

FORM 5

UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

ANNUAL STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP

OMB APPROVAL	
OMB Number:	3235-0362
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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).

Form 3 Holdings Reported.

Form 4 Transactions Reported.

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>KLEIN JOSEPH III</u> (Last) (First) (Middle) 2855 GAZELLE COURT (Street) CARLSBAD CA 92010 (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 Officer (give title below) Other (specify below)
	3. Statement for Issuer's Fiscal Year Ended (Month/Day/Year) 12/31/2021	
	4. If Amendment, Date of Original Filed (Month/Day/Year)	6. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person <input type="checkbox"/> Form filed by More than One Reporting Person

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 at end of Issuer's Fiscal Year (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
				Amount	(A) or (D)	Price			
Common Stock	11/30/2021		G ⁽¹⁾	6,000 ⁽¹⁾	D	\$0.0	12,126	D	
Common Stock	11/30/2021		G ⁽¹⁾	6,000 ⁽¹⁾	A	\$0.0	6,000	I	by Trust
Common Stock							100	I	by Son ⁽²⁾

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)
					(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Non-Qualified Stock Option (right to buy)	\$24.42	11/30/2021		G ⁽³⁾		12,000 ⁽³⁾	07/01/2017	06/30/2026	Common Stock	12,000	\$0.0	0	D	
Non-Qualified Stock Option (right to buy)	\$42.88	11/30/2021		G ⁽³⁾		12,000 ⁽³⁾	07/02/2019 ⁽⁴⁾	07/01/2028	Common Stock	12,000	\$0.0	4,000	D	
Non-Qualified Stock Option (right to buy)	\$52.22	11/30/2021		G ⁽³⁾		16,000 ⁽³⁾	07/03/2018	07/02/2027	Common Stock	16,000	\$0.0	0	D	
Non-Qualified Stock Option (right to buy)	\$57.16	11/30/2021		G ⁽³⁾		16,000 ⁽³⁾	07/01/2016	06/30/2025	Common Stock	16,000	\$0.0	0	D	
Non-Qualified Stock Option (right to buy)	\$60.2	11/30/2021		G ⁽³⁾		12,000 ⁽³⁾	07/01/2021	06/30/2030	Common Stock	12,000	\$0.0	0	D	
Non-Qualified Stock Option (right to buy)	\$64.8	11/30/2021		G ⁽³⁾		8,000 ⁽³⁾	07/01/2020 ⁽⁵⁾	06/30/2029	Common Stock	8,000	\$0.0	8,000	D	
Non-Qualified Stock Option (right to buy)	\$24.42	11/30/2021		G ⁽³⁾	12,000 ⁽³⁾		07/01/2017	06/30/2026	Common Stock	12,000	\$0.0	12,000	I	by Trust
Non-Qualified Stock Option (right to buy)	\$42.88	11/30/2021		G ⁽³⁾	12,000 ⁽³⁾		07/02/2019	07/01/2028	Common Stock	12,000	\$0.0	12,000	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)
					(A)	(D)	Date Exercisable	Expiration Date	Title	Amount or Number of Shares				
Non-Qualified Stock Option (right to buy)	\$52.22	11/30/2021		G ⁽³⁾	16,000 ⁽³⁾		07/03/2018	07/02/2027	Common Stock	16,000	\$0.0	16,000	I	by Trust
Non-Qualified Stock Option (right to buy)	\$57.16	11/30/2021		G ⁽³⁾	16,000 ⁽³⁾		07/01/2016	06/30/2025	Common Stock	16,000	\$0.0	16,000	I	by Trust
Non-Qualified Stock Option (right to buy)	\$60.2	11/30/2021		G ⁽³⁾	12,000 ⁽³⁾		07/01/2021	06/30/2030	Common Stock	12,000	\$0.0	12,000	I	by Trust
Non-Qualified Stock Option (right to buy)	\$64.8	11/30/2021		G ⁽³⁾	8,000 ⁽³⁾		07/01/2020	06/30/2029	Common Stock	8,000	\$0.0	8,000	I	by Trust

Explanation of Responses:

- The reported transaction reflects the gift of shares to trusts for the benefit of the reporting person's three children, of which the reporting person's wife is a trustee.
- The reporting person disclaims beneficial ownership of all securities held by his son, and this report should not be deemed an admission that the reporting person is the beneficial owner of such securities for purposes of Section 16 or for any other purpose.
- The reported transactions reflect the gift of vested stock options to trusts for the benefit of the reporting person's three children, of which the reporting person's wife is a trustee.
- Grant of 7/2/18 to reporting person of stock options under the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan. The option vests and becomes exercisable in four equal annual installments, with the first installment vesting on 7/2/19. The option shall be fully vested and exercisable on 7/2/22. The option was exercisable as to 12,000 shares on 11/30/21.
- Grant of 7/1/19 to reporting person of stock options under the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan. The option vests and becomes exercisable in four equal annual installments, with the first installment vesting on 7/1/20. The option shall be fully vested and exercisable on 7/1/23. The option was exercisable as to 8,000 shares on 11/30/21.

By: Patrick R. O'Neil, attorney-
in-fact For: Joseph Klein III 02/09/2022

** 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.