FORM 4

## UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

| OMB APPROVAL        |           |  |  |  |  |  |  |  |  |
|---------------------|-----------|--|--|--|--|--|--|--|--|
| OMB Number:         | 3235-0287 |  |  |  |  |  |  |  |  |
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hours per response:

|   | Check this box if no longer subject to |
|---|--|
| ١ | 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

|  |  |  |           |                  | 01 0  | COLIOII  | 00(11)  | OI LIIC  |   | CIII CC | прапу Аст             | 01 1340   |                            |  |                        |  |   |  |
|--|--|--|-----------|------------------|---|--|---|--|---|---------|-----------------------|---|----------------------------|--|------------------------|--|---|--|
| Name and Address of Reporting Person*     BENNETT C FRANK                  |  |  |           |                  |   | 2. Issuer Name and Ticker or Trading Symbol IONIS PHARMACEUTICALS INC I IONS |   |  |   |         |                       |   |                            | Relationship of Reporting Persor (Check all applicable)     Director     X     Officer (give title   |                        |  |   | Owner<br>(specify  |
| (Last) (First) (Middle) C/O IONIS PHARMACEUTICALS, INC. 2855 GAZELLE COURT |  |  |           |                  | 3. Date of Earliest Transaction (Month/Day/Year) 07/01/2018 |  |   |  |   |         |                       |   |                            | SVP, Antisense Research  |                        |  |   |  |
| (Street) CARLSBAD CA 92010 (City) (State) (Zip)                            |  |  |           |                  | 4. If A   | 4. If Amendment, Date of Original Filed (Month/Day/Year)                     |   |  |   |         |                       |   |                            | Individual or Joint/Group Filing (Check Applicable Line)     X Form filed by One Reporting Person     Form filed by More than One Reporting Person |                        |  |   |  |
|  |  | Tabl                                       | le I - N  | on-Deriv         | ative   | Secu   | ıritie  | s Ac   | quirec  | l, Di   | sposed o              | f, or E   | Benefic                    | ially (  | Owne                   | ed   |   |  |
| 1. Title of Security (Instr. 3)  2. Transacti Date (Month/Day              |  |  |           | (Year) Execution |   | A. Deemed<br>Execution Date,<br>f any<br>Month/Day/Year)                     |   | 3. 4. Securitie<br>Transaction<br>Code (Instr.<br>8) |   |         |                       |   | and 5) Secu<br>Bene<br>Own |  | icially<br>d Following | 6. Ownership<br>Form: Direct<br>(D) or Indirect<br>(I) (Instr. 4)                                | 7. Nature<br>of Indirect<br>Beneficial<br>Ownership               |  |
|  |  |  |           |                  |   |  |   |  | Code  | v       | Amount                | (A) 01<br>(D)   | Price                      | Tra  |                        | ted<br>action(s)<br>3 and 4)   |   | (Instr. 4)   |
| Common Stock 07/01/2   |  |  |           |                  |   | 2018 07/01/2018  |   | <b>J</b> <sup>(1)</sup>                              | V   | 282(1)  | A                     | \$35.4  | 85.4195                    |  | .9,396                 | D  |   |  |
|  |  | Та   | able II - |                  |   |  |   |  |   |         | osed of,<br>convertib |   |                            |  | vned                   |  |   |  |
|  |  | 3. Transaction<br>Date<br>(Month/Day/Year) | if any    | on Date,         | Code (Instr.  |  | 5. Nur<br>of<br>Deriva<br>Secur<br>Acqui<br>(A) or<br>Dispo<br>of (D)<br>(Instr.<br>and 5 | ative<br>rities<br>ired<br>osed                      | 6. Date Exercisable and Expiration Date (Month/Day/Year)  Date Expiration |         |                       | 7. Title and<br>Amount of<br>Securities<br>Underlying<br>Derivative<br>Security (Instr.<br>and 4) |                            | nt   |                        | 9. Number of derivative Securities Beneficially Owned Following Reported Transactions (Instr. 4) | Ownership<br>Form:<br>Direct (D)<br>or Indirect<br>(I) (Instr. 4) | 11. Nature<br>of Indirect<br>Beneficial<br>Ownership<br>(Instr. 4) |

## **Explanation of Responses:**

1. Reporting 282 shares acquired under the Ionis Pharmaceuticals, Inc. Amended and Restated 2000 Employee Stock Purchase Plan on July 1, 2018. These 282 shares may not be sold until January 2, 2019.

## Remarks:

/s/Patrick R. O'Neil, attorneyin-fact 07/03/2018

\*\* Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

- $^{\star}$  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.