

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).

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

1. Name and Address of Reporting Person* <u>O'NEIL PATRICK R.</u> (Last) (First) (Middle) <u>C/O IONIS PHARMACEUTICALS, INC.</u> <u>2855 GAZELLE COURT</u> (Street) <u>CARLSBAD CA 92010</u> (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) Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <u>SVP Legal & General Counsel</u>
	3. Date of Earliest Transaction (Month/Day/Year) <u>01/01/2019</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			
Common Stock	01/01/2019	01/01/2019	J ⁽¹⁾	V	66 ⁽¹⁾	A	\$36.448	14,584	D	
Common Stock	01/03/2019	01/03/2019	M ⁽³⁾		400 ⁽³⁾	A	\$10.82	14,984	D	
Common Stock	01/03/2019	01/03/2019	S ⁽³⁾		400 ⁽³⁾	D	\$54.8	14,584	D	
Common Stock	01/03/2019	01/03/2019	M ⁽³⁾		4,000 ⁽³⁾	A	\$39.87	18,584	D	
Common Stock	01/03/2019	01/03/2019	S ⁽³⁾		4,000 ⁽³⁾	D	\$54.8	14,584	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						Title
Employee Stock Option (right to buy)	\$53.77	01/02/2019	01/02/2019	A		49,800		01/02/2020 ⁽²⁾	01/01/2026	Common Stock	49,800	\$0	49,800	D	
Employee Stock Option (right to buy)	\$10.82	01/03/2019	01/03/2019	M		400		01/02/2017	01/01/2020	Common Stock	400	\$0	0	D	
Employee Stock Option (right to buy)	\$39.87	01/03/2019	01/03/2019	M		4,000		01/02/2018	01/01/2021	Common Stock	4,000	\$0	27,875	D	

Explanation of Responses:

- Reporting shares acquired under the Ionis Pharmaceuticals, Inc. Amended and Restated 2000 Employee Stock Purchase Plan on January 1, 2019. These shares may not be sold until July 2, 2019.
- Grant of 01/02/2019 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 01/02/2020. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments over the next 3 years. Following this transaction, the option was exercisable as to 0 on 01/02/2019.
- Acquired as a result of exercising a stock option pursuant to Rule 10b5-1 Trading Plan. The purchase and sale reported on this Form 4 was effective pursuant to Rule 10b5-1 Trading Plan adopted by the reporting person on 08/29/18.

Remarks:

Patrick R. O'Neil

01/03/2019

** 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.

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