

STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

| OMB APPROVAL | |
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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

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| 1. Name and Address of Reporting Person* <u>Monia Brett P</u> <hr/> (Last) (First) (Middle) 2855 GAZELLE COURT <hr/> (Street) CARLSBAD CA 92010 <hr/> (City) (State) (Zip) | 2. Issuer Name and Ticker or Trading Symbol <u>IONIS PHARMACEUTICALS INC [IONS]</u> | 5. Relationship of Reporting Person(s) to Issuer (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) Chief Executive Officer |
| | 3. Date of Earliest Transaction (Month/Day/Year) 01/26/2022 | |
| | 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 | 01/26/2022 | 01/26/2022 | A | | 2,194 ⁽¹⁾ | A | \$0.0 | 82,424 | D | |
| Common Stock | 01/26/2022 | 01/26/2022 | A | | 14,004 ⁽²⁾ | A | \$0.0 | 96,428 | D | |
| Common Stock | 01/26/2022 | 01/26/2022 | F | | 8,032 ⁽³⁾ | D | \$31.44 | 88,396 | 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) |
|--|--|--------------------------------------|--|--------------------------------|--|--|-----------------|---|--|--|---|--|
| | | | | | | Date Exercisable | Expiration Date | | | | | |

Explanation of Responses:

- Represents shares earned upon the vesting of performance based restricted stock units ("PRSUs") for the second performance period of the grant to the reporting person reported on January 17, 2020. The Compensation Committee certified achievement of the pre-established performance goal based on the Issuer's relative total shareholder return as compared to a peer group of companies at a level resulting in a vest of 58.06% of target shares. As reported at grant, the PRSUs could result in a payout of 0% to 150% based on actual achievement of the goal.
- Represents shares earned upon the vesting of performance based restricted stock units ("PRSUs") for the first performance period of the grant to the reporting person reported on January 20, 2021. The Compensation Committee certified achievement of the pre-established performance goal based on the Issuer's relative total shareholder return as compared to a peer group of companies at a level resulting in a vest of 81.37% of target shares. As reported at grant, the PRSUs could result in a payout of 0% to 150% based on actual achievement of the goal.
- Shares withheld to cover the required tax withholding obligations pursuant to the Ionis Pharmaceuticals, Inc. Amended and Restated 2011 Equity Incentive Plan.

By: Patrick R. O'Neil,
 attorney-in-fact For: Brett P. Monia 01/28/2022

** 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.