

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

SCHEDULE 14A

**Proxy Statement Pursuant to Section 14(a) of
the Securities Exchange Act of 1934 (Amendment No.)**

Filed by the Registrant

Filed by a Party other than the Registrant

Check the appropriate box:

- Preliminary Proxy Statement
 Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))
 Definitive Proxy Statement
 Definitive Additional Materials
 Soliciting Material Pursuant to §240.14a-12

Ionis Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

(Name of Person(s) Filing Proxy Statement, if other than the Registrant)

Payment of Filing Fee (Check the appropriate box):

- No fee required.
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IONIS PHARMACEUTICALS, INC.
2855 Gazelle Court
Carlsbad, CA 92010

NOTICE OF 2020 ANNUAL MEETING OF STOCKHOLDERS
TO BE HELD ON JUNE 4, 2020

Dear Stockholders,

I am pleased to invite you to Ionis Pharmaceuticals, Inc.'s 2020 Annual Meeting of Stockholders. In light of the COVID-19 pandemic, to support the health and well-being of our stockholders, employees and directors, and taking into account recent federal, state and local guidance, the Annual Meeting will be held in a virtual meeting format only, via live webcast on the Internet, with no physical in-person meeting. You can attend and participate in the Annual Meeting online by visiting www.virtualshareholdermeeting.com/IONS2020, where you will be able to listen to the meeting live, submit questions and vote. As always, we encourage you to vote your shares prior to the Annual Meeting.

This booklet includes the agenda for this year's Annual Meeting and the Proxy Statement. We will cover the formal items on the agenda during the Annual Meeting. Following the formal Annual Meeting, we will review the major developments of the past year and our plans for 2020 via webcast. You can find information regarding how to join the webcast on our website at <https://ir.ionispharma.com/events/event-details/2020-annual-meeting-stockholders-and-general-corporate-update>. The Proxy Statement explains the matters we will discuss in the meeting and provides additional information about us.

Your vote is very important. Whether or not you plan to attend the meeting, please be sure to vote your shares as soon as possible to ensure your representation at the meeting. We are distributing our proxy materials under a Securities and Exchange Commission rule that allows us to furnish proxy materials to our stockholders over the Internet rather than in paper form. We believe this method of distribution reduces our environmental impact and costs without hindering our stockholders' timely access to such important material. As a result, if you are a stockholder of record (that is, if your stock is registered with us in your own name) you will receive a Notice Regarding the Availability of Proxy Materials in the mail, which contains instructions on how to access our proxy materials and vote electronically through the Internet or to request printed proxy materials so you may vote by telephone or mail.

If your shares are registered in the name of a broker or other nominee, that nominee will forward the Notice Regarding the Availability of Proxy Materials to you and you can direct that nominee to vote your shares. Alternatively, if your nominee participates in a program provided through Broadridge Financial Solutions, Inc. that allows you to vote by telephone or through the Internet, your nominee will send you a voting form with telephone and Internet voting instructions.

If you plan to attend the virtual meeting and prefer to vote online, you may still do so even if you have already returned your proxy.

PLEASE NOTE, HOWEVER, THAT IF A BROKER, BANK OR OTHER NOMINEE HOLDS YOUR SHARES OF RECORD AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN A PROXY ISSUED IN YOUR NAME FROM THE BROKER, BANK OR OTHER NOMINEE.

In this document, unless the context requires otherwise, the words "Ionis," "Company," "we," "our" and "us" refer only to Ionis Pharmaceuticals, Inc. and its subsidiaries and not to any other person or entity.

Sincerely,

Patrick R. O'Neil
Corporate Secretary

IONIS PHARMACEUTICALS, INC.
2855 Gazelle Court
Carlsbad, CA 92010

NOTICE OF 2020 ANNUAL MEETING OF STOCKHOLDERS

Date: Thursday, June 4, 2020
Time: 2:00 p.m. Pacific Time
Place: www.virtualshareholdermeeting.com/IONS2020

Dear Stockholders,

At our 2020 Annual Meeting of Stockholders, we will ask you to:

- Proposal 1: elect Joseph Wender, B. Lynne Parshall, Spencer Berthelsen and Joan Herman to serve as Directors for a three-year term;
- Proposal 2: approve an amendment and restatement of the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 800,000 shares to an aggregate of 2,800,000 shares, reduce the amount of the automatic awards under the plan, revise the vesting schedule of awards and extend the term of the plan;
- Proposal 3: ratify amending the existing stock option and restricted stock unit awards of directors to adjust vesting;
- Proposal 4: make an advisory vote on executive compensation; and
- Proposal 5: ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2020 fiscal year.
- Transact any other business that may be properly presented at the Annual Meeting.

The foregoing items of business are more fully described in the enclosed Proxy Statement. If you were an Ionis stockholder of record at the close of business on April 6, 2020 you may vote at the Annual Meeting.

The Annual Meeting will be a completely virtual meeting. To participate, vote or submit questions during the Annual Meeting via live webcast, please visit www.virtualshareholdermeeting.com/IONS2020. **You will not be able to attend the Annual Meeting in person.**

By order of the Board of Directors,

Patrick R. O'Neil
Corporate Secretary

Carlsbad, California
April 24, 2020

ALL STOCKHOLDERS ARE CORDIALLY INVITED TO ATTEND THE VIRTUAL MEETING VIA LIVE WEBCAST. WHETHER OR NOT YOU EXPECT TO ATTEND THE MEETING, PLEASE VOTE BY TELEPHONE OR INTERNET BY FOLLOWING THE INSTRUCTIONS INCLUDED IN THIS PROXY STATEMENT AND YOUR NOTICE REGARDING THE AVAILABILITY OF PROXY MATERIALS OR PROXY CARD. ALTERNATIVELY, YOU MAY REQUEST A WRITTEN PROXY STATEMENT, AND COMPLETE, DATE, SIGN AND RETURN YOUR PROXY AS PROMPTLY AS POSSIBLE TO ENSURE YOUR REPRESENTATION AT THE MEETING. IF YOU RECEIVE YOUR PROXY MATERIALS BY MAIL, WE WILL INCLUDE A RETURN ENVELOPE (WHICH IS POSTAGE PREPAID IF MAILED IN THE UNITED STATES) FOR THAT PURPOSE. EVEN IF YOU HAVE GIVEN YOUR PROXY, YOU MAY STILL VOTE AT THE VIRTUAL MEETING VIA LIVE WEBCAST. PLEASE NOTE, HOWEVER, THAT IF YOUR SHARES ARE HELD OF RECORD BY A BROKER, BANK OR OTHER NOMINEE AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN FROM THE BROKER, BANK OR OTHER NOMINEE A PROXY ISSUED IN YOUR NAME.

PROXY STATEMENT
FOR THE 2020 ANNUAL MEETING OF STOCKHOLDERS

To Be Held on June 4, 2020

QUESTIONS AND ANSWERS ABOUT THESE PROXY MATERIALS AND VOTING

Why did I receive a Notice Regarding the Availability of Proxy Materials on the Internet?

Ionis' Board of Directors (the "Board") is soliciting your proxy to vote at the 2020 Annual Meeting of Stockholders, including at any adjournments or postponements of the meeting. We are distributing our Notice of Annual Meeting and Proxy Materials (the "Notice") by mail using the Notice and Access procedures established by the United States Securities and Exchange Commission (the "SEC"). The Notice is important because it contains a control number and instructions that will allow you to access our proxy materials and vote electronically through the Internet or to request printed proxy materials so you may vote by telephone or mail. Your vote is very important. Whether or not you plan to attend the meeting, please be sure to vote your shares as soon as possible to ensure your representation at the meeting. All stockholders will have the ability to access the proxy materials on the website referred to in the Notice or request to receive a printed set of the proxy materials. You can find instructions on how to access the proxy materials over the Internet or to request a printed copy in the Notice.

We intend to mail the Notice on or before April 24, 2020 to all stockholders of record entitled to vote at the Annual Meeting.

Will I receive any other proxy materials by mail?

We may send you a proxy card, along with a second Notice, on or after May 4, 2020.

Where and when is the Annual Meeting?

The Annual Meeting will be held on Thursday, June 4, 2020, at 2:00 p.m. Pacific Time. In light of the COVID-19 pandemic, to support the health and well-being of our stockholders, employees and directors, and taking into account recent federal, state and local guidance, the Annual Meeting will be held in a virtual meeting format only, via live webcast on the Internet, with no physical in-person meeting. To participate, vote or submit questions during the Annual Meeting via live webcast, please visit www.virtualshareholdermeeting.com/IONS2020.

If you cannot attend, please note that we will make a webcast of the presentation that follows the Annual Meeting available on the day of the meeting and for a limited time following the meeting at www.ionispharma.com.¹

If you plan to attend the virtual meeting and prefer to vote online, you may still do so even if you have already returned your proxy.

How do I attend the Annual Meeting?

We will be hosting the Annual Meeting via live webcast on the Internet. **You will not be able to attend the Annual Meeting in person.** All stockholders at the close of business on April 6, 2020 can listen to and participate in the Annual Meeting live via the Internet at www.virtualshareholdermeeting.com/IONS2020. **The webcast will begin at 2:00 p.m. Pacific Time on June 4, 2020. Stockholders may vote and submit questions while connected to the Annual Meeting on the Internet.** A summary of the information you need to attend the Annual Meeting online is provided below.

¹ Any information that is included on or linked to our website is not part of this Proxy Statement or any registration statement or report that incorporates this Proxy Statement by reference.

What do I need in order to be able to participate in the Annual Meeting online?

You will need the 16-digit control number included on your proxy card in order to be able to vote your shares or submit questions during the virtual Annual Meeting. **Instructions on how to connect and participate in the Annual Meeting via the Internet, including how to demonstrate proof of stock ownership, are posted at www.virtualshareholdermeeting.com/IONS2020.**

What if I have technical difficulties or trouble accessing the live webcast of the Annual Meeting?

If you encounter any difficulties accessing the live webcast of the Annual Meeting or during the Annual Meeting, please call (844) 916-0608 for assistance. If you misplace the 16-digit control number that is required to enter the Annual Meeting webcast and are a stockholder of record, operators providing assistance at this telephone number will be able to provide it to you. However, if you need your 16-digit control number and hold your shares in an account at a brokerage firm, bank, dealer, or other similar organization, you must contact that organization to obtain your 16-digit control number prior to the Annual Meeting webcast.

Who can attend and vote at the virtual Annual Meeting?

Only stockholders at the close of business on April 6, 2020 may attend and vote at the virtual Annual Meeting. On this record date, there were 139,287,505 shares of common stock outstanding and entitled to vote.

Stockholder of Record: Shares Registered in Your Name

If on April 6, 2020 your shares were registered directly in your name with our transfer agent, American Stock Transfer & Trust Company, then you are a stockholder of record. As a stockholder of record, you may vote online at the virtual meeting or vote by proxy over the telephone, by mail, or the Internet as instructed under the section below titled “How do I vote?” Whether or not you plan to attend the meeting, we urge you to fill out and return the proxy card or vote over the telephone or Internet to ensure your vote is counted.

Beneficial Owner: Shares Registered in the Name of a Broker or Bank

If on April 6, 2020 you did not own shares in your name, but rather in an account at a brokerage firm, bank, dealer or other similar organization, then you are the beneficial owner of shares held in “street name” and that organization is forwarding the Notice to you. The organization holding your account is the stockholder of record for purposes of voting at the Annual Meeting. As a beneficial owner, you may direct your broker or other agent regarding how to vote the shares in your account. If your shares are registered in the name of a broker or other nominee, your nominee may be participating in a program provided through Broadridge Financial Solutions, Inc. (“Broadridge”) that also allows you to vote by telephone or through the Internet. If so, the voting form your nominee sends you will provide telephone and Internet instructions. You are also invited to attend the virtual Annual Meeting via live webcast.

PLEASE NOTE, HOWEVER, THAT IF A BROKER, BANK OR OTHER NOMINEE HOLDS YOUR SHARES OF RECORD AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN A PROXY ISSUED IN YOUR NAME FROM THE BROKER, BANK OR OTHER NOMINEE.

What am I voting on?

The following matters are scheduled for a vote:

- Proposal 1: elect Joseph Wender, B. Lynne Parshall, Spencer Berthelsen and Joan Herman to serve as Directors for a three-year term;
- Proposal 2: approve an amendment and restatement of the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 800,000 shares to an aggregate of 2,800,000 shares, reduce the amount of the automatic awards under the plan, revise the vesting schedule of awards and extend the term of the plan;
- Proposal 3: ratify amending the existing stock option and restricted stock unit awards of directors to adjust vesting;
- Proposal 4: make an advisory vote on executive compensation; and

- Proposal 5: ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2020 fiscal year.

What if another matter is properly brought before the meeting?

The Board knows of no other matters that will be presented for consideration at the Annual Meeting. If any other matters are properly brought before the meeting, the persons named in the accompanying proxy intend to vote on those matters in accordance with their best judgment.

How do I vote?

You may vote in one of the following ways:

- vote through the Internet by following the instructions included with your Notice or proxy card;
- vote by telephone by following the instructions included with your proxy card if you have received proxy materials electronically or by mail;
- vote by mail by completing, signing, dating and returning your proxy card in the postage paid envelope provided; or
- vote during the virtual Annual Meeting by following the instructions posted at www.virtualshareholdermeeting.com/IONS2020.

The procedures for voting are fairly simple:

For Shares Registered in Your Name:

If you are a stockholder of record, you may go to www.proxyvote.com to vote your shares through the Internet up until 11:59 P.M. Eastern Time on June 3, 2020. The votes represented by your proxy will be displayed on the computer screen and you will be prompted to submit or revise your votes as desired.

To vote your shares by telephone, you must first request that we send proxy materials to you by following the instructions included in your Notice. Once you have received your proxy materials, you may vote using a touch-tone telephone by calling 1-800-690-6903 up until 11:59 P.M. Eastern Time on June 3, 2020 and following the recorded instructions. Please have your proxy card available at the time you vote.

To vote using the proxy card, simply complete, sign and date the proxy card that may be delivered to you and return it promptly in the envelope provided. If you return your signed proxy card to us before the Annual Meeting, we will vote your shares as you direct.

For Shares Registered in the Name of a Broker or Bank:

If your broker or bank holds your shares in "street name," you will need to obtain a proxy form from the institution that holds your shares and follow the instructions included on that form regarding how to instruct your broker to vote your shares. If you do not give instructions to your broker, your broker can vote your shares with respect to "discretionary" items, but not with respect to "non-discretionary" items. Discretionary items are proposals considered routine under the rules of the New York Stock Exchange (NYSE) on which a broker may vote shares held in street name in the absence of your voting instructions. While Ionis is listed with the Nasdaq Stock Market (Nasdaq), NYSE rules affect how brokers licensed by the NYSE can vote in a director election of any company, including companies listed with Nasdaq. The proposal to ratify Ernst & Young LLP as independent auditors is a discretionary item. Proposals 1-4 regarding (1) the election of Directors, (2) approval of an amendment and restatement of the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 800,000 shares to an aggregate of 2,800,000 shares, reduce the amount of the automatic awards under the plan, revise the vesting schedule of awards and extend the term of the plan, (3) ratification of amending the existing stock option and restricted stock unit awards of directors to adjust vesting, and (4) approval, on an advisory basis, of our executive compensation, are non-discretionary items. If you do not give your broker instructions for a non-discretionary item, the inspector of elections will treat your shares as broker non-votes. Broker non-votes will have no effect.

A number of brokers and banks are participating in a program provided by Broadridge that allows proxies to vote shares by means of the telephone and Internet. If your shares are held in an account with a broker or bank

participating in the Broadridge program, you may vote your shares by telephone or through the Internet by having the voting form in hand and calling the number or going to the website indicated on the form and following the instructions.

What if I return a proxy card or otherwise vote but do not make specific choices?

If you return a signed and dated proxy card or otherwise vote without marking voting selections, one of the individuals named on your proxy card will vote your shares as follows:

- “For” the election of the nominees for Director named in the Proxy Statement;
- “For” the approval of an amendment and restatement of the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 800,000 shares to an aggregate of 2,800,000 shares, reduce the amount of the automatic awards under the plan, revise the vesting schedule of awards and extend the term of the plan;
- “For” ratification of amending the existing stock option and restricted stock unit awards of directors to adjust vesting;
- “For” the approval, on an advisory basis, of executive compensation; and
- “For” the ratification of the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2020 fiscal year.

If any other matter is properly presented at the meeting, one of the individuals named on your proxy card will vote your shares using his or her best judgment.

Who is paying for this proxy solicitation?

Our Board is soliciting your proxy to vote at the Annual Meeting. We will bear the entire cost of soliciting proxies, including preparing, assembling, making available on the Internet and printing and mailing this Proxy Statement, the proxy card and any additional information furnished to stockholders. We will furnish copies of solicitation materials to banks, brokerage houses, fiduciaries and custodians holding our common stock in “street name” on behalf of beneficial owners of such shares. We may reimburse persons representing beneficial owners of our common stock for their costs of forwarding solicitation materials to such beneficial owners. Our Directors, officers or other employees may supplement original solicitation of proxies by telephone, electronic mail or personal solicitation. We will not pay our Directors, officers or employees any additional compensation for soliciting proxies. However, please be aware that you must bear any costs associated with your Internet service, such as usage charges from Internet access providers or telephone companies.

What does it mean if I receive more than one Notice?

If you receive more than one Notice or proxy card, your shares are registered in more than one name or are registered in different accounts. Please complete, sign, date and return *each* separate proxy card or vote by telephone or through the Internet by following the instructions included with *each* Notice or proxy card to properly vote your shares.

Can I change my vote after submitting my proxy?

Yes. Once you have submitted your proxy by mail, Internet or telephone, you may revoke it at any time before we exercise it at the Annual Meeting. You may revoke your proxy by any one of the following four ways:

- you may mail another proxy marked with a later date;
- you may revoke it through the Internet;
- you may notify our corporate secretary in writing sent to 2855 Gazelle Court, Carlsbad, California 92010 that you wish to revoke your proxy before the Annual Meeting takes place; or
- you may vote during the virtual Annual Meeting. *Attending* the meeting *will not*, by itself, revoke a proxy.

If your shares are held by your broker, bank or other agent, you should follow the instructions provided by your broker, bank or other agent.

When are stockholder proposals due for next year’s Annual Meeting?

If you have a proposal that you would like us to include in our Proxy Statement and form of proxy for, or to present at the 2021 Annual Meeting of Stockholders, you must send the proposal to us by no later than December 25, 2020. Stockholders wishing to submit proposals or Director nominations that are not to be included in such Proxy Statement and form of proxy must do so no later than the close of business on February 4, 2021. Stockholders should also review our bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and Director nominations.

What is the quorum requirement?

A quorum of stockholders is necessary to hold a valid meeting. A quorum will be present at the meeting if at least a majority of the outstanding shares entitled to vote are represented at the meeting or by proxy. We will count your shares towards the quorum only if you submit a valid proxy vote (or one is submitted on your behalf by your broker, bank or other nominee) or vote at the meeting. We will count abstentions and broker non-votes towards the quorum requirement.

If there is no quorum, the holders of a majority of shares present at the meeting or represented by proxy may adjourn the meeting to another date.

How are votes counted?

Each share of our common stock you own entitles you to one vote. Your Notice and proxy card indicates the number of shares of our common stock you owned at the close of business on April 6, 2020. The inspector of elections will count votes for the meeting and will separately count “For” and “Against” votes, abstentions, and broker non-votes. With respect to Proposal 1, the election of Directors, stockholders do not affirmatively vote “Against” nominees. Instead, if you do not want to elect a particular nominee, you should choose to “Withhold” a vote in favor of the applicable nominee for Director and the inspector of elections will count each “Withhold” for each nominee. Abstentions will have no effect on Proposals 1, 3 and 5. Abstentions will count towards the vote total for Proposals 2 and 4, and in each case, will have the same effect as “Against” votes. Broker non-votes have no effect and the inspector of elections will not count them towards the vote total for any proposal.

What are “broker non-votes”?

Broker non-votes occur when a beneficial owner of shares held in “street name” does not give instructions to the broker or nominee holding the shares as to how to vote on matters deemed “non-routine.” If your broker holds your shares in “street name,” and you do not give instructions to your broker, your broker can vote your shares with respect to “discretionary” items, but not with respect to “non-discretionary” items. The proposal to ratify Ernst & Young LLP as independent auditors is a discretionary item. Proposals 1-4 regarding (1) the election of Directors, (2) approval of an amendment and restatement of the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 800,000 shares to an aggregate of 2,800,000 shares, reduce the amount of the automatic awards under the plan, revise the vesting schedule of awards and extend the term of the plan, (3) ratification of amending the existing stock option and restricted stock unit awards of directors to adjust vesting, and (4) approval, on an advisory basis, of our executive compensation, are non-discretionary items. If you do not give your broker instructions for a non-discretionary item, the inspector of elections will treat your unvoted shares as broker non-votes.

How many votes are needed to approve each proposal?

- Proposal 1: For the election of Directors in an uncontested election, a Director nominee must receive a majority of the votes cast in the election such that the number of shares voted “For” the nominee must exceed 50% of the votes cast with respect to that Director. Only “For” and “Withhold” votes will affect the outcome. Abstentions and broker non-votes will have no effect.
- Proposal 2: To be approved, the amendment and restatement of the 2002 Non-Employee Directors’ Stock Option Plan must receive “For” votes from the holders of a majority of shares entitled to vote on the matter. If you “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes will have no effect.

- Proposal 3: To be approved, ratification of amending the existing stock option and restricted stock unit awards of directors to adjust vesting must receive “For” votes from a majority of shares entitled to vote on the matter. Abstentions and broker non-votes will have no effect.
- Proposal 4: We will consider the advisory approval of the compensation of our executive officers to be approved if it receives “For” votes from the holders of a majority of shares entitled to vote on the matter. If you “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes will have no effect.
- Proposal 5: To be approved, the ratification of the selection of Ernst & Young LLP as our independent auditors for our 2020 fiscal year must receive “For” votes from a majority of shares entitled to vote on the matter. Abstentions and broker non-votes will have no effect.

How can I find out the results of the voting at the Annual Meeting?

We will announce preliminary voting results at the Annual Meeting. In addition, we will publish final voting results in a current report on Form 8-K that we expect to file within four business days after the Annual Meeting. If final voting results are not available to us in time to file as part of a Form 8-K within four business days after the Annual Meeting, we intend to file a Form 8-K to publish preliminary results and, within four business days after we know the final results, file an additional Form 8-K to publish final results.

How can I elect to receive materials for future Annual Meetings electronically?

We are pleased to offer to our stockholders the benefits and convenience of electronic delivery of Annual Meeting materials, including:

- delivering the Proxy Statement, Annual Report on Form 10-K, and related materials by email to our stockholders;
- stockholder voting online;
- helping the environment by decreasing the use of paper documents;
- reducing the amount of bulky documents stockholders receive; and
- reducing our printing and mailing costs associated with more traditional delivery methods.

We encourage you to conserve natural resources and to reduce printing and mailing costs by signing up for electronic delivery of our stockholder communications after you place your current vote at www.proxyvote.com.

List of Shareholders

A list of shareholders of record will be available during the virtual Annual Meeting for inspection by shareholders for any legally valid purpose related to the Annual Meeting at www.virtualshareholdermeeting.com/IONS2020.

PROPOSAL 1

ELECTION OF DIRECTORS

Information about our Board

The Board is divided into three classes. Presently, the Board has twelve members with each class consisting of four Directors. Each class serves a three-year term and we hold elections each year at the Annual Meeting to elect the Directors whose terms are expiring.

In addition, the Board may elect a new Director to fill any vacant spot, including a vacancy caused by an increase in the size of the Board, such as the case with Ms. Herman. However, the Board believes it is important for our stockholders to ratify any member of the Board whom the Board appoints. As a result, whenever the Board appoints a new member, the Board will submit such new member's directorship for ratification at the next regularly scheduled Annual Meeting of Stockholders, unless such new director is up for election at the next regularly scheduled Annual Meeting of Stockholders.

The Board represents the interests of our stockholders by overseeing the Chief Executive Officer and other members of senior management in our operation. The Board's goal is to optimize long-term value by providing guidance and strategic oversight to Ionis' management on our stockholders' behalf.

Information about the 2020 Elections

The Board has nominated four individuals for election at the Annual Meeting. Each of the nominees currently serves as one of our Directors. Mr. Wender, Ms. Parshall, Dr. Berthelsen and Ms. Herman have each served as a Director for the periods set forth in the table below.

Name	Commencement of Ionis Directorship
Joseph Wender	January 1994
B. Lynne Parshall	September 2000
Spencer Berthelsen	May 2002
Joan Herman	June 2019

Mr. Wender, Ms. Parshall and Dr. Berthelsen have been re-elected by our stockholders each successive term. This is the first time Ms. Herman is a nominee for election by our stockholders. If re-elected or elected, as applicable, Mr. Wender, Ms. Parshall, Dr. Berthelsen and Ms. Herman will serve until the 2023 Annual Meeting or, in each case, until his or her successor is elected and has qualified, or until his or her earlier death, resignation or removal.

Our bylaws provide a majority vote standard for the election of directors in uncontested elections. In an uncontested election, the majority vote standard means that to be elected, a Director nominee must receive a majority of the votes cast in the election such that the number of shares voted "For" the nominee must exceed 50% of the votes cast with respect to that Director. The number of votes cast with respect to a Director's election excludes abstentions and broker non-votes. In contested elections where the number of nominees exceeds the number of Directors to be elected, the vote standard will be a plurality of the shares present or represented by proxy and entitled to vote.

If a nominee who already serves as a Director is not elected, and no successor is elected, the Director will offer to tender his or her resignation to the Board. The Nominating, Governance and Review Committee will make a recommendation to the Board on whether to accept or reject the resignation, or whether to take other action. The Board will act on the Nominating, Governance and Review Committee's recommendation and publicly disclose its decision and the rationale behind it within 90 days from the date of the certification of the election results. The Director who tenders his or her resignation will not participate in the recommendation of the Nominating, Governance and Review Committee or in the Board's decision. If a nominee's failure to be elected at the Annual Meeting results in a vacancy on the Board, then the Board can fill the vacancy.

The Nominating, Governance and Review Committee delivered its report to the Board providing its recommendations for Director nominees to stand for election at the Annual Meeting on March 23, 2020.

Following that report, the Board determined it would be in the best interests of Ionis and its stockholders to nominate Mr. Wender, Ms. Parshall, Dr. Berthelsen and Ms. Herman to be elected as Directors at the Annual Meeting. We provide below a short biography for each nominee. Mr. Wender, Ms. Parshall, Dr. Berthelsen and Ms. Herman have agreed to serve if elected, and we have no reason to believe that they cannot serve. However, if they cannot serve, we may vote your proxy for another nominee proposed by the Board, or the Board may reduce the number of authorized Directors.

Biographies of the Nominees for Election for a Three-Year Term Expiring at the 2023 Annual Meeting

Spencer R. Berthelsen, M.D., age 67², has served as a Director of Ionis since May 2002. Dr. Berthelsen practiced Internal Medicine with the Kelsey Seybold Clinic, a 400-physician medical group based in the Texas Medical Center in Houston, until March 2017. Dr. Berthelsen began at Kelsey Seybold in 1980 and served in various senior leadership positions throughout his nearly four-decade career at the clinic, including Chairman of the Department of Internal Medicine, Medical Director and Managing Director. He also served as Chairman of its board of directors from October 2001 through April 2016. He has served as Clinical Professor of Medicine at both Baylor College of Medicine and The University of Texas Health Science Center. Dr. Berthelsen served on the board of the Texas Academy of Internal Medicine in the past and the Caremark National Pharmacy and Therapeutics Committee from 1999 through 2005.

The Board believes Dr. Berthelsen is uniquely suited to serve on the Board because of his experience advising a large multispecialty group practice and almost 40 years of experience as a practicing physician.

Joan E. Herman, age 66, has served as a Director of Ionis since June 2019. Since 2008, Ms. Herman has served as President and Chief Executive Officer of Herman & Associates, a management consulting firm that specializes in advising private equity firms investing in healthcare. She has experience leading healthcare and payor companies, serving in several executive positions at Anthem (formerly WellPoint), including as President and Chief Executive Officer of several different business units. Ms. Herman also served as a Senior Vice President of Phoenix Life Insurance Company. Since January 2013, Ms. Herman has served on the board of directors for Encompass Health (formerly HealthSouth). She previously served on the boards of both Convergys and AARP Services, Inc.

The Board believes Ms. Herman is uniquely suited to serve on the Board because of her experience leading healthcare and payor companies.

B. Lynne Parshall, age 65, has served as a Director of Ionis since September 2000 and as a Senior Strategic Advisor to Ionis since January 2018. Previously she served as our Chief Operating Officer from December 2007 through January 2018 and as our Chief Financial Officer from June 1994 through December 2012. She also served as our Corporate Secretary through 2014 and has served with the Company in various executive roles since November 1991. Prior to joining Ionis, Ms. Parshall practiced law at Cooley LLP, outside counsel to Ionis, where she was a partner from 1986 to 1991. Ms. Parshall is a member of the American and California bar associations. Ms. Parshall has served on the boards of directors of Cytokinetics, Inc. since February 2013, and Akcea Therapeutics, Inc., since January 2015, both public biopharmaceutical companies.

The Board believes Ms. Parshall is uniquely suited to serve on the Board primarily because, as the former Chief Operating Officer and former executive of the Company for over 26 years, she has valuable Company-specific experience and expertise. In addition, Ms. Parshall has over 33 years of experience structuring and negotiating strategic licensing and financing transactions in the life sciences field.

Joseph H. Wender, age 75, has served as a Director of Ionis since January 1994. Mr. Wender began with Goldman, Sachs & Co. in 1971 and became a General Partner of that firm in 1982, where he headed the Financial Institutions Group for over a decade. Since January 2008, he has been a Senior Consultant to Goldman Sachs & Co. He is a former Independent Trustee of the Schwab Family of Funds and Director of Grandpoint Capital, a bank holding company. Mr. Wender also is co-CEO and partner of Colgin Cellars. Since March 2014, Mr. Wender has been a Director of Outfront Media, a lessor of advertising space on out-of-home advertising structures, and has served as its Lead Independent Director since 2016.

² The ages of all our Directors are as of March 1, 2020.

The Board believes Mr. Wender is uniquely suited to serve on the Board primarily because, with over 48 years of experience as an investment banker with Goldman, Sachs & Co., he provides Ionis important advice regarding our financial reporting, corporate finance matters, strategic transactions, and compensation matters.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE “FOR” THE ELECTION OF THE ABOVE NOMINEES.

Biographies of the Directors Whose Terms Expire at the 2021 Annual Meeting

Breaux B. Castleman, age 79, has served as a Director of Ionis since June 2013. Since August 2001, Mr. Castleman has been President and Chief Executive Officer of Syntiro Healthcare Services, Inc., a healthcare investment company, which sold its operations as a service provider of integrated care management and disease management. Since January 2008, Mr. Castleman has been a Senior Advisor of McNally Capital, LLC, a private equity and merchant banking firm focused on investments in private equity, both direct to companies and through private equity partnerships. Mr. Castleman was a director of USMD Holdings, Inc., a physician-led integrated healthcare system, from August 2010 until September 2016.

The Board believes Mr. Castleman is uniquely suited to serve on the Board and the Audit Committee because he has significant experience in strategic planning and financial structuring matters for Fortune 1000 companies and has financial advisory expertise in the life sciences industry.

Frederick T. Muto, age 66, has served as a Director of Ionis since March 2001. Mr. Muto joined the law firm of Cooley LLP, outside counsel to Ionis, in 1980, became a partner in 1986 and senior counsel in 2018. He is a founder of Cooley LLP’s San Diego office and was chair of the firm’s Business Department for a number of years.

The Board believes Mr. Muto is uniquely suited to serve on the Board and the Audit Committee primarily because, with over 39 years of experience at one of the country’s leading law firms focused on life sciences and technology companies, he provides us important advice regarding our strategic transactions, corporate governance and compensation matters.

Peter N. Reikes, age 59, has served as a Director of Ionis since September 2018. Mr. Reikes is a Vice Chairman in the Investment Banking Division at Stifel, Nicolaus & Company, Inc., which he joined in late 2010. Over the course of his extensive career in investment banking, Mr. Reikes has completed a wide range of financing and merger and acquisition transactions for companies in the life sciences, medical technology and healthcare services sectors. Prior to joining Stifel, Nicolaus, he spent 11 years at Cowen and Company, LLC, where he was Vice Chairman and Head of Healthcare Investment Banking, and over 14 years at PaineWebber Incorporated, where he was a Managing Director and Head of Healthcare Investment Banking and began his career in 1985. Mr. Reikes is also a director of the Heart & Soul Foundation, an organization that supports a range of community service programs in the greater New York City area. Mr. Reikes is a former director of Ricerca Biosciences, LLC, Biocompatibles, Ltd., and the affiliated partnership boards of Alkermes, Inc., Cephalon, Inc., Gensia, Inc., Genzyme Corporation and Repligen Corporation, as well as the Institute for Quality Improvement of the Accreditation Association for Ambulatory Health Care. Mr. Reikes received his B.A. in Economics from the University of California at Los Angeles and his M.B.A. in Finance from The Wharton School at the University of Pennsylvania.

The Board believes Mr. Reikes is uniquely suited to serve on the Board primarily because of his extensive experience in finance and strategic transactions for companies in the life sciences, medical technology and healthcare services industries.

Brett Monia, Ph.D., age 58, has served as a Director of Ionis since March 2019. Dr. Monia was promoted to Chief Executive Officer in January 2020. From January 2018 to December 2019, Dr. Monia served as our Chief Operating Officer, from January 2012 to January 2018, as our Senior Vice President, Drug Discovery, from February 2009 to January 2012, as our Vice President, Drug Discovery, and from October 2000 to February 2009, as our Vice President, Preclinical Drug Discovery. From October 1989 to October 2000, he held various positions within our Molecular Pharmacology department.

The Board believes Dr. Monia is uniquely suited to serve on the Board primarily because, as an executive officer of the Company since 2012 and a founder of Ionis, he has dedicated more than 30 years to discovering and developing antisense-based drugs. Dr. Monia is the inventor on over 100 issued patents and has directly supervised programs resulting in the clinical development of more than 40 antisense-based drugs across a broad range of therapeutic areas.

Biographies of the Nominees for Election for a Three-Year Term Expiring at the 2022 Annual Meeting

Stanley T. Croke, M.D., Ph.D., age 74, is a founder of Ionis and is our Executive Chairman of the Board. He has been a Director since January 1989. He served as our Chief Executive Officer from February 1989 until January 2020. In January 2020, Dr. Croke was elected Executive Chairman of the Board, and he has served as Chairman of the Board since February 1991. Prior to founding Ionis, from 1980 until January 1989, Dr. Croke worked for SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories. Dr. Croke served on the board of directors of Akcea Therapeutics, Inc., a public biopharmaceutical company, from January 2015 through October 2018.

The Board believes Dr. Croke is uniquely suited to serve on the Board primarily because, as the founder of Ionis and its former Chief Executive Officer, he has dedicated over 31 years to discovering and developing antisense, our technology platform. He is the named inventor on some of the key patents in the field of RNA-targeted therapeutics and has nearly 41 years of drug discovery and development experience.

Joseph Klein, III, age 58, has served as a Director of Ionis since December 2005. Mr. Klein is currently Managing Director of Gauss Capital Advisors, LLC, a financial consulting and investment advisory firm focused on biopharmaceuticals, which he founded in March 1998. From September 2003 to December 2008, Mr. Klein also served as a Venture Partner of Red Abbey Venture Partners, L.P., a life science private equity fund. From September 2001 to September 2002, Mr. Klein was a Venture Partner of MPM Capital, a healthcare venture capital firm. From June 1999 to September 2000 when it merged with WebMD Corporation, Mr. Klein served as Vice President, Strategy, for Medical Manager Corporation, a leading developer of physician office management information systems. For over nine years from 1989 to 1998, Mr. Klein was a health care investment analyst at T. Rowe Price Associates, Inc., where he was the founding portfolio manager of the T. Rowe Price Health Sciences Fund, Inc. Mr. Klein has served on the boards of directors of The Prospector Funds, Inc., an SEC Registered Investment Company that manages two no-load mutual funds, since September 2007 and Akcea Therapeutics, Inc., a public biopharmaceutical company, since September 2019. Mr. Klein also serves on the boards of private and non-profit entities.

The Board believes Mr. Klein is uniquely suited to serve on the Board and as Chairman of the Audit Committee because he is a Chartered Financial Analyst and has extensive public company, venture investment, board, and financial advisory expertise in the life sciences industry, including previously serving as Chairman of the Audit Committee at several public biopharmaceutical companies.

Joseph Loscalzo, M.D., Ph.D., age 68, has served as a Director of Ionis since February 2014. Dr. Loscalzo is Hersey Professor of the Theory and Practice of Medicine at Harvard Medical School, Chairman of the Department of Medicine, and Physician-in-Chief at Brigham and Women's Hospital. Dr. Loscalzo received his A.B. degree, *summa cum laude*, his Ph.D. in biochemistry, and his M.D. from the University of Pennsylvania. He completed his clinical training at Brigham and Women's Hospital and Harvard Medical School, where he served as Resident and Chief Resident in medicine and Fellow in cardiovascular medicine. Post-training, Dr. Loscalzo joined the Harvard faculty and staff at Brigham and Women's Hospital in 1984. He rose to the rank of Associate Professor of Medicine, Chief of Cardiology at the West Roxbury Veterans Administration Medical Center, and Director of the Center for Research in Thrombolysis at Brigham and Women's Hospital. He joined the faculty of Boston University in 1994, first as Chief of Cardiology and, in 1997, Wade Professor and Chair of Medicine, Professor of Biochemistry, and Director of the Whitaker Cardiovascular Institute. He returned to Harvard and Brigham and Women's Hospital in 2005. Since January 2016, Dr. Loscalzo has served on the board of directors of Leap Therapeutics, Inc., a public biopharmaceutical company.

The Board believes Dr. Loscalzo is uniquely suited to serve on the Board primarily because of his extensive scientific expertise, including 29 years of research in the areas of vascular biology, thrombosis, and atherosclerosis, and practical knowledge as a practicing physician. Dr. Loscalzo's expertise and role as a leading cardiologist is particularly valuable as we advance and grow our cardiovascular franchise.

Michael Hayden, CM, OBC, MB, ChB, Ph.D., FRCP(C), FRSC, age 68, has served as a Director of Ionis since September 2018. Dr. Hayden is a Killam Professor at the University of British Columbia and the Director of the Translational Laboratory in Genetic Medicine at the National University of Singapore and the Agency for Science, Technology and Research (A*STAR). From 2012 to 2017, he served as President of Global R&D and Chief Scientific Officer at Teva Pharmaceutical Industries Ltd. Dr. Hayden has founded three biotechnology companies and has been the recipient of numerous prestigious honors and awards, including being inducted into the Canadian Medical Hall of Fame, receiving the July 2012 Diamond Jubilee Medal, on behalf of HRH Queen Elisabeth II and the Margolese National Brain Disorder Prize, awarded to Canadians who have made outstanding contributions to the treatment, amelioration or cure of brain diseases. He has also received the Canada Gairdner Wightman award for his outstanding leadership in medicine and medical science as a physician-scientist. Dr. Hayden was awarded the Order of Canada, the Order of British Columbia, named Canada's Health Researcher of the Year by Canadian Institutes of Health Research, and has received the Prix Galien Award for his contribution to Canadian pharmaceutical research. Dr. Hayden has served on the boards of Aurinia Pharmaceuticals since February 2018 and Xenon Pharmaceuticals since November 1996, both public biopharmaceutical companies.

The Board believes Dr. Hayden is uniquely suited to serve on the Board because he has significant expertise in pharmaceutical research and development, both in academia and in commercial settings. In addition, Dr. Hayden has made substantial research contributions to advance treatments for brain diseases, which is particularly valuable as we grow our neurology franchise.

Independence of the Board

As required under Nasdaq listing standards, a majority of the members of a listed company's board of directors must qualify as "independent," as evaluated by our Nominating, Governance and Review Committee and affirmed by our Board. Our Nominating, Governance and Review Committee consults with our legal counsel to ensure that the Committee's determinations are consistent with all relevant securities and other laws and regulations regarding the definition of "independent," including those set forth in the applicable Nasdaq listing standards and applicable SEC rules and regulations, as in effect from time to time.

Consistent with these considerations, after review of all relevant transactions or relationships between each Director, or any of his or her family members, and Ionis, its senior management and its independent auditors, the Board affirmatively has determined that all of our Directors are independent Directors within the meaning of the applicable Nasdaq listing standards and SEC rules and regulations, except for Dr. Crooke, Ms. Parshall and Dr. Monia, our former Chief Executive Officer, former Chief Operating Officer, and current Chief Executive Officer, respectively. In making this determination, the Board found that none of these independent Directors has a material or other disqualifying relationship with us. Notably, Mr. Muto is no longer a partner at Cooley LLP, Ionis' outside counsel. Also, although the Company does business with Stifel, Nicolaus & Company, Inc., Mr. Reikes does not receive any personal compensation directly from revenue received by Ionis.

Information Regarding the Board and its Committees

Leadership Structure

Until January 2020, our Chief Executive Officer was the Chairman of the Board. In January 2020, Dr. Monia assumed the position of Chief Executive Officer and Dr. Crooke transitioned to Executive Chairman of the Board. The Board believes our current leadership structure is effective and serves the best interests of our stockholders at this time by allowing Dr. Monia to focus on his duties managing the day-to-day operations of the Company while benefiting from Dr. Crooke's invaluable knowledge and expertise. The Board believes that the newly separated roles of Executive Chairman of the Board and Chief Executive Officer reinforces the independence of the Board in its oversight of the business and affairs of the Company.

Risk Oversight

Our Board administers its risk oversight function directly and through both its Audit Committee and its Nominating, Governance and Review Committee. The Audit Committee oversees management of financial risks and related party transactions. In 2019, the Audit Committee authorized the formation of an internal audit function known as "Advisory Services" that reports to the Audit Committee. Advisory Services strives to accomplish its mission of adding value to and improving the Company's operations through sustaining a systematic, disciplined, and transparent approach to evaluating the effectiveness of governance, risk management, and control processes. The scope of Advisory Services is to determine if the control environment and internal control structure, as designed and represented by Company management, are adequate and functioning in a manner to enable the Company to meet its business objectives and satisfy its responsibilities.

The Nominating, Governance and Review Committee manages risks associated with the independence of the Board and potential conflicts of interests at the Board level, and periodically reviews our policies and procedures and makes recommendations when appropriate. We provide a complete description of each committee and its respective roles and responsibilities on pages [14](#) through [18](#) of this Proxy Statement. While each of these committees is responsible for evaluating certain risks and overseeing how we manage risk, these committees regularly inform the entire Board about such risks through committee reports.

In addition to the formal compliance program, the Board, the Audit Committee, the Nominating, Governance and Review Committee and the Science/Medical Committee encourage management to promote a corporate culture that understands risk management and incorporates it into the overall corporate strategy and day-to-day business operations. Our risk management structure also includes an ongoing effort to assess and analyze the most likely areas of future risk for Ionis. As a result, the Board, the Audit Committee, the Nominating, Governance and Review Committee and the Science/Medical Committee periodically ask our executives to discuss the most likely sources of material future risks and how we are addressing any significant potential vulnerability.

Board Committees

The Board has six committees: an Audit Committee, a Compensation Committee, a Nominating, Governance and Review Committee, an Agenda Committee, a Science/Medical Committee and a Finance Committee. Below is a description of each committee of our Board. Each of the committees has authority to engage legal counsel or other experts or consultants as it deems appropriate to carry out its responsibilities. The Board has determined that each member of our Audit Committee, Compensation Committee, and Nominating, Governance and Review Committee:

- meets the applicable rules and regulations regarding “independence,” including, but not limited to, Rule 5605(a)(2) of the Nasdaq listing standards and applicable SEC rules and regulations;
- is not an officer or employee of Ionis; and
- is free of any relationship that would interfere with his or her individual exercise of independent judgment with regard to Ionis.

Meetings and Attendance; Committee Members

The Board met seven times in 2019. During 2019, each Director attended 75% or more of the aggregate number of meetings of the Board and the committees on which such Director served. We encourage each member of the Board to attend the Annual Meeting of Stockholders.

Board Committee Members

The table below provides membership and meeting information for fiscal 2019 for each of the Board committees.

Name	Audit	Compensation	Nominating, Governance and Review	Agenda	Science/ Medical	Finance**	Attended 2019 Annual Meeting
Dr. Spencer R. Berthelsen	—	X*	X	—	X	—	
Mr. Breaux B. Castleman	X	—	—	—	—	—	X
Dr. Stanley T. Crooke	—	—	—	X*	X*	—	X
Dr. Michael Hayden	—	—	—	—	X	—	X
Ms. Joan E. Herman	X	—	—	—	—	—	
Mr. Joseph Klein, III	X*	—	—	—	—	—	X
Dr. Joseph Loscalzo	—	—	X	X	X	—	
Dr. Brett Monia	—	—	—	X	—	—	X
Mr. Frederick T. Muto	X	X	X	X ⁽¹⁾	—	X	X
Ms. B. Lynne Parshall	—	—	—	X	—	X	X
Mr. Peter Reikes	—	—	—	X	—	X	X
Mr. Joseph H. Wender	X ⁽²⁾	X	X*	—	—	X*	X
Total meetings in fiscal year 2019	7	4	4	4	2	6	

* Committee Chairperson

** Finance Committee formed in May 2019.

(1) Served on the Agenda Committee until March 22, 2019.

(2) Served on the Audit Committee until March 22, 2019.

The table below identifies our current Board and committee members.

Name	Audit	Compensation	Nominating, Governance and Review	Agenda	Science/ Medical	Finance
Dr. Spencer R. Berthelsen	—	X*	X	—	X	—
Mr. Breaux B. Castleman	X	—	—	—	—	—
Dr. Stanley T. Crooke	—	—	—	X*	X*	—
Dr. Michael Hayden	—	—	—	—	X	—
Ms. Joan E. Herman	X	—	—	—	—	—
Mr. Joseph Klein, III	X*	—	—	—	—	—
Dr. Joseph Loscalzo	—	—	X	X	X	—
Dr. Brett Monia	—	—	—	X	—	—
Mr. Frederick T. Muto	X	X	X	—	—	X
Ms. B. Lynne Parshall	—	—	—	X	—	X
Mr. Peter Reikes	—	—	—	X	—	X
Mr. Joseph H. Wender	—	X	X*	—	—	X*

* Committee Chairperson

Audit Committee

The Audit Committee of the Board oversees our corporate accounting and financial reporting process, including audits of our financial statements. For this purpose, the Audit Committee performs several functions.

The Audit Committee:

- reviews the annual and quarterly financial statements, including the disclosures contained under the caption “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” and oversees the annual and quarterly financial reporting processes, including sessions with the independent auditors and internal auditors in which Ionis’ employees and management are not present;
- selects and hires our independent auditors;
- oversees the independence of our independent auditors;
- evaluates our independent auditors’ performance; and
- has the authority to hire its own outside consultants and advisors, if necessary.

In addition to the responsibilities listed above, the Audit Committee has the following functions:

- receiving and considering our independent auditors’ comments as to the audit of the financial statements and internal controls, adequacy of staff and management performance and procedures in connection with internal controls;
- reviewing and, if appropriate, approving related party transactions;
- establishing and enforcing procedures for the receipt, retention and treatment of complaints regarding accounting or auditing improprieties;
- pre-approving all audit and non-audit services provided by our independent auditors that are not prohibited by law;
- overseeing cybersecurity preparedness; and
- meeting regularly with members of the internal audit/Advisory Services team.

Our Audit Committee utilizes an Audit Committee calendar to manage and track its key duties and responsibilities throughout each year.

Our Audit Committee charter requires that each member must be independent. We consider the members to be independent as long as they:

- do not accept any consulting, advisory or other compensatory fee from us, except in connection with their service as a Director;
- are not an affiliate of Ionis or one of its subsidiaries; and
- meet all of the other Nasdaq independence requirements.

In addition, all Audit Committee members must be financially literate and at least one member must be a “financial expert,” as defined by SEC regulations. Our Board has determined that the Audit Committee’s financial expert is Mr. Klein based on, among other things, his status as a Chartered Financial Analyst and his extensive public company, venture investment, board, and financial advisory expertise in the life sciences industry, including previously serving as Chairman of the Audit Committee at several public biopharmaceutical companies. We provide the Audit Committee with the funding it needs to perform its duties.

The Audit Committee typically meets twice each quarter: once face-to-face in connection with quarterly Board of Director meetings, and once by teleconference to review quarterly financial results and Form 10-Q or annual financial results and Form 10-K. In 2019, the Audit Committee met seven times. The Board has adopted a written Audit Committee charter, which you can find on our corporate website at www.ionispharma.com.³ Each member meets the membership criteria set forth in the Audit Committee charter and as stated above.

Compensation Committee

The primary function of the Compensation Committee of the Board is to review, modify (as needed) and approve our overall compensation strategy and policies and approve the compensation and other terms of employment of our executive officers, including our Chief Executive Officer. We include a full list of the Compensation Committee’s responsibilities as part of the Compensation Discussion and Analysis (“CD&A”) set forth on pages 37 through 61 of this Proxy Statement. The charter of the Compensation Committee grants the Compensation Committee full access to all of our books, records, facilities and personnel, and authority to obtain, at our expense, advice and assistance from internal and external legal, accounting or other advisors and consultants and other external resources that the Compensation Committee considers necessary or appropriate in the performance of its duties. In particular, the Compensation Committee has the sole authority to retain independent compensation consultants to help the Compensation Committee evaluate executive and Director compensation, including the authority to approve the consultants’ reasonable fees and other retention terms.

We also have a Non-Management Stock Option Committee that, as delegated by the Compensation Committee, may award stock options and RSUs to employees who are below director level in accordance with guidelines adopted by the Compensation Committee. The Non-Management Stock Option Committee has one member, Dr. Crooke.

The Compensation Committee met four times in 2019 and acted by unanimous written consent 12 times. The Board has adopted a written Compensation Committee charter, which you can find on our corporate website at www.ionispharma.com.⁴

The Compensation Committee reviews with management Ionis’ CD&A to consider whether to recommend that we include the CD&A in our Proxy Statements and other filings.

Compensation Committee Interlocks and Insider Participation

As noted above, during the fiscal year ended December 31, 2019, our Compensation Committee was composed of Dr. Berthelsen, Mr. Wender and Mr. Muto. In each case, none of the members of the Compensation Committee has ever been an employee or officer of Ionis. None of our executive officers serves as a member of the board of directors or compensation committee of any other entity that has one or more executive officers serving as a member of our Board or Compensation Committee.

³ Any information that is included on or linked to our website is not part of this Proxy Statement or any registration statement or report that incorporates this Proxy Statement by reference.

⁴ Any information that is included on or linked to our website is not part of this Proxy Statement or any registration statement or report that incorporates this Proxy Statement by reference.

Nominating, Governance and Review Committee

The Nominating, Governance and Review Committee of the Board is responsible for:

- interviewing, evaluating, nominating and recommending individuals for membership on our Board, and considering proposed changes to the Board for approval;
- managing risks associated with the independence of the Board and potential conflicts of interests at the Board level, and periodically reviewing our policies and procedures and making recommendations when appropriate; and
- performing such other functions as may be necessary or convenient for the efficient discharge of the foregoing.

The Nominating, Governance and Review Committee met four times during 2019. You can find our Nominating, Governance and Review Committee charter on our corporate website at www.ionispharma.com.⁵

Director Nominations - Approach to Board Composition

The Nominating, Governance and Review Committee believes that candidates for Director should have certain minimum qualifications. As a result, the Board adopted membership standards and believes that the Board members should meet the minimum membership requirements listed below.

The minimum membership requirements are as follows:

- members must be able to read and understand basic financial statements;
- members must demonstrate high personal integrity and ethics;
- members cannot serve as a director on the board of more than five other publicly traded companies;
- members cannot serve more than ten consecutive terms on the Board, except that Stanley T. Croke, a founder of the Company, may serve for no more than 15 consecutive terms; and
- members cannot run for re-election or serve on the Board once they have reached the age of 80.

In addition to these minimum standards, the Nominating, Governance and Review Committee will consider such factors as:

- possessing relevant expertise to offer advice and guidance to management;
- having sufficient time to devote to Ionis' affairs;
- demonstrating excellence in his or her field;
- having sound business judgment; and
- being committed to vigorously representing the long-term interests of our stockholders.

Director Nominations - Diversity Discussion

In considering Director nominations, the Nominating, Governance and Review Committee considers the total mix of competencies represented on the Board as a whole, as well as the competencies each member, or nominee, brings to the Board. In general, our Board members' experience falls into three large categories: (1) investment banking, financial accounting and corporate governance experience; (2) medical and scientific expertise; and (3) employee versus non-employee Directors. By selecting individuals who have investment banking, financial accounting and corporate governance backgrounds, we gain valuable experience that ensures we are managing our financial resources appropriately, reporting our financial results fairly and accurately, and generally running our business consistent with current good corporate practices. As a cutting-edge drug discovery and development company, we also greatly benefit from Board members who themselves are scientists and medical doctors and can help set and adjust our strategy and objectives based on the results we generate from our research and development efforts. In different ways, these first two categories allow us to effectively manage our cash and make prudent investments in our technology to achieve the greatest likelihood of success. We try to evenly balance the Board members across these first two categories.

⁵ Any information that is included on or linked to our website is not part of this Proxy Statement or any registration statement or report that incorporates this Proxy Statement by reference.

Regarding the third category, we believe that employee Directors can provide the Board valuable insight regarding our day-to-day operations, which can offer the Board a different perspective and help the Board make important management and compensation decisions. Our non-employee Directors can compare the opportunities and challenges presented to Ionis against the facts and circumstances they are experiencing outside Ionis. We have more non-employee Directors than employee Directors and believe that the current mix in this respect provides consistent leadership balanced with appropriate independent oversight. Additionally, the non-employee Directors regularly meet in executive session without employee Directors present. Finally, we do not discriminate against nominees on the basis of gender, race, religion, national origin, sexual orientation, disability or any other basis prohibited by applicable law.

Director Nominations - Process

The Nominating, Governance and Review Committee will consider Director candidates our stockholders recommend. The Nominating, Governance and Review Committee does not intend to alter the manner in which it evaluates candidates, including the minimum criteria set forth above, based on whether or not a stockholder recommended the candidate.

The Nominating, Governance and Review Committee reviews new candidates for Director in the context of the Board's composition, our operating requirements and our stockholders' long-term interests. In conducting this assessment, the Nominating, Governance and Review Committee considers diversity, maturity, skills, the minimum membership requirements discussed above, and such other factors as it deems appropriate given the current needs of the Board and Ionis, to maintain a balance of knowledge, experience and capability. The Nominating, Governance and Review Committee then uses its network of contacts to compile a list of potential candidates, but may also engage, if it deems appropriate, a paid professional search firm. The Nominating, Governance and Review Committee conducts any appropriate and necessary inquiries into the backgrounds and qualifications of possible candidates after considering the function and needs of the Board. In the case of incumbent Directors whose terms of office are set to expire, the Nominating, Governance and Review Committee reviews such Directors' overall service to Ionis during their term, including the number of meetings attended, level of participation, quality of performance, and any other relationships and transactions that might impair such Directors' independence.

The Nominating, Governance and Review Committee meets to discuss and consider the candidates' qualifications and determines whether each candidate is independent based upon applicable Nasdaq listing standards, SEC rules and regulations, and the advice of counsel, if necessary. Finally, the Nominating, Governance and Review Committee then selects a nominee for recommendation to the Board by majority vote.

Stockholder Recommendations for Directors

Stockholders who wish to recommend individuals for consideration by the Nominating, Governance and Review Committee to become nominees for election to the Board may do so by delivering a written recommendation to Ionis' corporate secretary at the following address: 2855 Gazelle Court, Carlsbad, CA 92010. Submissions must include:

- the name, age, business address and residence address of the nominee;
- the principal occupation or employment of the nominee;
- the stock ownership in Ionis of the nominee;
- the stock ownership in Ionis of the stockholder making the nomination, including any trading in derivative securities that may disguise ownership occurring within the last 12 months;
- the information relating to the nominee that is required to be disclosed in solicitations of proxies under applicable securities laws;
- the nominee's written consent to being named in the Proxy Statement as a nominee and to serving as a Director if elected;
- other information as we may reasonably require to determine the eligibility of the proposed nominee to serve as an independent Director or that could be material to a reasonable stockholder's understanding of the independence of the proposed nominee; and
- any voting commitments the nominee has to third parties.

In addition, the nominee will need to complete a written questionnaire regarding the background and qualifications of the nominee, and the background of any other person or entity on whose behalf the nomination is being made. The nominee must also agree to comply with all of our applicable publicly disclosed corporate governance, conflict of interest, confidentiality and stock ownership and trading policies and guidelines. The description of the requirements for Director nomination set forth above is qualified in its entirety by reference to our full and complete bylaws, which is an exhibit to our Current Report on Form 8-K filed with the SEC on December 18, 2015, a copy of which is available by contacting our corporate secretary. To date, the Board has not received or rejected a timely Director nominee for election at the upcoming stockholder meeting from a stockholder or stockholders holding more than 5% of our voting stock.

Agenda Committee

The primary function of the Agenda Committee of the Board is to determine the matters to be considered by the Board at each of its meetings and prepare an agenda accordingly. The Agenda Committee discussed in advance and set the agenda for each regularly scheduled Board meeting held in 2019.

Science/Medical Committee

The primary functions of the Science/Medical Committee of the Board are to focus on the key scientific and development issues facing our technology and medicines in development and help set our strategy in such areas. The Science/Medical Committee met two times in 2019.

Finance Committee

The primary function of the Finance Committee of the Board is to advise the Board on certain corporate finance matters for the Company and its subsidiaries, including capital structures, equity and debt financings, investments, and share repurchase activities. The Finance Committee was formed in May 2019 and met six times in 2019.

Stockholder Communications with the Board

We make every effort to ensure that our Board or individual Directors, as applicable, hear our stockholders' views, and provide appropriate responses to stockholders in a timely manner. Stockholders who wish to communicate with the Board, or individual Directors, may do so by sending written communications addressed to Ionis' corporate secretary at 2855 Gazelle Court, Carlsbad, CA 92010. If you wish to communicate with the independent Directors about your concerns or issues, you may address correspondence to a particular Director or to the independent Directors generally. If you do not name a particular Director, depending on the subject matter, we will forward the letter to the Chair of the Audit, Compensation, or Nominating, Governance and Review Committee. One or more of our employees designated by the Board will review these communications and will determine whether to present the materials to the Board. The purpose of this screening is to allow the Board to avoid having to consider irrelevant or inappropriate communications, such as advertisements, commercial solicitations and hostile communications. In accordance with our Code of Ethics and Business Conduct policy, all communications that relate to questionable accounting or auditing matters involving Ionis will be promptly and directly forwarded to the Audit Committee. Other than the processes described above, our Board has not adopted a formal written process for stockholder communications with the Board. We believe our Board's responsiveness to stockholder communications has been excellent.

Code of Ethics and Business Conduct

We have adopted a Code of Ethics and Business Conduct that applies to all officers, Directors and employees. We have posted our Code of Ethics and Business Conduct on our website. If we make any substantive amendments to the Code of Ethics and Business Conduct or grant any waiver from a provision of the Code of Ethics and Business Conduct to any executive officer or Director, we will promptly disclose the nature of the amendment or waiver on our website at www.ionispharma.com.⁶

⁶ Any information that is included on or linked to our website is not part of this Proxy Statement or any registration statement or report that incorporates this Proxy Statement by reference.

Corporate Governance Guidelines

The Board has adopted corporate governance guidelines to ensure that the Board will have the necessary authority and practices in place to review and evaluate our business operations as needed and to make decisions that are independent of our management. The guidelines are also intended to align our Directors' and management's interests with those of our stockholders. The corporate governance guidelines set forth the practices the Board intends to follow with respect to board composition and selection, board meetings and involvement of senior management, Chief Executive Officer performance evaluation, succession planning for Board committees and compensation, "clawbacks" of executive compensation, and share retention guidelines for our executive officers and Directors. The Board adopted the corporate governance guidelines to, among other things, reflect changes to the Nasdaq listing standards and SEC rules adopted to implement provisions of the Sarbanes-Oxley Act of 2002. You may view our corporate governance guidelines, as well as the charters for the Audit, Compensation and Nominating, Governance and Review committees at www.ionispharma.com.⁷

Anti-Hedging Policy and Anti-Pledging Policy

All employees, including our named executive officers, are prohibited from taking a "short" position in our stock and otherwise hedging their position in our stock against a future drop in our stock price. In addition, we specifically prohibit all of our employees from trading derivative instruments based on our common stock (e.g. put or call options for our stock) and prohibit pledging our stock as collateral.

⁷ Any information that is included on or linked to our website is not part of this Proxy Statement or any registration statement or report that incorporates this Proxy Statement by reference.

PROPOSAL 2

APPROVAL OF AN AMENDMENT AND RESTATEMENT OF OUR 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

On March 24, 2020, our Board of Directors amended and restated the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan (the "Directors' Plan"), subject to stockholder approval to, among other things, increase the number of shares of common stock authorized for issuance under the Directors' Plan by 800,000 shares; reduce the amount of the automatic awards under the Directors' Plan; revise the vesting schedule of awards granted under the Directors' Plan; and extend the term of the Directors' Plan by an additional ten years such that it will terminate on June 1, 2030. We refer to the Directors' Plan, as amended and restated on March 24, 2020, as the "Amended Directors' Plan" throughout this Proposal 2. References in this Proposal 2 to our Board of Directors include the Compensation Committee of the Board, where applicable.

In this Proposal 2, we are requesting our stockholders approve an amendment and restatement of the Directors' Plan (the "Amended Directors' Plan"). The material differences between the Directors' Plan and the Amended Directors' Plan are as follows:

- i. the Amended Directors' Plan provides for an increase to the aggregate number of shares of common stock authorized for issuance under such plan by 800,000 shares to an aggregate of 2,800,000 shares;
- ii. the Amended Directors' Plan provides for a reduced number of shares subject to automatic grants of stock options and provides a fixed number of shares underlying automatic grants of restricted stock units ("RSUs"), with automatic initial grants of stock options to new Board members being reduced from 32,000 to 24,000 stock options, automatic annual grants of stock options to new Board members being reduced from 16,000 to 12,000, and with automatic initial grants of RSUs to new Board members being changed from the product of 32,000 multiplied by a fraction (as determined by the Compensation Committee from time to time, known as the RSU/Option Factor and described herein) to a fixed 10,667 shares, and with automatic annual grants of RSUs being changed from the product of 16,000 multiplied by the RSU/Option Factor to a fixed 5,333 shares;
- iii. the Amended Directors' Plan revises the vesting schedule of awards from vesting in equal annual installments over four years to vesting at the end of one year; and
- iv. the Amended Directors' Plan extends the term of the Directors' Plan by an additional ten years such that it will terminate on June 1, 2030.

Background for the Current Request and Expected Future Grant Practices

Our management, Board and Compensation Committee believe that stock options and RSUs are a key aspect of our ability to attract and retain qualified non-employee Directors. The Board, upon the recommendation of the Compensation Committee, has approved an increase in the aggregate number of shares of common stock authorized for issuance under the Directors' Plan by 800,000 shares to an aggregate of 2,800,000 shares to ensure that for a period of at least three years, we can continue to grant stock options and RSUs to non-employee Directors at the current award amounts. If the stockholders do not approve this Proposal 2, and as a consequence, we cannot continue to grant options and RSUs at competitive levels, we believe that it will negatively affect our ability to recruit and retain highly qualified non-employee Directors. As of March 31, 2020, 143,441 shares were available for future grant under the Directors' Plan.

After a review of the Company's non-employee Director compensation and comparison to that of its peer companies, the Compensation Committee and Board decided it would be in the best interest of the Company to propose a reduction in the current size of automatic equity awards granted to non-employee Directors of the Company each year. In 2019, pursuant to section 6(b) of the Directors' Plan, each Director received an annual grant of 16,000 stock options and 7,110 RSUs. Under the Amended Directors' Plan described in this Proposal 2, the annual grants will be reduced to 12,000 stock options and 5,333 RSUs.

The affirmative vote of a majority of the shares present or represented by proxy and entitled to vote at the Annual Meeting is required to approve the proposed amendment and restatement of the Directors' Plan discussed above. If you hold your shares through a broker and you do not instruct the broker on how to vote on this Proposal 2, your broker will not have the authority to vote your shares. Abstentions and broker non-votes will

each be counted as present for purposes of determining the presence of a quorum. If you indicate on your proxy to “Abstain” from voting, it will have the same effect as an “Against” vote for this Proposal 2. Broker non-votes will not have any effect on the outcome of this Proposal 2.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE “FOR” APPROVAL OF PROPOSAL 2.

The following description of the Amended Directors’ Plan is qualified in all respects by the specific terms of the Amended Directors’ Plan, a copy of which was filed with this Proxy Statement.

Purpose

The purpose of the Amended Directors’ Plan is to:

- retain the services of persons now serving as our non-employee Directors;
- attract and retain the services of persons capable of serving on our Board; and
- incentivize our non-employee Directors to exert maximum efforts to promote our success.

Administration

Our Board administers the Amended Directors’ Plan. Our Board currently may not delegate administration of the Directors’ Plan to a committee, but under the Amended Directors’ Plan as described in this Proposal 2, the Board will be empowered to delegate administration of the Plan to a committee of the Board. The Board has the power to construe and interpret the Amended Directors’ Plan and stock awards granted under it, and to establish, amend and revoke rules and regulations for its administration.

Stock Subject to the Amended Directors’ Plan

An aggregate of 2,000,000 shares of common stock were authorized by the Board for issuance under the Directors’ Plan and was approved by the stockholders at the June 30, 2015 Annual Meeting. As of March 31, 2020, 143,441 shares were available for future grants under the Directors’ Plan. If this Proposal 2 is approved, there will be 2,800,000 shares of common stock authorized for issuance under the Directors’ Plan. Assuming stockholder approval of this Proposal 2, we expect to grant options to purchase a total of 120,000 shares and RSUs worth 53,330 shares under the Amended Directors’ Plan on July 1 of each year.

Equity Award Grant History Under the Directors’ Plan

	2017	2018 ⁽¹⁾	2019 ⁽¹⁾	2020 (through March 31) ⁽²⁾
Shares subject to stock options granted	96,000	176,000	192,000	0
Shares subject to RSUs granted	16,002	39,105	85,321	0
Shares subject to equity awards canceled	0	0	0	0
Net shares subject to equity awards ⁽³⁾	112,002	215,105	277,321	0

- (1) The number of equity awards granted in 2018 and 2019 was higher due in part to the addition of new directors.
- (2) We grant nondiscretionary equity awards to non-employee Directors for each year in July of such year.
- (3) Shares subject to equity awards that are canceled or expire become available for re-issuance under the equity plan. Therefore, net shares for any year is the total shares subject to awards granted in that year less the shares subject to awards canceled in such year.

On March 31, 2020, the last reported sales price of our common stock on the Nasdaq Global Select Market was \$47.28 per share.

If options granted under the Amended Directors’ Plan expire or otherwise terminate without being exercised, the shares of common stock not acquired pursuant to such options again become available for issuance under the Amended Directors’ Plan.

Eligibility, Option Grants, RSU Awards

The Amended Directors’ Plan provides that we may only grant options and RSU awards to a non-employee Director. Under the Amended Directors’ Plan a “non-employee Director” is a Director of Ionis or one of our affiliates who is not otherwise an employee of Ionis or any affiliate. Ten of our twelve current Directors, all except Dr. Crooke and Dr. Monia, are eligible to participate in the Amended Directors’ Plan.

Options granted under the Amended Directors' Plan are nonstatutory stock options, meaning they are not intended to qualify as incentive stock options within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended (the "Code").

Under the Amended Directors' Plan as described in this Proposal 2, awards will not be subject to the RSU/Option Factor calculation described below and instead will be set at reduced, fixed amounts as follows:

- *Initial Grants*
 - o An initial grant of a stock option to purchase shares of common stock to each person when he or she first becomes a non-employee Director of Ionis equal to 24,000; and
 - o An initial grant of an RSU award on the 15th of the month following the end of the quarter in which he or she first becomes a non-employee Director of Ionis in an amount equal to 10,667.
- *Annual Grants*
 - o An annual grant, on July 1, or the next business day should such date be on a Saturday, Sunday or holiday, of a stock option to purchase 12,000 shares of common stock to each non-employee Director; and
 - o An annual grant, on July 1, or the next business day should such date be on a Saturday, Sunday or holiday, of an RSU award to each non-employee Director in an amount equal to 5,333.

In contrast, the Directors' Plan *currently* provides for nondiscretionary grants of stock options and RSU awards to the non-employee Directors as follows:

- *Initial Grants*
 - o An initial grant of a stock option to purchase 32,000 shares of common stock and an RSU award in an amount equal to 32,000 multiplied by the then applicable RSU/Option Factor described below to each person when he or she first becomes a non-employee Director.
 - o The RSU/Option Factor is a ratio, represented by a fraction, as approved by the Compensation Committee when it sets the allocation of equity compensation for our employees between options and RSU awards. The RSU/Option Factor can be as low as zero and as high as one. The RSU/Option Factor approved by the Compensation Committee as of the date the Board approved the amendment and restatement of the Directors' Plan was 1/6.
- *Annual Grants*
 - o An annual grant, on July 1, or the next business day should such date be on a Saturday, Sunday or holiday, of a stock option to purchase 16,000 shares of common stock and an RSU award in an amount equal to 16,000 multiplied by the then applicable RSU/Option Factor to each non-employee Director.

Terms of Options

Each option under the Amended Directors' Plan is subject to the following terms and conditions:

Vesting Schedule and Option Exercise. The Directors' Plan *currently* provides for options granted under the Directors' Plan to vest in four equal annual installments beginning on the first anniversary of the grant of the option. Under the proposed amendments described in this Proposal 2, options granted under the Amended Directors' Plan shall vest as follows:

- *Initial Grants:* 100% of the shares subject to the option shall vest on the first anniversary of the date of grant, provided that he or she has, during the entire year prior to such vesting date, continuously served as a non-employee Director, employee or consultant of Ionis or one of our affiliates.
- *Annual Grants:* 100% of the shares subject to the option shall vest on the first anniversary of the date of grant or the next regularly scheduled annual meeting of stockholders, whichever occurs earlier, provided that he or she has, during the entire period from the date of grant through such vesting date, continuously served as a non-employee Director, employee, or consultant of Ionis or one of our affiliates.

Vesting is conditioned upon continued service as a Director or as an employee or consultant of Ionis or one of our affiliates.

The Board has the power to accelerate the time during which an option may vest or be exercised. Options granted under the Amended Directors' Plan do not permit exercise prior to vesting.

A Director may exercise an option under the Amended Directors' Plan by written notice to us, specifying the number of full shares of common stock to be purchased accompanied by payment of the purchase price.

Exercise Price; Payment. The exercise price of options granted under the Amended Directors' Plan is equal to 100% of the fair market value of the common stock on the date granted; however, an option may be granted with a lower exercise price if the option is granted pursuant to an assumption or substitution for another option in a manner that satisfies Section 424(a) of the Code. Optionholders must pay the exercise price of options granted under the Amended Directors' Plan in cash, or pursuant to a "same-day-sale" under Regulation T. To the extent provided by the terms of an option, an optionholder may satisfy any federal, state or local tax withholding obligation relating to the exercise of such option by a cash payment upon exercise.

Transferability; Term. Under the Amended Directors' Plan, an optionholder may not transfer an option, except as determined by the Board and as set forth in the option agreement. Currently, the Board has determined, and Director option agreements provide, that in addition to the ability to transfer an option by will or the laws of descent and distribution, a Director may transfer part or all of an option to any of the following:

- an optionholder's spouse, children (by birth or adoption), stepchildren, grandchildren, or parents;
- a trust or other entity established solely for the optionholder's benefit or the benefit of the optionholder's spouse, children (by birth or adoption), stepchildren, grandchildren, or parents for estate planning purposes; or
- an organization that 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, an optionholder may, by delivering written notice to us, in a form satisfactory to us, designate a third party who, in the event of the optionholder's death, will thereafter be entitled to exercise the option.

No option granted under the Amended Directors' Plan is exercisable by any person after the expiration of ten years from the date the option is granted.

Other Provisions. The option agreement may contain such other terms, provisions and conditions not inconsistent with the Amended Directors' Plan as may be determined by the Board.

Terms of Restricted Stock Unit Awards

Each RSU award under the Amended Directors' Plan is subject to the following terms and conditions:

Consideration. At the time of grant of an RSU award, the Board will determine the consideration, if any, to be paid by the Participant upon delivery of each share of common stock subject to the RSU award. The consideration to be paid (if any) by the Participant for each share of common stock subject to an RSU award may be paid in any form of legal consideration that may be acceptable to the Board, in its sole discretion, and permissible under applicable law.

Vesting. The Directors' Plan *currently* provides that each RSU award will vest as follows: one-fourth of the shares subject to the RSU award shall vest on each anniversary of the date of grant provided that the RSU award recipient has, during the entire year prior to such vesting date, continuously served as a non-employee Director or as an employee of or consultant to Ionis or one of our affiliates. Under the Amended Directors' Plan as described in this Proposal 2, RSU awards granted after approval of this amendment shall vest as follows:

- *Initial Grants:* 100% of the shares subject to the RSU shall vest on the first anniversary of the date of grant provided that he or she has, during the entire year prior to such vesting date, continuously served as a non-employee Director, employee or consultant of Ionis or one of our affiliates.
- *Annual Grants:* 100% of the shares subject to the RSU shall vest on the first anniversary of the date of grant or the next regularly scheduled annual meeting of stockholders, whichever occurs earlier, provided that he or she has, during the entire period from the date of grant through such vesting date, continuously served as a non-employee Director, employee or consultant of Ionis or one of our affiliates.

Payment. An RSU award may be settled by the delivery of shares of common stock, their cash equivalent, any combination thereof or in any other form of consideration, as determined by the Board and contained in the RSU award agreement. Under the proposed amendments to the Directors' Plan described in this Proposal 2, annual RSUs that are granted and vest after approval of this amendment will settle on July 15th of the year in which they vest.

Additional Restrictions. At the time of the grant of an RSU award, the Board, as it deems appropriate, may impose such restrictions or conditions that delay the delivery of the shares of common stock (or their cash equivalent) subject to an RSU award to a time after the vesting of such RSU award.

Dividend Equivalents. Dividend equivalents may be credited in respect of shares of common stock covered by an RSU award, as determined by the Board and contained in the RSU award agreement. At the sole discretion of the Board, such dividend equivalents may be converted into additional shares of common stock covered by the RSU award in such manner as determined by the Board. Any additional shares covered by the RSU award credited by reason of such dividend equivalents will be subject to all of the same terms and conditions of the underlying RSU award agreement to which they relate.

Termination of Continuous Service. Except as otherwise provided in the applicable award agreement, under the current Directors' Plan such portion of the RSU award that has not vested will be forfeited upon the RSU award recipient's termination of continuous service as a non-employee Director, or as an employee or consultant of Ionis or one of our affiliates.

Adjustment Provisions

If any change is made in, or other event occurs with respect to, the common stock subject to the Amended Directors' Plan, or subject to any stock award, without the receipt of consideration by Ionis (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by Ionis) (each, a "Capitalization Adjustment"), the Amended Directors' Plan will be appropriately adjusted in the class(es) and maximum number of securities subject both to the Amended Directors' Plan pursuant to the shares reserve and to the nondiscretionary stock awards, and the outstanding stock awards will be appropriately adjusted in the class(es) and number of securities and price per share, if applicable, of common stock subject to such outstanding stock awards. The Board will make such adjustments, and its determination will be final, binding and conclusive. The conversion of any convertible securities of Ionis will not be treated as a transaction "without receipt of consideration" by Ionis.

If there is (i) a sale or other disposition of all or substantially all of our assets, (ii) a sale or other disposition of at least 90% of our outstanding securities, or (iii) certain specified types of merger, consolidation or similar transactions (each, a "Corporate Transaction" as defined more specifically in the Amended Directors' Plan), any surviving or acquiring corporation may assume stock awards outstanding under the Amended Directors' Plan or may substitute similar stock awards. If any surviving or acquiring corporation does not assume the stock awards or substitute similar stock awards, then with respect to stock awards held by optionholders whose service with Ionis or an affiliate of Ionis has not terminated as of the effective date of the Corporate Transaction, the vesting of such stock awards (and, if applicable, the time during which such stock awards may be exercised) will be accelerated in full and the stock awards will terminate if not exercised (if applicable) at or prior to such effective date. With respect to stock awards outstanding under the Amended Directors' Plan that have been neither assumed nor substituted and that are held by award holders whose continuous service has terminated prior to the effective time of the Corporate Transaction, the vesting of the stock awards, and, if applicable, the time at which such stock awards may be exercised will not be accelerated unless otherwise provided in a written agreement between Ionis or any affiliate and the holder of the stock award, and such stock awards will terminate if not vested and exercised, as applicable, prior to the effective time of the Corporate Transaction.

If there is a dissolution or liquidation of Ionis, then all outstanding stock awards under the Amended Directors' Plan will terminate immediately prior to the completion of the dissolution or liquidation.

In the event of (i) a qualifying merger or consolidation or similar transaction, as described in the Amended Directors' Plan, whereby following such transaction the stockholders of Ionis immediately prior to such transaction do not own outstanding voting securities representing more than 50% of the combined voting power

of the entity (or parent of the entity) surviving such transaction, (ii) a qualifying sale, lease, license or other disposition of all or substantially all of our assets, (iii) certain entities reporting under Section 13(d) or 14(d) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") acquire more than 50% of our voting power under certain qualifying circumstances, or (iv) a majority of our Board is replaced by individuals who are not nominated by members of our current Board or members nominated by our current Board or their nominees (each such event, a "Change of Control" for purposes of the Amended Directors' Plan), the vesting of any outstanding stock awards under the Amended Directors' Plan held by persons whose continuous service with Ionis or an affiliate of Ionis has not terminated prior to the effective date of the Change of Control will accelerate in full, and the stock awards will terminate on the earlier of 12 months following the date of the Change of Control or the expiration date set forth in the stock award grant.

The acceleration of an option in the event of a Corporate Transaction or a Change in Control event may be viewed as an anti-takeover provision, which may have the effect of discouraging a proposal to acquire or otherwise obtain control of Ionis.

No Repricing, "Cash-Out," or Cancellation and Re-Grant of Options without Stockholder Approval

Under the Amended Directors' Plan, the Board cannot reprice any outstanding options by reducing the exercise price of the stock award or cancel any outstanding options in exchange for cash or other stock awards without obtaining the approval of our stockholders within 12 months prior to the repricing or cancellation and re-grant event.

Duration, Amendment and Termination

The Board at any time, and from time to time, may amend the Amended Directors' Plan. However, except as relating to Capitalization Adjustments (described above), no amendment will be effective unless approved by our stockholders to the extent stockholder approval is necessary to satisfy the requirements of SEC Rule 16b-3 or any Nasdaq or securities exchange listing requirements or such amendment seeks to amend the prohibition on option repricing/ "cashing-out." The Board, in its sole discretion, may submit any other amendment to the Amended Directors' Plan for stockholder approval. Rights under any outstanding stock award granted before amendment of the Amended Directors' Plan will not be impaired by any amendment of the Amended Directors' Plan unless we request the consent of the award holder and the award holder consents in writing.

Unless sooner terminated by our Board and if this Proposal 2 is not approved, the Directors' Plan will terminate effective June 1, 2020. Under the proposed amendments described in this Proposal 2, the Amended Directors' Plan will terminate on June 1, 2030.

Federal Income Tax Information

Nonstatutory Stock Options

Nonstatutory stock options granted under the Amended Directors' Plan generally have the following federal income tax consequences.

There are no tax consequences to the optionholder or us by reason of the grant of a nonstatutory stock option. Upon exercise of a nonstatutory stock option, the optionholder normally will recognize taxable ordinary income equal to the excess of the stock's fair market value on the date of exercise over the option exercise price. In the unlikely event the optionholder becomes an employee, we are required to withhold from regular wages or supplemental wage payments an amount based on the ordinary income recognized. Subject to the requirement of reasonableness and the satisfaction of a tax reporting obligation, we will generally be entitled to a business expense deduction equal to the taxable ordinary income realized by the optionholder.

Upon disposition of the stock, the optionholder will recognize a capital gain or loss equal to the difference between the selling price and the sum of the amount paid for such stock plus any amount recognized as ordinary income upon exercise of the option. Such gain or loss will be long-term or short-term depending on whether the stock was held for more than one year.

Restricted Stock Unit Awards

Generally, the recipient of a stock unit structured to conform to the requirements of Section 409A of the Code or an exception to Section 409A of the Code will recognize ordinary income at the time the stock is delivered equal to the excess, if any, of the fair market value of the shares of our common stock received over

any amount paid by the recipient in exchange for the shares of our common stock. To conform to the requirements of Section 409A of the Code, the shares of our common stock subject to a stock unit award may generally be delivered only upon one of the following events: a fixed calendar date (or dates), separation from service, death, disability or a change in control. If delivery occurs on another date, unless the stock units otherwise comply with or qualify for an exception to the requirements of Section 409A of the Code, in addition to the tax treatment described above, the recipient will owe an additional 20% federal tax and interest on any taxes owed.

The recipient's basis for the determination of gain or loss upon the subsequent disposition of shares acquired from stock units will be the amount paid for such shares plus any ordinary income recognized when the stock is delivered.

Subject to the requirement of reasonableness, the provisions of Section 162(m) of the Code and the satisfaction of a tax reporting obligation, we will generally be entitled to a tax deduction equal to the taxable ordinary income realized by the recipient of the stock award.

New Plan Benefits Table

The following table presents certain information with respect to stock options and RSU awards we expect to grant under the Amended Directors' Plan for services rendered during the fiscal year ending December 31, 2020 to our non-employee Directors, assuming stockholder approval of this Proposal 2. This table assumes that each non-employee Director continues as one of our Directors throughout the year and that we do not elect any additional non-employee Directors. This information is for illustration only and may not be indicative of grants that are made in the future under the Directors' Plan.

NEW PLAN BENEFITS AMENDED AND RESTATED 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

Name of Non-Employee Director⁽¹⁾	Number of Option Shares	Number of Restricted Stock Unit Awards
Spencer R. Berthelsen	12,000	5,333
Breaux B. Castleman	12,000	5,333
Michael Hayden	12,000	5,333
Joan Herman	12,000	5,333
Joseph Klein, III	12,000	5,333
Joseph Loscalzo	12,000	5,333
Frederick Muto	12,000	5,333
B. Lynne Parshall	12,000	5,333
Peter Reikes	12,000	5,333
Joseph Wender	12,000	5,333
Non-Employee Directors as a Group	120,000	53,330

(1) We have omitted all employees and groups of employees required to be disclosed pursuant to Item 10 of Schedule 14A (17 C.F.R. §240.14a-101), as employees are not eligible to receive awards under the Amended Directors' Plan.

Plan Benefits under the Directors' Plan

The following table sets forth, for each of the individuals indicated, the total number of shares subject to awards that have been granted under the Directors' Plan as of April 6, 2020.

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

Name of Non-Employee Director ⁽¹⁾	Total Number of Shares	Options	RSUs
Spencer R. Berthelsen	287,958	263,500	24,458
Breaux B. Castleman	156,708	129,750	26,958
Michael Hayden	62,220	48,000	14,220
Joan Herman	69,331	48,000	21,331
Joseph Klein, III	247,958	223,500	24,458
Joseph Loscalzo	143,583	118,500	25,083
Frederick Muto	267,958	243,500	24,458
B. Lynne Parshall	42,665	32,000	10,665
Peter Reikes	62,220	48,000	14,220
Joseph Wender	267,958	243,500	24,458
Non-Employee Directors as a Group	1,608,559	1,398,250	210,309

(1) We have omitted all employees and groups of employees required to be disclosed pursuant to Item 10 of Schedule 14A (17 C.F.R. §240.14a-101), as employees are not eligible to receive awards under the Directors' Plan.

Please see page 36 for information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of March 31, 2020.

PROPOSAL 3

RATIFY AMENDING THE EXISTING STOCK OPTION AND RESTRICTED STOCK UNIT AWARDS OF DIRECTORS TO ADJUST VESTING

In this Proposal 3, we are requesting our stockholders to ratify amending existing annual stock option and annual restricted stock unit awards of our Directors to adjust vesting such that all annual awards granted under the Directors' Plan will vest equally over four years on each anniversary of the date of grant or the next regularly scheduled annual meeting of stockholders, whichever occurs earlier.

Background for the Current Request

The Company currently grants annual stock option and annual restricted stock unit awards to Directors in July of each year and such awards vest equally over four years on each anniversary of the date of grant. The Company typically holds its Annual Meeting of Stockholders in June of each year. Based on the Company's established grant schedule and customary Annual Meeting date, there is the potential for an unintended forfeiture of a year of vesting for a departing Board member. Under the proposed amended vesting schedule of this Proposal 3, each vesting date of existing annual stock option and annual restricted stock unit awards for all Board members will be changed to the date of the next regularly scheduled annual meeting of stockholders (recognizing the service year of the Board member from one annual meeting to the next) or the anniversary of the grant date, whichever occurs earlier. The Company believes this change is in the Company's best interest so that it and its Board members can effectively plan for departures from the Board. This change also ensures the Company's Directors are treated fairly since the vesting of awards will now be directly tied to each Director's period of performance as a Board member.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE "FOR" APPROVAL OF PROPOSAL 3.

PROPOSAL 4

ADVISORY VOTE ON EXECUTIVE COMPENSATION

The Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010, called the “Dodd-Frank Act,” entitles Ionis’ stockholders to vote to approve, on an advisory (nonbinding) basis, the compensation of our Chief Executive Officer, Chief Financial Officer and our three other most highly compensated executive officers (at December 31, 2019), called our “named executive officers” as disclosed in this Proxy Statement in accordance with the SEC’s rules.

We are asking our stockholders to indicate their support for our named executive officers’ compensation as described in this Proxy Statement. This Proposal 4, commonly known as a “say on pay” proposal, gives our stockholders the opportunity to express their views on the compensation paid to our named executive officers. This vote is not intended to address any specific item of compensation, but rather the overall compensation of our named executive officers and the philosophy, policies and practices described in this Proxy Statement. Accordingly, we are asking our stockholders to vote “FOR” the following resolution at the Annual Meeting:

“RESOLVED, that Ionis’ stockholders approve, on an advisory basis, the compensation of the named executive officers, as disclosed in this Proxy Statement for the 2020 Annual Meeting of Stockholders pursuant to the compensation disclosure rules of the Securities and Exchange Commission.”

We recommend you carefully review the EXECUTIVE COMPENSATION section of this Proxy Statement located on pages [37](#) through [61](#). Below is a high-level summary of some of our compensation practices. This summary is qualified by the detailed disclosure contained in the EXECUTIVE COMPENSATION section of this Proxy Statement.

The table below summarizes some of our executive compensation practices, both the practices we implement because we believe they are consistent with our vision and long-term stockholder value (see “What We Do” below), and those that we choose not to implement as we believe they are counter to our vision and long-term stockholder value (see “What We Don’t Do” below):

What We Do	What We Don’t Do
<ul style="list-style-type: none"> ✓ In 2020 we began allocating 20% of our Chief Executive Officer’s equity awards as performance-based restricted stock units ✓ Demand more of every employee: more commitment, more knowledge, more intensity, more innovation, more productivity ✓ Reward productivity and performance ✓ Recognize the value of long-term employees and low turnover ✓ Use a balanced mix of fixed and variable cash incentives and long-term equity incentives ✓ Review compensation compared to the 25th, 50th and 75th percentiles of our peer group ✓ Design our compensation philosophy and objectives to mitigate unnecessary or imprudent business risk taking ✓ Set explicit and demanding objectives at the beginning of each year from which we measure performance for the year ✓ Place a maximum limit on Performance Management By Objective (MBO) awards ✓ Set a strict budget for equity awards and salary increases ✓ Set the size of equity awards based on individual and company performance ✓ Require minimum vesting periods for equity awards ✓ Maintain equity holding periods that require our executive officers and non-employee Directors to hold shares received from their RSUs until they meet certain ownership thresholds or no longer serve the Company ✓ Maintain equity holding periods that require our employees to hold ESPP shares for a minimum of six months ✓ Require our executive officers and VPs to trade Ionis’ stock through Rule 10b5-1 trading plans ✓ Use a “double trigger” for cash payments for change of control ✓ Use a “double trigger” for equity acceleration for change of control for our executive officers ✓ Use an executive “clawback” policy ✓ Use an independent compensation consultant engaged by the Compensation Committee 	<ul style="list-style-type: none"> ✗ Do not guarantee a cash bonus – cash bonuses can, and have been, zero ✗ Do not provide perquisites for any employees ✗ Do not provide “gross-up” payments, other than for relocation ✗ Do not allow pledging, shorting or hedging against our stock ✗ Do not reprice or “cash-out” stock options without stockholder approval

**CEO Compensation vs. Total Return
(Over Five Years)**

The graph below shows the relationship of our CEO’s compensation (\$ in thousands) as calculated pursuant to SEC rules compared to the total shareholder return (“TSR”) on \$100 invested on December 31, 2015 in our common stock through December 31, 2019. While stock price is only one of the measures of performance we use to set executive compensation, including for our CEO, over the past five-year period, our CEO’s compensation has generally aligned with our stock performance. Over this period, TSR has generally increased year over year.

For 2016, however, Ionis’ one-year TSR was negative. Our CEO’s compensation for that period increased, largely due to an increase in the Company Performance Factor for the Performance MBO for 2016. Due to Ionis’ significant strategic and financial achievements during 2016, including, among other things, exceeding our financial guidance and obtaining FDA approval of SPINRAZA just three months after the FDA’s acceptance of the NDA filing, the Compensation Committee felt that the increased Company Performance Factor was appropriate.

The many achievements of the Company in 2016 laid the foundation for significant growth in 2017, 2018 and 2019. Ionis ended 2019 in a very strong financial position, with 2019 revenues of over \$1 billion, a nearly 50% increase from 2018, and Ionis’ eighth consecutive year of revenue growth. For the fourth year in a row, Ionis was profitable, with non-GAAP⁸ net income in 2019 of over \$400 million. As shown in the graph below, our CEO’s compensation aligned with TSR for 2017, 2018 and 2019.⁹



The affirmative vote of a majority of the holders of shares present or represented by proxy at the Annual Meeting and entitled to vote on the matter is required to adopt the resolution. If you indicate on your proxy to “Abstain” from voting, it will have the same effect as a vote “Against” this Proposal 4. Brokers do not have

⁸ We use “non-GAAP” in place of “pro-forma” when discussing our financial results that exclude non-cash compensation expense related to equity awards because we believe that non-GAAP financial results better represent the economics of our business and how we manage our business.

⁹ This graph is not “soliciting material,” is not deemed “filed” with the SEC, is not subject to the liabilities of Section 18 of the Exchange Act and is not to be incorporated by reference in any of our filings under the Securities Act of 1933, as amended (the “Securities Act”) or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

discretion to vote uninstructed shares with respect to this Proposal 4. Accordingly, if brokers do not receive voting instructions from beneficial owners of the shares, they cannot vote the shares. Therefore, broker non-votes will not affect the outcome of the voting on this Proposal 4.

The “say on pay” vote is advisory, and therefore is not binding on Ionis, the Compensation Committee or the Board. However, Ionis’ management, the Board and the Compensation Committee value the opinions of the stockholders. As such, if there is any significant vote against the named executive officers’ compensation as disclosed in this Proxy Statement, the Board will consider the stockholders’ concerns and the Board and Compensation Committee will evaluate whether any actions are necessary to address those concerns.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE “FOR” APPROVAL OF PROPOSAL 4.

RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

The Audit Committee has selected Ernst & Young LLP as our independent registered public accounting firm for our 2020 fiscal year and has requested management to ask for stockholder ratification at the Annual Meeting. Ernst & Young LLP has audited our financial statements since we were founded in 1989. Representatives of Ernst & Young LLP will be at the virtual Annual Meeting to answer any questions and make a statement should they desire to do so.

Although our bylaws do not require stockholders to ratify our independent registered public accounting firm, the Audit Committee would like our stockholders' opinion as a matter of good corporate practice. If the stockholders do not ratify the selection of Ernst & Young LLP, the Audit Committee will reconsider whether to keep the firm. However, even if the stockholders ratify the selection, the Audit Committee may choose to appoint a different independent accounting firm at any time during the year if it believes that a change would be in the best interests of our stockholders and Ionis.

The affirmative vote of the holders of a majority of the shares present or represented by proxy at the Annual Meeting and entitled to vote on the matter will be required to ratify the selection of Ernst & Young LLP. Abstentions and broker non-votes will have no effect on this Proposal 5.

Independent Auditors' Fees; Pre-Approval Policies and Procedures

The Audit Committee has adopted a policy and procedure for the pre-approval of audit and permissible non-audit services rendered by our independent registered public accounting firm, Ernst & Young LLP. The policy generally pre-approves specific services in the defined categories of audit services, audit-related services, and tax services up to pre-determined amounts. The Audit Committee may pre-approve services as part of its approval of the scope of the engagement of the independent auditor or on an individual explicit case-by-case basis before the Audit Committee engages the independent registered public accounting firm to provide each service. The Audit Committee pre-approved all of the services described below.

Audit Fees

For the fiscal years ended December 31, 2019 and 2018, Ernst & Young LLP billed us approximately \$1.6 million and \$1.3 million for each year, respectively, primarily related to the integrated audit of our financial statements and reviews of our interim financial statements. In addition, Ernst & Young LLP billed us approximately \$220,000 and approximately \$500,000 in 2019 and 2018, respectively, related to corporate transactions, of which approximately \$85,000 and \$350,000 was billed to Akcea Therapeutics, Inc. ("Akcea"), our affiliate, for each year, respectively. Additionally, for the fiscal years ended December 31, 2019 and 2018, Ernst & Young LLP billed us approximately \$750,000 and \$450,000, respectively, related to the audit of the financial statements of Akcea.

Audit Related Fees

For the fiscal years ended December 31, 2019 and 2018, there were no audit related fees billed by Ernst & Young LLP.

Tax Fees

For the fiscal years ended December 31, 2019 and 2018, Ernst & Young LLP billed us approximately \$225,000 and \$350,000 for each year, respectively, primarily related to professional services on tax projects, including services related to Akcea's international tax planning, of which approximately \$15,000 and \$125,000 was billed to Akcea in 2019 and 2018, respectively.

All Other Fees

During the fiscal years ended December 31, 2019 and 2018, all other fees billed by Ernst & Young LLP were approximately \$6,000 and \$5,000, respectively. These fees were for a subscription to an online accounting and tax information service. The Audit Committee has determined that the rendering of all non-audit services by Ernst & Young LLP is compatible with maintaining the auditor's independence. During the fiscal year ended December 31, 2019, none of the total hours expended on our financial audit by Ernst & Young LLP were provided by persons other than Ernst & Young LLP's employees.

THE BOARD UNANIMOUSLY RECOMMENDS A VOTE "FOR" APPROVAL OF PROPOSAL 5.

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of March 3, 2020 by:

- each Director and nominee for Director;
- each executive officer named in the Summary Compensation Table under “Executive Compensation— Compensation of Executive Officers”;
- all Directors and executive officers as a group; and
- every entity that we know beneficially owns more than five percent of our common stock.

Beneficial Owner	Beneficial Ownership ⁽¹⁾	
	Number of Shares	Percent of Total ⁽²⁾
FMR LLC ⁽³⁾ 245 Summer Street Boston, MA 02210	21,124,062	15.17%
The Vanguard Group ⁽⁴⁾ 100 Vanguard Boulevard Malvern, PA 19355	11,966,392	8.59%
Baillie Gifford & Co ⁽⁵⁾ Calton Square 1 Greenside Row Edinburgh EH1 3AN Scotland UK	8,790,025	6.31%
BlackRock, Inc. ⁽⁶⁾ 55 East 52 nd Street New York, NY 10055	8,402,389	6.03%
BB Biotech AG ⁽⁷⁾ Schwertstrasse 6 CH-8200, Schaffhausen Switzerland	7,994,955	5.74%
ClearBridge Investments, LLC ⁽⁸⁾ 620 8 th Avenue New York, NY 10018	7,947,576	5.71%
Spencer R. Berthelsen ⁽⁹⁾	205,553	*
Breaux B. Castleman ⁽¹⁰⁾	104,933	*
Stanley T. Crooke ⁽¹¹⁾	1,504,382	1.08%
Michael Hayden ⁽¹²⁾	9,778	*
Joan Herman	—	*
Joseph Klein, III ⁽¹³⁾	48,783	*
Joseph Loscalzo ⁽¹⁴⁾	91,808	*
Frederick T. Muto ⁽¹⁵⁾	116,183	*
B. Lynne Parshall ⁽¹⁶⁾	472,304	*
Peter Reikes ⁽¹⁷⁾	9,778	*
Joseph H. Wender ⁽¹⁸⁾	140,305	*
Richard S. Geary ⁽¹⁹⁾	192,749	*
Elizabeth L. Hougen ⁽²⁰⁾	233,932	*
Brett Monia ⁽²¹⁾	272,701	*
Patrick R. O’Neil ⁽²²⁾	81,794	*
All Directors and executive officers as a group (eighteen persons) ⁽²³⁾	3,716,250	2.67%

* Less than one percent

- (1) We base this table upon information supplied by officers, Directors, principal stockholders and Form 3s, Form 4s, Form 5s, Schedules 13D and 13G filed with the SEC. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, we believe that each of the stockholders named in this table has sole voting and investment power with respect to the shares indicated as beneficially owned.
- (2) Applicable percentages are based on 139,231,034 shares of common stock outstanding on March 3, 2020, adjusted as required by rules promulgated by the SEC.
- (3) Abigail P. Johnson is a Director, the Chairman, and the Chief Executive Officer of FMR LLC. Members of the Johnson family, including Abigail P. Johnson, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders' voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders' voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC.
Neither FMR LLC nor Abigail P. Johnson has the sole power to vote or direct the voting of the shares owned directly by the various investment companies registered under the Investment Company Act ("Fidelity Funds") advised by Fidelity Management & Research Company ("FMR Co"), a wholly owned subsidiary of FMR LLC, which power resides with the Fidelity Funds' Boards of Trustees. FMR Co carries out the voting of the shares under written guidelines established by the Fidelity Funds' Boards of Trustees.
- (4) The Vanguard Group has sole voting power to direct the vote of 100,184 shares, shared voting power to direct the vote of 36,447 shares, sole power to dispose or direct the disposition of 11,840,798 shares, and shared dispositive power for 125,594 shares. Vanguard Fiduciary Trust Company, a wholly owned subsidiary of The Vanguard Group, Inc., is the beneficial owner of 57,428 shares of our common stock outstanding as a result of its serving as investment manager of collective trust accounts. Vanguard Investments Australia, Ltd., a wholly owned subsidiary of The Vanguard Group, Inc., is the beneficial owner of 110,992 shares of our common stock outstanding as a result of its serving as investment manager of Australian investment offerings.
- (5) Securities reported as beneficially owned by Baillie Gifford & Co are held by Baillie Gifford & Co. and/or one of more of its investment advisor subsidiaries, which may include Baillie Gifford Overseas Limited, on behalf of investment advisory clients, which may include investment companies registered under the Investment Company Act. Baillie Gifford has sole voting power to direct the vote of 4,046,041 shares and sole power to dispose or direct the disposition of 8,790,025 shares.
- (6) BlackRock, Inc. is a parent holding company and various persons have the right to receive or the power to direct the receipt of dividends from, or the proceeds from the sale of shares of our common stock. BlackRock has sole voting power to direct the vote of 7,668,838 shares and sole power to dispose or direct the disposition of 8,402,389 shares.
- (7) BB Biotech AG shares voting and dispositive powers for its shares with Biotech Invest N.V.
- (8) ClearBridge Investments, LLC is an investment adviser registered under the Investment Advisers Act. ClearBridge Investments has sole voting power to direct the vote of 7,729,495 shares and sole power to dispose or direct the disposition of 7,947,576 shares.
- (9) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 108,500 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before May 2, 2020.
- (10) Includes 89,750 shares of common stock issuable upon exercise of options held by Mr. Castleman that are exercisable on or before May 2, 2020.
- (11) Includes 659,879 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before May 2, 2020. Also includes 700,391 shares of common stock held in a family trust for which Dr. Crooke shares voting and investment power. Also includes 44,596 shares of common stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, which are exercisable on or before May 2, 2020. Dr. Crooke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.
- (12) Includes 8,000 shares of common stock issuable upon exercise of options held by Dr. Hayden that are exercisable on or before May 2, 2020.
- (13) Includes 100 shares of common stock beneficially owned by Mr. Klein's son and 36,000 shares of common stock issuable upon exercise of options held by Mr. Klein that are exercisable on or before May 2, 2020.
- (14) Includes 78,500 shares of common stock issuable upon exercise of options held by Dr. Loscalzo that are exercisable on or before May 2, 2020.
- (15) Includes 1,500 shares of common stock beneficially owned through the Cooley LLP Salary Deferral and Profit Sharing Plan and 100,500 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before May 2, 2020.
- (16) Includes 407,507 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before May 2, 2020.
- (17) Includes 8,000 shares of common stock issuable upon exercise of options held by Mr. Reikes that are exercisable on or before May 2, 2020.
- (18) Includes shares of common stock held by Mr. Wender in a trust, and 78,500 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before May 2, 2020.
- (19) Includes 162,303 shares of common stock issuable upon exercise of options held by Dr. Geary that are exercisable on or before May 2, 2020.
- (20) Includes 201,558 shares of common stock issuable upon exercise of options held by Ms. Hougen that are exercisable on or before May 2, 2020.
- (21) Includes 243,744 shares of common stock issuable upon exercise of options held by Dr. Monia that are exercisable on or before May 2, 2020.
- (22) Includes 60,785 shares of common stock issuable upon exercise of options held by Mr. O'Neil that are exercisable on or before May 2, 2020.
- (23) Includes an aggregate of 2,566,663 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before May 2, 2020.

Securities Authorized for Issuance Under Equity Compensation Plans

The following table sets forth information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of March 31, 2020:

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders ⁽¹⁾	13,201,975	\$53.14	5,172,193 ⁽²⁾
Total	13,201,975	\$53.14	5,172,193

(1) Consists of four Ionis plans: 1989 Stock Option Plan, Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, 2011 Equity Incentive Plan, and Employee Stock Purchase Plan, or ESPP.

(2) Of these shares, 686,336 remained available for purchase under the ESPP as of March 31, 2020.

Compensation Discussion and Analysis

Business and Compensation Overview and 2019 Corporate Performance Achievement

Our Mission. Since inception, the Ionis mission has been to create a new, more efficient technology for drug discovery and development – antisense technology – and exploit that technology to create a pipeline of first-in-class and/or best-in-class medicines to treat a wide range of diseases. Today, thanks to the innovation and perseverance of Ionis, we believe antisense technology has the potential to treat diseases where no other therapeutic approach has proved effective.

Through the efficiency of our technology platform and business strategy we have built a pipeline of medicines in development with approximately 520 employees, representing a ratio of 1 medicine: 13 employees.

Ionis is focused on innovation. Ionis has implemented a business strategy intended to support long-term innovation based on the efficiency of antisense technology. Ionis has created an innovation-focused, science-driven culture that couples with the technology and business model to ensure long-term productivity and a commitment to the patients we serve and our stockholders.

Innovation Drives Our Success. Antisense technology exists today primarily because of the innovation at Ionis, with more than 1,800 issued patents that provide substantial control of key elements of the technology for many years to come. Our sizable collection of issued patents is all the more remarkable given that Ionis has approximately 520 employees. This means Ionis has produced over three issued patents per employee. Our intellectual property has been critical in the completion of strategic partnerships through which we have earned significant commercial revenue and a broad sustaining base of R&D revenue and the development of a consortium of companies that advance the technology alongside us, thereby increasing our reach. We achieved our eighth consecutive year of revenue growth in 2019, establishing our ability to generate sustainable revenue from our commercial medicines and numerous partnerships. We should continue to realize value from our majority owned affiliate, Akcea, and our partnerships, for many years to come in the form of commercial sales, license fees, upfront payments, milestone payments and royalties. Ionis has been recognized as one of the top ten most innovative companies in the biotechnology industry, based on number of granted patents, scientific strength, industry impact, technology strength and research intensity. In addition, Ionis and Biogen received the prestigious International Prix Galien Award for the Best Biotechnology Product in 2018 for SPINRAZA. In 2019, Ionis' founder and current Executive Chairman of the Board, Dr. Stanley Crooke, was awarded the Massry Prize for his pioneering work to establish an entirely new class of medicines and was one of several Ionis scientists to be honored with the prestigious Paper of the Year award at the Oligonucleotide Therapeutics Society Annual Meeting for the most impactful paper in the field of oligonucleotide therapeutics.

Commercial Medicines and Robust Pipeline. We have three commercial medicines approved in major markets around the world, SPINRAZA, TEGSEDI and WAYLIVRA. In 2019, Ionis received the Pantheon DiNA Award for Company of the Year by the California Life Sciences Association for achieving the approval and commercialization of these medicines. We also have four medicines that entered pivotal studies in 2019, and we anticipate 10 or more NDA submissions by the end of 2025. These medicines, along with the more than 30 additional medicines in our pipeline, represent multiple potential drivers of value for years to come. We believe our efficient drug discovery platform, coupled with our innovation-centric business model, provides us with the flexibility to determine the optimal development and commercialization strategy to maximize the commercial opportunity for each of our medicines and ensure that we continue to produce transformative medicines for patients who need them. We believe we are positioned to continue to drive substantial value for patients and stockholders.

Organizational Strategy. A key component of our business and organizational strategy is to operate with a workforce of a sufficient size to allow us to meet our goals but that also continues to foster innovation. We license our medicines at key value inflection points during development, thus avoiding the need to build the large, complex, inefficient organizations associated with fully integrated pharmaceutical companies. We also demand more of every employee at Ionis and do not tolerate mediocrity. We have been remarkably successful in achieving these goals. Today we have over 40 new medicines in development; one medicine in development per

13 employees. And we believe this productivity is sustainable. We have consistently added, and plan to continue to add, three to five new medicines to the pipeline every year without significant increases in the number of employees.

Our Compensation System. By design, Ionis demands more of every employee. This requires us to design our compensation system to recruit, motivate and retain outstanding individuals. Here too, we have been successful. Our average employee turnover rate over the last five years (reflected as of the third quarter each year) has averaged 8.9% per year, while the average turnover in the San Diego/La Jolla area for biotech/pharmaceutical companies over this period was 16.5% according to a survey published by Radford – an Aon Hewitt Company. Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees. The experience and seniority of our employees is as critical to our future success as it has been to the success we have enjoyed to date.

Our Vision. At Ionis our vision is clear and designed to create sustainable long-term value through innovation and to transform the lives of generations of patients in need across a wide variety of diseases. Our vision is to:

- work with the understanding that patients depend on us;
- continuously maintain an environment of cutting-edge innovation;
- create and constantly advance a more efficient drug discovery platform – antisense technology;
- pursue a business model and maintain a culture committed to creating long-term value through innovation;
- broaden, deepen and advance our pipeline of antisense medicines;
- demand more of every employee – more commitment, more knowledge, more intensity, more innovation and more productivity;
- aggressively manage average and below average performance so every employee produces more; and
- demand great performance and pay for that performance.

Summary of Compensation Practices

Below we summarize some of our compensation practices, both the practices we implement because we believe they are consistent with our vision and building long-term stockholder value (see “What We Do” below), and those we choose not to implement as we believe they are counter to our vision and building long-term stockholder value (see “What We Don’t Do” below):

What We Do	What We Don’t Do
<ul style="list-style-type: none"> ✓ In 2020 we began allocating 20% of our Chief Executive Officer’s equity awards as performance-based restricted stock units ✓ Demand more of every employee: more commitment, more knowledge, more intensity, more innovation, more productivity ✓ Reward productivity and performance ✓ Recognize the value of long-term employees and low turnover ✓ Use a balanced mix of fixed and variable cash incentives and long-term equity incentives ✓ Review compensation compared to the 25th, 50th and 75th percentiles of our peer group ✓ Design our compensation philosophy and objectives to mitigate unnecessary or imprudent business risk taking ✓ Set explicit and demanding objectives at the beginning of each year from which we measure performance for the year ✓ Place a maximum limit on Performance Management By Objectives (MBO) awards ✓ Set a strict budget for equity awards and salary increases ✓ Set the size of equity awards based on individual and company performance ✓ Require minimum vesting periods for equity awards ✓ Maintain equity holding periods that require our executive officers and non-employee Board members to hold shares received from their RSUs until they meet certain ownership thresholds or no longer serve the Company ✓ Maintain equity holding periods that require our employees to hold ESPP shares for a minimum of six months ✓ Require our executive officers and VPs to trade Ionis’ stock through Rule 10b5-1 trading plans ✓ Use a “double trigger” for cash payments for change of control ✓ Use a “double trigger” for equity acceleration for change of control for our officers ✓ Use an executive “clawback” policy ✓ Use an independent compensation consultant engaged by the Compensation Committee 	<ul style="list-style-type: none"> ✗ Do not guarantee a cash bonus – cash bonuses can, and have been, zero ✗ Do not provide perquisites for any employees ✗ Do not provide “gross-up” payments, other than for relocation ✗ Do not allow pledging, shorting or hedging against our stock ✗ Do not reprice or “cash-out” stock options without stockholder approval

2020 CEO Transition

After 30 years as Ionis' Chief Executive Officer, in January 2020, Dr. Crooke, our founder, transitioned to Executive Chairman of the Board. As Executive Chairman, Dr. Crooke is responsible for the activities of the Board and will remain active in the Company, providing strategic advice and continuing to participate in the Company's scientific activities. Dr. Monia, who was our Chief Operating Officer, assumed the position of Chief Executive Officer in January 2020; the position of Chief Operating Officer is currently vacant. The historical information contained in this Proxy Statement provides compensation data for Dr. Crooke and Dr. Monia with respect to each of their roles in 2019.

Compensation Overview and the Role of the Compensation Committee

We have designed our executive compensation program to attract and retain executives who can help us meet our business objectives and to motivate our executive officers to enhance long-term stockholder value. The Compensation Committee, with input from an independent compensation consultant, manages and oversees our executive compensation program. At the end of each year, and as otherwise required, the Compensation Committee approves the total compensation for each of our executive officers. In addition, the full Board reviews and ratifies the Compensation Committee's decisions regarding the compensation of our executive officers.

The Compensation Committee's responsibilities include:

- reviewing and approving overall compensation strategy;
- reviewing and approving corporate performance goals and objectives relevant to the compensation of our executive officers;
- evaluating and recommending to the Board the compensation plans and programs advisable for Ionis, as well as modifying or terminating existing plans and programs;
- establishing policies with respect to stock compensation arrangements;
- reviewing and approving compensation arrangements for our executive officers, including our Chief Executive Officer;
- reviewing and approving compensation arrangements for our Directors;
- administering our stock-based awards and ESPP;
- evaluating risks associated with our compensation policies and practices and assessing whether these risks are reasonably likely to have a material adverse effect on us;
- selecting and retaining a qualified, independent compensation consultant;
- performing other functions as may be necessary or convenient in the efficient discharge of the foregoing; and
- reporting to the Board from time to time, or whenever it is called upon to do so.

Independent Compensation Consultant

The Compensation Committee has the authority and budget to hire an independent compensation consultant as it deems necessary. The Compensation Committee has retained Marsh & McLennan Agency as its independent compensation consultant. For 2019, Marsh & McLennan Agency primarily provided the Compensation Committee advice in the following areas:

- selecting the 2019 Executive Peer Group;
- reviewing new hire awards and target annual equity awards for employees;
- evaluating the pay mix for our executive officers;
- assessing senior management compensation;
- evaluating Board member compensation;
- analyzing CEO compensation with respect to TSR; and
- evaluating our named executive officer equity awards.

Marsh & McLennan Agency did not provide any additional services to us or our affiliates in 2019.

Compensation Philosophy

Our compensation philosophy supports and rewards the characteristics and behaviors we believe will make us successful:



Pay for Performance. We incorporate a number of features into our compensation structure to mitigate the risk that our compensation policies and practices could encourage unnecessary or imprudent business risk taking. We use a combination of compensation vehicles that provide a balanced mix of fixed and variable cash incentives, and long-term stock incentives. Our Performance Management By Objective (“MBO”) awards are not guaranteed (i.e., are 100% at risk) and include a multiplier, or performance factor, based on Ionis’ and the employee’s performance (respectively, the “Company Performance Factor” and the “Individual Performance Factor”). Therefore, if either Ionis or the employee performs poorly, the Performance MBO can be, and has been, zero.

Beginning in 2020, we added performance-based restricted stock unit (“PRSU”) awards to the compensation for our Chief Executive Officer. As further described below, certain stockholders previously requested we implement performance-based stock awards and after thoughtful deliberation, the Compensation Committee decided to grant our CEO awards that provide him the opportunity to earn a defined number of shares of our common stock if we achieve pre-determined performance goals. The PRSU awards represent 20% of our CEO’s equity compensation. We believe these PRSU awards provide a challenging incentive to the CEO to significantly grow the Company. One third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (*i.e.*, the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant; the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant; and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on the Company’s relative TSR as compared to a peer group of companies and as measured, in each case, at the end of the applicable performance period. No number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 150% of the target number depending on the Company’s relative TSR.

Beginning in 2020, we added performance-based restricted stock unit (“PRSU”) awards to the compensation for our Chief Executive Officer.

CEO Pay Ratio. An executive officer’s salary plus bonus represents the officer’s total cash compensation. Our philosophy has been to have the CEO’s total cash compensation be between 20-30 times the lowest levels of compensation received by an employee. Dr. Crooke’s total cash compensation, over the last three years, was on average approximately 30 times that of the average cash compensation for our lowest level employees, and for 2019, decreased to approximately 28 times that of our lowest level employees. Dr. Crooke’s total cash compensation, over the last three years, was on average 2.29 times greater than the average of that of our other executive officers.

We cover the specific elements of our compensation structure in more detail below.

Business Objectives

As noted above, our vision is clear and is designed to promote long-term creation of value through innovation and to bring benefit to generations of patients with many diseases. Our vision is to:

- work with the understanding that patients depend on us;
- continuously maintain an environment of cutting-edge innovation;
- create and constantly advance a more efficient drug discovery platform – antisense technology;
- pursue a business model and maintain a culture committed to creating long-term value through innovation;
- broaden, deepen and advance our pipeline of antisense medicines;
- demand more of every employee – more commitment, more knowledge, more intensity, more innovation, more productivity;
- aggressively manage average and below average performance so that every employee produces more; and
- demand great performance and pay for that performance.

Overview of Our Compensation Program

Drug discovery and development across a portfolio of many medicines (currently over 40) is a long process that spans many years, where decisions we make today can have a positive or negative consequence five years, ten years, and even further into the future. As such, it is essential we set goals that incentivize our employees to execute our long-term strategy, because we believe our long-term strategy should continue to reward our stockholders into the future.

Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees.

For us to retain our technology leadership and effectively manage the technical complexity and broad scope of our development pipeline, our most senior executives and the members of their teams must advance multiple drug strategies and collaborative partnerships in parallel and consistently over many years, versus emphasizing one or two at the expense of others that deserve attention. As a result, other than stock price, budget and our annual financial guidance to Wall Street, we currently do not use financial-based metrics as objectives, such as earnings per share, because financial metrics typically overly emphasize two or three annual business metrics and ignore the complexity of the tasks we are undertaking. By taking this approach, we avoid the temptation to deviate from creating fundamental long-term value to meet a short-term metric.

We structure our corporate objectives so they are results driven rather than task driven. We typically include a number of objectives that are based on achieving positive data in the clinic. For example, in 2019 we had corporate objectives to (i) advance our pipeline to enable ten or more Phase 3 studies in the next two years with one of the measures being to obtain positive clinical proof-of-concept on at least five medicines in 2019; (ii) make our relationship with AstraZeneca successful with one of the measures being to achieve positive data from a Phase 1 study; and (iii) achieve key technology advancements with one of the measures being to achieve a five- to ten-fold potency increase in a particular area. These types of objectives only reward our employees if the data are positive – we do this to encourage the prudent spending of stockholder money on development decisions. In other words, we want to structure our objectives to reward success based on judgment, rather than the making of “bad bets.”

At the beginning of each year, we set aggressive corporate objectives, including objective measures, that our Board approves. On at least a quarterly basis, the Board evaluates our progress in achieving these objectives. We define excellent performance as a year in which we have met most of our objectives.

Importance of Tenure; Our Investment in Knowledge-Rich Employees

It takes a significant period of time and a substantial investment to recruit and develop employees who possess the experience and talent necessary to lead at Ionis given our transformative technology, innovative business strategy and complex drug development pipeline. Senior executives must have experience with all aspects of our business to be effective leaders. Our drug technology is a “platform technology,” which means the more knowledge and experience an employee has with our technology platform, the better equipped she or he is to create value at Ionis. Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees. The experience and seniority of our employees is critical to our future success. For these reasons, it is our objective to attract and retain the best talent available and to invest in those individuals who deliver long-term productivity.

- Long tenure among a dedicated and highly skilled workforce, combined with the highest performance standards, contributes to our leadership in the industry and serves the interests of stockholders.
- Our focus on retention is coupled with a strong belief that executive talent most often should be developed and promoted from within Ionis.
 - The long tenure of high-performing executive officers reflects this strategy at all levels of the organization. Our executive officers who served as of December 31, 2019 have on average approximately 25 years and individually as much as over 30 years of tenure at Ionis.

- The Company has carefully evaluated and selected each of our executive officers through a rigorous performance assessment process over a long career. In their current assignments, they remain subject to a challenging annual performance assessment in which they must continue to meet the highest standards or be reassigned or separated from the Company.

To recognize our employees, including our named executive officers, who deliver long-term productivity to the Company, Ionis has implemented two awards. In 2019, we implemented the “Lifetime Achievement Award” to recognize our distinguished, long-tenured, senior-level contributors who had extraordinary contributions that helped determine the Company’s future with a \$50,000 cash award. In 2018, we implemented the “Commitment to Ionis Award” to thank employees for their commitment to the Company. The amount of the Commitment to Ionis Award correlates to the employee’s length of service with the Company and is paid on the employee’s milestone anniversary as shown below. When we implemented this award in 2018, every employee with five or more years of service who was not scheduled to receive a Commitment to Ionis Award in 2018 or 2019 received a one-time “catch-up” award for one-half of the amount of the milestone award immediately preceding his or her actual length of service.

Years of Service	Award
5	\$5,000
10	\$10,000
20	\$20,000
30	\$30,000

In 2019, Drs. Crooke and Monia were each awarded a Lifetime Achievement Award and a Commitment to Ionis Award, the latter of which was based on their respective service with the Company, in each case since 1989.

Elements of Executive Compensation

Employees in our organization do not share either accountability or responsibility equally for strategic and/or tactical decisions. It is well ingrained in our culture that not everyone should share the same level of risk/reward for the consequences of these decisions. As a result, we have structured the various components of our compensation system to reflect accountability both for the successes and failures (both long-term and short-term) of Ionis and our employees. We pay our senior management team for results and their use of judgment in executing the strategies they have established. Therefore, the more senior a person becomes within Ionis, the more the person’s cash compensation will be “at risk.” We compensate the more junior employees for accomplishing their work well and, therefore, a lower portion of their cash compensation is “at risk.”

The more senior role a person plays, the more that person’s cash compensation will be “at risk.”

Our executive officers’ total compensation consists of four elements:

- (1) base salary;
- (2) Performance MBO – performance-based, at-risk cash compensation, *no portion of which is guaranteed*;
- (3) stock-based compensation, including performance-based restricted stock unit awards for our CEO; and
- (4) the same benefits, including 401(k) matching, that we provide to all employees.

The Performance MBO (performance-based, at-risk cash compensation) and performance-based restricted stock unit awards are the only elements that do not apply to all employees. Employees at the director level and above are eligible to receive Performance MBO awards, and our CEO receives performance-based restricted stock unit awards.

We consider many factors in determining the amounts we grant to our executive officers for all of the compensation elements listed above, with the exception of item 4. These factors include:

- company-wide performance, including achievement of pre-established corporate objectives;
- the Compensation Committee’s assessment of our CEO’s and executive officers’ individual performance;
- competitive compensation practices;
- increased efficiencies and process improvements;
- effective collaboration and teamwork;
- individual expertise, skills and knowledge;
- the need to retain and motivate;
- the impact an individual’s judgment has on our success or failure; and
- the advice of the Compensation Committee’s independent compensation consultant.

At the beginning of each year, we set aggressive corporate objectives, including objective measures, that our Board approves. On at least a quarterly basis, the Board evaluates our progress in achieving these objectives.

The Compensation Committee relies on these and other factors such as general economic conditions, industry conditions, and the Compensation Committee’s collective business judgment in setting and/or approving the appropriate increases. We do not have specific weightings assigned to these factors, as the importance of each factor can vary among the executive officers and from year to year.

Executive Peer Group

The Compensation Committee considers relevant market pay practices when setting executive compensation to ensure our ability to recruit and retain high performing talent. Although we do not benchmark or target our compensation to any particular level in relation to the compensation of the Executive Peer Group (as defined below), the Compensation Committee compares the compensation opportunity for our named executive officers to similarly-situated executives at the 25th, 50th and 75th percentiles of the Executive Peer Group (as defined below) as a “market check” to ensure, in its judgment, that the named executive officers’ compensation remains appropriate. The Executive Peer Group data is just one factor considered in the annual compensation approval process, in addition to the factors described above under “Elements of Executive Compensation.”

The Compensation Committee, in consultation with its independent compensation consultant, evaluated and selected a peer group of 20 life science companies for evaluating Ionis’ compensation (the “Executive Peer Group”). The Compensation Committee reviews the compensation of our named executive officers against the Executive Peer Group’s executive compensation to ensure that our compensation is competitive and to inform and shape its decision-making when setting compensation. While the Compensation Committee uses these data to inform and shape decision-making, it does not strictly adhere to quantitative benchmarks.

The Executive Peer Group, which the Compensation Committee reviews on an annual basis, consists of companies that generally:

- are similar to Ionis in terms of certain factors, including one or more of the following: size (*i.e.*, revenue, market capitalization), industry, stage of development and location;
- have named executive officer positions that are comparable to ours in terms of breadth, complexity and scope of responsibilities; and
- compete with us for executive talent.

The Executive Peer Group generally does not include companies headquartered outside the United States (because compensation and benefit practices are generally different outside the United States, the comparable compensation data for the named executive officers is not available and cost of living is different) or companies in industries whose compensation programs are not comparable to our programs, such as non-life science companies.

In June 2019, the Compensation Committee reviewed the Executive Peer Group using the criteria listed above and publicly available data as of May 2019. The Compensation Committee noted Ionis' market capitalization was approximately \$10.3 billion and revenue for the year ending December 31, 2018 was approximately \$600 million. As part of this process, the Compensation Committee looked at companies in Ionis' industry with an emphasis on companies with market capitalizations of between \$5 billion and \$20 billion, and revenue less than \$1.2 billion. The Compensation Committee also looked at companies that identified Ionis as a peer, so called "reverse peers." Based on this evaluation, the Compensation Committee added Array BioPharma, BioMarin Pharmaceuticals, Incyte Corporation and Jazz Pharmaceuticals to the Executive Peer Group. These companies all fell within the market capitalization range and were in Ionis' sector. BioMarin Pharmaceuticals, Incyte Corporation and Jazz Pharmaceuticals had revenue above the \$1.2 billion guideline, but each company was identified as a "reverse peer." Additionally, the Compensation Committee removed Akorn, Horizon Pharma and Portola Pharmaceuticals because these companies fell well below the market capitalization range and removed Tesaro because this company was acquired by GlaxoSmithKline.

The following table lists the companies in the 2019 Executive Peer Group, along with Ionis' rankings among these companies, based on market capitalization and financial data reported by each company for the most recently-reported fiscal year at the time the Compensation Committee selected the Executive Peer Group in June 2019.

Company (ticker)	Annual Revenues (in millions)	Market Capitalization (in millions)	Stage of Lead Drug
Acadia Pharmaceuticals (ACAD)	\$223.8	\$3,411.1	Market
Agios Pharmaceuticals (AGIO)	\$94.4	\$10,296.0	Market
Alkermes (ALKS)	\$1,094.3	\$4,471.7	Market
Alnylam Pharmaceuticals (ALNY)	\$74.9	\$8,837.7	Market
Array BioPharma (ARRY)	\$173.8	\$4,877.0	Phase III
BioMarin Pharmaceuticals (BMRN)	\$1,491.2	\$15,074.1	Market
bluebird bio (BLUE)	\$54.6	\$7,695.9	Phase III
Clovis Oncology (CLVS)	\$95.4	\$938.6	Market
Exact Sciences Corp (EXAS)	\$454.5	\$12,541.4	Market
Exelixis (EXEL)	\$853.8	\$5,828.1	Market
Incyte Corporation (INCY)	\$1,881.9	\$16,921.5	Market
Intercept Pharmaceuticals (ICPT)	\$179.8	\$2,548.0	Market
Ironwood Pharmaceuticals (IRWD)	\$346.6	\$1,833.3	Market
Jazz Pharmaceuticals (JAZZ)	\$1,890.9	\$7,358.5	Market
Ligand Pharmaceuticals (LGND)	\$251.5	\$2,471.9	Market
Nektar Therapeutics (NKTR)	\$1,193.3	\$5,514.5	Market
Neurocrine Biosciences (NBIX)	\$451.2	\$6,806.6	Market
Sarepta (SRPT)	\$301.0	\$8,571.7	Market
Seattle Genetics (SGEN)	\$654.7	\$10,808.4	Market
The Medicines Company (MDCO)	\$6.1	\$2,350.0	Market
Ionis Pharmaceuticals, Inc. (IONS)	\$599.7 ¹⁰	\$10,282.1	Market
Ionis' Ranking	8	6	N/A
Ionis' Percentile Rank	67%	79%	N/A

¹⁰ As reported in our Annual Report on Form 10-K for the year ended December 31, 2018.

Our Productivity vs. Industry Peers

All companies in all industries strive to be more productive than their peers. Leadership management and compensation systems are all focused on enhancing long-term productivity. However, measuring productivity is challenging, particularly in biotechnology.

Even for established R&D-based pharmaceutical companies for which the comparator group is obvious, comparisons of productivity are challenging. While revenues and profits per employee may be good measures for a portion of the equation, they provide

little insight into potential for topline sales growth and no insight into innovation, which is the foundation for long-term sustainable growth. To provide insight into these attributes, measures of the size, maturity and potential value of the drug pipeline as well as the number of issued patents are useful and, viewed in the context of the Company's financial performance, they help show a comprehensive picture of the Company's productivity and strength. We have historically been, and continue to be, at the top of the Executive Peer Group in these measures. For example, of the companies in the Executive Peer Group, we have the fewest employees per medicine in clinical trial. With approximately 25 medicines in clinical trials and just 520 employees, we are able to develop more medicines more efficiently, all while continuing to achieve exceptional financial results.¹¹

In 2019, we earned an all-time high for revenue of \$1.1 billion, nearly doubling our revenue from that of 2018, substantially exceeded our financial guidance and advanced a diverse pipeline of over 40 potentially transformative medicines.

In 2019, a number of achievements demonstrated our productivity and strength:

- We earned an all-time high for revenue of \$1.1 billion, substantially exceeded our 2019 financial guidance, achieved non-GAAP net income of over \$400 million and ended the year with \$2.5 billion in cash – exceptional financial performance that resulted from increased commercial revenue and R&D revenue that nearly doubled that of 2018.
- We achieved these financial successes while advancing four medicines into pivotal studies, achieving positive clinical proof-of-concept results from five medicines, advancing numerous medicines into earlier stages of development (including six new Ionis-owned medicines) and investing in complementary new technologies to facilitate continued pipeline growth.
- We launched WAYLIVRA in Europe and grew TEGSEDI sales globally, achieving \$42 million in product sales.

Our business model and efficient platform enabled us to accomplish these robust results and they set us apart from our peers.

¹¹ Based on data reported on each reporting company's website and Annual Report on Form 10-K for the year ended December 31, 2019.

We do more with less. With a workforce far smaller than most of our peers in the industry, we do more: more targets, more mechanisms, more organs, more routes of delivery and more issued patents per employee. We are the innovation leader in RNA-targeted therapeutics and aim to continue to be, thereby creating value for patients and stockholders in 2020 and beyond.

3
Commercial medicines



4
Phase 3 programs

Tominersen (IONIS-HTT_{Rx})
Huntington's disease

Tofersen (IONIS-SOD1_{Rx})
SOD1 ALS

AKCEA-APO(a)-L_{Rx}
(TQJ230)
Lp(a)-driven CVD

AKCEA-TTR-L_{Rx}
hATTR polyneuropathy

≥5

New **Phase 3** starts expected in 2020-2021

≥10

New **Phase 2 starts** expected in 2020

≥10

NDA submissions expected through 2025

Revenue Growth; Financial Performance

Additional evidence of our productivity and the benefit of our business strategy is reflected by our strong financial position. Ionis ended 2019 in a very strong financial position, with 2019 revenues of over \$1 billion, a nearly 50% increase from 2018, and Ionis' eighth consecutive year of revenue growth. For the fourth year in a row, Ionis was profitable, with non-GAAP¹² net income in 2019 of over \$400 million. This success is driven by the strength of our business strategy, which leverages numerous sources of revenue, with multiple opportunities for upside, while reducing risk.

\$1.1 billion in revenue

Nearly doubled over 2018



\$293 million in royalty revenue

>20% increase over 2018

\$513 million
of operating income*

\$402 million
of net income*

\$2.5 billion of cash
Enabling investment across the business to drive value creation

* Non-GAAP

¹² We use "non-GAAP" in place of "pro-forma" when discussing our financial results that exclude non-cash compensation expense related to equity awards because we believe that non-GAAP financial results better represent the economics of our business and how we manage our business.

Compensation Allocation/Pay Mix

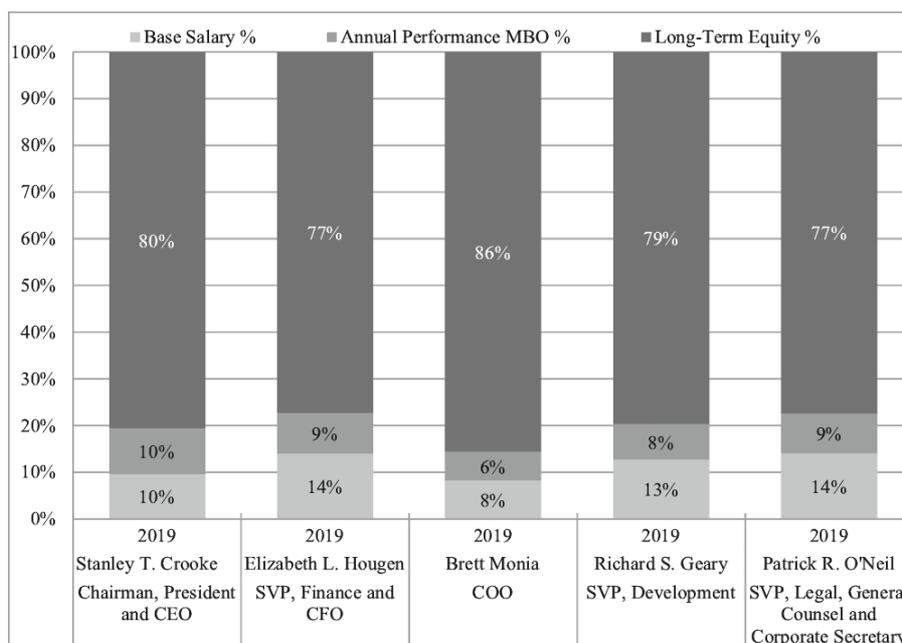
A key element of our compensation philosophy is to monitor and adjust our pay mix for our senior management team so the pay mix is less heavily weighted on fixed compensation (salary) and more heavily weighted on at-risk cash compensation and long-term equity incentive compensation. As part of the Compensation Committee’s review of our total pay mix for executive officers, the Compensation Committee focuses on the following:

- *A significant portion of cash compensation is at risk.* The Compensation Committee structures cash compensation such that a significant proportion of our CEO’s and other named executive officers’ cash compensation is at risk;
- *More of total compensation is long-term equity.* The Compensation Committee structures the total pay mix for our CEO and other named executive officers such that more of their compensation is in the form of long-term equity compensation; and
- *Less of total compensation is salary.* The Compensation Committee strives to have the total pay mix for our CEO and other named executive officers such that less of their compensation is in the form of salary. For example, in previous years, the Compensation Committee did not increase salaries for the CEO or our named executive officers to allow an increasing percentage of total compensation to be at risk.

An annual review of our total pay mix helps Ionis compete for and retain talent in the competitive marketplace and maintain compensation equity and balance among positions with similar responsibilities. The target pay mix for our named executive officers is a result of the compensation targets that emphasize long-term compensation versus short-term compensation. Actual salary levels, annual Performance MBO awards and long-term incentive awards vary based on one or more of the following: an individual’s responsibilities, tenure in a particular position, experience, individual performance and company performance.

2019 Compensation Decisions and Results

The following chart illustrates the portions of actual total direct compensation for the named executive officers that are composed of base salary, annual Performance MBO and long-term equity (\$ shown in thousands) for 2019:



Name	Year	Base Salary	Annual Performance MBO	Long-Term Equity	% of Total Direct Compensation		
					Base Salary %	Annual Performance MBO %	Long-Term Equity %
Stanley T. Crooke Chairman, President and CEO ⁽¹⁾	2019	\$911,506	\$925,748	\$7,623,978	10%	10%	80%
Elizabeth L. Hougen SVP, Finance and CFO	2019	\$479,880	\$299,925	\$2,647,671	14%	9%	77%
Brett Monia COO ⁽²⁾	2019	\$527,850	\$395,888	\$5,470,759	8%	6%	86%
Richard Geary SVP, Development	2019	\$491,186	\$294,712	\$3,078,281	13%	8%	79%
Patrick O'Neil SVP, Legal, General Counsel and Corporate Secretary	2019	\$483,052	\$289,831	\$2,647,671	14%	9%	77%

(1) As of January 2020, Dr. Crooke transitioned to Executive Chairman of the Board.

(2) As of January 2020, Dr. Brett Monia became Chief Executive Officer.

Base Salary

The fixed component of our compensation structure is base salary. We categorize our jobs in a system called broad banding. That is to say there are relatively few job levels within Ionis, specifically eleven levels, but the scope of responsibility and accountability an employee may assume is broad. We do not have salary ranges, and therefore we do not set salary minimums or maximums. It is therefore possible that someone may be in a lower job level, but his or her salary may reach levels that exceed those of someone in a higher job level. We have chosen not to have salary ranges because years of experience have shown that this approach often creates unnecessary bureaucracy and a loss of talented individuals. Our aim is to attract and retain the most highly qualified employees in an extremely competitive market.

We determine base compensation levels for all our employees primarily by market forces. Accordingly, the Compensation Committee believes that it is important when making its compensation decisions to be informed as to the current practices of comparable publicly held companies with which we compete for top talent. To this end, the Compensation Committee reviews market and peer company data, which includes competitive information relating to the mix and levels of compensation for executives in the life sciences industry. We obtain this information for the Executive Peer Group based on recent public filings with the SEC. In addition, we also review data from the Radford Global Life Sciences Survey, which is a summary of compensation data submitted by over 500 life sciences companies. The Compensation Committee uses these data to inform and shape its decision-making but does not strictly adhere to quantitative benchmarks. In addition, we assess whether the scope of job responsibilities and internal equity warrant a given base salary.

For most of our executive officers, and all of our named executive officers, salary represents 20% or less of total compensation.

We guarantee base salary to all employees as wages for hours worked. It represents consideration for the performance of job responsibilities. This portion of total cash compensation is not at risk and may increase as a result of how well an individual performs his or her job responsibilities.

Each year our employees are eligible to receive an appropriate merit salary increase. The Compensation Committee sets a Company-wide merit increase budget percentage based on Ionis' performance and external factors such as the average merit budget of comparable companies. The actual merit increase award for each

employee, including our executive officers, will vary depending upon the respective employee's contributions to Ionis. For example, for 2019 performance the Company-wide merit increase budget was 3.3%, with a range of individual merit award increases of 0% to 6%. However, regardless of individual employee variances, we do not exceed the Company-wide approved merit budget.

The Compensation Committee evaluates each executive officer's performance to set his or her annual merit increase. As part of this process, the Compensation Committee reviews the written reports prepared by the CEO evaluating the performance of each individual executive officer. The Compensation Committee carefully considers these reports since our CEO is in the best position to evaluate our executive officers' day-to-day and overall performance. The Compensation Committee meets in executive session and evaluates the CEO's performance, primarily based upon the CEO's achievement of our company's objectives for the year. At the end of this process, the Compensation Committee determines the CEO's merit increase and approves or recommends changes to the merit increases for the remaining executive officers. Our CEO has no role in determining his own compensation.

The executive officers' new salaries for each year are calculated as follows:

- Current Base Salary (x) Merit Increase = Increase to Base Salary
- Current Base Salary (+) Increase to Base Salary = New Base Salary

For example, Ms. Hougen's 2020 salary of \$499,555 was calculated as follows¹³:

<u>2019 Base Salary</u>	(x)	<u>Merit Increase</u>	=	<u>Increase to Base Salary</u>
\$479,880	(x)	4.1%	=	\$19,675
<u>Current Base Salary</u>	(+)	<u>Increase to Base Salary</u>	=	<u>New Base Salary in 2020</u>
\$479,880	(+)	\$19,675	=	\$499,555

When reviewing salaries, the Compensation Committee noted that the salary of most of our named executive officers was within the competitive range of the Executive Peer Group. The Compensation Committee also noted its desired target mix of compensation that is less weighted on salary. Given Ionis' strong 2019 performance, the Compensation Committee approved merit increases to the 2020 salaries of the named executive officers other than Dr. Crooke and Dr. Monia of 3.8% on average, which were consistent with the budget for merit increases approved by the Compensation Committee. As a result of their respective transitions to Executive Chairman and Chief Executive Officer, neither Dr. Crooke nor Dr. Monia received a merit increase for 2020. Instead, the Compensation Committee evaluated the salary levels for each of these positions with assistance from Marsh & McLennan Agency, which prepared a comprehensive assessment of the compensation of a newly appointed CEO and Executive Chairman, and approved the salaries for each position following review of such assessment. Consistent with their new roles and responsibilities, Dr. Crooke's annual salary decreased to \$683,630 and Dr. Monia's annual salary increased to \$700,000.

Performance MBO Program – Performance-Based, At-Risk Cash Compensation

The next component of an executive officer's compensation, and the compensation of our employees at the director level and above, is a performance-based cash payment through our Performance MBO program. While an employee's base salary compensates the employee for his or her continued service and performance, our Performance MBO program rewards employees for reaching specific objectives and for the judgment they use in making decisions. We do not guarantee a Performance MBO award as compensation. It is totally at risk. As such, a Performance MBO award represents an opportunity for reward based upon the individual's level of accountability and depends on the relative success of both Ionis and the individual. Our approach for awarding Performance MBO bonuses differs from salary increases because, unlike salary increases, market forces do not impact bonus amounts.

We calculate the actual amount of each executive officer's respective Performance MBO award based on the following formula:

$$\text{Base Salary (x) Target Performance MBO \% (x) Company Performance Factor (x) Individual Performance Factor} = \text{Performance MBO Amount}$$

¹³ We elected to use Ms. Hougen's data as an illustration of the 2020 salary calculation, as Dr. Crooke's 2020 salary was evaluated separately in connection with his transition to Executive Chairman of the Board in January 2020.

Performance MBO Awards can be zero. The multipliers in this formula ensure we award bonuses based on *both* Ionis' performance and individual performance. This means an employee may not receive a Performance MBO even if he or she performed well in a year in which the Company does not meet its corporate objectives. Similarly, if an employee performed poorly in a year in which the Company met its corporate objectives, he or she may not receive a Performance MBO.

Performance MBO awards can be, and have in the past been, zero. Performance MBO awards have a maximum amount.

For example, in a prior year, we did not pay Performance MBOs to executive officers due to the failures we faced at the time. In another year, our CEO's Performance MBO was 64% of the Performance MBO he received in the immediately preceding year because of disappointing clinical trial results; the Company Performance Factor was 50% that year. Conversely, in successful years, we reward our executive officers consistent with Ionis' success.

Performance MBOs have a maximum limit. Performance MBOs are limited by a maximum Company Performance Factor, maximum Individual Performance Factor and Target Performance MBO Percentage:

- We have a maximum Company Performance Factor of 200% and a maximum Individual Performance Factor of 160%. This range represents the boundary conditions for our Performance Factors and ensures we reward our employees consistent with Ionis' success.
- We base Target Performance MBO percentages on position levels within Ionis. The Target Performance MBO percentages for 2019 were: Directors 20%; Executive Directors 25%; Vice Presidents 30% or 35%; Senior Vice Presidents 40%; COO 50%; and CEO 65%.

An individual's Target Performance MBO percentage does not change unless he or she changes position level or the Compensation Committee sets a new target for that level. The table below summarizes the minimum and maximum Performance MBO for 2019 as a percentage of salary:

Name	Minimum Performance MBO Percentage of Salary	Maximum Performance MBO Percentage of Salary
Stanley T. Crooke	0%	208%
Elizabeth L. Hougen	0%	128%
Brett Monia	0%	160%
Richard Geary	0%	128%
Patrick O'Neil	0%	128%

The Compensation Committee sets the Company Performance Factor based on the following process:

- At the end of each year, the Compensation Committee meets to evaluate Ionis' overall performance for the year. As described below in the chart called "Evaluation of 2019 Corporate Objectives," the Compensation Committee measures Ionis' performance based upon the achievement of goals set at the beginning of the year with objective measures and agreed upon by our Board and upper management.
- In addition, the Compensation Committee considers our one-, three- and five-year TSRs, and based on these returns has *negative discretion to reduce the Corporate Performance Factor and Individual Performance Factors for our executive officers*.
- The Compensation Committee then reviews the Company Performance Factor history from the prior ten years to form a comparison for our current year's successes and/or failures.
- Finally, the Compensation Committee approves each executive officer's Individual Performance Factor based on the individual's performance.

Based on our one-, three- and five-year TSRs, the Compensation Committee has negative discretion to reduce the Corporate Performance Factor and Individual Performance Factors for our executive officers.

Once the Compensation Committee has determined the elements of the formula above, we use that formula to calculate each executive officer's Performance MBO.

Evaluation of 2019 Corporate Objectives. On December 18, 2019, the Compensation Committee completed its evaluation of the Company's performance against the 2019 Corporate Objectives.

The Compensation Committee set the Company Performance Factor for the 2019 Performance MBO at 125% due to our strong achievements for the year across drug discovery, development, corporate development and financial performance, particularly given:

- We earned an all-time high for revenue of \$1.1 billion, substantially exceeded our 2019 financial guidance, achieved non-GAAP net income of over \$400 million and ended the year with \$2.5 billion in cash – exceptional financial performance that resulted from increased commercial revenue and R&D revenue that nearly doubled that of 2018.
- We achieved these financial successes while advancing four medicines into pivotal studies, achieving positive clinical proof-of-concept results from five medicines, advancing numerous medicines into earlier stages of development (including six new Ionis-owned medicines) and investing in complementary new technologies to facilitate continued pipeline growth.
- We launched WAYLIVRA in Europe and grew TEGSEDI sales globally, achieving \$42 million in product sales.

The Compensation Committee evaluates performance based on the achievement of goals (*including objective measures*) that the Board and management set at the beginning of each year. The table below provides a detailed evaluation of each objective and the related achievements for 2019, as well as a description of notable unplanned accomplishments that the Compensation Committee considered in evaluating the Company's performance. Going forward, the Company will reduce the total number of corporate objectives in order to increase the Company's focus on key objectives we consider most important for that year.

Evaluation of 2019 Corporate Objectives		
	Objective & Pre-Approved Objective Measures	Evaluation
1	<p>Meet budget/projections:</p> <ul style="list-style-type: none"> Achieve a specified target in pro forma operating profit Meet financial guidance 	<p>Ionis <u>exceeded</u> this objective:</p> <ul style="list-style-type: none"> Ionis significantly exceeded the specified target by earning more than \$500 million in non-GAAP operating income Ionis substantially exceeded financial guidance
2	<p>Strengthen Akcea/Ionis partnership to improve performance:</p> <ul style="list-style-type: none"> Optimize Akcea pipeline and strategic investment plan and enhance intercompany communications to achieve greater efficiency and effectiveness 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> Ionis and Akcea achieved significantly improved intercompany operational performance
3	<p>Make TEGSEDI (inotersen) commercially successful:</p> <ul style="list-style-type: none"> 2019 sales \geq a specified sales target Achieve acceptable pricing approvals in key jurisdictions Achieve approval in Brazil 	<p>Ionis <u>partially met</u> this objective:</p> <ul style="list-style-type: none"> Did not achieve; however, we attained a substantial percentage of the specified sales target Successfully achieved acceptable pricing approvals in multiple key jurisdictions Achieved approval in Brazil
4	<p>Initiate four pivotal studies</p>	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> Ionis initiated four Phase 3 studies (for tominersen, tofersen, AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx})
5	<p>Advance pipeline to enable ten or more Phase 3 studies in next two years:</p> <ul style="list-style-type: none"> Positive clinical proof-of-concept results (Phase 2 or otherwise at study completion) from \geq five medicines 	<p>Ionis <u>exceeded</u> this objective:</p> <ul style="list-style-type: none"> Ionis achieved positive clinical proof-of-concept for eight medicines
6	<p>Facilitate the scientific and regulatory communities' understanding and appreciation of the benefits of our LICA technology</p>	<p>Ionis <u>met</u> this objective</p>
7	<p>Increase stock price performance by a specified target percentage greater than or equal to median of the companies listed in the Nasdaq Biotechnology Index.</p>	<p>Ionis <u>exceeded</u> this objective:</p> <ul style="list-style-type: none"> Ionis' stock price outperformed the median stock price change for companies listed in the Nasdaq Biotechnology Index by a percentage greater than the specified target
8	<p>Achieve successful executive level transition:</p> <ul style="list-style-type: none"> Achieve positive CEO transition Establish effective senior level organization to support successful 2020 transition 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> Ionis successfully prepared for the transition of the CEO role from Dr. Crooke to Dr. Monia Ionis made several senior level organizational changes to support the 2020 CEO transition, specifically, Ionis appointed Frank Bennet, Ph.D., to Chief Scientific Officer and promoted Eric Swayze, Ph.D., to Senior Vice President of Research
9	<p>SPINRAZA – Achieve successful commercialization:</p> <ul style="list-style-type: none"> 2019 sales \geq a specified target with royalties \geq a specified target 	<p>Ionis <u>substantially met</u> this objective:</p> <ul style="list-style-type: none"> Ionis achieved an overwhelming percentage of its SPINRAZA sales and royalty targets for 2019

Evaluation of 2019 Corporate Objectives		
	Objective & Pre-Approved Objective Measures	Evaluation
10	<p>WAYLIVRA – Achieve successful commercialization:</p> <ul style="list-style-type: none"> • Achieve approval in EU • Define path with FDA for US approval • 2019 sales \geq a specified sales target (contingent on EU approval) 	<p>Ionis <u>substantially met</u> this objective:</p> <ul style="list-style-type: none"> • Achieved EU approval in May 2019 • Made significant progress with FDA defining a path for US approval • Did not achieve
11	<p>Achieve sufficient R&D revenue to meet a specified target in pro forma operating profit</p>	<p>Ionis <u>exceeded</u> this objective</p>
12	<p>Progress rapid development of AKCEA-TTR-L_{Rx} for both hereditary and wild type:</p> <ul style="list-style-type: none"> • Successfully complete Phase 1 study to support Phase 3 development • Initiate Phase 3 study for AKCEA-TTR-L_{Rx} 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> • Achieved • Ionis initiated a Phase 3 study of AKCEA-TTR-L_{Rx} in patients with polyneuropathy driven by hereditary TTR amyloidosis
13	<p>Make Novartis relationship successful:</p> <ul style="list-style-type: none"> • Successful end of Phase 2 meeting with FDA for AKCEA-APO(a)-L_{Rx} • Achieve positive option for AKCEA-APO(a)-L_{Rx} • Novartis initiation of AKCEA-APO(a)-L_{Rx} Phase 3 study • Complete dosing for Phase 2 AKCEA-APOCIII-L_{Rx} study 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> • Achieved • Novartis exercised its option to license AKCEA-APO(a)-L_{Rx} • Novartis initiated a Phase 3 study of AKCEA-APO(a)-L_{Rx} • Dosing completed for Phase 2 study of AKCEA-APOCIII-L_{Rx}
14	<p>Make Biogen relationship successful:</p> <ul style="list-style-type: none"> • Achieve enrollment targets for IONIS-MAPT_{Rx} study • Initiate Phase 3 study for tofersen • Dose first patient for two specified programs • Achieve initiation of IND-tox studies for three new drug programs • Achieve \geq two new target sanctions and acceptance by Biogen • Identify \geq three development candidates and acceptance by Biogen 	<p>Ionis <u>substantially met</u> this objective:</p> <ul style="list-style-type: none"> • Ionis achieved its enrollment targets for IONIS-MAPT_{Rx} study • Achieved • Achieved for one program • Achieved • Ionis achieved two new target sanctions for Biogen • Ionis identified three development candidates for Biogen
15	<p>Make Roche relationship successful:</p> <ul style="list-style-type: none"> • Roche dosing of first patient in IONIS-HTT_{Rx} registration study • Initiate Phase 2 AMD study for FB and enroll a target number of patients with study on budget • Oversee safety for FB AMD study 	<p>Ionis <u>substantially met</u> this objective:</p> <ul style="list-style-type: none"> • Roche dosed first patient in IONIS-HTT_{Rx} registration study • Ionis initiated a Phase 2 study for FB in AMD and is continuing to enroll patients • Ionis oversaw safety for FB AMD study
16	<p>Make AstraZeneca relationship successful:</p> <ul style="list-style-type: none"> • Advance danvatirsen to registration study • Initiate IND-toxicology study for a specified program • AZ positive completion of subcutaneous and oral Phase 1 studies and decision to advance to Phase 2 for a specified program • Achieve positive oral Phase 1 study with \geq a target percentage bioavailability for a specified program • AZ dosing of first patient in Phase 1 study for two specified programs • Achieve development candidate approval and license fee from AZ for a specified program • Achieve two target sanctions 	<p>Ionis <u>partially met</u> this objective:</p> <ul style="list-style-type: none"> • Did not advance to registration study • IND-toxicology study was initiated and completed • Subcutaneous Phase 1a completed and oral study ongoing • Oral study ongoing • Achieved for one program • Did not achieve • Ionis achieved two target sanctions for AZ programs

Evaluation of 2019 Corporate Objectives		
	Objective & Pre-Approved Objective Measures	Evaluation
17	Advance pipeline: <ul style="list-style-type: none"> Initiate Phase 2 clinical trials on \geq four medicines (dose first patient) Initiate Phase 1 clinical trials on \geq four medicines (dose first patient/subject) Advance \geq six new medicines into the pipeline Achieve \geq five target sanctions Define regulatory path for mixed-dyslipidemia 	Ionis <u>exceeded</u> this objective: <ul style="list-style-type: none"> Ionis initiated Phase 2 clinical trials on five medicines Ionis initiated Phase 1 clinical trials on four medicines Ionis advanced ten new medicines into its pipeline Ionis achieved five target sanctions Achieved
18	Achieve key technology advancements: <ul style="list-style-type: none"> Advance new ASO design into development as general approach Optimize screening Achieve positive oral Phase 1 study with \geq a target percentage bioavailability Achieve five- to ten-fold increase in certain target tissues Successfully complete Phase 1 aerosol study 	Ionis <u>substantially met</u> this objective: <ul style="list-style-type: none"> Achieved Achieved Oral study ongoing Achieved Achieved
19	Achieve key transactions for pipeline on attractive terms	Ionis <u>met</u> this objective: <ul style="list-style-type: none"> Ionis successfully partnered AKCEA-ANGPTL3-L_{Rx} Ionis made significant progress on other key transactions for pipeline
Unplanned Accomplishments for 2019		
20	Positive IONIS-FXI _{Rx} FDA meeting	
21	Highly positive WAYLIVRA FPL data	
22	Positive Bayer IONIS-FXI-L _{Rx} advancement decision	
23	Implemented first stock buyback program	

Once the Committee establishes the Company Performance Factor, the Committee next reviews each executive officer's individual performance and contribution towards the corporate objectives and other accomplishments set forth above and sets each executive officer's MBO award accordingly. The following table illustrates the Performance MBO awards approved for 2019 performance:

Name	Base Salary	Target Performance MBO %	Company Performance Factor	Individual Performance Factor ⁽¹⁾	Resulting Performance MBO	Results Considered When Setting Individual Performance Factor ⁽¹⁾
Stanley T. Crooke ⁽²⁾	\$911,506	65%	125%	125%	\$925,748	1-23
Elizabeth L. Hougen	\$479,880	40%	125%	125%	\$299,925	1-3, 7-11, 19 & 23
Brett Monia ⁽²⁾	\$527,850	50%	125%	120%	\$395,888	1-23
Richard Geary	\$491,186	40%	125%	120%	\$294,712	1-2, 4-6, 8, 11-18 & 20-22
Patrick O'Neil	\$483,052	40%	125%	120%	\$289,831	1-2, 6-8, 13-19 & 23

(1) The numbers correspond to the enumerated objectives in the table entitled "Evaluation of 2019 Corporate Objectives" on pages 54 through 56. The Compensation Committee reviews the individual's contribution towards the corporate objectives and other accomplishments set forth above when determining the Individual Performance Factors.

(2) Since our CEO and COO are ultimately responsible for the Company's performance, their Individual Performance Factors are usually the same as the Company Performance Factor, up to an Individual Performance Factor maximum of 160%.

Stock Compensation

We use stock options and RSUs to give all employees, including Ionis' executive officers, an economic interest in the long-term appreciation of our common stock. We believe awarding a combination of stock options and RSUs provides a number of benefits. Stock options provide a way to align employee interests with those of upper management and the stockholders because as our stock price increases, so too does the employee's compensation. In 2012, we started granting RSUs as part of the annual merit equity awards. RSUs are a strong retention vehicle for employees as the RSUs vest in annual installments over four years and have value upon vesting, but at the same time, require fewer shares than stock option awards.

Our stock awards reward performance and incentivize long-term stock appreciation and increased stockholder returns.

We grant existing employees new stock options and RSUs annually to provide a continuing incentive in Ionis' long-term success. Each year, the Compensation Committee sets a budget of option equivalents for our named executive officers and a budget of option equivalents for all other employees. From these budgets, we set a target number of option equivalents for each employee level in the Company. The actual award for each employee can be higher or lower than the target for their level depending on individual performance, but the total awards cannot exceed the budget set by the Compensation Committee. In January 2019, we allocated option equivalents among stock options and RSUs as follows: 60% of option equivalents was allocated to stock options and 40% of option equivalents was allocated to RSUs.

We do not use Black-Scholes calculations to set the size of our equity awards. Instead, once we identify the number of stock options and RSUs to be awarded from the option equivalent budget for our named executive officers, we calculate the Black-Scholes value of the stock option awards. As a market check, we then compare the resulting values to the Black-Scholes value of awards granted by the companies in the Executive Peer Group and make adjustments to the size of the awards when appropriate. When our stock price is high, the Black-Scholes value of the awards is also high. Unlike other companies, when our stock price is low, we do not increase the equity awards to achieve a pre-defined Black-Scholes value of the stock options and RSUs to be awarded.

Performance-Based Stock Awards

Beginning in 2020, we began allocating 20% of our CEO's equity compensation in the form of performance-based restricted stock unit awards that vest based on our relative stock price performance compared to a peer group. We believe these performance-based restricted stock unit ("PRSU") awards provide a challenging incentive to the CEO to significantly grow the Company. One third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (*i.e.*, the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant; the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant; and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on the Company's relative TSR as compared to a peer group of companies, and as measured, in each case, at the end of the applicable performance period. No number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 150% of the target number depending on the Company's relative total shareholder return.

Over the past several years we discussed our use of time-vested stock options and RSU awards with our institutional stockholders. The results of this process were that many of our stockholders acknowledged that stock options are prevalent in the biopharmaceutical industry and are considered performance-based because they require the stock price to appreciate following the grant date and prior to vesting and exercise to provide economic value to the recipient. In addition, many of our stockholders agreed that we had the right mix of equity vehicles for our industry and stage. Our independent compensation consultant also believes time-vested stock options are performance-based compensation and an appropriate equity vehicle for Ionis and did not recommend making any changes to our equity vehicles for 2019. *Some of our stockholders, however, have requested we incorporate performance-based stock awards into our executive compensation program. As noted above, beginning in 2020, we added performance-based restricted stock unit awards to the compensation for our Chief Executive Officer, which provide him the opportunity to earn a defined number of shares of our common stock if we achieve pre-determined performance goals.* As such, for his promotion, Dr. Monia received 85,045 option

equivalents that were allocated among time-vested stock options, time-vested RSUs and PRSUs as follows: 40,822 time-vested stock options (80% of option equivalents allocated 60% to stock options), 18,143 time-vested RSUs (80% of option equivalents allocated 40% to RSUs, divided by 1.5) and 17,009 PRSUs (20% of option equivalents, divided by 1.5 to establish the target payout of 11,339, multiplied by 150% to account for potential upside).

Vesting of Stock Awards

Vesting schedules reward long-term performance and incentivize long-term stock appreciation and increased stockholder returns. For each stock option and RSU granted (except PRSUs), the Compensation Committee sets a vesting schedule over four years, with no vesting during the first year. Therefore, the stock options and RSUs granted to our executive officers directly align the interests of our executive officers with the interests of our stockholders and Ionis' long-term success. The actual economic value of stock option awards depends directly on the performance of our stock price over the period during which the awards vest and the period during which the stock options may be exercised. In other words, the stock options are not worth anything if our stock price does not increase above the exercise price. Our executive officers will only realize economic value when our stock price, and consequently stockholder value, increases. Similarly, in the same way our stockholder returns increase and decrease based on our stock's performance, the value to our employees of the RSUs increases and decreases based on our stock's performance.

With the exception of PRSUs awarded to our CEO, we do not tie vesting to the achievement of specific events, such as annual metrics, because we do not want to encourage our employees to deviate from our company objectives, which we believe optimizes sustained stockholder value; nor do we want our employees to take unnecessary risks just to meet a short-term metric.

Each year the Compensation Committee approves a stock option and RSU budget for annual employee merit awards. We do not grant options or RSUs in excess of this budget without Compensation Committee approval.

The stock option vesting schedule is typically over a four-year period at the rate of 25% at the end of the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment. The RSU vesting schedule is typically over a four-year period at the rate of 25% per year. In addition, as further described below, our executive officers must hold shares received upon vesting of their RSUs until they

meet certain ownership thresholds or no longer serve the Company. These practices align our employee compensation with our stockholders' interests because if stockholder value declines over time, so too will the value of the equity compensation provided to all employees. We have historically had low employee turnover, particularly in our management team, and the members of our management have traditionally held their stock options for a long period of time before exercise. Our low turnover is indicative of our employees' commitment to Ionis and its technology and reflects our executive officers' belief in the long-term value of our stock.

Our stock compensation budget minimizes dilution.

Each year the Compensation Committee approves a budget that sets the number of stock options and RSUs we can grant our employees for annual merit awards. We do not grant stock options or RSUs that exceed this budget without the Compensation Committee's approval. Over the past three years, the average merit award stock budget set by the Compensation Committee has been approximately 2.2% of our outstanding common stock on an issued and outstanding basis. This stock compensation budget, and therefore our equity compensation burn rate, is well below the Executive Peer Group average of 4% from 2016 through 2018. We believe this stock budget is an important tool to balance our compensation objectives with stockholder interests. For 2019 performance, the Compensation Committee set a merit stock award budget that resulted in approximately 2 million stock options and approximately 900,000 RSUs awarded to employees, including the executive officers. Together these shares represent approximately 2% of our outstanding common stock on an issued and outstanding basis for that year. This budget, as well as each employee's position level and performance in the previous year, ultimately determines the size of the individual annual stock grants.

Over the past 3 years, the average merit award stock budget set by the Compensation Committee has been approximately 2.2% of our outstanding common stock on an issued and outstanding basis.

Corporate Governance

Stock Ownership Guidelines and Holding Periods

Our executive officers and members of our Board of Directors must hold the shares issued under their RSUs until they have met an ownership guideline and all employees must hold shares purchased under our ESPP for six months.

Our Compensation Committee and our Board set stock ownership and holding guidelines for our executive officers and members of the Board. These guidelines require our executive officers and non-employee Board members to hold the shares they receive under their RSU awards until they achieve the guidelines or no longer serve the Company. Shares sold or surrendered to pay for withholding taxes associated with the RSU awards are exempt from these holding requirements.

The table below indicates the stock ownership guidelines for our executive officers and Board members:

Executive Officer/Director	Stock Ownership Guideline (as a multiple of base salary/annual cash retainer)
CEO	3 times Base Salary
COO	2 times Base Salary
All other executive officers	1 times Base Salary
Non-employee Directors	4 times Base Annual Cash Retainer

As of March 31, 2020, all of our non-employee Directors, except Dr. Hayden, Mr. Reikes and Ms. Herman, and all of our current executive officers except Dr. Monia, Dr. Swayze and Ms. Cadoret-Manier, meet these guidelines. Due to the recent appointments of Dr. Hayden, Mr. Reikes and Ms. Herman, the number of shares sufficient to meet such guidelines have not yet vested. Similarly, due to Dr. Monia's and Dr. Swayze's transitions in January 2020, and the recent appointment of Ms. Cadoret-Manier, they do not yet hold enough shares sufficient to meet the guidelines.

In addition, our ESPP has a six-month minimum holding period for shares purchased under the ESPP.

As of December 31, 2019, Dr. Crooke held approximately 700,000 shares of our common stock and has held most of these shares throughout his over 30-year tenure. Dr. Crooke's holding represented over 47 times his Base Salary at December 31, 2019.

Clawback Policy

We have a recoupment/"clawback" policy. If we are required to prepare an accounting restatement due to the material noncompliance of Ionis, as a result of misconduct, with any financial reporting requirement under the securities laws, Ionis' Chief Executive Officer and Chief Financial Officer must reimburse Ionis for:

- any bonus or other incentive-based or equity-based compensation received by that person from Ionis during the 12-month period following the first public issuance or filing with the SEC (whichever first occurs) of the financial document embodying such financial reporting requirement; and
- any profits realized from such executive's sale of Ionis' securities during that 12-month period.

The SEC may exempt any person from the application of this executive recoupment policy, as it deems necessary and appropriate.

In addition, if and when the SEC adopts implementing regulations under Section 954, "Recovery of Erroneously Awarded Compensation" under the Dodd-Frank Wall Street Reform and Consumer Protection Act, our Nominating, Governance and Review Committee will promptly adopt appropriate updates to this policy to comport with such implementing regulations.

Anti-Hedging Policy and Anti-Pledging Policy

We explicitly prohibit employees from "shorting" and hedging against our stock. To help avoid situations in which our employees may benefit from transactions that harm our stockholders, our policies specifically prohibit

all employees, including our executive officers, from taking a “short” position in our stock and otherwise hedging their position in our stock against a future drop in our stock price. In addition, we specifically prohibit all of our employees from trading derivative instruments based on our common stock (e.g. put or call options for our stock) and prohibit pledging our stock as collateral.

Rule 10b5-1 Trading Program

10b5-1 plan required for executive officers and vice presidents. We have a Rule 10b5-1 trading program. Our Rule 10b5-1 trading program allows our executive officers, vice presidents and other employees to establish plans that permit prearranged future sales of his or her stock when there is no material non-public information available. We do not allow our executive officers or vice presidents to buy or sell our stock outside of the Rule 10b5-1 trading program except for purchases of our stock under our ESPP (but not subsequent sales of the stock) and transactions that are automatically effected by Ionis’ stock administrator in connection with the vesting and release of RSUs.

Perquisites

We are committed to using stockholder money responsibly, to building stockholder value and ensuring our processes are entirely transparent. As a result, Ionis’ policies do not provide for perquisites for any employees, including our executive officers.

Retirement & Other Benefits

We maintain a highly competitive position with regard to the benefits offered to all regular employees, including our executive officers. These benefits include medical, dental and vision insurance, EAP, basic life insurance, short-term disability/sick pay, long-term disability, vacation, holidays, a 401(k) plan with employer match, an ESPP and Accidental Death & Dismemberment (AD&D) insurance.

Recognizing that health care costs constitute a greater fraction of disposable income for lower paid employees, we have a progressive contribution premium for our health care benefits, which means the more money an Ionis employee makes, the more he or she contributes to the costs of his or her family’s health care.

Retention and Change of Control Agreements

As part of our normal course of business and as a result of our business strategy, we engage in discussions with other biotechnology and pharmaceutical companies about possible collaborations, licensing and/or other ways in which the companies may work together to further our respective long-term objectives. In addition, many larger established pharmaceutical companies consider companies at similar stages of development to ours as potential acquisition targets. Occasionally, a transaction in the biotech/biopharmaceutical industry may start as a licensing transaction, but ultimately result in an acquisition. In certain scenarios, the potential for merger or being acquired may be in the best interests of our stockholders. As further described on page 65, we adopted a Change in Control and Severance Benefit Plan to provide certain economic benefits to our executive officers if their employment is terminated in certain circumstances, including as a result of a transaction that results in a change in control of the Company.

Tax and Accounting Considerations

Under Section 162(m) of the Internal Revenue Code (“Section 162(m)”), compensation paid to any publicly held corporation’s “covered employees” that exceeds \$1 million per taxable year for any covered employee is generally non-deductible.

Prior to the enactment of the Tax Cuts and Jobs Act, Section 162(m) provided a performance-based compensation exception, pursuant to which the deduction limit under Section 162(m) did not apply to any compensation that qualified as “performance-based compensation” under Section 162(m). Pursuant to the Tax Cuts and Jobs Act, the performance-based compensation exception under Section 162(m) was repealed with respect to taxable years beginning after December 31, 2017, except that certain transition relief is provided for compensation paid pursuant to a written binding contract that was in effect on November 2, 2017, and that is not modified in any material respect on or after such date.

Compensation paid to each of the Company’s “covered employees” in excess of \$1 million per taxable year generally will not be deductible unless it qualifies for the performance-based compensation exception under Section 162(m) pursuant to the transition relief described above. Because of certain ambiguities and uncertainties

regarding the application and interpretation of Section 162(m), as well as other factors beyond the control of the Compensation Committee, there is no guarantee that any compensation paid by the Company will be eligible for such transition relief and be deductible by the Company in the future. Although the Compensation Committee will continue to consider tax implications as one factor in determining executive compensation, the Compensation Committee also looks at other factors in making its decisions and retains the flexibility to provide compensation for the Company's named executive officers in a manner consistent with the goals of the Company's executive compensation program and the best interests of the Company and its stockholders, which may include providing for compensation that is not deductible by the Company due to the deduction limit under Section 162(m). The Compensation Committee also retains the flexibility to modify compensation that was initially intended to be exempt from the deduction limit under Section 162(m) if it determines that such modifications are consistent with the Company's business needs.

Under FASB Topic ASC 718 ("ASC 718"), the Company is required to estimate and record an expense for each award of equity compensation over the vesting period of the award. We record share-based compensation expense on an ongoing basis according to ASC 718.

Compensation of Executive Officers

The following table shows for the fiscal years ended December 31, 2019, 2018, and 2017, compensation awarded to or paid to, or earned by, our Chief Executive Officer, Chief Financial Officer, and our three other most highly compensated executive officers at December 31, 2019, called our "named executive officers."

Summary Compensation Table

Name and Principal Position	Year	Salary (\$)	Bonus ⁽¹⁾ (\$)	Stock Awards ⁽²⁾⁽³⁾ (\$)	Option Awards ⁽²⁾ (\$)	All Other Compensation ⁽⁴⁾ (\$)	Total (\$)
Stanley T. Crooke ⁽⁵⁾ Chairman, President, Chief Executive Officer	2019	\$911,506	\$ 925,748	\$3,712,677	\$3,911,301	\$137,598	\$9,598,830
	2018	\$883,242	\$ 759,257	\$1,870,630	\$4,073,394	\$ 39,056	\$7,625,579
	2017	\$849,271	\$1,006,068	\$1,306,509	\$4,113,250	\$ 39,554	\$7,314,652
Elizabeth L. Hougen Senior Vice President, Finance and Chief Financial Officer	2019	\$479,880	\$ 299,925	\$1,289,352	\$1,358,319	\$ 54,382	\$3,481,858
	2018	\$448,363	\$ 245,985	\$ 645,931	\$1,406,573	\$ 47,214	\$2,794,066
	2017	\$425,224	\$ 264,064	\$ 362,454	\$1,141,147	\$ 38,887	\$2,231,776
Brett Monia ⁽⁶⁾ Chief Operating Officer	2019	\$527,850	\$ 395,888	\$2,664,113	\$2,806,646	\$133,466	\$6,527,963
	2018	\$508,124	\$ 351,900	\$1,042,207	\$2,331,712	\$ 41,756	\$4,275,699
	2017	\$443,480	\$ 335,271	\$ 384,720	\$1,211,167	\$ 38,254	\$2,412,892
Richard S. Geary Senior Vice President, Development	2019	\$491,186	\$ 294,712	\$1,499,030	\$1,579,251	\$ 43,896	\$3,908,075
	2018	\$474,576	\$ 261,966	\$ 687,390	\$1,496,862	\$ 48,403	\$2,969,196
	2017	\$456,323	\$ 320,339	\$ 362,454	\$1,141,147	\$ 31,219	\$2,311,482
Patrick R. O'Neil Senior Vice President, Legal, General Counsel and Corporate Secretary	2019	\$483,052	\$ 289,831	\$1,289,352	\$1,358,319	\$ 43,347	\$3,463,901
	2018	\$468,074	\$ 236,845	\$ 646,144	\$1,407,061	\$ 37,090	\$2,795,214
	2017	\$454,000	\$ 294,192	\$ 362,454	\$1,141,147	\$ 31,851	\$2,283,644

- (1) We present bonuses in the years they were earned, not in the year paid. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; for example, in January 2020 we paid bonuses for 2019 performance.
- (2) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock and option awards granted to our named executive officers. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 4, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2019 regarding assumptions underlying valuation of equity awards.
- (3) Stock awards for our named executive officers increased in 2019 due primarily to a shift in allocation of option equivalents from 75% stock options/25% RSUs to 60% stock options/40% RSUs.

- (4) Includes AD&D, Basic Life, Medical, Dental, Vision and 401(k) matching contributions, which are available to all employees. For Drs. Crooke and Monia, also includes a Lifetime Achievement Award and Commitment to Ionis Award for 2019.
- (5) As of January 2020, Dr. Crooke transitioned to Executive Chairman of the Board.
- (6) As of January 2020, Dr. Brett Monia became Chief Executive Officer.

Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2019, certain information regarding grants of plan-based awards to our named executive officers:

Grants of Plan-Based Awards in Fiscal 2019

Name	Grant Date	All Other Stock Awards: Number of Shares of Stock or Units (#)	All Other Option Awards: Number of Securities Underlying Options (#)	Exercise or Base Price of Option Awards (\$/Sh)	Grant Date Fair Value of Stock and Option Awards ⁽¹⁾ (\$)
Stanley T. Crooke	1/2/19		143,400	\$53.77	\$3,911,301
	1/15/19	63,726			\$3,712,677
Elizabeth L. Hougen	1/2/19		49,800	\$53.77	\$1,358,319
	1/15/19	22,131			\$1,289,352
Brett Monia	1/2/19		102,900	\$53.77	\$2,806,646
	1/15/19	45,728			\$2,664,113
Richard S. Geary	1/2/19		57,900	\$53.77	\$1,579,251
	1/15/19	25,730			\$1,499,030
Patrick R. O'Neil	1/2/19		49,800	\$53.77	\$1,358,319
	1/15/19	22,131			\$1,289,352

- (1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock and option awards granted to our named executive Officers. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 4, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2019 regarding assumptions underlying valuation of equity awards.

Narrative to Summary Compensation Table and Grants of Plan-Based Awards Table

The Compensation Committee granted merit non-statutory stock options to the executive officers on January 2, 2019. All of these stock options were granted out of our 2011 Plan. The options have a term of seven years and vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment.

The Compensation Committee granted RSUs to the executive officers on January 15, 2019. All of these RSUs were granted out of our 2011 Plan. The RSUs vest at the rate of 25% per year over four years with a vesting commencement date of January 15, 2019.

Outstanding Equity Awards at Fiscal Year-End – Executive Officers.

The following table shows for the fiscal year ended December 31, 2019, certain information regarding outstanding equity awards at fiscal year-end for our named executive officers.

Other than the equity awards described in the table below, there were no equity incentive plan awards outstanding for our named executive officers at December 31, 2019.

Outstanding Equity Awards as of December 31, 2019

Name	Grant Date	Option Awards				Stock Awards	
		Number of Securities Underlying Unexercised Options (#) Exercisable ⁽¹⁾	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price (\$)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested ⁽²⁾	Market Value of Shares or Units of Stock that Have Not Vested ⁽³⁾ (\$)
Stanley T. Crooke	1/2/2014	27,180	—	\$39.87	1/1/2021	—	—
	1/2/2015	165,000	—	\$61.57	1/1/2022	—	—
	1/4/2016	191,115	4,067	\$61.68	1/3/2023	—	—
	1/3/2017	118,863	44,150	\$47.34	1/2/2024	—	—
	1/2/2018	75,792	82,383	\$49.25	1/1/2025	—	—
	1/2/2019	—	143,400	\$53.77	1/1/2026	—	—
	1/15/2016	—	—	—	—	8,132	\$ 491,254
	1/15/2017	—	—	—	—	13,584	\$ 820,609
	1/15/2018	—	—	—	—	26,361	\$1,592,468
	1/15/2019	—	—	—	—	63,726	\$3,849,688
Elizabeth L. Hougen	1/2/2014	45,000	—	\$39.87	1/1/2021	—	—
	1/2/2015	33,112	—	\$61.57	1/1/2022	—	—
	1/4/2016	37,443	797	\$61.68	1/3/2023	—	—
	1/3/2017	32,976	12,249	\$47.34	1/2/2024	—	—
	1/2/2018	26,172	28,447	\$49.25	1/1/2025	—	—
	1/2/2019	—	49,800	\$53.77	1/1/2026	—	—
	1/15/2016	—	—	—	—	1,593	\$ 96,233
	1/15/2017	—	—	—	—	3,768	\$ 227,625
	1/15/2018	—	—	—	—	9,102	\$ 549,852
	1/15/2019	—	—	—	—	22,131	\$1,336,934
Brett Monia	1/2/2014	45,000	—	\$39.87	1/1/2021	—	—
	1/2/2015	36,423	—	\$61.57	1/1/2022	—	—
	1/4/2016	37,443	797	\$61.68	1/3/2023	—	—
	1/3/2017	35,000	13,000	\$47.34	1/2/2024	—	—
	1/2/2018	27,852	30,273	\$49.25	1/1/2025	—	—
	1/14/2018	14,375	15,625	\$53.22	1/13/2025	—	—
	1/2/2019	—	102,900	\$53.77	1/1/2026	—	—
	1/15/2016	—	—	—	—	1,593	\$ 96,233
	1/15/2017	—	—	—	—	4,000	\$ 241,640
	1/15/2018	—	—	—	—	9,687	\$ 585,192
	1/15/2018	—	—	—	—	5,000	\$ 302,050
1/15/2019	—	—	—	—	45,728	\$2,762,428	

Name	Grant Date	Option Awards				Stock Awards	
		Number of Securities Underlying Unexercised Options (#) Exercisable ⁽¹⁾	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price (\$)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested ⁽²⁾	Market Value of Shares or Units of Stock that Have Not Vested ⁽³⁾ (\$)
Richard Geary	1/2/2014	25,000	—	\$39.87	1/1/2021	—	—
	1/2/2015	33,112	—	\$61.57	1/1/2022	—	—
	1/4/2016	37,443	797	\$61.68	1/3/2023	—	—
	1/3/2017	8,976	12,249	\$47.34	1/2/2024	—	—
	1/2/2018	27,852	30,273	\$49.25	1/1/2025	—	—
	1/2/2019	—	57,900	\$53.77	1/1/2026	—	—
	1/15/2016	—	—	—	—	1,593	\$ 96,233
	1/15/2017	—	—	—	—	3,768	\$ 227,625
	1/15/2018	—	—	—	—	9,687	\$ 585,192
1/15/2019	—	—	—	—	25,730	\$1,554,349	
Patrick R. O'Neil	1/4/2016	7,170	797	\$61.68	1/3/2023	—	—
	1/3/2017	8,576	12,249	\$47.34	1/2/2024	—	—
	1/2/2018	18,181	28,457	\$49.25	1/1/2025	—	—
	1/2/2019	—	49,800	\$53.77	1/1/2026	—	—
	1/15/2016	—	—	—	—	1,593	\$ 96,233
	1/15/2017	—	—	—	—	3,768	\$ 227,625
	1/15/2018	—	—	—	—	9,105	\$ 550,033
	1/15/2019	—	—	—	—	22,131	\$1,336,934

- (1) The options granted to our employees have a term of seven years and vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment.
- (2) The RSUs granted to our employees were granted out of our 2011 Plan. The RSUs vest at the rate of 25% per year over four years.
- (3) Market value of stock awards was determined by multiplying the number of unvested shares by \$60.41, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 31, 2019, the last trading day of fiscal 2019.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2019, certain information regarding option exercises and stock awards vesting during the last fiscal year with respect to our named executive officers:

Name	Option Awards		Stock Awards	
	Number of Shares Acquired on Exercise (#) ⁽¹⁾	Value Realized on Exercise (\$)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting (\$)
Stanley T. Crooke	177,000	\$ 5,125,547	30,587	\$1,781,999
Elizabeth L. Hougen	23,200	\$ 1,185,698	7,891	\$ 459,730
Brett Monia	—	—	10,006	\$ 582,950
Richard Geary	61,240	\$ 2,673,225	8,085	\$ 471,032
Patrick R. O'Neil	126,405	\$ 2,792,358	7,823	\$ 455,768

- (1) Each individual executed each option exercise and resulting sales pursuant to the individual's Rule 10b5-1 trading plan.

Post-Employment Compensation

Pension Benefits and Nonqualified Deferred Compensation

In January 2018, B. Lynne Parshall transitioned from our then Chief Operating Officer to a Senior Strategic Advisor to Ionis and she continues to be a member of the Board of Directors of Ionis. Ionis entered into a Strategic Advisory Services Agreement with Ms. Parshall, as amended on March 22, 2019 and January 9, 2020 (the "Amended Advisory Services Agreement"), to reflect her new role. Pursuant to such agreement, if in the future Ms. Parshall ends her board of director service for the Company, for 18 months following such date, the

Company will pay Ms. Parshall's COBRA premium payments, or if COBRA is not available, an amount equal to the cost of comparable health insurance coverage. See page 71 of this Proxy Statement for further information regarding the Amended Advisory Services Agreement.

Our executive officers are eligible to participate in our 401(k) contributory defined contribution plan. In 2019, we contributed to each participant a matching contribution equal to 100% of the first 5% of the participant's compensation he or she contributed to the plan. In 2019, the maximum matching contribution was \$14,000. The Compensation Committee can also grant discretionary contributions under our 401(k) plan. We do not provide any nonqualified defined contribution or other deferred compensation plans.

Employment Agreements

Our executive officers do not have employment contracts with us; however, they are entitled to participate in our Change of Control and Severance Benefit Plan, as described below.

Potential Payments Upon Termination or Change-of-Control

Severance and Change of Control Arrangements

On October 18, 2018, the Company implemented a Change of Control and Severance Benefit Plan (the "Plan") that provides for change of control and severance benefits to the Company's executive officers, including but not limited to the Chief Executive Officer and the Chief Financial Officer. The Plan provides that if an officer is terminated without "cause" (as defined in the Plan) or resigns for "good reason" (as defined in the Plan), except in connection with a "change in control" of the Company (as defined in the Plan), the officer will generally be entitled to receive the following severance benefits upon termination:

- A lump sum payment of the officer's then-current annual base salary (multiplied by 1.5 for the Chief Executive Officer);
- Accelerated vesting of stock options and restricted stock units previously granted by the Compensation Committee and outstanding as of the termination date that otherwise would have vested over a period of 18 months for the Chief Executive Officer and 12 months for the other executive officers; and
- Continued medical group health and dental plan coverage (for a period of 18 months for the Chief Executive Officer, and 12 months for the other executive officers).

If the officer's termination or resignation occurs during the period that begins three months before and ends twelve months following a change in control, the officer will generally be entitled to receive the following severance benefits upon termination:

- A lump sum payment of the officer's then-current annual base salary (multiplied by 1.5 for the Chief Executive Officer);
- Payment of the officer's then-current target bonus (multiplied by 1.5 for the Chief Executive Officer);
- Accelerated vesting of all stock options and restricted stock units previously granted by the Compensation Committee and outstanding as of the termination date; and
- Continued medical group health and dental plan coverage (for a period of 18 months for the Chief Executive Officer, and 12 months for the other executive officers).

Payments under the Plan will be subject to all required taxes. The Plan includes provisions for adjustment to the timing of payments to minimize accelerated or additional tax pursuant to Section 409A of the Internal Revenue Code. The Plan does not include any tax gross-up or other tax indemnity related to payments made to officers under the Plan; however, payments, benefits or distributions to or for the benefit of the officer under the Plan may be reduced if doing so would result in a more favorable after-tax position for the officer.

Conditions

As a condition to receiving benefits under the Change of Control and Severance Benefit Plan described above, the officer is required to execute and not revoke a release in favor of the Company, which release will contain standard release from liability, non-solicitation and non-disparagement provisions, and a reaffirmation of the officer's confidentiality obligations to the Company.

Estimate of Benefits under Change of Control and Severance Benefit Plan

The following table estimates the lump sum payments and health benefits that would be required to be paid to our named executive officers under the Change of Control and Severance Benefit Plan as of December 31, 2019. This table estimates the lump sum payments based upon either a termination without cause, a resignation with good reason or a termination in connection with a change of control, assuming such event occurred on December 31, 2019. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 77 of this Proxy Statement.

Name	Total – Change of Control Event	Total – Non-Change of Control Event
Stanley T. Crooke	\$2,295,531	\$1,406,813
Elizabeth L. Hougen	\$ 701,563	\$ 509,611
Brett Monia	\$ 821,506	\$ 557,581
Richard S. Geary	\$ 708,437	\$ 511,963
Patrick R. O’Neil	\$ 697,050	\$ 503,829

In addition, in the case of a termination or resignation with good reason in connection with a change of control, stock options and restricted stock units previously granted by the Compensation Committee and outstanding as of the termination date will accelerate as described above.

Director Compensation

For the fiscal year ending December 31, 2019, we paid our non-employee Directors a base cash retainer of \$55,000 with additional role-based compensation as noted below:

Role	2019 Cash Compensation
Board Member (Base)	\$55,000
Committee Chairs (Additional)	
Agenda	\$10,000
Audit	\$24,000
Compensation	\$20,000
Finance	\$20,000
Nominating, Governance and Review	\$10,000
Science/Medical	\$ 0
Committee Member (Additional)	
Agenda	\$ 5,000
Audit	\$12,000
Compensation	\$10,000
Finance	\$10,000
Nominating, Governance and Review	\$ 5,000
Science/Medical	\$10,000

If the Board creates new committees, we anticipate that the non-employee members of such new committees will receive additional compensation for their role on those committees. We do not pay Board members additional compensation for attending Board meetings, but we do reimburse them for the expenses they incur to attend the meetings.

In 2019, each non-employee Director also received automatic stock award grants under our Non-Employee Director Plan. On July 1, 2019, under the Non-Employee Director Plan, each of our non-employee Directors serving at that time received an option to purchase 16,000 shares of our common stock, at an exercise price of \$64.80 per share, the fair market value of the common stock on the date of the grant, based on the closing sales price reported on the Nasdaq Global Select Market, and an RSU award for 7,110 shares. Upon her appointment to the Board in June 2019, Ms. Herman received an option to purchase 32,000 shares of our common stock, at

an exercise price of \$63.90, the fair market value of the common stock on the date of the grant, based on the closing price reported on the Nasdaq Global Select Market, and an RSU award for 14,221 shares. The options and RSUs vest over a four-year period in equal annual installments.

The Compensation Committee reviews pay levels for non-employee Directors at least every other year with assistance from Marsh & McLennan Agency, which prepares a comprehensive assessment of Ionis' non-employee Director compensation program. That assessment includes benchmarking of director compensation against the same peer group used for executive compensation purposes, an update on recent trends in director compensation, and a review of related corporate governance best practices. The Compensation Committee reviews these assessments prior to making recommendations to the Board regarding non-employee Director compensation. As a result of such review in 2019, the Compensation Committee and Board decided it would be in the best interest of the Company to propose a reduction in the size of initial awards granted to non-employee Directors of the Company upon commencement of Board service and automatic equity awards granted to non-employee Directors of the Company each year. Under the proposed amendments to the Non-Employee Director Plan described on page 20 of this Proxy Statement, the initial and annual grants to each Director will be reduced as follows: 24,000 stock options and 10,667 RSUs for initial grants and 12,000 stock options and 5,333 RSUs for annual grants.

The following table shows for the fiscal year ended December 31, 2019 certain information with respect to the compensation of all our non-employee Directors:

Director Compensation for Fiscal 2019

Name	Cash Compensation Earned or Paid (\$)	Stock Awards (\$)(1)	Option Awards (\$)(1)	All Other Compensation (\$)(2)	Total (\$)
Spencer R. Berthelsen	\$91,250	\$ 460,728	\$ 607,645	\$ —	\$1,159,623
Breaux B. Castleman	\$67,000	\$ 460,728	\$ 607,645	\$ 15,426	\$1,150,799
Michael Hayden	\$62,500	\$ 460,728	\$ 607,645	\$ 15,246	\$1,146,299
Joan Herman	\$35,083	\$1,369,450 ⁽³⁾	\$1,821,936 ⁽³⁾	\$ —	\$3,226,469
Joseph Klein, III	\$76,000	\$ 460,728	\$ 607,645	\$ 22,074	\$1,166,447
Joseph Loscalzo	\$75,000	\$ 460,728	\$ 607,645	\$ —	\$1,143,373
Frederick T. Muto	\$80,250	\$ 460,728	\$ 607,645	\$ —	\$1,148,623
B. Lynne Parshall	\$67,500	\$ 460,728	\$ 607,645	\$1,291,989 ⁽⁴⁾	\$2,427,862
Peter N. Reikes	\$66,250	\$ 460,728	\$ 607,645	\$ —	\$1,134,623
Joseph H. Wender	\$94,750	\$ 460,728	\$ 607,645	\$ —	\$1,163,123

- (1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with ASC 718 for stock and option awards granted to the Directors. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 4, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2019 regarding assumptions underlying valuation of equity awards.
- (2) For Mr. Castleman, Dr. Hayden, Mr. Klein and Ms. Parshall, includes medical, dental and vision benefits, which are available to all employees of the Company.
- (3) Includes an initial award granted to Ms. Herman when she became a Director.
- (4) On January 15, 2018, Ms. Parshall transitioned out of her role as Chief Operating Officer and retired from Ionis after 28 years of service. Thereafter, she became a Senior Strategic Advisor to the Company and entered into the Amended Advisory Services Agreement. As a result of this transition, Ms. Parshall's "All Other Compensation" for 2019 includes consulting fees and bonuses earned under the Amended Advisory Services Agreement.

Outstanding Equity Awards at Fiscal Year-End – Directors

The following table shows for the fiscal year ended December 31, 2019, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors:

Outstanding Equity Awards as of December 31, 2019

Name	Option Awards				Stock Awards	
	Number of Securities Underlying Unexercised Options (#) Exercisable ⁽¹⁾	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price (\$)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested ^{(2) (3)}	Market Value of Shares or Units of Stock that Have Not Vested ⁽⁴⁾
Spencer R. Berthelsen	15,000	—	\$ 9.22	6/30/2020	11,775	\$711,328
	15,000	—	\$ 9.30	6/30/2021		
	11,250	—	\$12.94	7/1/2022		
	11,250	—	\$28.47	6/30/2023		
	16,000	—	\$35.53	6/30/2024		
	16,000	—	\$57.16	6/30/2025		
	12,000	4,000	\$24.42	6/30/2026		
	8,000	8,000	\$52.22	7/2/2027		
	4,000	12,000	\$42.88	7/1/2028		
—	16,000	\$64.80	6/30/2029			
Breaux B. Castleman	22,500	—	\$26.66	6/24/2023	11,775	\$711,328
	11,250	—	\$28.47	6/30/2023		
	16,000	—	\$35.53	6/30/2024		
	16,000	—	\$57.16	6/30/2025		
	12,000	4,000	\$24.42	6/30/2026		
	8,000	8,000	\$52.22	7/2/2027		
	4,000	12,000	\$42.88	7/1/2028		
	—	16,000	\$64.80	6/30/2029		
Joseph Klein, III	16,000	—	\$57.16	6/30/2025	11,775	\$711,328
	8,000	4,000	\$24.42	6/30/2026		
	8,000	8,000	\$52.22	7/2/2027		
	4,000	12,000	\$42.88	7/1/2028		
	—	16,000	\$64.80	6/30/2029		
Joseph Loscalzo	22,500	—	\$49.09	2/2/2024	11,775	\$711,328
	16,000	—	\$35.53	6/30/2024		
	16,000	—	\$57.16	6/30/2025		
	12,000	4,000	\$24.42	6/30/2026		
	8,000	8,000	\$52.22	7/2/2027		
	4,000	12,000	\$42.88	7/1/2028		
—	16,000	\$64.80	6/30/2029			
Frederick T. Muto	15,000	—	\$ 9.22	6/30/2020	11,775	\$711,328
	15,000	—	\$ 9.30	6/30/2021		
	11,250	—	\$12.94	7/1/2022		
	11,250	—	\$28.47	6/30/2023		
	16,000	—	\$35.53	6/30/2024		
	16,000	—	\$57.16	6/30/2025		
	4,000	4,000	\$24.42	6/30/2026		
	8,000	8,000	\$52.22	7/2/2027		
	4,000	12,000	\$42.88	7/1/2028		
—	16,000	\$64.80	6/30/2029			

Name	Option Awards				Stock Awards	
	Number of Securities Underlying Unexercised Options (#) Exercisable ⁽¹⁾	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price (\$)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested ^{(2) (3)}	Market Value of Shares or Units of Stock that Have Not Vested ⁽⁴⁾
Joseph H. Wender	11,250	—	\$12.94	7/1/2022	11,775	\$ 711,328
	11,250	—	\$28.47	6/30/2023		
	16,000	—	\$35.53	6/30/2024		
	16,000	—	\$57.16	6/30/2025		
	12,000	4,000	\$24.42	6/30/2026		
	8,000	8,000	\$52.22	7/2/2027		
	4,000	12,000	\$42.88	7/1/2028		
	—	16,000	\$64.80	6/30/2029		
B. Lynne Parshall ⁽⁵⁾	7,500	—	\$39.87	1/1/2021	41,321	\$2,496,202
	132,458	—	\$61.57	1/1/2022		
	105,308	2,241	\$61.68	1/3/2023		
	85,778	31,860	\$47.34	1/2/2024		
	49,630	53,945	\$49.25	1/1/2025		
	4,000	12,000	\$42.88	7/1/2028		
	—	16,000	\$64.80	6/30/2029		
Michael Hayden	8,000	24,000	\$50.80	9/18/2028	12,442	\$ 751,621
	—	16,000	\$64.80	6/30/2029		
Peter N. Reikes	8,000	24,000	\$49.14	9/21/2028	12,442	\$ 751,621
	—	16,000	\$64.80	6/30/2029		
Joan Herman	—	32,000	\$63.90	6/8/2029	21,331	\$1,288,606
	—	16,000	\$64.80	6/30/2019		

- (1) Except for the awards Ms. Parshall received when she was an employee, the options were granted out of our Non-Employee Director Plan and have a term of ten years and vest at the rate of 25% per year over four years. The options Ms. Parshall received as an employee vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter.
- (2) Except for the awards Ms. Parshall received when she was an employee, the RSUs were granted out of our Non-Employee Director Plan. Each RSU award vests at the rate of 25% per year over four years.
- (3) All of our non-employee Directors are subject to our Stock Holding and Ownership Guidelines for RSU Shares, which requires each non-employee Director to accumulate and maintain shares of common stock issued pursuant to RSUs until he or she has accumulated shares of common stock equal to four times such non-employee Director's base annual cash retainer for service as a Director (but not for service on a Board committee), or until his or her termination of service.
- (4) Market value of stock awards was determined by multiplying the number of unvested shares by \$60.41, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 31, 2019, the last trading day of fiscal year 2019.
- (5) Includes awards received by Ms. Parshall during her tenure as an executive officer of the Company.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2019, certain information regarding option exercises and stock awards vested during the last fiscal year with respect to all of our non-employee Directors:

Option Exercises and Stock Vested in Fiscal 2019

Name	Option Awards		Stock Awards	
	Number of Shares Acquired on Exercise (#)	Value Realized on Exercise (\$)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting (\$)
Spencer R. Berthelsen	15,000	\$ 710,313	2,889	\$ 188,790
Breaux B. Castleman	—	—	2,889	\$ 188,790
Joseph Klein, III	4,000	\$ 113,028	2,889	\$ 188,790
Joseph Loscalzo	—	—	2,889	\$ 188,790
Frederick T. Muto	23,000	\$1,121,192	2,889	\$ 188,790
Joseph H. Wender	—	—	2,889	\$ 188,790
B. Lynne Parshall ⁽¹⁾	66,667	\$2,300,982	21,545	\$1,262,101
Michael Hayden	—	—	1,778	\$ 109,276
Peter N. Reikes	—	—	1,778	\$ 109,276
Joan Herman	—	—	—	—

(1) Includes shares received by Ms. Parshall pursuant to awards granted during her tenure as an executive officer of the Company.

Certain Relationships and Related Transactions

We have provided some of the information below because you may find it useful when evaluating the proposals contained in this Proxy Statement. When we include a transaction in this section, we do not necessarily mean that the transaction qualifies as a related party transaction under the securities laws.

Until January 2020, Dr. Rosanne Crooke, the wife of Dr. Stanley Crooke, our Executive Chairman and former Chief Executive Officer, was one of our non-executive officers working part time at 30 hours per week. The Compensation Committee approves Dr. Rosanne Crooke's compensation. Her compensation was commensurate with the compensation of other employees at the same level at Ionis. For the fiscal years ended 2019, 2018 and 2017, she received the following compensation:

Name and Principal Position	Year	Salary (\$)	Bonus ⁽¹⁾ (\$)	Stock Awards ⁽²⁾ (\$)	Option Awards ⁽²⁾ (4) (\$)	All Other Compensation ⁽³⁾ (\$)	Total (\$)
Rosanne Crooke VP, Cardiovascular Diseases Drug Discovery Research	2019	\$252,199	\$113,490	\$310,642	\$327,305	\$45,583	\$1,049,220
	2018	\$244,142	\$101,075	\$208,143	\$453,320	\$12,889	\$1,019,569
	2017	\$235,658	\$114,530	\$129,458	\$407,684	\$12,785	\$ 900,115

- (1) We present bonuses in the years they were earned, not in the year paid. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; for example, in January 2020 we paid bonuses for 2019 performance.
- (2) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with ASC 718 for stock and option awards granted to Dr. Rosanne Crooke. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 4, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2019 regarding assumptions underlying valuation of equity awards.
- (3) Includes AD&D, Basic Life, and 401(k) matching contributions, which are available to all employees of the Company.
- (4) These amounts represent the estimated fair values of stock option grants we recognized as share-based compensation expense. The estimated fair value amounts were determined using an option-pricing model and are not indicative of whether Dr. Rosanne Crooke will realize the estimated fair value or any financial benefits from the award. The applicable amounts represent:
- 16,157 shares at \$47.34 per share received on January 3, 2017;
 - 17,603 shares at \$49.25 per share received on January 2, 2018; and
 - 12,477 shares at \$60.89 per share received on January 2, 2019.

One of our Directors, Mr. Muto, who was elected to the Board in March 2001, is senior counsel at Cooley LLP, our outside legal counsel. We paid Cooley LLP an aggregate of approximately \$1.5 million in fees in 2019 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2019 fiscal year. Notably, Mr. Muto is no longer a partner at Cooley.

B. Lynne Parshall, who was employed by Ionis for 28 years, became a Senior Strategic Advisor to the Company effective January 2018. Under the Amended Advisory Services Agreement, Ms. Parshall provides strategic advisory services to the Company, including in strategic planning, business development, and with the Company's important relationships with Biogen and Akcea. Pursuant to the Amended Advisory Services Agreement, Ms. Parshall received consulting fees of \$1,276,563 (including bonuses to recognize the significant value Ms. Parshall contributes to the Company) for services provided in 2019. The Audit Committee of the Board approved the Amended Advisory Services Agreement, and the Compensation Committee of the Board approved Ms. Parshall's consideration under the Amended Advisory Services Agreement, including her bonuses.

Ms. Parshall also serves on the boards of directors of the Company and Akcea. Ms. Parshall receives for her board service the same compensation as the Company and Akcea provide their other non-employee Directors. If in the future Ms. Parshall ends her board of director service for the Company, for 18 months following such date, the Company will pay Ms. Parshall's COBRA premium payments, or if COBRA is not available, an amount equal to the cost of comparable health insurance coverage. The Amended Advisory Services Agreement will continue until termination by us or Ms. Parshall upon 120 days' advance written notice.

One of our Directors, Peter Reikes, is a Vice Chairman in the Investment Banking Division at Stifel, Nicolaus & Company, Inc., a firm we engage from time to time for investment banking services. We paid Stifel an aggregate of approximately \$1 million in 2019, which amount is substantially less than 5% of Stifel's gross revenues for its 2019 fiscal year.

In late 2019, the n-Lorem Foundation, a non-profit organization, was formed to provide advanced, experimental RNA-targeted medicines free of charge for life to patients living with ultra-rare diseases. The n-Lorem Foundation was established with an initial investment by our Executive Chairman of the Board and former Chief Executive Officer, Dr. Stanley Crooke, and his wife, Dr. Rosanne Crooke. The Company made a donation of \$1.5 million to support the launch of the n-Lorem Foundation. Several of the Company's Directors, including Dr. Crooke, Ms. Parshall, Dr. Berthelsen, Dr. Hayden and Dr. Loscalzo, also serve as Directors for the n-Lorem Foundation. Additionally, Mr. O'Neil, our SVP, General Counsel and Corporate Secretary, serves as the Corporate Secretary for the n-Lorem Foundation. None of our executive officers or Directors is compensated for his or her service to the n-Lorem Foundation.

We have entered into indemnity agreements with each of our executive officers and Directors and certain non-executive officers which provide, among other things, that we will indemnify such officer or Director, under the circumstances and to the extent provided for therein, for expenses, damages, judgments, fines and settlements he or she may be required to pay in actions or proceedings which he or she is or may be made a party by reason of his or her position as a Director, officer or other agent of Ionis, and otherwise to the fullest extent permitted under Delaware law and our bylaws. Our bylaws provide that we will indemnify our Directors and executive officers to the fullest extent not prohibited by Delaware law or any other applicable law, except that we will generally not be required to indemnify a Director or executive officer in connection with any proceeding initiated by such Director or executive officer.

Policies and Procedures Regarding Related Party Transactions

A committee of the Board composed entirely of independent Directors approves transactions with related persons, as defined under SEC regulations. The Compensation Committee approves all compensation we pay to employees who may qualify as related persons, and the Audit Committee approves all other related party transactions, as specified in its charter.

For transactions that do not qualify as related party transactions, but may otherwise present a conflict of interest, our Code of Ethics and Business Conduct requires the Board (for our executive officers and Directors) or the Chief Executive Officer or Chief Operating Officer (for non-executive officers) to determine that no conflict of interest exists.

Our written policies and procedures specifically prohibit personal loans to our executive officers and any officer with a title of Vice President or higher.

CEO Pay Ratio

Under SEC rules, we disclose below the annual total compensation of our median employee, and the ratio of the annual total compensation of our CEO compared to the annual total compensation of our median employee ("CEO Pay Ratio"). We identified our median employee in 2018 using the following methodology:

- We included all employees of Ionis or our affiliate, Akcea, who were employed by us on December 31, 2018.
- We identified our median employee from this employee population based on the W-2 income (for U.S.-based employees) and W-2-equivalent income (for non-U.S.-based employees) for 2018. For non-U.S.-based employees, we converted foreign currency amounts using the exchange rates in effect as of December 31, 2018, consistent with the preparation of our financial statements. We did not annualize any of these amounts.

Using this approach, we determined our median employee for 2018. We used the same employee as our median employee for 2019, as there have not been changes to our employee population or employee compensation arrangements that we reasonably believe would significantly affect our pay ratio disclosure. Using the median employee from 2018, we calculated the annual total compensation of this employee for 2019 in accordance with the requirements of the Summary Compensation Table.

For 2019, the median of the annual total compensation of our employees (other than our CEO) was \$270,956 and the annual total compensation of our CEO, as reported in the Summary Compensation Table included in this Proxy Statement, was \$9,598,830. Based on this information, the ratio of the annual total compensation of our CEO to the median of the annual total compensation of all employees was 35 to 1.

The CEO Pay Ratio above represents our reasonable estimate calculated in a manner consistent with SEC rules and applicable guidance. SEC rules and guidance provide significant flexibility in how companies identify the median employee, and each company may use a different methodology and make different assumptions particular to that company. As a result, and as explained by the SEC when it adopted these rules, in considering the pay ratio disclosure, stockholders should keep in mind that the rule was not designed to facilitate comparisons of pay ratios among different companies, even companies within the same industry, but rather to allow stockholders to better understand and assess each particular company's compensation practices and pay ratio disclosures.

Currently, neither the Compensation Committee nor our management used the CEO Pay Ratio described above to make compensation decisions. The Compensation Committee does, however, consider the cash pay ratios described on page [42](#) of this Proxy Statement when making compensation decisions.

COMPENSATION COMMITTEE REPORT*

The Compensation Committee has:

- reviewed and discussed the Compensation Discussion and Analysis included in this Proxy Statement with management; and
- based on this review and discussion, the Compensation Committee recommended to the Board of Directors that the Compensation Discussion and Analysis be included in our Proxy Statement relating to the 2020 Annual Meeting of Stockholders.

The Compensation Committee

Spencer R. Berthelsen, *Chairman*

Frederick T. Muto

Joseph H. Wender

- * This Section is not “soliciting material,” is not deemed filed with the SEC and is not to be incorporated by reference in any filing of Ionis under the Securities Act or the Exchange Act.

AUDIT COMMITTEE REPORT*

The Audit Committee is made up entirely of independent Directors and operates under a written charter that has been adopted by the Board of Directors and is reviewed annually. During fiscal year 2019, the Audit Committee fulfilled its duties and responsibilities as outlined in the charter. At its meetings, the Audit Committee meets as a group with members of the Company's financial management, the independent auditors, and the internal auditors (a function that was enhanced in 2019). In addition, the Audit Committee regularly holds separate, private, executive sessions with senior management, the independent auditors, and internal audit team to discuss applicable audit matters and provide oversight.

The Audit Committee oversees our financial reporting process on behalf of the Board of Directors. Management has the primary responsibility for the financial statements and the financial reporting process, including the systems of internal controls. In fulfilling its oversight responsibilities, the Audit Committee reviewed the audited consolidated financial statements and the related schedules in our Annual Report on Form 10-K for the fiscal year ended December 31, 2019 with management, including a discussion of the quality, not just the acceptability, of the accounting principles, the reasonableness of significant judgments, and the clarity of disclosures in the financial statements.

The Audit Committee reviewed with our independent registered public accounting firm, who are responsible for expressing an opinion on the conformity of our audited consolidated financial statements with U.S. generally accepted accounting principles, their judgments as to the quality, not just the acceptability, of our accounting principles and any other matters as are required to be discussed with the Audit Committee under Public Company Accounting Oversight Board (United States) (PCAOB) standards. In addition, the Audit Committee has discussed with the independent auditors, the auditors' independence from management and Ionis, including the matters in the written disclosures required by PCAOB Rule 3526. The Audit Committee received from Ernst & Young LLP written disclosure and the letter regarding its independence as required by applicable requirements of the Public Company Accounting Oversight Board regarding Ernst & Young LLP's communications with the Audit Committee concerning independence. The Audit Committee also discussed with our independent auditors the matters required by Auditing Standard No. 1301, *Communications with Audit Committees*, issued by the PCAOB.

The Audit Committee also reviewed and discussed together with management and the independent auditors the audited consolidated financial statements for the fiscal year ended December 31, 2019, and the results of management's assessment of the effectiveness of the Company's internal control over financial reporting and the independent auditor's audit of internal control over financial reporting.

The Audit Committee discussed with our independent auditors the overall scope and plans for their audit. The Audit Committee met with the independent auditors, with and without management present, to discuss the results of their examinations, their evaluations of our internal controls, including internal control over financial reporting, and the overall quality of our financial reporting.

In reliance on the reviews and discussions referred to above, the Audit Committee recommended to the Board of Directors, and the Board has approved, that the audited financial statements be included in our Annual Report on Form 10-K for the fiscal year ended December 31, 2019 for filing with the SEC. The Audit Committee and the Board have also recommended, subject to stockholder approval, the selection of Ernst & Young LLP as our independent auditors for 2020.

The Audit Committee

Joseph Klein, III, *Chairman*

Breaux B. Castleman

Joan Herman

Frederick T. Muto

* This Section is not "soliciting material," is not deemed filed with the SEC and is not to be incorporated by reference in any filing of Ionis under the Securities Act or the Exchange Act.

HOUSEHOLDING OF PROXY MATERIALS

The SEC has adopted rules that permit companies and intermediaries (e.g. brokers) to satisfy the delivery requirements for Notice Regarding the Availability of Proxy Materials with respect to two or more stockholders sharing the same address by delivering a single Notice Regarding the Availability of Proxy Materials addressed to those stockholders. This process, which is commonly referred to as “householding,” potentially means extra convenience for stockholders and cost savings for companies.

This year, a number of brokers with account holders who are our stockholders will be “householding” our proxy materials. A single Notice Regarding the Availability of Proxy Materials will be delivered to multiple stockholders sharing an address unless contrary instructions have been received from the affected stockholders. Once you have been notified by your broker that they will be “householding” communications to your address, “householding” will continue until you are notified otherwise or until you revoke your consent. If, at any time, you no longer wish to participate in “householding” and would prefer to receive a separate Notice Regarding the Availability of Proxy Materials, please notify your broker and direct your written request to Ionis Pharmaceuticals, Inc., Attn: Corporate Secretary, 2855 Gazelle Court, Carlsbad, California 92010, or contact our stock administrator at (760) 931-9200, and we will promptly provide you a separate Notice Regarding the Availability of Proxy Materials. Stockholders who currently receive multiple copies of the Proxy Statement or Notice Regarding the Availability of Proxy Materials at their address and would like to request “householding” of their communications should contact their broker.

Other Matters

The Board of Directors knows of no other matters that will be presented for consideration at the Annual Meeting. If any other issues are properly brought before the meeting, we will ask our proxy holders to vote on the matters using their best judgment.

For further information about Ionis Pharmaceuticals, Inc., please request a free copy of our Annual Report on Form 10-K for the year ended December 31, 2019 that we filed with the SEC. Please send written requests to:

**Patrick R. O’Neil, Corporate Secretary
Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010**

You may also visit our website (www.ionispharma.com¹⁴) to view our 2019 Annual Report on Form 10-K. The Annual Report on Form 10-K is not incorporated into this Proxy Statement and is not considered soliciting material.

By Order of the Board of Directors,

Patrick R. O’Neil
Corporate Secretary

April 24, 2020

¹⁴ Any information that is included on or linked to our website is not part of this Proxy Statement or any registration statement or report that incorporates this Proxy Statement by reference.

Special Note Regarding Forward-Looking Statements

This Proxy Statement and the information incorporated herein by reference includes forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen) and our technologies and products in development, including the business of Akcea Therapeutics, Inc., our majority-owned affiliate. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2019, which is on file with the SEC. Copies of the 10-K and other documents are available from the Company.

In this Proxy Statement, unless the context requires otherwise, “Ionis,” “Company,” “we,” “our,” and “us” refers to Ionis Pharmaceuticals, Inc. and its subsidiaries.

“Ionis,” the Ionis logo, and other trademarks or service marks of Ionis Pharmaceuticals, Inc. appearing in this Proxy Statement are the property of Ionis Pharmaceuticals, Inc. “Akcea,” the Akcea logo, and other trademarks or service marks of Akcea Therapeutics, Inc. appearing in this Proxy Statement are the property of Akcea Therapeutics, Inc. This Proxy Statement contains additional trade names, trademarks and service marks of others, which are the property of their respective owners. Solely for convenience, trademarks and trade names referred to in this Proxy Statement may appear without the ® or TM symbols.

AMENDED AND RESTATED

2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

ADOPTED BY THE BOARD OF DIRECTORS SEPTEMBER 11, 2001
APPROVED BY STOCKHOLDERS MAY 31, 2002
EFFECTIVE DATE: MAY 31, 2002

AMENDED: APRIL 20, 2006 (Amendment approved by Board on December 12, 2005 and April 20, 2006 and by the Stockholders on May 3, 2006)

AMENDED: JUNE 5, 2008 (Amendment approved by Board on September 13, 2007 and February 22, 2008 and by the Stockholders on June 5, 2008)

AMENDED AND RESTATED: JUNE 2, 2010 (Amendment and Restatement approved by Board on February 26, 2010 and by the Stockholders on June 2, 2010)

AMENDED AND RESTATED: JUNE 7, 2012 (Amendment and Restatement approved by Board on March 27, 2012 and by the Stockholders on June 7, 2012)

AMENDED AND RESTATED: JUNE 10, 2014 (Amendment and Restatement approved by Board on February 11, 2014 and by the Stockholders on June 10, 2014)

AMENDED AND RESTATED: JUNE 30, 2015 (Amendment and Restatement approved by Board on March 20, 2015 and by the Stockholders on June 30, 2015)

Amendment and Restatement approved by Board on
March 24, 2020

SUBJECT TO APPROVAL BY STOCKHOLDERS

1. PURPOSES.

(a) **Amendment and Restatement.** This Plan was originally an amendment and restatement of the Ionis Pharmaceuticals, Inc. 1992 Non-Employee Directors' Stock Option Plan, and is an amendment and restatement of the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan, as amended through June 30, 2015. Effective upon approval by the Company's stockholders, this Amended and Restated Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan will amend, replace and supersede the 2002 Non-Employee Director's Stock Option Plan adopted by the Company's stockholders on June 30, 2015. The amendment and restatement of the Plan shall not amend or cancel any options granted and outstanding under this Plan as of the amendment and restatement date.

(b) **Eligible Recipients.** The persons eligible to receive Stock Awards are the Non-Employee Directors of the Company.

(c) **Available Stock Awards.** The purpose of the Plan is to provide a means by which Non-Employee Directors may be given an opportunity to benefit from increases in value of the Common Stock through the granting of Stock Awards.

(d) **General Purpose.** The Company, by means of the Plan, seeks to retain the services of its Non-Employee Directors, to secure and retain the services of new Non-Employee Directors and to provide incentives for such persons to exert maximum efforts for the success of the Company and its Affiliates.

2. DEFINITIONS.

(a) **"Affiliate"** means any parent corporation or subsidiary corporation of the Company, whether now or hereafter existing, as those terms are defined in Sections 424(e) and (f), respectively, of the Code.

(b) **“Annual Grant”** means an Option and/or RSU Award granted annually to all Non-Employee Directors who meet the criteria specified in subsection 6(b) of the Plan.

(c) **“Board”** means the Board of Directors of the Company.

(d) **“Capitalization Adjustment”** has the meaning ascribed to that term in Section 12(a).

(e) **“Change in Control”** means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) any Exchange Act Person becomes the Owner, directly or indirectly, of securities of the Company representing more than 50% of the combined voting power of the Company’s then outstanding securities other than by virtue of a merger, consolidation or similar transaction and other than by a purchase of securities directly from the Company;

Notwithstanding the foregoing, a Change in Control shall not be deemed to occur solely because the level of Ownership held by any Exchange Act Person (the “Subject Person”) exceeds the percentage threshold specified above of the outstanding voting securities as a result of a repurchase or other acquisition of voting securities by the Company reducing the number of shares outstanding, *provided* that if a Change in Control would occur (but for the operation of this sentence) as a result of the acquisition of voting securities by the Company, and after such share acquisition, the Subject Person becomes the Owner of any additional voting securities (other than through a purchase directly from the Company) that, assuming the repurchase or other acquisition had not occurred, increases the percentage of the then outstanding voting securities Owned by the Subject Person over the percentage threshold specified above, then a Change in Control shall be deemed to occur.

(ii) there is consummated a merger, consolidation or similar transaction involving (directly or indirectly) the Company and, immediately after the consummation of such merger, consolidation or similar transaction, the stockholders of the Company immediately prior thereto do not Own, directly or indirectly, outstanding voting securities representing more than 50% of the combined outstanding voting power of the surviving Entity in such merger, consolidation or similar transaction or more than 50% of the combined outstanding voting power of the parent of the surviving Entity in such merger, consolidation or similar transaction;

(iii) the stockholders of the Company approve or the Board approves a plan of complete dissolution or liquidation of the Company, or a complete dissolution or liquidation of the Company shall otherwise occur;

(iv) there is consummated a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries, other than a sale, lease, license or other disposition of all or substantially all of the consolidated assets of the Company and its Subsidiaries to an Entity, more than 50% of the combined voting power of the voting securities of which are Owned by stockholders of the Company in substantially the same proportions as their Ownership of the Company immediately prior to such sale, lease, license or other disposition; or

(v) individuals who, on the date this Plan is adopted by the Board, are members of the Board (the “Incumbent Board”) cease for any reason to constitute at least a majority of the members of the Board; (*provided, however,* that if the appointment or election (or nomination for election) of any new Board member was approved or recommended by a majority vote of the members of the Incumbent Board then still in office, such new member shall, for purposes of this Plan, be considered as a member of the Incumbent Board).

Notwithstanding the foregoing or any other provision of this Plan, the definition of Change in Control (or any analogous term) in an individual written agreement between the Company or any Affiliate and the Holder shall supersede the foregoing definition with respect to Stock Awards subject to such agreement (it being understood, however, that if no definition of Change in Control or any analogous term is set forth in such an individual written agreement, the foregoing definition shall apply).

(f) **“Code”** means the Internal Revenue Code of 1986, as amended.

(g) **“Common Stock”** means the common stock of the Company.

(h) **“Company”** means Ionis Pharmaceuticals, Inc., a Delaware corporation.

(i) **“Consultant”** means any person, including an advisor, (i) engaged by the Company or an Affiliate to render consulting or advisory services and who is compensated for such services or (ii) serving as a member of

the Board of Directors of an Affiliate and who is compensated for such services. However, the term “Consultant” shall not include Directors who are not compensated by the Company for their services as Directors, and the payment of a director’s fee by the Company for services as a Director shall not cause a Director to be considered a “Consultant” for purposes of the Plan.

(j) **“Continuous Service”** means that the Holder’s service with the Company or an Affiliate, whether as an Employee, Director or Consultant, is not interrupted or terminated. A change in the capacity in which the Holder renders service to the Company or an Affiliate as an Employee, Consultant or Director or a change in the entity for which the Holder renders such service, provided that there is no interruption or termination of the Holder’s service with the Company or an Affiliate, shall not terminate a Holder’s Continuous Service. For example, a change in status from a Non-Employee Director of the Company to a Consultant of an Affiliate or an Employee of the Company shall not constitute an interruption of Continuous Service. The Board or the chief executive officer of the Company, in that party’s sole discretion, may determine whether Continuous Service shall be considered interrupted in the case of any leave of absence approved by that party, including sick leave, military leave or any other personal leave.

(k) **“Corporate Transaction”** means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) a sale or other disposition of all or substantially all, as determined by the Board in its discretion, of the consolidated assets of the Company and its Subsidiaries;

(ii) a sale or other disposition of at least 90% of the outstanding securities of the Company;

(iii) a merger, consolidation or similar transaction following which the Company is not the surviving corporation; or

(iv) a merger, consolidation or similar transaction following which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger, consolidation or similar transaction are converted or exchanged by virtue of the merger, consolidation or similar transaction into other property, whether in the form of securities, cash or otherwise.

(l) **“Director”** means a member of the Board of Directors of the Company.

(m) **“Disability”** means the permanent and total disability of a person within the meaning of Section 22(e)(3) of the Code.

(n) **“Employee”** means any person employed by the Company or an Affiliate. Service as a Director or payment of a director’s fee by the Company or an Affiliate shall not be sufficient to constitute “employment” by the Company or an Affiliate.

(o) **“Entity”** means a corporation, partnership or other entity.

(p) **“Exchange Act”** means the Securities Exchange Act of 1934, as amended.

(q) **“Exchange Act Person”** means any natural person, Entity or “group” (within the meaning of Section 13(d) or 14(d) of the Exchange Act), except that “Exchange Act Person” shall not include (A) the Company or any Subsidiary of the Company, (B) any employee benefit plan of the Company or any Subsidiary of the Company or any trustee or other fiduciary holding securities under an employee benefit plan of the Company or any Subsidiary of the Company, (C) an underwriter temporarily holding securities pursuant to an offering of such securities, or (D) an Entity Owned, directly or indirectly, by the stockholders of the Company in substantially the same proportions as their Ownership of stock of the Company.

(r) **“Fair Market Value”** means, as of any date, the value of the Common Stock determined as follows:

(i) If the Common Stock is listed on any established stock exchange or traded on the Nasdaq National Market or the Nasdaq SmallCap Market, the Fair Market Value of a share of Common Stock shall be the closing sales price for such stock (or the closing bid, if no sales were reported) as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the last market trading day prior to the day of determination, as reported in The Wall Street Journal or such other source as the Board deems reliable.

(ii) In the absence of such markets for the Common Stock, the Fair Market Value shall be determined in good faith by the Board.

(s) **“Holder”** means a person to whom an Option or RSU Award is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Option or RSU Award.

(t) **“Initial Grant”** means an Option and/or RSU granted to a Non-Employee Director who meets the criteria specified in subsection 6(a) of the Plan.

(u) **“Non-Employee Director”** means a Director who is not an Employee.

(v) **“Nonstatutory Stock Option”** means an Option not intended to qualify as an incentive stock option within the meaning of Section 422 of the Code and the regulations promulgated thereunder.

(w) **“Officer”** means a person who is an officer of the Company within the meaning of Section 16 of the Exchange Act and the rules and regulations promulgated thereunder.

(x) **“Option”** means a Nonstatutory Stock Option granted pursuant to the Plan.

(y) **“Option Agreement”** means a written agreement between the Company and a Holder evidencing the terms and conditions of an individual Option grant. Each Option Agreement shall be subject to the terms and conditions of the Plan.

(z) **“Own,” “Owned,” “Owner,” “Ownership”** A person or Entity shall be deemed to “Own,” to have “Owned,” to be the “Owner” of, or to have acquired “Ownership” of securities if such person or Entity, directly or indirectly, through any contract, arrangement, understanding, relationship or otherwise, has or shares voting power, which includes the power to vote or to direct the voting, with respect to such securities.

(aa) **“Plan”** means this Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan, which is an amendment and restatement of the Ionis Pharmaceuticals, Inc. 1992 Non-Employee Directors’ Stock Option Plan.

(bb) **“RSU Award”** means a right to receive shares of Common Stock which is granted pursuant to the terms and conditions of Section 8.

(cc) **“RSU Award Agreement”** means a written agreement between the Company and a holder of a RSU Award evidencing the terms and conditions of a RSU Award grant. Each RSU Award Agreement shall be subject to the terms and conditions of the Plan.

(dd) **“Rule 16b-3”** means Rule 16b-3 promulgated under the Exchange Act or any successor to Rule 16b-3, as in effect from time to time.

(ee) **“Securities Act”** means the Securities Act of 1933, as amended.

(ff) **“Stock Award”** means an Option or RSU Award, as applicable.

(gg) **“Subsidiary”** means, with respect to the Company, (i) any corporation of which more than 50% of the outstanding capital stock having ordinary voting power to elect a majority of the board of directors of such corporation (irrespective of whether, at the time, stock of any other class or classes of such corporation shall have or might have voting power by reason of the happening of any contingency) is at the time, directly or indirectly Owned by the Company, and (ii) any partnership in which the Company has a direct or indirect interest (whether in the form of voting or participation in profits or capital contribution) of more than 50%.

3. ADMINISTRATION.

(a) **Administration by Board.** The Board shall administer the Plan. The Board may delegate administration of the Plan to a committee. If delegated to a committee, references to the Board will include a reference to the committee, as applicable.

(b) **Powers of Board.** The Board shall have the power, subject to, and within the limitations of, the express provisions of the Plan:

(i) To determine the provisions of each Stock Award to the extent not specified in the Plan.

(ii) To construe and interpret the Plan and Stock Awards granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any

defect, omission or inconsistency in the Plan or in any Option Agreement or RSU Agreement, in a manner and to the extent it shall deem necessary or expedient to make the Plan fully effective.

(iii) To amend the Plan or a Stock Award as provided in Section 13.

(iv) To terminate or suspend the Plan as provided in Section 14.

(v) Generally, to exercise such powers and to perform such acts as the Board deems necessary or expedient to promote the best interests of the Company and that are not in conflict with the provisions of the Plan.

(c) **Effect of Board's Decision.** All determinations, interpretations and constructions made by the Board in good faith shall not be subject to review by any person and shall be final, binding and conclusive on all persons.

(d) **Arbitration.** Any dispute or claim concerning any Stock Award granted (or not granted) pursuant to the Plan or any disputes or claims relating to or arising out of the Plan shall be fully, finally and exclusively resolved by binding arbitration conducted pursuant to the Commercial Arbitration Rules of the American Arbitration Association in San Diego, California. The Company shall pay all arbitration fees. In addition to any other relief, the arbitrator may award to the prevailing party recovery of its attorney's fees and costs. By accepting a Stock Award, Holders and the Company waive their respective rights to have any such disputes or claims tried by a judge or jury.

4. SHARES SUBJECT TO THE PLAN.

(a) **Share Reserve.** Subject to the provisions of Section 12(a) relating to Capitalization Adjustments, the Common Stock that may be issued pursuant to Stock Awards shall not exceed in the aggregate **2,800,000** shares of Common Stock.

(b) **Reversion of Shares to the Share Reserve.** If any Stock Award shall for any reason expire or otherwise terminate, in whole or in part, without having been exercised or vested in full, the shares of Common Stock not issued under such Stock Award shall revert to and again become available for issuance under the Plan.

(c) **Source of Shares.** The shares of Common Stock subject to the Plan may be unissued shares or reacquired shares, bought on the market or otherwise.

5. ELIGIBILITY.

The Stock Awards as set forth in Section 6 of the Plan automatically shall be granted under the Plan to all Non-Employee Directors.

6. NON-DISCRETIONARY GRANTS.

(a) **Initial Grants.** Without any further action of the Board, each person who is elected or appointed for the first time after the Company's stockholders approve this amendment and restatement of the Plan to be a Non-Employee Director shall automatically be granted, on the terms and conditions set forth herein, an Initial Grant of Option and RSU Awards as follows:

(i) An Option to purchase 24,000 shares of Common Stock; and

(ii) An RSU Award of 10,667 RSUs.

(iii) The grant date for such initial options will be the date the Non-Employee Director was elected or appointed by the Board or stockholders of the Company, as applicable. The grant date for such initial RSU Awards will be the 15th of the month following the end of the quarter in which such Non-Employee Director was elected or appointed by the Board or stockholders of the Company, as applicable.

(b) **Annual Grants.** Without any further action of the Board, after the effective date of this amendment and restatement of the Plan, a Non-Employee Director shall be granted an Annual Grant as follows: On July 1 of each year, beginning on July 1, 2020, each person who is then a Non-Employee Director automatically shall be granted, on the terms and conditions set forth herein, an Annual Grant of Option and RSU Awards as follows:

(i) An Option to purchase 12,000 shares of Common Stock; and

(ii) An RSU Award of 5,333 RSUs.

7. OPTION PROVISIONS.

Each Option shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. Each Option shall include (through incorporation of provisions hereof by reference in the Option or otherwise) the substance of each of the following provisions:

(a) **Term.** No Option shall be exercisable after the expiration of 10 years from the date it was granted.

(b) **Exercise Price.** The exercise price of each Option shall be 100% of the Fair Market Value of the Common Stock subject to the Option on the date the Option is granted. Notwithstanding the foregoing, an Option may be granted with an exercise price lower than that set forth in the preceding sentence if such Option is granted pursuant to an assumption or substitution for another option in a manner satisfying the provisions of Section 424(a) of the Code.

(c) **Consideration.** The purchase price of Common Stock acquired pursuant to the exercise of an Option shall be paid, to the extent permitted by applicable law, by any combination of the following methods of payment:

(i) by cash, check, bank draft or money order payable to the Company; or

(ii) pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board that, prior to the issuance of the stock subject to the Option, results in either the receipt of cash (or check) by the Company or the receipt of irrevocable instructions to pay the aggregate exercise price to the Company from the sales proceeds.

(d) **Transferability.** An Option will not be transferable except as determined by the Board.

(e) **Exercise Schedule.** The Option shall be exercisable as the shares of Common Stock subject to the Option vest.

(f) **Vesting Schedule.** The Option shall vest and become exercisable as follows:

(i) **Initial Grants:** 100% of the shares subject to the Option shall vest on the annual anniversary of the date of grant, provided that the Holder has, during the entire year prior to such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate, whereupon such option shall become fully exercisable in accordance with its terms with respect to that portion of the shares represented by that installment.

(ii) **Annual Grants:** 100% of the shares subject to the Option shall vest on (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier, provided that the Holder has, during the entire period from the date of grant through such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate, whereupon such option shall become fully exercisable in accordance with its terms with respect to that portion of the shares represented by that installment.

(g) **Termination of Continuous Service.** In the event that an Holder's Continuous Service terminates (other than upon the Holder's death or Disability), the Holder may exercise his or her Option (to the extent that the Holder was entitled to exercise such Option as of the date of termination) but only within such period of time ending on the earlier of (i) the date 3 months following the termination of the Holder's Continuous Service (or such longer or shorter period specified in the Option Agreement), or (ii) the expiration of the term of the Option as set forth in the Option Agreement. If, after termination, the Holder does not exercise his or her Option within the time specified in the Option Agreement, the Option shall terminate.

(h) **Extension of Termination Date.** An Holder's Option Agreement may also provide that if the exercise of the Option following the termination of the Holder's Continuous Service (other than upon the Holder's death or Disability) would be prohibited at any time solely because the issuance of shares of Common Stock would violate the registration requirements under the Securities Act, then the Option shall terminate on the earlier of (i) the expiration of the term of the Option set forth in subsection 7(a) or (ii) the expiration of a period of 3 months after the termination of the Holder's Continuous Service during which the exercise of the Option would not be in violation of such registration requirements. In addition, unless otherwise provided in an Holder's Option Agreement, if the immediate sale of any Common Stock received upon exercise of an Option following the termination of the Holder's Continuous Service would violate the Company's insider trading policy, then the

Option shall terminate on the earlier of (i) the expiration of a period equal to the applicable post-termination exercise period after the termination of the Holder's Continuous Service during which the sale of Common Stock received upon exercise of the Option would not be in violation of the Company's insider trading policy, or (ii) the expiration of the term of the Option as set forth in the applicable Option Agreement.

(i) Disability of Holder. In the event that an Holder's Continuous Service terminates as a result of the Holder's Disability, the Holder may exercise his or her Option (to the extent that the Holder was entitled to exercise such Option as of the date of termination), but only within such period of time ending on the earlier of (i) the date 12 months following such termination (or such longer or shorter period specified in the Option Agreement) or (ii) the expiration of the term of the Option as set forth in the Option Agreement. If, after termination, the Holder does not exercise his or her Option within the time specified herein, the Option shall terminate.

(j) Death of Holder. In the event that (i) an Holder's Continuous Service terminates as a result of the Holder's death or (ii) the Holder dies within the period (if any) specified in the Option Agreement after the termination of the Holder's Continuous Service for a reason other than death, then the Option may be exercised (to the extent the Holder was entitled to exercise such Option as of the date of death) by the Holder's estate, by a person who acquired the right to exercise the Option by bequest or inheritance or by a person designated to exercise the Option upon the Holder's death pursuant to subsection 7(d), but only within the period ending on the earlier of (1) the date 18 months following the date of death (or such longer or shorter period specified in the Option Agreement) or (2) the expiration of the term of such Option as set forth in the Option Agreement. If, after death, the Option is not exercised within the time specified herein, the Option shall terminate.

8. RESTRICTED STOCK UNIT PROVISIONS.

Each Restricted Stock Unit Award Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The terms and conditions of Restricted Stock Unit Award Agreements may change from time to time, and the terms and conditions of separate Restricted Stock Unit Award Agreements need not be identical; *provided, however*, that each Restricted Stock Unit Award Agreement shall conform to (through incorporation of the provisions hereof by reference in the Agreement or otherwise) the substance of each of the following provisions:

(a) Consideration. At the time of grant of a Restricted Stock Unit Award, the Board will determine the consideration, if any, to be paid by the Holder upon delivery of each share of Common Stock subject to the Restricted Stock Unit Award. The consideration to be paid (if any) by the Holder for each share of Common Stock subject to a Restricted Stock Unit Award may be paid in any form of legal consideration that may be acceptable to the Board, in its sole discretion, and permissible under applicable law.

(b) Vesting. Each RSU Award under this Plan shall vest as follows:

(i) Initial Grants: 100% of the shares subject to the RSU shall vest on the annual anniversary of the date of grant, provided that the Holder has, during the entire year prior to such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate.

(ii) Annual Grants: 100% of the shares subject to the RSU shall vest on (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier, provided that the Holder has, during the entire period from the date of grant through such vesting date, continuously served as a Non-Employee Director or as an Employee of or Consultant to the Company or any Affiliate; provided such RSU Awards, once vested, will be settled on the July 15th following the vesting date.

(c) Payment. A Restricted Stock Unit Award may be settled by the delivery of shares of Common Stock, their cash equivalent, any combination thereof or in any other form of consideration, as determined by the Board and contained in the Restricted Stock Unit Award Agreement.

(d) Additional Restrictions. At the time of the grant of a Restricted Stock Unit Award, the Board, as it deems appropriate, may impose such restrictions or conditions that delay the delivery of the shares of Common Stock (or their cash equivalent) subject to a Restricted Stock Unit Award to a time after the vesting of such Restricted Stock Unit Award.

(e) Dividend Equivalents. Dividend equivalents may be credited in respect of shares of Common Stock covered by a Restricted Stock Unit Award, as determined by the Board and contained in the Restricted Stock

Unit Award Agreement. At the sole discretion of the Board, such dividend equivalents may be converted into additional shares of Common Stock covered by the Restricted Stock Unit Award in such manner as determined by the Board. Any additional shares covered by the Restricted Stock Unit Award credited by reason of such dividend equivalents will be subject to all of the same terms and conditions of the underlying Restricted Stock Unit Award Agreement to which they relate.

(f) Termination of Holder's Continuous Service. Except as otherwise provided in the applicable Restricted Stock Unit Award Agreement, such portion of the Restricted Stock Unit Award that has not vested will be forfeited upon the Holder's termination of Continuous Service.

9. COVENANTS OF THE COMPANY.

(a) Availability of Shares. During the terms of the Stock Awards, the Company shall keep available at all times the number of shares of Common Stock required to satisfy such Stock Awards.

(b) Securities Law Compliance. The Company shall seek to obtain from each regulatory commission or agency having jurisdiction over the Plan such authority as may be required to grant Stock Awards and to issue and sell shares of Common Stock upon exercise of the Stock Awards; provided, however, that this undertaking shall not require the Company to register under the Securities Act the Plan, any Stock Award or any Common Stock issued or issuable pursuant to any such Stock Award. If, after reasonable efforts, the Company is unable to obtain from any such regulatory commission or agency the authority which counsel for the Company deems necessary for the lawful issuance and sale of Common Stock under the Plan, the Company shall be relieved from any liability for failure to issue and sell Common Stock upon exercise of such Stock Awards unless and until such authority is obtained. A Non-Employee Director shall not be eligible for the grant of a Stock Award or the subsequent issuance of Common Stock pursuant to the Stock Award if such grant or issuance would violate any applicable securities law.

(c) No Obligation to Notify or Minimize Taxes. The Company shall have no duty or obligation to any Holder to advise such Holder (or the estate of, or transferee of, such Holder) as to the time or manner of exercising such Stock Award. Furthermore, the Company shall have no duty or obligation to warn or otherwise advise such Holder (or the estate of, or transferee of, such Holder) of a pending termination or expiration of a Stock Award or a possible period in which the Stock Award may not be exercised. The Company has no duty or obligation to minimize the tax consequences of a Stock Award to the Holder of such Stock Award.

10. USE OF PROCEEDS FROM STOCK.

Proceeds from the sale of Common Stock pursuant to Options or RSU Awards (if any) shall constitute general funds of the Company.

11. MISCELLANEOUS.

(a) Acceleration of Exercisability and Vesting. The Board shall have the power to accelerate the time at which a Stock Award may first be exercised or the time during which a Stock Award or any part thereof will vest in accordance with the Plan, notwithstanding the provisions in the Stock Award stating the time at which it may first be exercised or the time during which it will vest.

(b) Stockholder Rights. No Holder shall be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares of Common Stock subject to such Stock Award unless and until such Holder has satisfied all requirements for exercise of the Option or settlement of the RSU Award, as applicable, pursuant to its terms.

(c) No Service Rights. Nothing in the Plan or any instrument executed or Stock Award granted pursuant thereto shall confer upon any Holder any right to continue to serve the Company as a Non-Employee Director or shall affect the right of the Company or an Affiliate to terminate (i) the employment of an Employee with or without notice and with or without cause, (ii) the service of a Consultant pursuant to the terms of such Consultant's agreement with the Company or an Affiliate or (iii) the service of a Director pursuant to the Bylaws of the Company or an Affiliate, and any applicable provisions of the corporate law of the state in which the Company or the Affiliate is incorporated, as the case may be.

(d) Investment Assurances. The Company may require a Holder, as a condition of exercising or acquiring Common Stock under any Award, (i) to give written assurances satisfactory to the Company as to the Holder's

knowledge and experience in financial and business matters and/or to employ a purchaser representative reasonably satisfactory to the Company who is knowledgeable and experienced in financial and business matters and that he or she is capable of evaluating, alone or together with the purchaser representative, the merits and risks of exercising the Stock Award; and (ii) to give written assurances satisfactory to the Company stating that the Holder is acquiring the Common Stock subject to the Stock Award for the Holder's own account and not with any present intention of selling or otherwise distributing the Common Stock. The foregoing requirements, and any assurances given pursuant to such requirements, shall be inoperative if (1) the issuance of the shares of Common Stock upon the exercise or acquisition of Common Stock under the Stock Award has been registered under a then currently effective registration statement under the Securities Act or (2) as to any particular requirement, a determination is made by counsel for the Company that such requirement need not be met in the circumstances under the then applicable securities laws. The Company may, upon advice of counsel to the Company, place legends on stock certificates issued under the Plan as such counsel deems necessary or appropriate in order to comply with applicable securities laws, including, but not limited to, legends restricting the transfer of the Common Stock.

(e) Withholding Obligations. To the extent provided by the terms of the applicable Option Agreement or RSU Award Agreement, the Holder may satisfy any federal, state or local tax withholding obligation relating to the exercise or acquisition of Common Stock under a Stock Award by any of the following means (in addition to the Company's right to withhold from any compensation paid to the Holder by the Company) or by a combination of such means: (i) tendering a cash payment; (ii) authorizing the Company to withhold shares of Common Stock from the shares of Common Stock otherwise issuable to the Holder as a result of the exercise or acquisition of Common Stock under the Stock Award, *provided, however*, that no shares of Common Stock are withheld with a value exceeding the minimum amount of tax required to be withheld by law (or such lower amount as may be necessary to avoid variable award accounting); or (iii) delivering to the Company owned and unencumbered shares of Common Stock.

(f) Electronic Delivery. Any reference herein to a "written" agreement or document shall include any agreement or document delivered electronically or posted on the Company's intranet (or other shared electronic medium controlled by the Company to which the Holder has access).

12. ADJUSTMENTS UPON CHANGES IN STOCK.

(a) Capitalization Adjustments. If any change is made in, or other event occurs with respect to, the Common Stock subject to the Plan, or subject to any Stock Award, without the receipt of consideration by the Company (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by the Company) (each, a "Capitalization Adjustment"), the Plan will be appropriately adjusted in the class(es) and maximum number of securities subject both to the Plan pursuant to subsection 4(a) and to the nondiscretionary Stock Awards specified in Section 6, and the outstanding Stock Awards will be appropriately adjusted in the class(es) and number of securities and price per share of Common Stock subject to such outstanding Stock Awards. The Board shall make such adjustments, and its determination shall be final, binding and conclusive. (The conversion of any convertible securities of the Company shall not be treated as a transaction "without receipt of consideration" by the Company.)

(b) Dissolution or Liquidation. In the event of a dissolution or liquidation of the Company, then all outstanding Stock Awards shall terminate immediately prior to the completion of such dissolution or liquidation.

(c) Corporate Transaction. In the event of a Corporate Transaction, any surviving corporation or acquiring corporation may assume any or all Stock Awards outstanding under the Plan or may substitute similar stock awards for Stock Awards outstanding under the Plan (it being understood that similar stock awards include, but are not limited to, options to acquire, or restricted stock unit rights to receive, the same consideration paid to the stockholders or the Company, as the case may be, pursuant to the Corporate Transaction). In the event that any surviving corporation or acquiring corporation does not assume any or all such outstanding Stock Awards or substitute similar stock awards for such outstanding Stock Awards, then with respect to Stock Awards that have been neither assumed nor substituted and that are held by Holders whose Continuous Service has not terminated prior to the effective time of the Corporate Transaction, the vesting of such Stock Awards (and, if applicable, the time at which such Stock Awards may be exercised) shall (contingent upon the effectiveness of the Corporate

Transaction) be accelerated in full to a date prior to the effective time of such Corporate Transaction as the Board shall determine (or, if the Board shall not determine such a date, to the date that is 5 days prior to the effective time of the Corporate Transaction), and the Stock Awards shall terminate if not exercised at or prior to such effective time. With respect to Stock Awards outstanding under the Plan that have been neither assumed nor substituted and that are held by Holders whose Continuous Service has terminated prior to the effective time of the Corporate Transaction, the vesting of such Stock Awards (and, if applicable, the time at which such Stock Award may be exercised) shall not be accelerated unless otherwise provided in a written agreement between the Company or any Affiliate and the holder of such Stock Award, and such Stock Awards shall terminate if not exercised prior to the effective time of the Corporate Transaction.

(d) Change in Control. Notwithstanding any other provisions of the Plan to the contrary, if a Change in Control occurs and the Holder's Continuous Service has not terminated prior to the effective date of such Change in Control, then the vesting and exercisability of the shares of Common Stock subject to the Holder's Stock Awards shall be accelerated in full as of the effective date of the Change in Control. Following such Change in Control (other than a Change in Control resulting from a plan of complete dissolution or liquidation of the Company) and notwithstanding any other provision of the Plan to the contrary and provided that the Holder's Continuous Service has not terminated prior to the effective date of the Change in Control, then the Holder's Options shall expire on the earliest of (i) 12 months following the effective date of such Change in Control or (ii) the Expiration Date indicated in the Holder's Grant Notice.

(e) Parachute Payments. If any payment or benefit the Holder would receive pursuant to a Change in Control from the Company or otherwise ("Payment") would (i) constitute a "parachute payment" within the meaning of Section 280G of the Code, and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then such Payment shall be reduced to the Reduced Amount. The "Reduced Amount" shall be either (x) the largest portion of the Payment that would result in no portion of the Payment being subject to the Excise Tax or (y) the largest portion, up to and including the total, of the Payment, whichever amount, after taking into account all applicable federal, state and local employment taxes, income taxes, and the Excise Tax (all computed at the highest applicable marginal rate), results in the Holder's receipt, on an after-tax basis, of the greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax. If a reduction in a Payment is required pursuant to the preceding sentence and the Reduced Amount is determined pursuant to clause (x) of the preceding sentence, the reduction shall occur in the manner (the "**Reduction Method**") that results in the greatest economic benefit for Holder. If more than one method of reduction will result in the same economic benefit, the items so reduced will be reduced pro rata (the "**Pro Rata Reduction Method**"). Notwithstanding the foregoing, if the Reduction Method or the Pro Rata Reduction Method would result in any portion of the Payment being subject to taxes pursuant to Section 409A of the Code that would not otherwise be subject to taxes pursuant to Section 409A of the Code, then the Reduction Method and/or the Pro Rata Reduction Method, as the case may be, shall be modified so as to avoid the imposition of taxes pursuant to Section 409A of the Code as follows: (A) as a first priority, the modification shall preserve to the greatest extent possible, the greatest economic benefit for Holder as determined on an after-tax basis; (B) as a second priority, Payments that are contingent on future events (e.g., being terminated without cause), shall be reduced (or eliminated) before Payments that are not contingent on future events; and (C) as a third priority, Payments that are "deferred compensation" within the meaning of Section 409A of the Code shall be reduced (or eliminated) before Payments that are not deferred compensation within the meaning of Section 409A of the Code.

The accounting firm engaged by the Company for general audit purposes as of the day prior to the effective date of the Change in Control shall perform the foregoing calculations. If the accounting firm so engaged by the Company is serving as accountant or auditor for the individual, entity or group effecting the Change in Control, the Company shall appoint a nationally recognized accounting firm to make the determinations required hereunder. The Company shall bear all expenses with respect to the determinations by such accounting firm required to be made hereunder.

The accounting firm engaged to make the determinations hereunder shall provide its calculations, together with detailed supporting documentation, to the Holder and the Company within 15 calendar days after the date on which the Holder's right to a Payment is triggered (if requested at that time by the Holder or the Company) or such other time as requested by the Holder or the Company. If the accounting firm determines that no Excise Tax is payable with respect to a Payment, either before or after the application of the Reduced Amount, it shall

furnish the Company and the Holder with an opinion reasonably acceptable to the Holder that no Excise Tax will be imposed with respect to such Payment. Any good faith determinations of the accounting firm made hereunder shall be final, binding and conclusive upon the Holder and the Company.

13. AMENDMENT OF THE PLAN AND STOCK AWARDS.

(a) Amendment of Plan. The Board at any time, and from time to time, may amend the Plan. However, except as provided in Section 12(a) relating to Capitalization Adjustments, no amendment shall be effective unless approved by the stockholders of the Company to the extent stockholder approval is necessary to satisfy the requirements of Rule 16b-3 or any Nasdaq or securities exchange listing requirements.

(b) Stockholder Approval. The Board, in its sole discretion, may submit any other amendment to the Plan for stockholder approval.

(c) No Impairment of Rights. Rights under any Stock Award granted before amendment of the Plan shall not be impaired by any amendment of the Plan unless (i) the Company requests the consent of the Holder and (ii) the Holder consents in writing.

(d) Amendment of Stock Awards. The Board at any time, and from time to time, may amend the terms of any one or more Stock Awards; *provided, however*, that the rights under any Stock Award shall not be impaired by any such amendment unless (i) the Company requests the consent of the Holder and (ii) the Holder consents in writing.

(e) Prohibition on Reduction of Exercise Prices, Cancellation and Re-Grant of Stock Awards. Neither the Board nor any Committee (or subcommittee) shall have the authority to: (i) reduce the exercise price of any outstanding Options under the Plan, or (ii) cancel any outstanding Options that have an exercise price or strike price greater than the current Fair Market Value of the Common Stock in exchange for cash or other Stock Awards under the Plan, unless the stockholders of the Company have approved such an action within 12 months prior to such an event. Notwithstanding the foregoing, this paragraph will not be construed to apply to "issuing or assuming a stock option in a transaction to which section 424(a) applies," within the meaning of Section 424 of the Code."

14. TERMINATION OR SUSPENSION OF THE PLAN.

(a) Plan Term. The Board may suspend or terminate the Plan at any time. Unless sooner terminated, the Plan shall terminate on June 1, 2030. No Stock Awards may be granted under the Plan while the Plan is suspended or after it is terminated.

(b) No Impairment of Rights. Suspension or termination of the Plan shall not impair rights and obligations under any Stock Award granted while the Plan is in effect except with the written consent of the Holder.

15. EFFECTIVE DATE OF PLAN.

The Plan shall become effective as determined by the Board, but no Stock Award shall be exercised unless and until the Plan has been approved by the stockholders of the Company, which approval shall be within 12 months before or after the date the Plan is adopted by the Board.

16. CHOICE OF LAW.

The law of the State of California shall govern all questions concerning the construction, validity and interpretation of this Plan without regard to such state's conflict of laws rules.

IONIS PHARMACEUTICALS, INC.
 2855 GAZELLE COURT
 CARLSBAD, CALIFORNIA 92010
 ATTN: CORPORATE SECRETARY

VOTE BY INTERNET
Before The Meeting - Go to www.proxyvote.com

Use the Internet to transmit your voting instructions and for electronic delivery of information up until 11:59 p.m. Eastern Time the day before the cut-off date or meeting date. Have your proxy card in hand when you access the web site and follow the instructions to obtain your records and to create an electronic voting instruction form.

During The Meeting - Go to www.virtualshareholdermeeting.com/IONS2020

You may attend the meeting via the Internet and vote during the meeting. Have the information that is printed in the box marked by the arrow available and follow the instructions.

VOTE BY PHONE - 1-800-690-6903
 Use any touch-tone telephone to transmit your voting instructions up until 11:59 p.m. Eastern Time the day before the cut-off date or meeting date. Have your proxy card in hand when you call and then follow the instructions.

VOTE BY MAIL
 Mark, sign and date your proxy card and return it in the postage-paid envelope we have provided or return it to Vote Processing, c/o Broadridge, 51 Mercedes Way, Edgewood, NY 11717.

TO VOTE, MARK BLOCKS BELOW IN BLUE OR BLACK INK AS FOLLOWS:

D10183-P33544

KEEP THIS PORTION FOR YOUR RECORDS
 DETACH AND RETURN THIS PORTION ONLY

THIS PROXY CARD IS VALID ONLY WHEN SIGNED AND DATED.

<p>IONIS PHARMACEUTICALS, INC.</p> <p>The Board of Directors recommends you vote FOR the following nominees to be elected for a term expiring in 2023:</p> <p>1. Election of Directors</p> <p>Nominees:</p> <p>01) Joseph Wender 02) B. Lynne Parshall 03) Spencer Berthelsen 04) Joan Herman</p> <p>The Board of Directors recommends you vote FOR proposals 2, 3, 4 and 5.</p> <p>2. To approve an amendment and restatement of the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 800,000 shares to an aggregate of 2,800,000 shares, reduce the amount of the automatic awards under the plan, revise the vesting schedule of awards and extend the term of the plan.</p> <p>3. To ratify amending the existing stock option and restricted stock unit awards of directors to adjust vesting.</p> <p>4. To approve, by non-binding vote, executive compensation.</p> <p>5. Ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for the 2020 fiscal year.</p> <p>NOTE: Such other business as may properly come before the meeting or any adjournment thereof.</p> <p>Please sign exactly as your name(s) appear(s) hereon. When signing as attorney, executor, administrator, or other fiduciary, please give full title as such. Joint owners should each sign personally. All holders must sign. If a corporation or partnership, please sign in full corporate or partnership name by authorized officer.</p>	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="text-align: center;">For All</td> <td style="text-align: center;">Withhold All</td> <td style="text-align: center;">For All Except</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	For All	Withhold All	For All Except	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>To withhold authority to vote for any individual nominee(s), mark "For All Except" and write the number(s) of the nominee(s) on the line below.</p> <p>_____</p>									
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<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%; height: 20px;"></td> <td style="width: 20%; height: 20px;"></td> </tr> </table> <p>Signature [PLEASE SIGN WITHIN BOX] Date</p>				<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%; height: 20px;"></td> <td style="width: 20%; height: 20px;"></td> </tr> </table> <p>Signature (Joint Owners) Date</p>													

Important Notice Regarding the Availability of Proxy Materials for the Annual Meeting:
The Form 10-K and Notice and Proxy Statement are available at www.proxyvote.com.

D10184-P33544

**IONIS PHARMACEUTICALS, INC.
Annual Meeting of Stockholders
June 4, 2020 2:00 PM Pacific Time**

This proxy is solicited by the Board of Directors of Ionis Pharmaceuticals, Inc.

The undersigned hereby appoints Brett Monia and Stanley T. Crooke, and each of them, with power to act without the other and with power of substitution, as proxies and attorneys-in-fact and hereby authorizes them to represent and vote, as provided on the other side, all the shares of Ionis Pharmaceuticals, Inc. Common Stock which the undersigned is entitled to vote and, in their discretion, to vote upon such other business as may properly come before the Annual Meeting of Stockholders of the Company to be held June 4, 2020 at www.virtualshareholdermeeting.com/IONS2020, or any adjournment thereof with all powers which the undersigned would possess if present at the meeting.

This proxy, when properly executed, will be voted in the manner directed herein by the undersigned. If no such direction is made but the card is signed, this proxy will be voted FOR the election of the nominees under Proposal 1, FOR Proposal 2, FOR Proposal 3, FOR Proposal 4, and FOR Proposal 5, and in the discretion of the proxies with respect to such other business as may properly come before the meeting.

Continued and to be signed on reverse side