (Instr. 4) Common Stock 03/07/2006 2. Issuer Name and Ticker or Trading Symbol ISIS PHARMACEUTICALS INC [ISIS] 1. Date of Earliest Transaction (Month/Day/Year) 03/07/2006 3. Date of Earliest Transaction (Month/Day/Year) 03/07/2006 4. If Armendment, Date of Original Filed (Month/Day/Year) (City) (State) (Zip) 5. Individual or Joint/Group Filing (Check Applicable Line) X Form filed by More than One Reporting Person Form filed by One Reporting P | | | | | | | | | | | | | | | | | | |
|--|---------------------------|------------|---------------|---------------------------------|--|--|---|------------------|---|--|-------------------------------------|--|---|--|--|--|--|--|
| Common Stock Comm | . 3 | | | | | | | | , | | | | | | | | | |
| Common Stock Common Stock Common Stock Columbra S | BROWN RICHARD K | | | | | THIRDITO | 10 11 | <u> </u> | <u>10 11 (C</u> [1 | | Director | 10% C | Owner | | | | | |
| (Carret) CARLSBAD CA 92008 Table 1 - Non-Derivative Securities Acquired, (Month/Day/Year) [Street) CARLSBAD [City] (State) Table 1 - Non-Derivative Securities Acquired, (Month/Day/Year) [Month/Day/Year] (Month/Day/Year) Todae (Month/Day/Year) [Month/Day/Year] (Month/Day/Year) [Month/Day/Year] (Month/Day/Year) [Month/Day/Year] (Month/Day/Year) [Month/Day/Year] (Month/Day/Year) [Month/Day/Year] (Month/Day/Year) [Month/Day/Year] (Month/Day/Year) [Month/Day/Year] (Month/Day/Year) [Month/Day/Year] (Month/Day/Year) (Month/Da | | | | | | | | | | | _ x | | | | | | | |
| Common Stock 03/07/2006 03/07/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D Common Stock 03/08/2006 M 2,770 A \$6.84 5,118 D C | (Last) (First) (Middle) | | | | ` ' ' | | | | | | | '''' | | | | | | |
| Carlor C | C/O ISIS PHAR | RMACEUTICA | ALS, INC. | | 03/07/2006 | | | | | | | Vice President | | | | | | |
| Carlor C | 1896 RUTHER | FORD ROAD | | | | | | | | | | | | | | | | |
| Carlo Carl | 1000 110 111210 | rond north | | Ì | 4 If Amendment Date of Original Filed (Month/Day/Year) | | | | | | | 6. Individual or Joint/Group Filing (Check Applicable | | | | | | |
| Carl Sand Carro Carl Carro | (Street) | | | | | , | Ü | | ` , | , | | · | | ·· | | | | |
| City (State) (Zip) | , | CA | 92008 | | | | | | | | X | Form filed by One | Reporting Person | on | | | | |
| City (State City | CHILDDID | CII | 32000 | | | | | | | | | | e than One Repo | orting | | | | |
| Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned 2. Transaction Date (Month/Day/Year) 2. Transaction Date (Indirect Date (In | (City) | (Stato) | (7in) | | | | | | | | | Person | | | | | | |
| 1. Title of Security (Instr. 3) 2. Transaction Date (Month/Day/Year) 2. Transaction Date (Month/Day/Year) 2. Transaction Date (Month/Day/Year) 2. Deemed Execution Date, if any (Month/Day/Year) Code v Amount (A) or (D) (Instr. 3, 4 and 5) Common Stock 03/07/2006 | (City) | (State) | (Zip) | | | | | | | - 1 | | | | | | | | |
| $ \begin{array}{c ccccccccccccccccccccccccccccccccccc$ | | | | | | | | | | | | | | | | | | |
| Common Stock 03/07/2006 03/07/2006 M 2,000 A \$6.84 4,348 D Common Stock 03/07/2006 03/07/2006 s(1) 2,000(1) D \$7.97 2,348 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D | | | Table I - Noi | า-Deriva | tive S | ecurities Acq | uired, | Disp | osed of, c | r Ben | eficially | Owned | | | | | | |
| Common Stock 03/07/2006 03/07/2006 s(1) 2,000(1) D \$7.97 2,348 D Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D | 1. Title of Security | (Instr. 3) | Table I - Noi | 2. Transac Date | ction | 2A. Deemed Execution Date, if any | 3. Transa Code (| ction | 4. Securities | Acquired | (A) or | 5. Amount of Securities Beneficially Owned Following | Form: Direct (D) or Indirect | of Indirect Beneficial Ownership | | | | |
| Common Stock 03/08/2006 03/08/2006 M 2,770 A \$6.84 5,118 D | 1. Title of Security | (Instr. 3) | Table I - Noi | 2. Transac Date | ction | 2A. Deemed Execution Date, if any | 3. Transa Code (8) | action Instr. | 4. Securities Disposed Of (5) | Acquired (D) (Instr. | (A) or 3, 4 and | 5. Amount of Securities Beneficially Owned Following Reported Transaction(s) | Form: Direct (D) or Indirect | of Indirect Beneficial Ownership | | | | |
| | | (Instr. 3) | Table I - Noi | 2. Transac Date (Month/Da | ction ay/Year) | 2A. Deemed Execution Date, if any (Month/Day/Year) | 3. Transa Code (8) | action Instr. | 4. Securities a Disposed Of (5) Amount | Acquired (D) (Instr. (A) or (D) | (A) or 3, 4 and | 5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4) | Form: Direct (D) or Indirect (I) (Instr. 4) | of Indirect Beneficial Ownership | | | | |
| Common Stock 03/08/2006 03/08/2006 s ⁽¹⁾ 500 ⁽¹⁾ D \$8.09 4,618 D | Common Stock | (Instr. 3) | Table I - Noi | 2. Transac Date (Month/Da | etion ay/Year) 2006 | 2A. Deemed Execution Date, if any (Month/Day/Year) | 3. Transa Code (8) Code | action Instr. | 4. Securities ADISPOSED OF (5) Amount 2,000 | Acquired (D) (Instr. | (A) or 3, 4 and Price \$6.84 | 5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4) | Form: Direct (D) or Indirect (I) (Instr. 4) | of Indirect Beneficial Ownership | | | | |
| | Common Stock Common Stock | (Instr. 3) | Table I - Nor | 2. Transac Date (Month/Da | 2006 2006 | 2A. Deemed Execution Date, if any (Month/Day/Year) 03/07/2006 03/07/2006 | 3. Transa Code (8) Code M | action Instr. | 4. Securities of Disposed Of (5) Amount 2,000 2,000(1) | (A) or (D) A | (A) or 3, 4 and Price \$6.84 \$7.97 | 5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4) 4,348 | Form: Direct (D) or Indirect (I) (Instr. 4) | of Indirect Beneficial Ownership | | | | |

Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

S⁽¹⁾

S⁽¹⁾

S⁽¹⁾

S⁽¹⁾

500(1)

500⁽¹⁾

500(1)

770(1)

\$8.15

\$8.07

\$8.04

\$8.01

D

D

D

4,118

3,618

3,118

2,348

D

D

D

03/08/2006

03/08/2006

03/08/2006

03/08/2006

| | | | | • | • | | | | | | | | | | |
|---|---|--|---|------------------------------|---|--|-------------------------|---------------------------|--|-----------------|--|-----|--|--|--|
| 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. Transa Code (8) | | of Deri Sec Acq (A) o Disp of (I | oosed O) tr. 3, 4 | Expiration Da | 6. Date Exercisable and Expiration Date (Month/Day/Year) | | 7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4) | | 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 | | | | |
| Employee Stock Option (right to buy) | \$6.84 | 03/07/2006 | 03/07/2006 | М | | | 2,000 | 01/02/2004 ⁽²⁾ | 05/24/2006 | Common Stock | 2,000 | \$0 | 2,770 | D | |
| Employee Stock Option (right to buy) | \$6.84 | 03/08/2006 | 03/08/2006 | M | | | 2,770 | 01/02/2004 ⁽³⁾ | 05/24/2006 | Common Stock | 2,770 | \$0 | 0 | D | |

Explanation of Responses:

Common Stock

Common Stock

Common Stock

Common Stock

 $1. \ The sale\ reported in this\ Form\ 4\ was\ effected\ pursuant\ to\ a\ Rule\ 10b5-1\ trading\ plan\ adopted\ by\ the\ reporting\ person\ on\ 2-16-06.$

03/08/2006

03/08/2006

03/08/2006

03/08/2006

- 2. Stock option under the Isis Pharmaceuticals, Inc. 2000 Broad-Based Equity Incentive Plan. 25% of the shares subject to the option vested and became exercisable on 1-2-04. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 4,125 shares per year. The option was exercisable as to 4770 shares on 3-7-06 prior to the reported exercise.
- 3. Stock option under the Isis Pharmaceuticals, Inc. 2000 Broad-Based Equity Incentive Plan. 25% of the shares subject to the option vested and became exercisable on 1-2-04. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 4,125 shares per year. The option was exercisable as to 2770 shares on 3-8-06 prior to the reported exercise.

Remarks:

/s/B. Lynne Parshall, Attorney-**In-Fact**

03/09/2006

** 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.

| Persons who respond to the collection of information of | contained in this form are not req | uired to respond unless the form di | splays a currently valid OMB Number. |
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