

| OMB APPROVAL | |
|--|-----------|
| OMB Number: | 3235-0287 |
| Estimated average burden hours per response: | 0.5 |

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* <u>Monia Brett P</u> <hr/> (Last) (First) (Middle) <u>C/O IONIS PHARMACEUTICALS, INC.</u> <u>2855 GAZELLE CT.</u> <hr/> (Street) <u>CARLSBAD, CA 92010</u> <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) <u>Chief Executive Officer</u> |
| | 3. Date of Earliest Transaction (Month/Day/Year) <u>01/04/2021</u> | |
| | 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 | | | |

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) | \$56.78 | 01/04/2021 | 01/04/2021 | A | | 149,872 | | 01/04/2022 ⁽¹⁾ | 01/03/2028 | Common Stock | 149,872 | \$0.0 | 149,872 | D | |

Explanation of Responses:

1. Grant on 01/04/2021 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 01/04/2021. 25% of the shares subject to the option will vest and become exercisable on 01/04/2022. Thereafter, the remaining shares subject to the option will vest and become exercisable in 36 equal monthly installments over the next 3 years.

Remarks:

/s/Patrick R. O'Neil, attorney-in-fact 01/06/2021

** 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.