

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

1. Name and Address of Reporting Person* <u>CROOKE STANLEY T</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) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <p style="text-align: center;">Chairman and CEO</p>
	3. Date of Earliest Transaction (Month/Day/Year) <u>01/04/2016</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	01/04/2016	01/04/2016	M ⁽³⁾		10,000 ⁽³⁾	A	\$10.29	24,642	D	
Common Stock	01/04/2016	01/04/2016	S ⁽³⁾		10,000 ⁽³⁾	D	\$61.05	14,642	D	
Common Stock	01/04/2016	01/04/2016	M ⁽⁴⁾		1,000 ⁽⁴⁾	A	\$9.22	2,297	I	By wife
Common Stock	01/04/2016	01/04/2016	S ⁽⁴⁾		1,000 ⁽⁴⁾	D	\$61.05	1,297	I	By wife
Common Stock								725,391	I	By Trust

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	Amount or Number of Shares				
Employee Stock Option (right to buy)	\$61.68	01/04/2016	01/04/2016	A		195,182		01/04/2017 ⁽¹⁾	01/03/2023	Common Stock	195,182	\$0	195,182	D	
Employee Stock Option (right to buy)	\$61.68	01/04/2016	01/04/2016	A		8,000		01/04/2017 ⁽²⁾	01/03/2023	Common Stock	8,000	\$0	8,000	I	By Wife
Employee Stock Option (right to buy)	\$10.29	01/04/2016	01/04/2016	M		10,000		01/03/2015	01/02/2018	Common Stock	10,000	\$0	91,259	D	
Employee Stock Option (right to buy)	\$9.22	01/04/2016	01/04/2016	M		1,000		07/19/2014	07/18/2017	Common Stock	1,000	\$0	1,000	I	By wife

Explanation of Responses:

- Grant of 1/4/2016 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 1/4/2017. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 48,796 shares per year. Following this transaction, the option was exercisable as to 0 on 1/4/2016.
- Grant of 1/4/2016 to reporting person's wife 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 1/4/2017. Thereafter, the remaining shares subject to the option vest and become exercisable in 36 equal monthly installments, at the rate of 2,000 shares per year. Following this transaction, the option was exercisable as to 0 on 1/4/2016.
- 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 9/21/2015.
- 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's wife on 9/21/2015.

Remarks:

/s/B. Lynne Parhsall, attorney-in-fact 01/04/2016

** 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.

