

**UNITED STATES**  
**SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549

**FORM S-8**

REGISTRATION STATEMENT UNDER THE SECURITIES ACT OF 1933

**IONIS PHARMACEUTICALS, INC.**

(Exact name of registrant as specified in its charter)

**Delaware**  
(State of Incorporation)

**33-0336973**  
(I.R.S. Employer Identification No.)

**2855 Gazelle Court**  
**Carlsbad, CA 92010**  
(Address of principal executive offices)

**Amended and Restated Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan**  
(Full title of the plan)

**Brett Monia**  
**Chief Executive Officer**  
**IONIS PHARMACEUTICALS, INC.**  
**2855 Gazelle Court**  
**Carlsbad, California 92010**  
**(760) 931-9200**

(Name, address, and telephone number, including area code, of agent for service)

Copies to:  
**Patrick R. O'Neil, Esq.**  
**Executive Vice President, Legal, General Counsel and Corporate Secretary**  
**IONIS PHARMACEUTICALS, INC.**  
**2855 Gazelle Court**  
**Carlsbad, California 92010**  
**(760) 931-9200**

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer   
Non-accelerated filer

Accelerated filer   
Smaller reporting company   
Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act.

**CALCULATION OF REGISTRATION FEE**

Title of Securities to be Registered	Amount to be Registered (1,2)	Proposed Maximum Offering Price per Share (3)	Proposed Maximum Aggregate Offering Price (3)	Amount of Registration Fee
Common Stock, par value \$.001 per share	800,000 shares	\$56.95	\$45,560,000	\$5,913.69

(1) In accordance with Rule 416 under the Securities Act of 1933, as amended (the "Securities Act"), this Registration Statement on Form S-8 (this "Registration Statement") shall be deemed to cover any additional securities that may from time to time be offered or issued by Ionis Pharmaceuticals, Inc. ("Ionis" or the "Registrant") to prevent dilution resulting from stock splits, stock dividends or similar transactions.

(2) Includes 800,000 shares issuable pursuant to the Registrant's Amended and Restated Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan (the "2002 NED Plan").

(3) Estimated solely for the purpose of calculating the amount of the registration fee pursuant to Rule 457(c) and Rule 457(h) of the Securities Act. The price per share and the aggregate offering price are calculated on the basis of \$56.95, the average of the high and low sales prices of Registrant's Common Stock on August 6, 2020, as reported on the NASDAQ Global Market for the shares subject to the 2002 NED Plan.

---

---

---

## EXPLANATORY NOTE

Pursuant to General Instruction E of Form S-8, this Registration Statement is being filed in order to register an additional 800,000 shares of Common Stock of the Registrant issuable under the 2002 NED Plan, which are securities of the same class and relate to the same employee benefit plan as those shares of Common Stock registered on the Registrant's registration statements on Form S-8 previously filed with the Securities and Exchange Commission (the "Commission") on [November 9, 2015 \(Registration No. 333-207900\)](#), [November 6, 2012 \(Registration No. 333-184788\)](#), [August 9, 2010 \(Registration No. 333-168674\)](#), [May 5, 2006 \(Registration No. 333-133853\)](#) and [June 28, 2002 \(Registration No. 333-91572\)](#), all of which are hereby incorporated by reference.

---

**INFORMATION REQUIRED IN THE REGISTRATION STATEMENT**

**Item 3. Incorporation of Documents by Reference.**

The following documents filed with the Commission by the Registrant are hereby incorporated by reference into this Registration Statement:

- (a) the Registrant's Annual Report on [Form 10-K](#) for the year ended December 31, 2019, as filed with the Commission on March 2, 2020;
- (b) the Registrant's Quarterly Report on [Form 10-Q for the quarterly period ended March 31, 2020](#), as filed with the Commission on May 6, 2020 and Quarterly Report on [Form 10-Q for the quarterly period ended June 30, 2020](#), as filed with the Commission on August 5, 2020;
- (c) the Registrant's Current Reports on Form 8-K filed with the Commission on [January 10, 2020](#), [January 17, 2020](#), [February 26, 2020](#), [May 6, 2020](#), [June 10, 2020](#) and [August 5, 2020](#); and
- (d) the sections of the Registrant's Definitive Proxy Statement on [Schedule 14A](#) for the 2020 Annual Meeting of Shareholders incorporated by reference in the Annual Report.

All documents filed by the Registrant with the Commission pursuant to Sections 13(a), 13(c), 14 and 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), after the date hereof and prior to the filing of a post-effective amendment which indicates that all securities offered pursuant to this Registration Statement have been sold or which deregisters all securities then remaining unsold, shall be deemed to be incorporated by reference herein and to be a part hereof from the date of filing of such documents.

**Item 5. Interests of Named Experts and Counsel.**

The validity of the issuance of the common stock offered in this Registration Statement will be passed upon for the Registrant by Patrick R. O'Neil, Executive Vice President, Legal, General Counsel and Corporate Secretary of Ionis.

Mr. O'Neil holds or has the right to acquire shares of Ionis' Common Stock in an aggregate amount that is less than 1% of Ionis' outstanding Common Stock.

**Item 6. Indemnification of Directors and Officers.**

Under Section 145 of the Delaware General Corporation Law (the "DGCL"), we have broad powers to indemnify our directors and officers against liabilities they may incur in such capacities, including liabilities under the Securities Act.

Our certificate of incorporation and bylaws include provisions to (i) eliminate the personal liability of its directors for monetary damages resulting from breaches of their fiduciary duty to the extent permitted by Section 102(b)(7) of the DGCL and (ii) require us to indemnify our directors and officers to the fullest extent permitted by Section 145 of the DGCL, including circumstances in which indemnification is otherwise discretionary. Pursuant to Section 145 of the DGCL, a corporation generally has the power to indemnify its present and former directors, officers, employees and agents against expenses incurred by them in connection with any suit to which they are, or are threatened to be made, a party by reason of their serving in such positions so long as they acted in good faith and in a manner they reasonably believed to be in, or not opposed to, the best interest of the corporation, and with respect to any criminal action, they had no reasonable cause to believe their conduct was unlawful. We believe that these provisions are necessary to attract and retain qualified persons as directors and officers. These provisions do not eliminate the directors' duty of care, and, in appropriate circumstances, equitable remedies such as injunctive or other forms of non-monetary relief will remain available under Delaware law. In addition, each director will continue to be subject to liability for breach of the director's duty of loyalty to us, for acts or omissions not in good faith or involving intentional misconduct, for knowing violations of law, for acts or omissions that the director believes to be contrary to the best interests of Ionis or our stockholders, for any transaction from which the director derived an improper personal benefit, for acts or omissions involving a reckless disregard for the director's duty to Ionis or our stockholders when the director was aware or should have been aware of a risk of serious injury to Ionis or our stockholders, for acts or omissions that constitute an unexcused pattern of inattention that amounts to an abdication of the director's duty to Ionis or our stockholders, for improper transactions between the director and us and for improper distributions to stockholders and loans to directors and officers. The provision also does not affect a director's responsibilities under any other law, such as the federal securities law or state or federal environmental laws.

We have entered into indemnity agreements with each of our directors and executive officers that require us to indemnify such persons against expenses, judgments, fines, settlements and other amounts incurred (including expenses of a derivative action) in connection with any proceeding, whether actual or threatened, to which any such person may be made a party by reason of the fact that such person is or was a director or an executive officer of Ionis or any of our affiliated enterprises, provided such person acted in good faith and in a manner such persons reasonably believed to be in, or not opposed to, the best interests of Ionis and, with respect to any criminal proceeding, has no reasonable cause to believe his conduct was unlawful. The indemnification agreements also set forth procedures that will apply in the event of a claim for indemnification thereunder.

We have an insurance policy covering our officers and directors with respect to certain liabilities, including liabilities arising under the Securities Act or otherwise.

---

## Item 8. Exhibits.

Exhibit Number	Description
<a href="#">5.1</a>	Opinion of Patrick R. O'Neil
<a href="#">23.1</a>	Consent of Independent Registered Public Accounting Firm
<a href="#">23.2</a>	Consent of Patrick R. O'Neil. Reference is made to Exhibit 5.1
<a href="#">24.1</a>	Power of Attorney is contained on the signature pages
<a href="#">99.1</a>	Amended and Restated Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan (1)
<a href="#">99.2</a>	Form of Option Agreement for options granted under the Amended and Restated Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan (2)
<a href="#">99.3</a>	Form of Restricted Stock Unit Agreement for restricted stock units granted under the Amended and Restated Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan (3)

(1) Filed as an appendix to the Registrant's [Notice of 2020 Annual Meeting of Stockholders and Proxy Statement](#) filed with the SEC on April 24, 2020, and incorporated herein by reference.

(2) Filed herewith.

(3) Filed herewith.

## Item 9. Undertakings.

(a) The undersigned Registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this Registration Statement:

(i) To include any prospectus required by section 10(a)(3) of the Securities Act;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the Registration Statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the Registration Statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective Registration Statement;

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the Registration Statement or any material change to such information in the Registration Statement;

*Provided, however,* that paragraphs (a)(1)(i) and (a)(1)(ii) of this section do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the Registrant pursuant to section 13 or section 15(d) of the Securities Exchange Act of 1934 (the "Exchange Act") that are incorporated by reference in the Registration Statement; and

(2) That, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered herein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

---

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability of the Registrant under the Securities Act to any purchaser in the initial distribution of the securities: The undersigned Registrant undertakes that in a primary offering of securities of the undersigned Registrant pursuant to this Registration Statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned Registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) Any preliminary prospectus or prospectus of the undersigned Registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned Registrant or used or referred to by the undersigned Registrant;

(iii) The portion of any other free writing prospectus relating to the offering containing material information about the undersigned Registrant or its securities provided by or on behalf of the undersigned Registrant; and

(iv) Any other communication that is an offer in the offering made by the undersigned Registrant to the purchaser.

(b) The undersigned Registrant hereby undertakes that, for purposes of determining any liability under the Securities Act, each filing of the Registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in the Registration Statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

(c) Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the Registrant pursuant to the foregoing provisions, or otherwise, the Registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

---

## SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-8 and has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Carlsbad, State of California, on August 7, 2020.

IONIS PHARMACEUTICALS, INC.

By:           /s/ Brett Monia            
Brett Monia  
Chief Executive Officer

## POWER OF ATTORNEY

**KNOW ALL PERSONS BY THESE PRESENTS**, that each person whose signature appears below constitutes and Brett Monia and Elizabeth Hougen, and each or any one of them, his or her true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments (including post-effective amendments) to this Registration Statement, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or any of them, or their or his or her substitutes or substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, as amended, this Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

<b>Signature</b>	<b>Title</b>	<b>Date</b>
<u>          /s/ Brett Monia          </u> Brett Monia	Chief Executive Officer (Principal Executive Officer)	August 7, 2020
<u>          /s/ Elizabeth Hougen          </u> Elizabeth Hougen	Chief Financial Officer (Principal Financial Officer)	August 7, 2020
<u>          /s/ Stanley T. Crooke          </u> Stanley T. Crooke	Executive Chairman	August 7, 2020
<u>          /s/ Breaux B. Castleman          </u> Breaux B. Castleman	Director	August 7, 2020
<u>          /s/ Spencer R. Berthelsen          </u> Spencer R. Berthelsen	Director	August 7, 2020
<u>          /s/ Joseph Klein, III          </u> Joseph Klein, III	Director	August 7, 2020
<u>          /s/ Joseph Loscalzo          </u> Joseph Loscalzo	Director	August 7, 2020
<u>          /s/ Frederick T. Muto          </u> Frederick T. Muto	Director	August 7, 2020
<u>          /s/ Joseph H. Wender          </u> Joseph H. Wender	Director	August 7, 2020
<u>          /s/ B. Lynne Parshall          </u> B. Lynne Parshall	Director	August 7, 2020
<u>          /s/ Peter Reikes          </u> Peter Reikes	Director	August 7, 2020
<u>          /s/ Michael Hayden          </u> Michael Hayden	Director	August 7, 2020
<u>          /s/ Joan E. Herman          </u> Joan E. Herman	Director	August 7, 2020

---

August 7, 2020

Ionis Pharmaceuticals, Inc.  
2855 Gazelle Court  
Carlsbad, CA 92010

Ladies and Gentlemen:

You have requested my opinion with respect to certain matters in connection with the filing by Ionis Pharmaceuticals, Inc. (the “Company”) of a Registration Statement on Form S-8 (the “Registration Statement”) with the Securities and Exchange Commission, covering the offering of an additional 800,000 shares of the Company’s Common Stock, \$.001 par value (the “Shares”), of which, 2,800,000 Shares are issuable pursuant to its Amended and Restated Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan (the “2002 NED Plan”) as described in the Registration Statement.

In connection with this opinion, I have examined and relied upon the Registration Statement, the Company’s Restated Certificate of Incorporation, as amended, and Bylaws and the originals or copies certified to my satisfaction, of such records, documents, certificates, memoranda and other instruments as in my judgment are necessary or appropriate to enable me to render the opinion expressed below.

On the basis of the foregoing, and in reliance thereon, I am of the opinion that the Shares, when issued and sold in accordance with the 2002 NED Plan and related prospectuses, will be validly issued, fully paid and nonassessable.

I consent to the reference to myself under the caption “Interests of Named Experts and Counsel” in the Registration Statement and to the filing of this opinion as an exhibit to the Registration Statement.

Very truly yours,

/s/ Patrick R. O’Neil

---

Patrick R. O’Neil  
Executive Vice President, Legal, General Counsel and Corporate Secretary

---

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statement (Form S-8) pertaining to the Amended and Restated Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan of Ionis Pharmaceuticals, Inc. of our reports dated March 2, 2020, with respect to the consolidated financial statements of Ionis Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Ionis Pharmaceuticals, Inc. included in its Annual Report (Form 10-K) for the year ended December 31, 2019, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

San Diego, California  
August 7, 2020

---

AMENDED AND RESTATED
2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN
GRANT NOTICE

Optionee: «Name»

Date of Grant: «Date»

Ionis Pharmaceuticals, Inc.
Non-Statutory Stock Option Agreement

IONIS PHARMACEUTICALS, INC. (the "Company"), pursuant to its Amended and Restated 2002 Non-Employee Directors' Stock Option Plan (the "Plan"), hereby grants to Optionholder an option to purchase the number of shares of the Company's Common Stock set forth below. This option is subject to all of the terms and conditions as set forth herein and in the Stock Option Agreement (Attachment I hereto), the Plan and the Notice of Exercise, all of which are attached hereto and incorporated herein in their entirety.

Number of Shares Subject to Option: 12,000

Vesting Schedule:

Number of Shares
12,000

Date of Earliest Exercise (vesting).
Either (1) the annual anniversary of the Date of Grant, or (2) the next regularly scheduled annual meeting of stockholders of the Company, whichever occurs earlier

Exercise Price Per \$«Price» 1
Share:

Expiration Date: «Date» 2

Ionis Pharmaceuticals, Inc.

By:
Duly authorized on behalf of
the Board of Directors

Optionee:
Address: «Address\_1»
«Address\_2»

Optionee:

Additional Terms/Acknowledgements: The undersigned Optionholder acknowledges receipt of, and understands and agrees to, this Grant Notice, the Stock Option Agreement and the Plan. Optionholder further acknowledges that as of the Date of Grant, this Grant Notice, the Stock Option Agreement and the Plan set forth the entire understanding between Optionholder and the Company regarding the acquisition of stock in the Company and supersede all prior oral and written agreements on that subject with the exception of (i) options previously granted and delivered to Optionholder under the Plan, and (ii) the following agreements only:

OTHER AGREEMENTS:

1 Not less than 100% of the fair market value of the Common Stock on the Date of Grant of this option.
2 Less than 10 years from the Date of Grant of this option.

**IONIS PHARMACEUTICALS, INC.**  
**AMENDED AND RESTATED 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN**  
**STOCK OPTION AGREEMENT**  
**(NONSTATUTORY STOCK OPTION)**

Pursuant to your Stock Option Grant Notice (“Grant Notice”) and this Stock Option Agreement, Ionis Pharmaceuticals, Inc. (the “Company”) has granted you an option under its Amended and Restated 2002 Non-Employee Directors’ Stock Option Plan (the “Plan”) to purchase the number of shares of the Company’s Common Stock indicated in your Grant Notice at the exercise price indicated in your Grant Notice. Defined terms not explicitly defined in this Stock Option Agreement but defined in the Plan shall have the same definitions as in the Plan.

The details of your option are as follows:

1. **VESTING.** Subject to the limitations contained herein, your option will vest as provided in your Grant Notice, provided that vesting will cease upon the termination of your Continuous Service.
  2. **NUMBER OF SHARES AND EXERCISE PRICE.** The number of shares of Common Stock subject to your option and your exercise price per share referenced in your Grant Notice may be adjusted from time to time for Capitalization Adjustments, as provided in the Plan.
  3. **METHOD OF PAYMENT.** Payment of the exercise price is due in full upon exercise of all or any part of your option. You may make payment of the exercise price in cash or by check or pursuant to a “same-day-sale” under Regulation T.
  4. **WHOLE SHARES.** You may exercise your option only for whole shares of Common Stock.
  5. **SECURITIES LAW COMPLIANCE.** Notwithstanding anything to the contrary contained herein, you may not exercise your option unless the shares of Common Stock issuable upon such exercise are then registered under the Securities Act or, if such shares of Common Stock are not then so registered, the Company has determined that such exercise and issuance would be exempt from the registration requirements of the Securities Act. The exercise of your option must also comply with other applicable laws and regulations governing your option, and you may not exercise your option if the Company determines that such exercise would not be in material compliance with such laws and regulations.
  6. **TERM.** You may not exercise your option before the commencement of its term or after its term expires. Unless otherwise provided in Section 11(d) of the Plan, the term of your option commences on the Date of Grant and expires upon the *earliest* of the following:
    - (a) 3 months after the termination of your Continuous Service for any reason other than your Disability or death, provided that if during any part of such 3 month period your option is not exercisable solely because of the condition set forth in the preceding paragraph relating to “Securities Law Compliance,” your option shall not expire until the earlier of the Expiration Date or until it shall have been exercisable for an aggregate period of 3 months after the termination of your Continuous Service;
    - (b) 12 months after the termination of your Continuous Service due to your Disability;
    - (c) 18 months after your death if you die either during your Continuous Service or within 3 months after your Continuous Service terminates; or
    - (d) 18 months after the termination of your Continuous Service due to your retirement, where (i) you were over the age of 55 at the time of such retirement; and (ii) you had been an employee, director or consultant (or any combination thereof) of the Company for a continuous and uninterrupted period of at least 5 years prior to such retirement (having satisfied all of the conditions set forth in clauses (i) and (ii) above, “Qualified Retirement”); or
    - (e) the day before the 10th anniversary of the Date of Grant.
-

**7. EXERCISE.**

(a) You may exercise the vested portion of your option during its term by delivering a Notice of Exercise (in a form designated by the Company) together with the exercise price to the Secretary of the Company, or to such other person as the Company may designate, during regular business hours, together with such additional documents as the Company may then require.

(b) The minimum number of shares with respect to which this option may be exercised at any one time is 1,000, unless the number of shares available for exercise (that is, the remaining vested shares) equals less than 1,000 shares, in which case the minimum number of shares exercised must equal the number of shares then vested.

(c) By exercising your option you agree that, as a condition to any exercise of your option, the Company may require you to enter into an arrangement providing for the payment by you to the Company of any tax withholding obligation of the Company arising by reason of (1) the exercise of your option, (2) the lapse of any substantial risk of forfeiture to which the shares of Common Stock are subject at the time of exercise, or (3) the disposition of shares of Common Stock acquired upon such exercise.

**8. TRANSFERABILITY.** This option is not transferable except by will or by the laws of descent and distribution, and is exercisable during your lifetime only by you; notwithstanding the foregoing, you may transfer part or all of this option to any of the following:

(i) your spouse, children (by birth or adoption), stepchildren, grandchildren, or parents;

(ii) a trust or other entity established solely for your benefit or the benefit of your spouse, children (by birth or adoption), stepchildren, grandchildren, or parents for estate planning purposes; or,

(iii) an organization which is exempt from taxation under Section 501(c)(3) of the Code or to which tax-deductible charitable contributions may be made under Section 170 of the Code.

Furthermore, you may, by delivering written notice to the Company, in a form satisfactory to the Company, designate a third party who, in the event of your death, will thereafter be entitled to exercise the option.

**9. RIGHT OF REPURCHASE.** To the extent provided in the Company's bylaws as amended from time to time, the Company shall have the right to repurchase all or any part of the shares of Common Stock you acquire pursuant to the exercise of your option.

**10. OPTION NOT A SERVICE CONTRACT.** Your option is not an employment or service contract, and nothing in your option shall be deemed to create in any way whatsoever any obligation on your part to continue in the employ of the Company or an Affiliate, or of the Company or an Affiliate to continue your employment. In addition, nothing in your option shall obligate the Company or an Affiliate, their respective stockholders, Boards of Directors, Officers or Employees to continue any relationship that you might have as a Director or Consultant for the Company or an Affiliate.

**11. WITHHOLDING OBLIGATIONS.** You may not exercise your option unless the tax withholding obligations of the Company and/or any Affiliate are satisfied. Accordingly, you may not be able to exercise your option when desired even though your option is vested, and the Company shall have no obligation to issue a certificate for such shares of Common Stock or release such shares of Common Stock from any escrow provided for herein.

**12. NOTICES.** Any notices provided for in your option or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by mail by the Company to you, 5 days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company.

**13. GOVERNING PLAN DOCUMENT.** Your option is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your option, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. In the event of any conflict between the provisions of your option and those of the Plan, the provisions of the Plan shall control.

---

IONIS PHARMACEUTICALS, INC.  
 RESTRICTED STOCK UNIT GRANT NOTICE  
 (AMENDED & RESTATED 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN)

Ionis Pharmaceuticals, Inc. (the "**Company**"), pursuant to its Amended & Restated 2002 Non-Employee Directors' Stock Option Plan (the "**Plan**"), hereby awards to Participant a Restricted Stock Unit Award for the number of stock units set forth below (the "**Award**"). The Award is subject to all of the terms and conditions as set forth herein; and in the Plan and the Restricted Stock Unit Agreement, both of which are attached hereto and incorporated herein in their entirety. Capitalized terms not otherwise defined herein shall have the meanings set forth in the Plan or the Restricted Stock Unit Agreement. In the event of any conflict between the terms in the Award and the Plan, the terms of the Plan shall control.

Participant: \_\_\_\_\_  
 Date of Grant: \_\_\_\_\_  
 Delivery Date: \_\_\_\_\_  
 Number of Stock Units Subject to Award: \_\_\_\_\_  
 Consideration: Participant's Services

**Vesting Schedule:** 100% of the Stock Units subject to this Award will vest either on (1) the annual anniversary of the Date of Grant, or (2) the next regularly scheduled annual meeting of stockholders of the Company, whichever occurs earlier. Notwithstanding the foregoing, vesting shall terminate upon the Participant's termination of Continuous Service.

**Issuance Schedule:** The shares of Common Stock to be issued in respect of the Award will be issued in accordance with the issuance schedule set forth in Section 6 of the Restricted Stock Unit Agreement.

**Additional Terms/Acknowledgements:** The undersigned Participant acknowledges receipt of, and understands and agrees to, this Restricted Stock Unit Grant Notice, the Restricted Stock Unit Agreement and the Plan. Participant further acknowledges that as of the Date of Grant, this Restricted Stock Unit Grant Notice, the Restricted Stock Unit Agreement and the Plan set forth the entire understanding between Participant and the Company regarding the Award and supersedes all prior oral and written agreements on that subject.

IONIS PHARMACEUTICALS, INC.  
 By: \_\_\_\_\_  
 Signature  
 Title: \_\_\_\_\_  
 Date: \_\_\_\_\_

PARTICIPANT:  
 \_\_\_\_\_  
 Signature  
 Date: \_\_\_\_\_

ATTACHMENTS: Restricted Stock Unit Agreement, Amended & Restated 2002 Non-Employee Directors' Stock Option Plan

IONIS PHARMACEUTICALS, INC.  
AMENDED & RESTATED 2002 NON-EMPLOYEE DIRECTORS'  
STOCK OPTION PLAN

RESTRICTED STOCK UNIT AGREEMENT

Pursuant to the Restricted Stock Unit Grant Notice (“**Grant Notice**”) and this Restricted Stock Unit Agreement and in consideration of your services, Ionis Pharmaceuticals, Inc. (the “**Company**”) has awarded you a Restricted Stock Unit Award (the “**Award**”) under its Amended & Restated 2002 Non-Employee Director’s Stock Option Plan (the “**Plan**”). Your Award is granted to you effective as of the Date of Grant set forth in the Grant Notice for this Award. This Restricted Stock Unit Award Agreement shall be deemed to be agreed to by the Company and you upon the earlier of (i) signing (or electronic acceptance) by you of the Restricted Stock Unit Grant Notice to which it is attached, and (ii) your receipt of shares of Common Stock under this Restricted Stock Unit Agreement. Capitalized terms not explicitly defined in this Restricted Stock Unit Agreement shall have the same meanings given to them in the Plan or the Grant Notice, as applicable. In the event of any conflict between the terms in this Restricted Stock Unit Agreement and the Plan, the terms of the Plan shall control. The details of your Award, in addition to those set forth in the Grant Notice and the Plan, are as follows.

**1. GRANT OF THE AWARD.** This Award represents the right to be issued on a future date the number of shares of the Company’s Common Stock that is equal to the number of stock units indicated in the Grant Notice (the “**Stock Units**”). As of the Date of Grant, the Company will credit to a bookkeeping account maintained by the Company for your benefit (the “**Account**”) the number of Stock Units subject to the Award. This Award was granted in consideration of your services to the Company. Except as otherwise provided herein, you will not be required to make any payment to the Company (other than past and future services to the Company) with respect to your receipt of the Award, the vesting of the Stock Units or the delivery of the Common Stock to be issued in respect of the Award.

**2. VESTING.**

**(a) In General.** Subject to the limitations contained herein, your Award will vest, if at all, in accordance with the vesting schedule provided in the Grant Notice, provided that vesting will cease upon the termination of your Continuous Service. Upon such termination of your Continuous Service, the Stock Units credited to the Account that were not vested on the date of such termination will be forfeited at no cost to the Company and you will have no further right, title or interest in the Stock Units or the shares of Common Stock to be issued in respect of the Award.

**3. NUMBER OF SHARES.**

**(a)** The number of Stock Units subject to your Award may be adjusted from time to time for Capitalization Adjustments, as provided in the Plan.

---

**(b)** Any additional Stock Units that become subject to the Award pursuant to this Section 3 and Section 7, if any, shall be subject, in a manner determined by the Board, to the same forfeiture restrictions, restrictions on transferability, and time and manner of delivery as applicable to the other Stock Units covered by your Award.

**(c)** Notwithstanding the provisions of this Section 3, no fractional shares or rights for fractional shares of Common Stock shall be created pursuant to this Section 3. The Board shall, in its discretion, determine an equivalent benefit for any fractional shares or fractional shares that might be created by the adjustments referred to in this Section 3.

**4. SECURITIES LAW COMPLIANCE.** You may not be issued any shares in respect of your Award unless either (i) the shares are registered under the Securities Act; or (ii) the Company has determined that such issuance would be exempt from the registration requirements of the Securities Act. Your Award also must comply with other applicable laws and regulations governing the Award, and you will not receive such shares if the Company determines that such receipt would not be in material compliance with such laws and regulations.

**5. TRANSFER RESTRICTIONS.** Prior to the time that shares of Common Stock have been delivered to you, you may not transfer, pledge, sell or otherwise dispose of this Award or the shares issuable in respect of your Award, except as expressly provided in this Section 5. For example, you may not use shares that may be issued in respect of your Award as security for a loan. The restrictions on transfer set forth herein will lapse upon delivery to you of shares in respect of your vested Award.

**(a) Death.** Your Award is transferable by will and by the laws of descent and distribution. In addition, upon receiving written permission from the Board or its duly authorized designee, you may, by delivering written notice to the Company, in a form provided by or otherwise satisfactory to the Company and any broker designated by the Company to effect transactions under the Plan, designate a third party who, in the event of your death, shall thereafter be entitled to receive any distribution of Common Stock or other consideration to which you were entitled at the time of your death pursuant to this Agreement. In the absence of such a designation, your executor or administrator of your estate shall be entitled to receive, on behalf of your estate, such Common Stock or other consideration.

**(b) Certain Trusts.** Upon receiving written permission from the Board or its duly authorized designee, you may transfer your Award to a trust if you are considered to be the sole beneficial owner (determined under Section 671 of the Code and applicable state law) while the Award is held in the trust, provided that you and the trustee enter into transfer and other agreements required by the Company.

**(c) Domestic Relations Orders.** Upon receiving written permission from the Board or its duly authorized designee, and provided that you and the designated transferee enter into transfer and other agreements required by the Company, you may transfer your Award or your right to receive the distribution of Common Stock or other consideration thereunder, pursuant to a domestic relations order that contains the information required by the Company to effectuate the transfer. You are encouraged to discuss the proposed terms of any division of this Award with the Company prior to finalizing the domestic relations order to help ensure the required information is contained within the domestic relations order.

---

(a) If the Award is exempt from application of Section 409A of the Code and the regulations and other guidance thereunder and any state law of similar effect (collectively "**Section 409A**"), the Company will deliver to you a number of shares of the Company's Common Stock equal to the number of vested Stock Units subject to your Award, including any additional Stock Units received pursuant to Section 3 above that relate to those vested Stock Units on the applicable delivery date. However, if a scheduled delivery date falls on a date that is not a business day, such delivery date shall instead fall on the next following business day. Notwithstanding the foregoing, in the event that (i) you are subject to the Company's policy permitting officers and directors to sell shares only during certain "window" periods, in effect from time to time (the "**Policy**") or you are otherwise prohibited from selling shares of the Company's Common Stock in the public market and any shares covered by your Award are scheduled to be delivered on a day (the "**Original Distribution Date**") that does not occur during an open "window period" applicable to you or a day on which you are permitted to sell shares of the Company's common stock pursuant to a written plan that meets the requirements of Rule 10b5-1 under the Exchange Act, in each case as determined by the Company in accordance with the Policy, or does not occur on a date when you are otherwise permitted to sell shares of the Company's common stock on the open market, and (ii) the Company elects not to satisfy its tax withholding obligations (if any) by withholding shares from your distribution, then such shares shall not be delivered on such Original Distribution Date and shall instead be delivered on the first business day of the next occurring open "window period" applicable to you pursuant to such policy (regardless of whether you are still providing continuous services at such time) or the next business day when you are not prohibited from selling shares of the Company's Common Stock in the open market, but in no event later than the fifteenth day of the third calendar month of the calendar year following the calendar year in which the shares covered by the Award vest. Delivery of the shares pursuant to the provisions of this Section 6(a) is intended to comply with the requirements for the short-term deferral exemption available under Treasury Regulation 1.409A-1(b)(4) and shall be construed and administered in such manner. The form of such delivery of the shares (*e.g.*, a stock certificate or electronic entry evidencing such shares) shall be determined by the Company.

(b) The provisions of this Section 6(b) are intended to apply if the Award is subject to Section 409A because of the terms of a severance arrangement or other agreement between you and the Company, if any, that provides for acceleration of vesting of the Award upon your separation from service (as such term is defined in section 409A(a)(2)(A)(i) of the Code and applicable guidance thereunder ("**Separation From Service**") and such severance benefit does not satisfy the requirements for an exemption from application of Section 409A provided under Treasury Regulations Sections 1.409A-1(b)(4) or 1.409A-1(b)(9) ("**Non-Exempt Severance Arrangement**"). If the Award is subject to and not exempt from application of Section 409A due to application of a Non-Exempt Severance Arrangement, the following provisions in this Section 6(b) shall supersede anything to the contrary in Section 6(a).

---

**(i)** If the Award vests in ordinary course during your Continuous Service in accordance with the vesting schedule set forth in the Grant Notice, in no event will the shares to be issued in respect of your Award be issued any later than the later of: (i) December 31<sup>st</sup> of the calendar year that includes the applicable vesting date, or (ii) the 60<sup>th</sup> day that follows the applicable vesting date.

**(ii)** If the Award accelerates vesting under the terms of your Non-Exempt Severance Arrangement in connection with your Separation From Service, and such vesting acceleration provisions of your Non-Exempt Severance Arrangement were in effect as of the date of grant of the Award and therefore part of the terms of the Award as of the date of grant, then the shares will be earlier issued in respect of your Award upon your Separation From Service in accordance with the terms of the Non-Exempt Severance Arrangement, but in no event later than the 60<sup>th</sup> day that follows the date of your Separation From Service. However, if at the time the shares would otherwise be issued you are subject to the distribution limitations contained in section 409A of the Code applicable to “specified employees” as defined in section 409A(a)(2)(B)(i) of the Code and applicable guidance thereunder, such share issuances shall not be made before the date which is six months following the date of your Separation From Service, or, if earlier, the date of your death that occurs within such six month period.

**(iii)** If the Award accelerates vesting under the terms of your Non-Exempt Severance Arrangement in connection with your Separation From Service, and such vesting acceleration provisions of your Non-Exempt Severance Arrangement were not in effect as of the date of grant of the Award and therefore not a part of the terms of the Award on the date of grant, then such acceleration of vesting of the Award shall not accelerate the issuance date of the shares, but the shares shall instead be issued on the same schedule as set forth on the Grant Notice as if they had vested in ordinary course during your Continuous Service, notwithstanding the vesting acceleration of the Award. Such issuance schedule is intended to satisfy the requirements of payment on a specified date or pursuant to a fixed schedule, as provided under Treas. Reg. 1.409A-3(a)(4).

**(c)** The provisions in this Agreement for delivery of the shares in respect of the Award are intended either to comply with the requirements of Section 409A or to provide a basis for exemption from such requirements so that the delivery of the shares will not trigger the additional tax imposed under Section 409A, and any ambiguities herein will be so interpreted.

**7. DIVIDENDS.** You shall be entitled to receive payments equal to any cash dividends and other distributions paid with respect to a corresponding number of shares to be issued in respect of the Stock Units covered by your Award, provided that if any such dividends or distributions are paid in shares, the Fair Market Value of such shares shall be converted into additional Stock Units covered by the Award, and further provided that such additional Stock Units shall be subject to the same forfeiture restrictions and restrictions on transferability as apply to the Stock Units subject to the Award with respect to which they relate.

**8. RESTRICTIVE LEGENDS.** The shares issued in respect of your Award shall be endorsed with appropriate legends determined by the Company.

---

**9. AWARD NOT A SERVICE CONTRACT.**

(a) Your Continuous Service with the Company or an Affiliate is not for any specified term and may be terminated by you or by the Company or an Affiliate at any time, for any reason, with or without cause and with or without notice. Nothing in this Restricted Stock Unit Agreement (including, but not limited to, the vesting of your Award pursuant to the schedule set forth in Section 2 herein or the issuance of the shares in respect of your Award), the Plan or any covenant of good faith and fair dealing that may be found implicit in this Restricted Stock Unit Agreement or the Plan shall: (i) confer upon you any right to continue in the employ of, or affiliation with, the Company or an Affiliate; (ii) constitute any promise or commitment by the Company or an Affiliate regarding the fact or nature of future positions, future work assignments, future compensation or any other term or condition of employment or affiliation; (iii) confer any right or benefit under this Restricted Stock Unit Agreement or the Plan unless such right or benefit has specifically accrued under the terms of this Agreement or Plan; or (iv) deprive the Company of the right to terminate you at will and without regard to any future vesting opportunity that you may have.

(b) By accepting this Award, you acknowledge and agree that the right to continue vesting in the Award pursuant to the schedule set forth in Section 2 is earned only by continuing as an employee, director or consultant at the will of the Company (not through the act of being hired, being granted this Award or any other award or benefit) and that the Company has the right to reorganize, sell, spin-out or otherwise restructure one or more of its businesses or Affiliates at any time or from time to time, as it deems appropriate (a "reorganization"). You further acknowledge and agree that such a reorganization could result in the termination of your Continuous Service, or the termination of Affiliate status of your employer and the loss of benefits available to you under this Restricted Stock Unit Agreement, including but not limited to, the termination of the right to continue vesting in the Award. You further acknowledge and agree that this Restricted Stock Unit Agreement, the Plan, the transactions contemplated hereunder and the vesting schedule set forth herein or any covenant of good faith and fair dealing that may be found implicit in any of them do not constitute an express or implied promise of continued engagement as an employee or consultant for the term of this Agreement, for any period, or at all, and shall not interfere in any way with your right or the Company's right to terminate your Continuous Service at any time, with or without cause and with or without notice.

**10. WITHHOLDING OBLIGATIONS.**

(a) On or before the time you receive a distribution of the shares subject to your Award, or at any time thereafter as requested by the Company, you hereby authorize any required withholding (if any) from the Common Stock issuable to you and/or otherwise agree to make adequate provision in cash for any sums required to satisfy the federal, state, local and foreign tax withholding obligations (if any) of the Company or any Affiliate which arise in connection with your Award (the "**Withholding Taxes**"). Additionally, the Company may, in its sole discretion, satisfy all or any portion of the Withholding Taxes obligation relating to your Award by any of the following means or by a combination of such means: (i) withholding from any compensation otherwise payable to you by the Company; (ii) causing you to tender a cash payment; or (iii) withholding shares of Common Stock from the shares of Common Stock issued or otherwise issuable to you in connection with the Award with a Fair Market Value (measured as of the date shares of Common Stock are issued pursuant to Section 6) equal to the amount of such Withholding Taxes; provided, however, that the number of such shares of Common Stock so withheld shall not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income.

---

**(b)** Unless the tax withholding obligations of the Company and/or any Affiliate are satisfied, the Company shall have no obligation to deliver to you any Common Stock.

**(c)** In the event the Company's obligation to withhold arises prior to the delivery to you of Common Stock or it is determined after the delivery of Common Stock to you that the amount of the Company's withholding obligation was greater than the amount withheld by the Company, you agree to indemnify and hold the Company harmless from any failure by the Company to withhold the proper amount.

**(d)** If specified in your Grant Notice and permitted by the Company, you may direct the Company to withhold shares of Common Stock with a Fair Market Value (measured as of the date shares of Common Stock are issued pursuant to Section 6) equal to the amount of such Withholding Taxes; provided, however, that the number of such shares of Common Stock so withheld shall not exceed the amount necessary to satisfy the Company's required tax withholding obligations using the minimum statutory withholding rates for federal, state, local and foreign tax purposes, including payroll taxes, that are applicable to supplemental taxable income.

**11. UNSECURED OBLIGATION.** Your Award is unfunded, and as a holder of a vested Award, you shall be considered an unsecured creditor of the Company with respect to the Company's obligation, if any, to issue shares pursuant to this Agreement. You shall not have voting or any other rights as a stockholder of the Company with respect to the shares to be issued pursuant to this Agreement until such shares are issued to you pursuant to Section 6 of this Agreement. Upon such issuance, you will obtain full voting and other rights as a stockholder of the Company. Nothing contained in this Agreement, and no action taken pursuant to its provisions, shall create or be construed to create a trust of any kind or a fiduciary relationship between you and the Company or any other person.

**12. OTHER DOCUMENTS.** You hereby acknowledge receipt or the right to receive a document providing the information required by Rule 428(b)(1) promulgated under the Securities Act, which includes the Plan prospectus. In addition, you acknowledge receipt of the Company's insider-trading policy and agree that you may sell shares only in compliance with such policy, in effect from time to time.

**13. NOTICES.** Any notices provided for in your Award or the Plan shall be given in writing and shall be deemed effectively given upon receipt or, in the case of notices delivered by the Company to you, five days after deposit in the United States mail, postage prepaid, addressed to you at the last address you provided to the Company. Notwithstanding the foregoing, the Company may, in its sole discretion, decide to deliver any documents related to participation in the Plan and this Award by electronic means or to request your consent to participate in the Plan by electronic means. You hereby consent to receive such documents by electronic delivery and, if requested, to agree to participate in the Plan through an on-line or electronic system established and maintained by the Company or another third party designated by the Company.

---

**14. MISCELLANEOUS.**

(a) The rights and obligations of the Company under your Award shall be transferable to any one or more persons or entities, and all covenants and agreements hereunder shall inure to the benefit of, and be enforceable by the Company's successors and assigns. Your rights and obligations under your Award may only be assigned with the prior written consent of the Company.

(b) You agree upon request to execute any further documents or instruments necessary or desirable in the sole determination of the Company to carry out the purposes or intent of your Award.

(c) You acknowledge and agree that you have reviewed your Award in its entirety, have had an opportunity to obtain the advice of counsel prior to executing and accepting your Award, and fully understand all provisions of your Award.

(d) This Agreement shall be subject to all applicable laws, rules, and regulations, and to such approvals by any governmental agencies or national securities exchanges as may be required.

(e) All obligations of the Company under the Plan and this Agreement shall be binding on any successor to the Company, whether the existence of such successor is the result of a direct or indirect purchase, merger, consolidation, or otherwise, of all or substantially all of the business and/or assets of the Company.

**15. GOVERNING PLAN DOCUMENT.** Your Award is subject to all the provisions of the Plan, the provisions of which are hereby made a part of your Award, and is further subject to all interpretations, amendments, rules and regulations which may from time to time be promulgated and adopted pursuant to the Plan. Except as expressly provided herein, in the event of any conflict between the provisions of your Award and those of the Plan, the provisions of the Plan shall control.

**16. SEVERABILITY.** If all or any part of this Agreement or the Plan is declared by any court or governmental authority to be unlawful or invalid, such unlawfulness or invalidity shall not invalidate any portion of this Agreement or the Plan not declared to be unlawful or invalid. Any Section of this Agreement (or part of such a Section) so declared to be unlawful or invalid shall, if possible, be construed in a manner which will give effect to the terms of such Section or part of a Section to the fullest extent possible while remaining lawful and valid.

**17. CHOICE OF LAW.** The interpretation, performance and enforcement of this Agreement will be governed by the law of the state of California without regard to such state's conflicts of laws rules.

**18. AMENDMENT.** This Agreement may not be modified, amended or terminated except by an instrument in writing, signed by you and by a duly authorized representative of the Company. Notwithstanding the foregoing, this Agreement may be amended solely by the Board by a writing which specifically states that it is amending this Agreement, so long as a copy of such amendment is delivered to you, and provided that no such amendment adversely affecting your rights hereunder may be made without your written consent. Without limiting the foregoing, the Board reserves the right to change, by written notice to you, the provisions of this Agreement in any way it may deem necessary or advisable to carry out the purpose of the grant as a result of any change in applicable laws or regulations or any future law, regulation, ruling, or judicial decision, provided that any such change shall be applicable only to rights relating to that portion of the Award which is then subject to restrictions as provided herein.

---