

| OMB APPROVAL | |
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STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934 or Section 30(h) of the Investment Company Act of 1940

Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

| | | | | | | | | |
|--|--|--|---|--|--|--|--|--|
| 1. Name and Address of Reporting Person* BENNETT C. FRANK | | | 2. Issuer Name and Ticker or Trading Symbol IONIS PHARMACEUTICALS, INC [IONS] | | | 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 | | |
| (Last) (First) (Middle) C/O IONIS PHARMACEUTICALS, INC. 2855 GAZELLE COURT | | | 3. Date of Earliest Transaction (Month/Day/Year) 01/01/2016 | | | | | |
| (Street) CARLSBAD CA 92010 | | | 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 <input type="checkbox"/> Form filed by More than One Reporting Person | | |
| (City) (State) (Zip) | | | | | | | | |

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 | 01/01/2016 | 01/01/2016 | j ⁽³⁾ | v | 89 | A | \$47.7105 | 7,405 | 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 | | | | | |
| Employee Stock Option (right to buy) | \$61.68 | 01/04/2016 | 01/04/2016 | A | | 38,240 | | 01/04/2017 ⁽²⁾ | 01/03/2023 | Common Stock | \$0 | 38,240 | D | |

Explanation of Responses:

- Reporting 89 shares acquired under the Ionis Pharmaceuticals, Inc. Amended and Restated 2000 Employee Stock Purchase Plan on January 1, 2016. These 89 shares may not be sold until July 2, 2016.
- Grant of 1/4/2016 to reporting person of stock options under the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan. 25% of the shares subject to the option vest and become exercisable on 1/4/2017. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 9,560 shares per year. Following this transaction, the option was exercisable as to 0 on 1/4/2016.

Remarks:

/s/B. Lynne Parshall, attorney-in-fact

01/04/2016

** 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.

POWER OF ATTORNEY

Know all by these presents, that the undersigned hereby constitutes and appoints each of Stanley T. Crooke and B. Lynne Parshall, signing individually, the undersigned (1) execute for and on behalf of the undersigned, an officer, director or holder of 10% or more of a registered class of securities of Isis Pharmaceuticals, Inc. (Isis), (2) do and perform any and all acts for and on behalf of the undersigned that may be necessary or desirable to complete and execute such Form 3, 4 or 5, complete and file such Form 3, 4 or 5, (3) take any other action of any nature whatsoever in connection with the foregoing which, in the opinion of such attorney-in-fact, may be of benefit, in the best interest of Isis. The undersigned hereby grants to each such attorney-in-fact full power and authority to do and perform any and every act and thing whatsoever requisite, necessary, convenient or proper in the premises, and which may in anywise relate to the foregoing, and to execute and file the same. This Power of Attorney shall remain in full force and effect until the earliest to occur of (a) the undersigned is no longer required to file Forms 3, 4 and 5 with the SEC.

IN WITNESS WHEREOF, the undersigned has caused this Power of Attorney to be executed as of this 22nd day of November, 2002.

/S/C. Frank Bennett