FORM 4

## UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

## STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

| OMB APPROVAL             |     |  |  |  |  |  |  |  |
|--------------------------|-----|--|--|--|--|--|--|--|
| OMB Number: 3235-0287    |     |  |  |  |  |  |  |  |
| Estimated average burden |     |  |  |  |  |  |  |  |
| hours per response:      | 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 or Section 30(h) of the Investment Company Act of 1940

| 1. Name and Address of Reporting Person*  Baroldi Joseph  (Last) (First) (Middle)  2855 GAZELLE COURT |         |            |                |                | 2. Issuer Name and Ticker or Trading Symbol IONIS PHARMACEUTICALS INC [ IONS ]  3. Date of Earliest Transaction (Month/Day/Year) 01/03/2023 |  |   |                           |  |                         |   |                 | 5. Relationship of Reporting Person(s) to Issuer (Check all applicable)  Director 10% Owner  X Officer (give title Other (specify below)  EVP, Chief Business Officer |                       |   |  |   |           |
|---|---------|------------|----------------|----------------|---|--|---|---------------------------|--|-------------------------|---|-----------------|---|-----------------------|---|--|---|-----------|
| (Street) CARLSI   |         |            | 92010<br>(Zip) |                | 4.1   | 4. If Amendment, Date of Original Filed (Month/Day/Year)                           |   |                           |  |                         |   |                 | ne)<br>X Foi<br>Foi   | ,                     |   |  |   |           |
| 1. Title of Security (Instr. 3)  2. Trans. Date   |         |            |                |                | active Securities Ac<br>action 2A. Deemed<br>Execution Date,<br>if any<br>(Month/Day/Yea  |  |   | 3. Transaction Dispose 5) |  | 4. Securiti<br>Disposed | of, or Beneficities Acquired (A) or d Of (D) (Instr. 3, 4 a |                 | 5. Amount of  |                       | 6. Ownership<br>Form: Direct<br>(D) or Indirect<br>(I) (Instr. 4) |  | 7. Nature of<br>Indirect<br>Beneficial<br>Ownership<br>(Instr. 4) |           |
| (e.g., p  1. Title of   |         |            |                | outs, calls, v |   | 5. Numb<br>of<br>Derivati<br>Securiti<br>Acquire<br>(A) or<br>Dispose<br>of (D) (I | 5. Number of Exportantive Securities Acquired |                           | uired, Disposed of,<br>c, options, convertible<br>6. Date Exercisable and<br>Expiration Date<br>(Month/Day/Year) |                         |   |                 | 8. Price<br>Derivat<br>Securit  | o of 9. Numl derivati | ve<br>ies<br>ially<br>ng<br>ed<br>ction(s)                        | 10.<br>Ownership<br>Form:<br>Direct (D)<br>or Indirect<br>(I) (Instr. 4) | Beneficial<br>Ownership<br>ct (Instr. 4)                          |           |
|   |         |            |                | c              | ode   | v  | (A)   | (D)                       | Date<br>Exercisabl   |                         | Expiration<br>Date  | Title           | Amour<br>or<br>Number<br>of<br>Shares   | er                    |   |  |   |           |
| Non-<br>Qualified<br>Stock<br>Option<br>(right to<br>buy)   | \$37.58 | 01/03/2023 |                |                | Α   |  | 19,665  |                           | 01/03/2024   | µ(1)                    | 01/02/2033  | Common<br>Stock | 19,66   | 5 \$0.0               | 19,0  | 665  | D   |           |
| Non-<br>Qualified<br>Stock<br>Option<br>(right to<br>buy)   | \$37.58 | 01/03/2023 |                |                | A   |  | 2,400   |                           | 01/03/2024   | μ <sup>(2)</sup> (      | 01/02/2033  | Common<br>Stock | 2,400   | \$0.0                 | 2,4   | 00   | I   | by Spouse |

1. Grant on 01/03/2023 to reporting person of stock options under the Ionis Pharmaceuticals, Inc. Amended and Restated 2011 Equity Incentive Plan. Following this transaction, the option was exercisable as to 0 shares on 01/03/2023. 25% of the shares subject to the option will vest and become exercisable on 01/03/2024. Thereafter, the remaining shares subject to the option will vest and become exercisable in 36 equal monthly installments over the next 3 years.

2. Grant on 01/03/2023 to reporting person's spouse of stock options under the Ionis Pharmaceuticals, Inc. Amended and Restated 2011 Equity Incentive Plan. Following this transaction, the option was exercisable as to 0 shares on 01/03/2023. 25% of the shares subject to the option will vest and become exercisable on 01/03/2024. Thereafter, the remaining shares subject to the option will vest and become exercisable in 36 equal monthly installments over the next 3 years.

> By: Patrick R. O'Neil, attorneyin-fact For: Joseph T. Baroldi

\*\* 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.