

| 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

| | | |
|---|---|---|
| 1. Name and Address of Reporting Person* BENNETT C FRANK (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 ISIS PHARMACEUTICALS INC [ISIS] | 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) SVP, Antisense Research |
| | 3. Date of Earliest Transaction (Month/Day/Year) 08/27/2014 | |
| 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 | 08/27/2014 | 08/27/2014 | M ⁽¹⁾ | | 2,000 ⁽¹⁾ | A | \$15.38 | 6,627 | D | |
| Common Stock | 08/27/2014 | 08/27/2014 | S ⁽¹⁾ | | 2,000 ⁽¹⁾ | D | \$40.5 | 4,627 | D | |
| Common Stock | 08/27/2014 | 08/27/2014 | M ⁽¹⁾ | | 1,000 ⁽¹⁾ | A | \$15.38 | 5,627 | D | |
| Common Stock | 08/27/2014 | 08/27/2014 | S ⁽¹⁾ | | 1,000 ⁽¹⁾ | D | \$40.53 | 4,627 | D | |
| Common Stock | 08/27/2014 | 08/27/2014 | M ⁽¹⁾ | | 2,000 ⁽¹⁾ | A | \$15.38 | 6,627 | D | |
| Common Stock | 08/27/2014 | 08/27/2014 | S ⁽¹⁾ | | 2,000 ⁽¹⁾ | D | \$40.55 | 4,627 | 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) | \$15.38 | 08/27/2014 | 08/27/2014 | M | | | 5,000 | 01/02/2012 | 01/01/2015 | Common Stock | 5,000 | \$0 | 0 | D | |

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 5/22/14.

Remarks:

/s/C. Frank Bennett 08/28/2014

** 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.