

**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 2021 ANNUAL MEETING OF STOCKHOLDERS
TO BE HELD ON JUNE 2, 2021

Dear Stockholders,

I am pleased to invite you to Ionis Pharmaceuticals, Inc.'s 2021 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 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/IONS2021, 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 2021 via webcast. You can find information regarding how to join the webcast on our website at ir.ionispharma.com. 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 2021 ANNUAL MEETING OF STOCKHOLDERS

Date: Wednesday, June 2, 2021
Time: 2:00 p.m. Pacific Time
Place: www.virtualshareholdermeeting.com/IONS2021

Dear Stockholders,

At our 2021 Annual Meeting of Stockholders, we will ask you to:

- Proposal 1: elect our nominees, Brett Monia, Frederick Muto, and Peter Reikes, to our Board of Directors to serve as Directors for a three-year term;
- Proposal 2: approve an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 6,700,000 shares to an aggregate of 29,700,000 shares and add a fungible share counting ratio;
- Proposal 3: make an advisory vote on executive compensation; and
- Proposal 4: ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2021 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 5, 2021 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/IONS2021. **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 23, 2021

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 2021 ANNUAL MEETING OF STOCKHOLDERS**

To Be Held on June 2, 2021

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 2021 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 23, 2021 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 3, 2021.

Where and when is the Annual Meeting?

The Annual Meeting will be held on Wednesday, June 2, 2021, 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 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/IONS2021.

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 5, 2021 can listen to and participate in the Annual Meeting live via the internet at www.virtualshareholdermeeting.com/IONS2021. **The webcast will begin at 2:00 p.m. Pacific Time on June 2, 2021. 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/IONS2021.**

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 the telephone number that is listed at www.virtualshareholdermeeting.com/IONS2021 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.

Who can attend and vote at the Annual Meeting?

Only stockholders at the close of business on April 5, 2021 may attend and vote at the Annual Meeting. On this record date, there were 140,929,256 shares of common stock outstanding and entitled to vote.

Stockholder of Record: Shares Registered in Your Name

If on April 5, 2021 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 5, 2021 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 our nominees, Brett Monia, Frederick Muto, and Peter Reikes, to our Board of Directors to serve as Directors for a three-year term;
- Proposal 2: approve an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 6,700,000 shares to an aggregate of 29,700,000 shares and add a fungible share counting ratio;
- Proposal 3: make an advisory vote on executive compensation; and
- Proposal 4: ratify the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2021 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/IONS2021.

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 1, 2021. 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 1, 2021 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 1-3 regarding (1) the election of Directors, (2) approval of an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 6,700,000 shares to an aggregate of 29,700,000 shares and add a fungible share counting ratio, and (3) 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. 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 of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 6,700,000 shares to an aggregate of 29,700,000 shares and add a fungible share counting ratio;
- “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 2021 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 2022 Annual Meeting of Stockholders, you must send the proposal to us by no later than December 24, 2021. 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 2, 2022. 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 5, 2021. 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 and 4. Abstentions will count towards the vote total for Proposals 2 and 3, 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 1-3 regarding (1) the election of Directors, (2) approval of an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 6,700,000 shares to an aggregate of 29,700,000 shares and add a fungible share counting ratio, and (3) 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, if any, will have no effect.
- Proposal 2: To be approved, the amendment of the 2011 Equity Incentive Plan must receive “For” votes from a majority of the holders of shares present or represented by proxy at the Annual Meeting and entitled to vote on the matter. If you “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes, if any, will have no effect.
- Proposal 3: We will consider the advisory approval of the compensation of our executive officers to be approved if it receives “For” votes from a majority of the holders of shares present or represented by proxy at the Annual Meeting and entitled to vote on the matter. If you “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes, if any, will have no effect.

- Proposal 4: To be approved, the ratification of the selection of Ernst & Young LLP as our independent auditors for our 2021 fiscal year must receive “For” votes from a majority of the holders of shares present or represented by proxy at the Annual Meeting and entitled to vote on the matter. Abstentions, if any, will have no effect. Because brokers have discretionary authority to vote on the ratification of the selection of Ernst & Young LLP, we do not expect any broker non-votes in connection with the ratification.

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 number 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 stockholders entitled to vote at the Annual Meeting will be available for examination at our principal executive offices at the address listed above for a period of 10 days prior to the Annual Meeting, and will be available during the virtual Annual Meeting for examination at www.virtualshareholdermeeting.com/IONS2021.

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. 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 2021 Elections

The Board has nominated three individuals for election at the Annual Meeting. Each of the nominees currently serves as one of our Directors. Dr. Monia, Mr. Muto and Mr. Reikes have each served as a Director for the periods set forth in the table below.

Name	Commencement of Ionis Directorship
Brett Monia	March 2019
Frederick Muto	March 2001
Peter Reikes	September 2018

In accordance with Ionis' Board membership requirement that prohibits members from running for re-election once they have reached the age of 80, Mr. Castleman will not be standing for re-election at the 2021 Annual Meeting. Ionis thanks Mr. Castleman for his eight years of Board service to the Company.

Mr. Muto has been re-elected by our stockholders each successive term. This is the first time Dr. Monia and Mr. Reikes are nominees for election by our stockholders. If re-elected or elected, as applicable, Dr. Monia, Mr. Muto and Mr. Reikes will serve until the 2024 Annual Meeting or, in each case, until his successor is elected and has qualified, or until his 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.

On March 22, 2021, 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. Following that

report, the Board determined it would be in the best interests of Ionis and its stockholders to nominate Dr. Monia, Mr. Muto and Mr. Reikes to be elected as Directors at the Annual Meeting. We provide below a short biography for each nominee. Dr. Monia, Mr. Muto and Mr. Reikes 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 2024 Annual Meeting

Brett Monia, Ph.D., age 59², 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. Following the Company's acquisition of all of the outstanding shares of Akcea Therapeutics, Inc. ("Akcea," and such acquisition, the "Akcea Acquisition"), Dr. Monia became the President of Akcea.

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 31 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.

Frederick T. Muto, age 67, 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 40 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 60, 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.

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

Biographies of the Directors Not Seeking Re-Election

Breaux B. Castleman, age 80, 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

² The ages of all our Directors are as of March 1, 2021.

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.

In accordance with Ionis' Board membership requirement that prohibits members from running for re-election once they have reached the age of 80, Mr. Castleman will not be standing for re-election at the 2021 Annual Meeting. Ionis thanks Mr. Castleman for his eight years of Board service to the Company.

Stanley T. Crooke, M.D., Ph.D., age 75, 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. Crooke was appointed 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. Crooke worked for SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories. Dr. Crooke served on the board of directors of Akcea Therapeutics, Inc. from January 2015 through October 2018.

Following the 2021 Annual Meeting of Stockholders, Dr. Crooke will step down from the Board and will serve as a Strategic Advisor to the Company, providing strategic advice and continuing to participate in the Company's scientific activities. Ionis thanks Dr. Crooke for his 32 years of service to the Company as its founder, former Chief Executive Officer and Executive Chairman of the Board.

Biographies of the Directors Whose Terms Expire at the 2022 Annual Meeting

Michael Hayden, CM, OBC, MB, ChB, Ph.D., FRCP(C), FRSC, age 69, has served as a Director of Ionis since September 2018. Dr. Hayden is a Killam Professor at the University of British Columbia, the highest honor UBC can confer on any faculty member. He is also an accomplished scientist and physician. He was the President of Global R&D and Chief Scientific Officer at Teva Pharmaceuticals from 2012-2017. During this time approximately 35 new products were approved in major markets with many for diseases of the central nervous system. In 2015 Teva R&D was recognized as one of the 10 most exciting innovators in the pharmaceutical industry by IDEA Pharma and in 2017 Teva R&D ranked top of the industry for central nervous system development and clinical trial success rate by Pharma Intelligence. 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 and receiving the July 2012 Diamond Jubilee Medal on behalf of HRH Queen Elisabeth II. He has also received the Canada Gairdner Wightman award. 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 received the Prix Galien Award in 2007. Dr. Hayden serves on the boards of Aurinia Pharmaceuticals, Xenon Pharmaceuticals, 89Bio and AbCellera.

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.

Joseph Klein, III, age 59, 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. 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., from September 2019 until the completion of the Akcea Acquisition. 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 69, 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 30 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.

Biographies of the Directors Whose Terms Expire at the 2023 Annual Meeting

Spencer R. Berthelsen, M.D., age 68, 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 67, 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 66, 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., a public biopharmaceutical company, since February 2013, and Akcea Therapeutics, Inc., from January 2015 until the completion of the Akcea Acquisition.

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 34 years of experience structuring and negotiating strategic licensing and financing transactions in the life sciences field.

Joseph H. Wender, age 76, has served as a Director of Ionis since January 1994 and our independent lead Director since December 2020. 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 2019 he has been an Advisory Director to Goldman Sachs & Co. and from January 2008 to December 2018 was 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.

The Board believes Mr. Wender is uniquely suited to serve on the Board and as our independent lead Director primarily because, with over 49 years of experience as an investment banker with Goldman, Sachs & Co., he provides Ionis important advice regarding our financial reporting, corporate finance, strategic transactions, and compensation matters.

Independence of the Board of Directors

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. Croke, 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., and Goldman Sachs & Co., neither Mr. Reikes nor Mr. Wender, respectively, receives any personal compensation directly from revenue received from 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. Croke transitioned to Executive Chairman of the Board. Following the 2021 Annual Meeting of Stockholders, Dr. Croke will step down from the Board and will serve as a Strategic Advisor to the Company, providing strategic advice and continuing to participate in the Company's scientific activities.

Independent Lead Director

In December 2020, the Board of Directors appointed Mr. Wender as the independent lead Director of the Board. The Board believes that the appointment of an independent lead Director and the separated roles of Executive Chairman of the Board and Chief Executive Officer reinforce 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 all of its current committees. We provide a complete description of each committee and its respective roles and responsibilities on pages [16](#) through [20](#) 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.

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. The Compensation Committee reviews risks to the Company related to our executive compensation program and our general compensation philosophies. The Finance

Committee evaluates risks to the Company associated with our corporate finance matters. The Science/Medical Committee identifies risks to the Company related to our technology platform. The newly formed Commercial Compliance Committee will be responsible for evaluating risks to the Company in connection with the commercialization of our medicines.

In addition to the formal compliance program, the Board and its committees 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 and most of its committees 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 had six committees as of December 31, 2020: an Audit Committee, a Compensation Committee, a Nominating, Governance and Review Committee, an Agenda Committee, a Science/Medical Committee, and a Finance Committee. As of March 26, 2021, the Board dissolved the Agenda Committee and formed a Commercial Compliance 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 2020. During 2020, 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. In 2020, due to the COVID-19 pandemic, the Company held a virtual Annual Meeting of Stockholders via live webcast and presented a Company update via a separate webcast following the Annual Meeting. Due to technical difficulties, only two Board members were able to attend the 2020 virtual Annual Meeting, but many of the Board members attended the Company update presentation that followed the Annual Meeting.

Board Committee Members

The table below provides membership and meeting information for fiscal 2020 for each of the Board committees.

Name	Audit	Compensation	Nominating, Governance and Review	Agenda	Science/ Medical	Finance	Attended 2020 Annual Meeting
Dr. Spencer R. Berthelsen	—	X*	X	—	X	—	X
Mr. Breaux B. Castleman	X	—	—	—	—	—	—
Dr. Stanley T. Croke	—	—	—	X*	X*	—	—
Dr. Michael Hayden	—	—	—	—	X	—	—
Ms. Joan E. Herman	X	—	—	—	—	—	X
Mr. Joseph Klein, III	X*	—	—	—	—	—	—
Dr. Joseph Loscalzo	—	—	X	X	X	—	—
Dr. Brett Monia	—	—	—	X	—	—	—
Mr. Frederick T. Muto	X	X	X	X	—	X	—
Ms. B. Lynne Parshall	—	—	—	X	—	X	—
Mr. Peter Reikes	—	—	—	X	—	X	—
Mr. Joseph H. Wender	—	X	X*	—	—	X*	—
Total meetings in fiscal year 2020	10	5	3	4	1	6	

* Committee Chairperson

The table below identifies our Board and committee members immediately following the 2021 Annual Meeting of Stockholders.

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

* Committee Chairperson

** Dr. C. Frank Bennett, the Company's EVP and Chief Scientific Officer, is the executive sponsor of the committee

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 2020, the Audit Committee met ten times, all via teleconference due to the COVID-19 pandemic. 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 40 through 65 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. Monia.

The Compensation Committee met five times in 2020, all via teleconference due to the COVID-19 pandemic, and acted by unanimous written consent 13 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, 2020, 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 three times during 2020. 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; 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.

We also value diversity on our Board and do not discriminate against nominees on the basis of gender, race, religion, national origin, sexual orientation, disability, or any other basis. Recognizing the importance of diversity on our Board, in December 2020, the Nominating, Governance and Review Committee approved authorizing the Company to begin a search for qualified Director candidates who are diverse and have commercial experience.

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 March 29, 2021, 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 2020. Since we now have an independent lead Director, we dissolved the Agenda Committee as of March 26, 2021.

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 one time in 2020 via teleconference due to the COVID-19 pandemic.

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, financings, investments, and share repurchase activities. The Finance Committee met six times in 2020, all via teleconference due to the COVID-19 pandemic.

Commercial Compliance Committee

The Commercial Compliance Committee was formed in March 2021. The primary function of the Commercial Compliance Committee is to provide oversight of compliance matters with respect to the commercialization and marketing of the Company's medicines.

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, 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 via an 8-K filing with the SEC or on our website at www.ionispharma.com.⁶

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.

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.

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 OF OUR 2011 EQUITY INCENTIVE PLAN

In March 2011, the Compensation Committee of the Board, and the Board, adopted the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan (the “2011 Plan”) and the stockholders approved the Plan on June 16, 2011. The stockholders have approved amendments to the 2011 Plan to increase the aggregate number of shares of common stock authorized for issuance under the 2011 Plan as follows: on June 30, 2015, an increase of 5,500,000 to an aggregate of 11,000,000 shares; on May 24, 2017, an increase of 5,000,000 to an aggregate of 16,000,000 shares; and on June 6, 2019, an increase of 7,000,000 to an aggregate of 23,000,000 shares. In March 2021, the Compensation Committee of the Board, and the Board, approved an amendment of the 2011 Plan as further described herein.

In this Proposal 2, we are requesting stockholders to approve an amendment of the 2011 Plan to:

- increase the aggregate number of shares of common stock authorized for issuance under the 2011 Plan by 6,700,000 to an aggregate of 29,700,000 shares;
- add a fungible share counting ratio so that the share reserve will be reduced or increased by 1.7 shares for each share of common stock issued pursuant to, or returning from, a Full Value Award (as defined below), respectively; and
- clarify the type of events that may trigger additional acceleration of vesting and exercisability of stock awards in connection with a change in control.

Our management, Board and Compensation Committee believe that stock options, restricted stock units (“RSUs”) and performance-based restricted stock units (“PRSUs”) are a key aspect of our ability to attract and retain qualified personnel in the face of intense competition for experienced scientists and other personnel among many pharmaceutical and health care companies. On March 26, 2021, the Board, upon the recommendation of the Compensation Committee, approved an amendment to the 2011 Plan to increase the aggregate number of shares of common stock authorized for issuance under the 2011 Plan by 6,700,000 to an aggregate of 29,700,000 shares, to ensure that for a period of at least two years, based on our current business plans, we can continue to grant stock options, RSUs and PRSUs to employees at appropriate levels as determined by the Compensation Committee; to add a fungible share counting ratio; and to clarify the type of events that may trigger additional acceleration of vesting and exercisability of stock awards in connection with a change in control. We refer to the 2011 Plan, as amended on March 26, 2021, as the “Amended 2011 Plan” throughout this Proposal 2. If the stockholders do not approve this Proposal 2, and as a consequence, we cannot continue to grant options, RSUs and PRSUs at competitive levels, we believe that it will negatively affect our ability to recruit and retain highly qualified personnel and our ability to manage future growth. Without these additional shares, management expects that the current shares available for grant under the 2011 Plan will not be sufficient to maintain our stock award practices for new employees or for promotions or merit awards for current employees.

Each year the Compensation Committee approves a budget that sets the number of stock options, RSUs and PRSUs we can grant our employees for annual merit awards. We do not grant options, RSUs or PRSUs 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 4.2% average of our peers.

The 2011 Plan was adopted to ultimately replace the Ionis Pharmaceuticals, Inc. 1989 Stock Option Plan (the “89 Plan”). There were only approximately 45,000 shares available as of March 31, 2021 for grant under the 89 Plan.

The 2011 Plan is our primary means of offering stock options, RSUs and PRSUs to our employees. There were only approximately 1.2 million shares available as of March 31, 2021 for grant under the 2011 Plan. The 2011 Plan also allows us to utilize a broad array of equity incentives and performance cash incentives to secure and retain the services of our employees and to provide long-term incentives that align the interests of our employees with the interests of our stockholders.

We also have the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan (the “2020 Plan”) that we assumed in connection with the Akcea Acquisition. Equity awards granted under the 2020 Plan are reserved primarily for legacy employees of Akcea who were employed as of October 12, 2020, which was the completion date of the Akcea Acquisition. There were approximately 2 million shares available as of March 31, 2021 for grant under the 2020 Plan.

The table below provides certain information regarding the 2020 Plan, 2011 Plan and the 89 Plan.

Employee Equity Incentive Plans (as of March 31, 2021)

	2020 Plan	2011 Plan	89 Plan
Total number of shares of common stock subject to outstanding stock options	363,350	13,453,327	31,070
Weighted-average exercise price of outstanding stock options	\$ 56.82	\$ 55.11	\$ 48.03
Weighted-average remaining term in years of outstanding stock options	6.74	4.25	1.47
Total number of shares of common stock subject to outstanding full value awards	161,483	2,658,712	—
Total number of shares of common stock available for grant under the plan	2,078,596	1,246,420	45,751
Total number of shares of common stock available for grant to non-employee Directors under the Non-Employee Director Plan ⁽¹⁾			770,111
Total number of shares of common stock available for grant under other equity incentive plans			—
Total number of shares of common stock outstanding			140,924,356
Per-share closing price of common stock as reported on Nasdaq Capital Market			\$ 44.96

(1) This amount reflects the number of shares of common stock available as of March 31, 2021 for grant under our 2002 Amended and Restated Non-Employee Directors’ Stock Option Plan (the “Non-Employee Director Plan”), which we use *solely* to offer equity awards to our non-employee Directors. With respect to the Non-Employee Director Plan, the total number of shares of common stock subject to outstanding stock options is 965,250, the weighted-average exercise price of outstanding stock options is \$47.66, the weighted-average remaining term in years of outstanding stock options is 6.11, the total number of shares of common stock subject to outstanding full value awards is 140,858, and the total number of shares of common stock available for grant under the Non-Employee Director Plan is 770,111. We have no equity incentive plans other than the 2020 Plan, 2011 Plan, 89 Plan and the Non-Employee Director Plan.

Required Vote and Board of Directors Recommendation

Approval of this Proposal 2 requires 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. Abstentions will be counted toward the tabulation of votes cast on the proposal and will have the same effect as “Against” votes. Broker non-votes will have no effect on the outcome of the vote.

Our Board believes that approval of Proposal 2 is in our best interests and the best interests of our stockholders for the reasons stated above.

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

DESCRIPTION OF THE AMENDED IONIS PHARMACEUTICALS, INC. 2011 EQUITY INCENTIVE PLAN

Below is a high-level summary of the terms of the Amended 2011 Plan. This summary is qualified in its entirety by reference to the complete text of the Amended 2011 Plan. We encourage our stockholders to read the actual text of the Amended 2011 Plan, as amended, in its entirety, a copy of which we filed with this Proxy Statement.

The Amended 2011 Plan:

- is administered by our Compensation Committee, which is composed entirely of independent Directors;
- has a term ending on June 15, 2031;
- contains a “fungible share counting” structure, whereby the number of shares of our common stock available for issuance under the Amended 2011 Plan will be reduced by (i) one share for each share issued pursuant to a stock option or stock appreciation right with an exercise price that is at least 100% of the fair market value of our common stock on the date of grant (an “Appreciation Award”) granted under the Amended 2011 Plan, and (ii) 1.7 shares for each share issued pursuant to a stock award that is not an Appreciation Award (a “Full Value Award”). As part of such fungible share counting structure, the number of shares of our common stock available for issuance under the Amended 2011 Plan will be increased by (i) one share for each share that becomes available again for issuance under the terms of the Amended 2011 Plan subject to an Appreciation Award, and (ii) 1.7 shares for each share that is granted after the effective date of the Amended 2011 Plan that becomes available again for issuance under the terms of the Amended 2011 Plan subject to a Full Value Award;
- prohibits the repricing of any option or stock appreciation rights outstanding under the Amended 2011 Plan, or “cashing out” underwater awards unless approved by our stockholders;
- is limited to the granting of stock options, SARs, restricted stock awards, RSUs, PRSUs, and performance cash awards;
- prohibits the payment of dividends and dividend equivalents with respect to shares subject to an award until such shares have vested in accordance with the terms of the corresponding award agreement;
- eliminates the recycling of shares forfeited to cover the exercise price or withholding taxes for stock options and SARs;
- requires that each newly granted stock option, restricted stock award, RSU, SAR and PRSU award not become fully vested until a date at least one year after the date of grant, except in the case of (1) a sale of all or substantially all of the assets of the Company, (2) a disposition of at least 90% of the Company’s securities, a merger or other similar transaction after which the Company is not the surviving corporation, (3) a merger or other similar transaction after which the Company is the surviving corporation but the shares of common stock immediately preceding the transaction are exchanged into other property, (4) an award granted in exchange for previously granted awards of a company acquired by the Company and (5) awards to non-employee directors that vest on the earlier of the one-year anniversary of the date of grant or the next annual meeting of stockholders, provided that such vesting period may not be less than 50 weeks; and Ionis may grant up to 1,485,000 shares worth of stock options, restricted stock awards, RSUs, SARs or PRSU awards that vest earlier than the minimum period described above;
- provides that if any stock awards held by participants who haven’t terminated service prior to a corporate transaction are not assumed, continued or substituted for by the acquiror (or its parent) in the transaction, then, contingent on the closing of the transaction, the vesting (and exercisability, if applicable) of such awards will be accelerated in full, and with respect to any awards subject to performance-based vesting conditions, vesting will be deemed satisfied at the greater of actual performance or target level; and
- requires all options and SARs outstanding under the Amended 2011 Plan to have an exercise or strike price of not less than 100% of the fair market value of our common stock on the date of grant.

Purpose

The main purpose of the Amended 2011 Plan is to allow us to give our employees (including officers), Directors and consultants an opportunity to benefit from increases in value of our common stock through the granting of a combination of stock options and RSUs. We believe providing our employees a combination of stock options and RSUs allows us to:

- retain the highest quality employees while motivating all employees to achieve key drivers of stock value;

- issue fewer shares, thereby reducing dilution;
- better align employee and stockholder interests; and
- encourage long-term holding by executive employees because stock settlement for RSUs does not require a same-day-sale.

In 2020, we granted our employees a combination of stock options and RSUs under our 2011 Plan, where we allocated 60% of the grant date dollar value to stock options and allocated 40% of the value to RSUs; and assumed that each share subject to an RSU was worth one-and-a-half shares subject to a stock option.

Background

The terms of the Amended 2011 Plan provide for the grant of stock options, SARs, restricted stock awards, RSUs, PRSU awards and performance cash awards that may be settled in cash, stock, or other property.

Shares Available for Awards

If this Proposal 2 is approved, there will be a total of 29,700,000 shares of our common stock authorized for issuance under the Amended 2011 Plan. If this Proposal 2 is not approved, there will only be approximately 1.2 million shares available for issuance under the Amended 2011 Plan as of March 31, 2021, which we expect will not be sufficient to maintain our stock award practices for new employees or for promotions or merit awards for current employees.

The following table summarizes the equity awards granted over the last three years, and through March 31, 2021, to our employees under our equity plans. We grant most of our equity awards for each year in January of such year as part of the annual merit compensation process. We have not attempted to forecast our future grant activity due to the number of assumptions that would be necessary to do so and the potential unpredictability of such underlying assumptions and estimates.

Equity Award Grant History Under Employee Equity Plans⁽¹⁾

	2018	2019	2020	2021 (through March 31)
Shares subject to equity awards granted	4,091,209	3,379,379	3,892,931	4,011,092
Shares subject to equity awards canceled, forfeited, or withheld for taxes	(612,762)	(465,440)	(712,131)	(487,992)
Net shares subject to equity awards ⁽²⁾	3,478,447	2,913,939	3,180,800	3,523,100

(1) Amounts shown reflect grants under our 2020 Plan, 2011 Plan and 89 Plan. We currently grant equity awards to our non-employee Directors separately under our Non-Employee Director Plan.

(2) Shares subject to equity awards that are canceled, forfeited, or withheld for taxes become available for re-issuance under the applicable 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, forfeited, or withheld for taxes in such year.

The number of shares of our common stock available for issuance under the Amended 2011 Plan will be reduced by (i) one share for each share of common stock issued pursuant to a stock option or stock appreciation right with an exercise or strike price of at least 100% of the fair market value of the underlying common stock on the date of grant, and (ii) 1.7 shares for each share of common stock issued pursuant to a Full Value Award.

If, under the Amended 2011 Plan, (i) any shares of common stock subject to a stock award are not issued because the stock award expires or otherwise terminates without all of the shares covered by the stock award having been issued or is settled in cash, (ii) any shares of common stock issued pursuant to a stock award are forfeited back to or repurchased by us because of the failure to meet a contingency or condition required for the vesting of such shares, or (iii) with respect to a Full Value Award, any shares of common stock are reacquired or withheld (or not issued) by us to satisfy a tax withholding obligation in connection with the award, then such shares will again become available for issuance under the Amended 2011 Plan (collectively, the “2011 Plan Returning Shares”). For each 2011 Plan Returning Share subject to a Full Value Award that is granted following the effective date of the Amended 2011 Plan, the number of shares of common stock available for issuance under the Amended 2011 Plan will increase by 1.7 shares.

We prohibit the recycling of shares we reacquire pursuant to our withholding obligations in connection with a stock option or SAR or as consideration for the exercise of a stock option or SAR and such reacquired shares will not become available for issuance under the Amended 2011 Plan.

Eligibility

All of our employees in the United States and our Directors and consultants are eligible to participate in the Amended 2011 Plan. Our practice, however, is not to grant awards to consultants or non-employee Directors under the Amended 2011 Plan. As of April 5, 2021, we had a total of 720 employees who were eligible to participate in the Amended 2011 Plan.

Administration

Our Board administers the Amended 2011 Plan. The Board may delegate authority to administer the Amended 2011 Plan to a committee but may retain the authority to concurrently administer the Amended 2011 Plan with the committee and may, at any time, revest in itself some or all of the powers previously delegated to the committee. Our Board has delegated administration of the Amended 2011 Plan to the Compensation Committee. Subject to the terms of the Amended 2011 Plan, the Compensation Committee may determine the recipients, numbers, and types of stock awards to be granted, and terms and conditions of the stock awards, including the period of their exercisability and vesting. Subject to the limitations set forth below, the Compensation Committee also determines the fair market value applicable to a stock award and the exercise price of stock options and SARs granted under the Amended 2011 Plan.

At the discretion of the Board, the Compensation Committee may consist solely of two or more “non-employee directors” within the meaning of Rule 16b-3 of the Securities Exchange Act of 1934, as amended (the “Exchange Act”). We also have a Non-Management Stock Award Committee that, as delegated by the Compensation Committee, awards stock awards to employees who are below director level in accordance with guidelines adopted by the Compensation Committee. The Non-Management Stock Award Committee has one member, Dr. Monia. As used herein, except as explicitly stated otherwise, with respect to the Amended 2011 Plan, the “Board” refers to any committee the Board appoints or, if applicable, any subcommittee, as well as to the Board itself.

No Repricing, “Cash-Out,” or Cancellation and Re-Grant of Stock Awards without Stockholder Approval

Under the Amended 2011 Plan, the Board cannot reprice any outstanding options or SARs by reducing the exercise price of the stock award or cancel any outstanding options or SARs 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.

Minimum Vesting; Restrictions on Accelerated Vesting

Under the Amended 2011 Plan, no stock award granted to an employee or member of the Board will become 100% vested in a period of less than one year after the grant of such award, *except that* the vesting of a stock award may accelerate (or may be accelerated by the Board or Compensation Committee) in the case of (1) a sale of all or substantially all of the assets of the Company, (2) a disposition of at least 90% of the Company’s securities, a merger or other similar transaction after which the Company is not the surviving corporation, (3) a merger or other similar transaction after which the Company is the surviving corporation but the shares of common stock immediately preceding the transaction are exchanged into other property, (4) an award granted in exchange for previously granted awards of a company acquired by the Company and (5) awards to non-employee directors that vest on the earlier of the one-year anniversary of the date of grant or the next annual meeting of stockholders, provided in such case that such vesting period may not be less than 50 weeks; and Ionis may grant up to 1,485,000 shares worth of stock options, restricted stock awards, RSUs, SARs or PRSU awards that vest earlier than the minimum period described above.

Dividends and Dividend Equivalents

The Amended 2011 Plan prohibits the payment of dividends and dividend equivalents with respect to shares subject to an award until such shares have vested in accordance with the terms of the corresponding award agreement.

No Evergreen

The Amended 2011 Plan does not include an automatic share reserve increase provision (i.e., an evergreen provision).

Stock Options

The Board grants stock options under the Amended 2011 Plan pursuant to stock option agreements. The Amended 2011 Plan permits the grant of stock options that qualify as nonstatutory stock options, or “NSOs.” Individual stock option agreements may be more restrictive as to any or all of the permissible terms described in this section.

Exercise Price; Payment

The exercise price of stock options may not be less than 100% of the fair market value of the common stock subject to the stock option on the date of grant. As of March 31, 2021, the closing price of our common stock as reported on the Nasdaq Global Select Market was \$44.96 per share.

Vesting

Stock options granted under the Amended 2011 Plan may become exercisable in cumulative increments, or “vest,” as determined by our Board at the rate specified in the stock option agreement, subject to the minimum vesting requirements described above. Shares covered by different stock options granted under the Amended 2011 Plan may be subject to different vesting schedules as our Board may determine.

Term

In general, the term of stock options granted under the Amended 2011 Plan is seven years, and the Amended 2011 Plan does not allow stock options to have a term that exceeds ten years. Unless the terms of an option holder’s stock option agreement or other agreement with the Company provides for earlier or later termination:

- if an option holder’s service relationship with us, or any affiliate of ours, ceases due to disability, the option holder may exercise any vested stock options for up to 12 months after the date the service relationship ends;
- if an option holder’s service relationship with us, or any affiliate of ours, ceases due to death, the option holder, or his or her beneficiary, may exercise any vested stock options for up to 18 months after the date the service relationship ends; and
- if an option holder’s service relationship with us, or any affiliate of ours, ceases for any reason, other than as described above, the option holder may exercise any vested stock options for up to three months after the date the service relationship ends.

Under the Amended 2011 Plan, the stock option term may be extended in the event that exercise of the stock option following termination of service is prohibited by applicable securities laws or if the sale of stock received upon exercise of a stock option would violate the Company’s insider trading policy. In no event may a stock option be exercised after its expiration date.

Consideration

Our Board determines the acceptable forms of consideration for the purchase of our common stock pursuant to the exercise of a stock option under the Amended 2011 Plan, which may include cash, check, bank draft or money order made payable to us, shares of our common stock, payment pursuant to a program developed under Regulation T as promulgated by the Federal Reserve Board, or a net exercise feature.

Transferability

Generally, an option holder may not transfer a stock option other than by will or the laws of descent and distribution or a domestic relations order. However, to the extent permitted under the terms of the applicable stock option agreement, an option holder may designate a beneficiary who may exercise the stock option following the option holder’s death.

Restricted Stock Unit Awards

RSUs are granted under the Amended 2011 Plan pursuant to restricted stock unit award agreements. Payment of any purchase price is made in any legal form acceptable to the Board. We settle a payment due to a recipient of a restricted stock unit award by delivery of shares of our common stock, by cash, by a combination of cash and stock, or in any other form of consideration determined by our Board and set forth in the restricted stock unit award agreement. We may credit dividend equivalents in respect of shares of our common stock covered by a restricted stock unit award; however, no dividend equivalents may be paid with respect to such shares before the date such shares have vested in accordance with the terms of the corresponding award agreement. RSUs are subject to vesting in accordance with a vesting schedule determined by our Board, subject to the minimum vesting requirements described earlier. Except as otherwise provided in the applicable RSU award agreement, RSUs that have not vested will be forfeited upon the participant's termination of continuous service for any reason.

Restricted Stock Awards

The Board may grant restricted stock awards under the Amended 2011 Plan pursuant to restricted stock award agreements. The Board may grant a restricted stock award in consideration for cash, check, bank draft or money order payable to us, the recipient's services performed for us or our affiliate, or any other form of legal consideration acceptable to the Board. Shares of our common stock acquired under a restricted stock award are subject to forfeiture to us in accordance with a vesting schedule determined by our Board. Holders of awards may only transfer their rights to acquire shares of our common stock under a restricted stock award upon such terms and conditions as are set forth in the restricted stock award agreement. We may credit dividend equivalents in respect of shares of our common stock covered by a restricted stock award; however, no dividend equivalents may be paid with respect to such shares before the date such shares have vested in accordance with the terms of the corresponding award agreement. Except as otherwise provided in the applicable restricted stock award agreement, restricted stock awards that have not vested will be forfeited upon the participant's termination of continuous service for any reason.

Stock Appreciation Rights

The Board may grant SARs under the Amended 2011 Plan pursuant to SAR agreements. Each SAR is denominated in common stock share equivalents. The Board will determine the strike price of each stock appreciation right but the strike price cannot be less than 100% of the fair market value of the stock subject to the SAR at the time of grant. Our Board may also impose restrictions or conditions upon the vesting of SARs that it deems appropriate, subject to the minimum vesting requirements described earlier. We may settle SARs in our common stock, in cash, in a combination of cash and stock, or in any other form of legal consideration approved by our Board and set forth in the stock appreciation right agreement. SARs will be subject to the same conditions upon termination and restrictions on transfer as stock options under the Amended 2011 Plan.

Performance Awards

The Amended 2011 Plan provides for the grant of two types of performance awards: PRSU awards and performance cash awards. The Board may grant, vest, or settle performance awards based upon the attainment of specified performance goals during a specified period of time. The Compensation Committee will determine the length of any performance period, the performance goals to be achieved during the performance period, and the measure of whether and to what degree such performance goals have been attained.

In granting a performance award, the Compensation Committee will set a period of time, called a performance period, over which the attainment of one or more performance goals will be measured for the purpose of determining whether the award recipient has a vested right in or to such award. The Compensation Committee will establish the performance goals, based upon one or more criteria, called performance criteria enumerated in the Amended 2011 Plan and described below. As soon as administratively practicable following the end of the performance period, the Compensation Committee will determine whether the performance goals have been satisfied.

The Board will determine performance goals under the Amended 2011 Plan, based on any one or more of the following performance criteria:

• earnings (including earnings per share and net earnings)	• earnings before interest, taxes, and depreciation
• earnings before interest, taxes, depreciation, and amortization	• total stockholder return
• return on equity or average stockholders' equity	• return on assets, investment, or capital employed
• stock price	• margin (including gross margin)
• income (before or after taxes)	• sales or revenue targets
• operating income	• expenses and cost reduction goals
• operating cash flow	• economic value added (or an equivalent metric)
• increases in revenue or product revenue	• cash flow
• improvement in or attainment of working capital levels	• share price performance
• market share	• stockholders' equity
• cash flow per share	• debt levels
• debt reduction	• workforce diversity
• customer satisfaction	• billings
• capital expenditures	• implementation or completion of projects or processes (including, but not limited to, development and regulatory milestones)
• operating profit	• other measures of performance selected by the Board
• growth of net income or operating income	

The Board is authorized to determine whether, when calculating the attainment of performance goals for a performance period, as follows:

- to exclude restructuring and/or other nonrecurring charges;
- to exclude exchange rate effects, as applicable, for non-U.S. dollar denominated performance goals;
- to exclude the effects of changes to generally accepted accounting principles;
- to exclude the effects of any statutory adjustments to corporate tax rates;
- to exclude the effects of items that are "unusual" in nature or occur "infrequently," as determined under generally accepted accounting principles; and
- to exclude accounting expenses relating to share-based compensation.

Changes to Capital Structure

If certain capitalization adjustments occur, the Board will appropriately adjust:

- the class(es) and maximum number of securities subject to the Amended 2011 Plan; and
- the class(es) and number of securities and price per share of stock subject to outstanding stock awards.

Corporate Transactions

Unless otherwise provided in the stock award agreement, any other written agreement between the Company or any of its affiliates and the participant, or in any director compensation policy of the Company, in the event of a corporate transaction (as specified in the Amended 2011 Plan and described below), all outstanding stock awards under the Amended 2011 Plan will be assumed, continued or substituted for by any surviving or acquiring entity (or its parent company). If the surviving or acquiring entity (or its parent company) elects not to assume, continue or substitute for such stock awards, then (i) with respect to any such stock awards that are held by individuals whose continuous service with us or an affiliate has not terminated prior to the effective date of the corporate transaction, the vesting and exercisability provisions of such stock awards will be accelerated in

full (and with respect to any performance stock awards, vesting will be deemed satisfied at the greater of actual performance or target level) and such awards will terminate if not exercised prior to the effective date of the corporate transaction, and (ii) with respect to any stock awards that are held by individuals whose continuous service with the Company or an affiliate of the Company has terminated prior to the effective date of the corporate transaction, the vesting and exercisability provisions of such stock awards will not be accelerated and such awards will terminate if not exercised prior to the effective date of the corporate transaction (except that any reacquisition or repurchase rights held by the Company with respect to such stock awards will not terminate and may continue to be exercised notwithstanding the corporate transaction).

For purposes of the Amended 2011 Plan, a corporate transaction will be deemed to occur in the event of the consummation of:

- a sale of all or substantially all of our consolidated assets;
- a sale of at least 90% of our outstanding securities;
- a merger or consolidation in which we are not the surviving corporation; or
- a merger or consolidation in which we are the surviving corporation but shares of our outstanding common stock are converted into other property by virtue of the transaction.

The acceleration of vesting of an award in the event of a corporate transaction under the Amended 2011 Plan may be viewed as an anti-takeover provision, which may have the effect of discouraging a proposal to acquire or otherwise obtain control of the Company.

Change in Control

A stock award will not be subject to additional acceleration of vesting and exercisability in connection with a change in control (as defined in the Amended 2011 Plan), except upon certain termination events that are in connection with a change in control as provided in the stock award agreement for such stock award or as otherwise may be provided in any other written agreement between us or any affiliate and the participant. In such a case, the stock award agreement or other written agreement may provide that vesting (and, if applicable, exercisability) of time-based awards will be accelerated in full and performance-based stock awards will be deemed to have been satisfied at the greater of actual performance or target level.

The acceleration of vesting of an award in the event of a change in control event under the Amended 2011 Plan may be viewed as an anti-takeover provision, which may have the effect of discouraging a proposal to acquire or otherwise obtain control of the Company.

Plan Amendments

Our Board has the authority to amend or terminate the Amended 2011 Plan. However, no amendment or termination of the plan will adversely affect any rights under awards already granted to a participant unless agreed to by the affected participant. We will obtain stockholder approval of any amendment to the Amended 2011 Plan as required by applicable law and listing requirements. We will not seek to amend the prohibition on option repricing or “cashing-out” without obtaining such stockholder approval.

Plan Termination

Unless sooner terminated by our Board, the Amended 2011 Plan will automatically terminate on June 15, 2031.

Federal Income Tax Information

The information set forth below is a summary only and does not purport to be complete. The information is based upon current federal income tax rules and therefore is subject to change when those rules change. Because the tax consequences to any recipient may depend on his or her particular situation, each recipient should consult the recipient’s tax adviser regarding the federal, state, local, and other tax consequences of the grant or exercise of an award or the disposition of stock acquired as a result of an award. The Amended 2011 Plan is not qualified under the provisions of Section 401(a) of the Code and is not subject to any of the provisions of the Employee Retirement Income Security Act of 1974. Our ability to realize the benefit of any tax deductions described below depends on our generation of taxable income, as well as the requirement of reasonableness and the satisfaction of our tax reporting obligations.

Nonstatutory Stock Options

Generally, there is no taxation upon the grant of an NSO if the stock option is granted with an exercise price equal to the fair market value of the underlying stock on the grant date. On exercise, an option holder will recognize ordinary income equal to the excess, if any, of the fair market value of the underlying stock on the date of exercise of the stock option over the exercise price. If the option holder is employed by us or one of our affiliates, that income will be subject to withholding taxes. The option holder's tax basis in those shares will be equal to their fair market value on the date of exercise of the stock option, and the option holder's capital gain holding period for those shares will begin on that date.

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

Restricted Stock Unit Awards

Generally, the recipient of a restricted stock unit award structured to comply with the requirements of Section 409A of the Code or an exemption 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 comply with the requirements of Section 409A of the Code, the shares of our common stock subject to a restricted stock unit award may generally only be delivered 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 restricted stock unit award otherwise complies with or qualifies for an exemption 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 a restricted stock unit award 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 our tax reporting obligation, we will generally be entitled to a tax deduction equal to the taxable ordinary income realized by the recipient of the restricted stock unit award.

Restricted Stock Awards

Generally, the recipient of a restricted stock award will recognize ordinary income at the time the stock is received equal to the excess, if any, of the fair market value of the stock received over any amount paid by the recipient in exchange for the stock. If, however, the stock is not vested when it is received (for example, if the employee is required to work for a period of time in order to have the right to sell the stock), the recipient generally will not recognize income until the stock becomes vested, at which time the recipient will recognize ordinary income equal to the excess, if any, of the fair market value of the stock on the date it becomes vested over any amount paid by the recipient in exchange for the stock. A recipient may, however, file an election with the Internal Revenue Service, within 30 days following his or her receipt of the stock award, to recognize ordinary income, as of the date the recipient receives the award, equal to the excess, if any, of the fair market value of the stock on the date the award is granted over any amount paid by the recipient for the stock.

The recipient's basis for the determination of gain or loss upon the subsequent disposition of shares acquired from a restricted stock award will be the amount paid for such shares plus any ordinary income recognized either when the stock is received or when the stock becomes vested.

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

Stock Appreciation Rights

We may grant stock appreciation rights under the Amended 2011 Plan separate from any other award or together with other awards under the Amended 2011 Plan.

Generally, if a stock appreciation right is granted with an exercise price equal to the fair market value of the underlying stock on the grant date, the recipient will recognize ordinary income equal to the fair market value of the stock or cash received upon such exercise.

Subject to the requirement of reasonableness, the provisions of Section 162(m) of the Code, and the satisfaction of our 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 appreciation right.

Section 162(m) Limitations

Section 162(m) of the Code disallows a deduction to any publicly held corporation and its affiliates for certain compensation paid to “covered employees” in a taxable year to the extent that compensation paid to a covered employee exceeds \$1 million. The exemption from Section 162(m)’s deduction limit for performance-based compensation has been repealed, effective for taxable years beginning after December 31, 2017, such that compensation paid to our covered employees in excess of \$1 million will not be deductible unless it qualifies for transition relief applicable to certain arrangements in place as of November 2, 2017, and not modified in any material respect on or after such date. As a result, compensation (including compensation pursuant to awards granted under the Amended 2011 Plan) paid to any of our “covered employees” under Section 162(m) of the Code in excess of \$1 million per taxable year generally will not be deductible.

New Plan Benefits

Awards granted under the Amended 2011 Plan to our executive officers and other employees are discretionary and are not subject to set benefits or amounts under the terms of the Amended 2011 Plan, and our Board and our Compensation Committee have not granted any awards under the Amended 2011 Plan subject to stockholder approval of this Proposal 2. Accordingly, the benefits or amounts that will be received by or allocated to our executive officers and other employees under the Amended 2011 Plan, as well as the benefits or amounts which would have been received by or allocated to our executive officers and other employees for fiscal year 2020 if the Amended 2011 Plan had been in effect, are not determinable.

Plan Benefits

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 2011 Plan as of March 31, 2021.

PLAN BENEFITS 2011 PLAN

Name and Position	Total Number of Shares	Options	RSUs	PRSUs ⁽¹⁾
Brett Monia Chief Executive Officer	872,884	612,014	197,900	62,970
Elizabeth L. Hougen Executive Vice President and Chief Financial Officer	430,533	342,336	88,197	—
Stanley T. Croke Executive Chairman of the Board	1,145,669	978,479	167,190	—
Richard Geary Executive Vice President, Chief Development Officer	423,735	338,170	85,565	—
Patrick R. O’Neil Executive Vice President, Legal, General Counsel and Chief Compliance Officer	384,912	300,567	84,345	—
All Executive Officers as a Group	4,267,635	3,360,701	843,964	62,970
All Non-Employee Directors as a Group	—	—	—	—
All Non-Executive Officer Employees as a Group	14,032,423	11,177,434	2,854,989	—

(1) Reflects the target payout of shares under the PRSU awards.

Please see page 39 for information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of March 31, 2021.

PROPOSAL 3

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, 2020), called our “named executive officers” as disclosed in this Proxy Statement in accordance with Section 14A of the Exchange Act.

We are asking our stockholders to indicate their support for our named executive officers’ compensation as described in this Proxy Statement. This Proposal 3, 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 2021 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 [40](#) through [65](#). 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
✓ In 2020 we began allocating 20% of our Chief Executive Officer’s equity awards as performance-based restricted stock units	✗ Do not guarantee a cash bonus – cash bonuses can be, and have been, zero
✓ Demand more of every employee: more commitment, more knowledge, more intensity, more innovation, more productivity	✗ Do not provide perquisites for any employees
✓ Reward productivity and performance	✗ Do not provide “gross-up” payments, other than for relocation
✓ Recognize the value of long-term employees and low turnover	✗ Do not allow pledging, shorting, or hedging against our stock
✓ Use a balanced mix of fixed and variable cash incentives and long-term equity incentives	✗ Do not reprice or “cash-out” stock options without stockholder approval
✓ Review compensation compared to the 25 th , 50 th and 75 th 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 that applies to all Section 16 Officers	
✓ Use an independent compensation consultant engaged by the Compensation Committee	

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 3. Brokers do not have discretion to vote uninstructed shares with respect to this Proposal 3. 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 3.

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 3.

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 2021 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 4.

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, 2020 and 2019, Ernst & Young LLP billed us approximately \$2.0 million and \$1.6 million, 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 \$90,000 and approximately \$220,000 in 2020 and 2019, respectively, related to corporate transactions, of which approximately \$10,000 and \$85,000 was billed to Akcea for each year, respectively. Additionally, for the fiscal years ended December 31, 2020 and 2019, Ernst & Young LLP billed us approximately \$415,000 and \$750,000, respectively, related to the audit of the financial statements of Akcea.

Audit Related Fees

For the fiscal years ended December 31, 2020 and 2019, there were no audit related fees billed by Ernst & Young LLP.

Tax Fees

For the fiscal years ended December 31, 2020 and 2019, Ernst & Young LLP billed us approximately \$640,000 and \$225,000 for each year, respectively, primarily related to professional services on tax projects, of which approximately \$195,000 in 2020 was related to the Akcea Acquisition.

All Other Fees

During the fiscal years ended December 31, 2020 and 2019, all other fees billed by Ernst & Young LLP were approximately \$6,000 each year. 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, 2020, 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 4.

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of March 1, 2021 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.

Except as otherwise indicated below, the address of each beneficial owner listed in this table is c/o Ionis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, California 92010.

Beneficial Owner	Beneficial Ownership ⁽¹⁾	
	Number of Shares	Percent of Total ⁽²⁾
FMR LLC ⁽³⁾ 245 Summer Street Boston, MA 02210	20,979,722	14.89%
T. Rowe Price Associates, Inc. ⁽⁴⁾ 100 E. Pratte Street Baltimore, MD 21202	13,114,967	9.31%
The Vanguard Group ⁽⁵⁾ 100 Vanguard Boulevard Malvern, PA 19355	12,244,388	8.69%
BlackRock, Inc. ⁽⁶⁾ 55 East 52 nd Street New York, NY 10055	9,750,502	6.92%
BB Biotech AG ⁽⁷⁾ Schwertstrasse 6 CH-8200, Schaffhausen Switzerland	8,220,000	5.84%
Spencer R. Berthelsen ⁽⁸⁾	210,553	*
Breaux B. Castleman ⁽⁹⁾	114,933	*
Stanley T. Crooke ⁽¹⁰⁾	1,333,990	*
Michael Hayden ⁽¹¹⁾	25,334	*
Joan Herman ⁽¹²⁾	17,334	*
Joseph Klein, III ⁽¹³⁾	65,894	*
Joseph Loscalzo ⁽¹⁴⁾	111,808	*
Frederick T. Muto ⁽¹⁵⁾	134,683	*
B. Lynne Parshall ⁽¹⁶⁾	519,178	*
Peter Reikes ⁽¹⁷⁾	25,334	*
Joseph H. Wender ⁽¹⁸⁾	160,305	*
Richard S. Geary ⁽¹⁹⁾	219,696	*
Elizabeth L. Hougen ⁽²⁰⁾	251,397	*
Brett Monia ⁽²¹⁾	348,651	*
Patrick R. O’Neil ⁽²²⁾	136,915	*
All Directors and executive officers as a group (nineteen persons) ⁽²³⁾	4,166,306	2.96%

* 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 140,867,798 shares of common stock outstanding on March 1, 2021, adjusted as required by rules promulgated by the SEC.
- (3) FMR LLC has sole voting power to direct the vote of 7,587,587 shares and sole power to dispose or direct the disposition of 20,979,722 shares. The Fidelity Growth Company Commingled Pool holds the interest of 7,553,613 shares of our common stock, which amounts to 5.36% of our total outstanding as of March 1, 2021.
- 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. LLC"), a wholly owned subsidiary of FMR LLC, which power resides with the Fidelity Funds' Boards of Trustees. FMR Co. LLC carries out the voting of the shares under written guidelines established by the Fidelity Funds' Boards of Trustees.
- (4) T. Rowe Price Associates, Inc. has sole voting power to direct the vote of 3,941,347 shares and sole power to dispose or direct the disposition of 13,114,967 shares.
- (5) The Vanguard Group has shared voting power to direct the vote of 136,226 shares, sole power to dispose or direct the disposition of 12,000,887 shares, and shared dispositive power for 243,501 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 9,045,495 shares and sole power to dispose or direct the disposition of 9,750,502 shares.
- (7) BB Biotech AG shares voting and dispositive powers for its shares with Biotech Invest N.V.
- (8) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 109,500 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before April 30, 2021.
- (9) Includes 95,750 shares of common stock issuable upon exercise of options held by Mr. Castleman that are exercisable on or before April 30, 2021.
- (10) Includes 776,658 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 30, 2021. Also includes 494,391 shares of common stock held in a family trust for which Dr. Crooke shares voting and investment power. Also includes 57,809 shares of common stock issuable upon exercise of options held by Rosanne Crooke, Dr. Crooke's wife, which are exercisable on or before April 30, 2021. Dr. Crooke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.
- (11) Includes 20,000 shares of common stock issuable upon exercise of options held by Dr. Hayden that are exercisable on or before April 30, 2021.
- (12) Includes 12,000 shares of common stock issuable upon exercise of options held by Ms. Herman that are exercisable on or before April 30, 2021.
- (13) Includes 100 shares of common stock beneficially owned by Mr. Klein's son and 52,000 shares of common stock issuable upon exercise of options held by Mr. Klein that are exercisable on or before April 30, 2021.
- (14) Includes 94,500 shares of common stock issuable upon exercise of options held by Dr. Loscalzo that are exercisable on or before April 30, 2021.
- (15) Includes 1,500 shares of common stock beneficially owned through the Cooley LLP Salary Deferral and Profit Sharing Plan and 101,500 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before April 30, 2021.
- (16) Includes 453,800 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 30, 2021.
- (17) Includes 20,000 shares of common stock issuable upon exercise of options held by Mr. Reikes that are exercisable on or before April 30, 2021.
- (18) Includes 88,305 shares of common stock held by Mr. Wender in a trust, and 72,000 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 30, 2021.
- (19) Includes 189,390 shares of common stock issuable upon exercise of options held by Dr. Geary that are exercisable on or before April 30, 2021.
- (20) Includes 207,810 shares of common stock issuable upon exercise of options held by Ms. Hougen that are exercisable on or before April 30, 2021.
- (21) Includes 298,537 shares of common stock issuable upon exercise of options held by Dr. Monia that are exercisable on or before April 30, 2021.
- (22) Includes 110,216 shares of common stock issuable upon exercise of options held by Mr. O'Neil that are exercisable on or before April 30, 2021.
- (23) Includes an aggregate of 3,100,461 shares issuable upon exercise of options held by all current Directors and executive officers as a group that are exercisable on or before April 30, 2021.

Delinquent Section 16(a) Reports

Section 16(a) of the Exchange Act requires our Directors, executive officers, and persons who own more than ten percent of a registered class of our equity securities, to file with the SEC initial reports of ownership and reports of changes in ownership of our common stock and other equity securities. Officers, Directors and greater than ten percent stockholders are required by SEC regulation to furnish us with copies of all Section 16(a) forms they file.

To our knowledge, based on a review of Section 16 reports submitted on EDGAR and written representations from the reporting persons that no Form 5 was required, during the fiscal year ended December 31, 2020, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with except for a release of restricted stock units to Ms. Herman on June 10, 2020, which was reported on June 17, 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, 2021:

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⁾	14,812,997	\$54.65	4,736,141 ⁽²⁾
Total	14,812,997	\$54.65	4,736,141

(1) Consists of five Ionis plans: 1989 Stock Option Plan, Amended and Restated 2002 Non-Employee Directors' Stock Option Plan, 2011 Equity Incentive Plan, 2020 Equity Incentive Plan and Employee Stock Purchase Plan, or ESPP.

(2) Of these shares, 624,857 remained available for purchase under the ESPP as of March 31, 2021.

Compensation Discussion and Analysis

Business and Compensation Overview and 2020 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, due to our innovation and perseverance, we believe antisense technology has the potential to treat diseases where no other therapeutic approach has proved effective.

Antisense technology exists today primarily because of the innovation at Ionis, with almost 1,100 issued patents that provide substantial control of key elements of the technology for many years to come.

Ionis is focused on innovation. 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, our employees, and our stockholders.

As a company focused on improving the health of people around the world, our priority during the COVID-19 pandemic is the safety of our employees, their families, the healthcare workers who work with us and the patients who rely on our medicines. We are also focused on maintaining the quality of our studies and minimizing the impact to timelines. While the COVID-19 pandemic has impacted some areas of our business, we believe our mitigation efforts and financial strength will enable us to continue to manage through the pandemic and execute on our strategic initiatives.

Innovation Drives Our Success. Antisense technology exists today primarily because of the innovation at Ionis, with almost 1,100 issued patents that provide substantial control of key elements of the technology for many years to come. 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. 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, and Ionis received the Prix Galien USA Award for the Best Biotechnology Product in 2020 for TEGSEDI. In 2020, Dr. C. Frank Bennett, Ionis' Executive Vice President and Chief Scientific Officer, was awarded the Lifetime Achievement Award by the Oligonucleotide Therapeutics Society for his important contributions to basic science and for being instrumental in the development of antisense oligonucleotide drugs that modulate splicing to correct severe genetic disease.

Commercial Medicines and Robust Pipeline. We are primarily focused on two core franchises: neurology and cardiometabolic. We have three commercial medicines approved in major markets around the world: SPINRAZA, TEGSEDI and WAYLIVRA. These medicines, along with the more than 30 additional medicines in our pipeline, represent multiple potential drivers of value for years to come. In 2020, we initiated multiple phase 3 studies and reported clinical proof-of-concept results from six medicines. In addition, we made significant progress across the rest of our pipeline by advancing more than ten medicines into Phase 2 studies, four of which were wholly owned medicines. We also broadened the scope of our antisense technology by demonstrating clinical proof-of-concept for aerosol delivery of an antisense medicine directly to the lungs. These accomplishments enabled us to achieve revenues of over \$700 million and a year-end cash balance of \$1.9 billion. 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. 2020 was a transformational year for Ionis. With new leadership in place that has established a new strategy for Ionis to commercialize medicines from our wholly owned pipeline, and to accelerate progress across our entire pipeline, we took important steps towards realizing our goal of having 12 or more medicines on the market in 2026. Key to our new strategy is maximizing the value of each medicine in our wholly owned portfolio. To that end, we invested in strengthening our commercial capabilities and expanded our wholly owned pipeline, accelerated by the Akcea Acquisition. With this acquisition, we believe we are stronger and more efficient, with enhanced ability to achieve even greater future success. We should continue to realize value from our wholly owned and partnered medicines for many years to come in the form of product sales, license fees, upfront payments, milestone payments and royalties.

2020 was a transformational year for Ionis. With new leadership in place that has established a new strategy for Ionis to commercialize medicines from our wholly owned pipeline, and to accelerate progress across our entire pipeline, we took important steps towards realizing our goal of having 12 or more medicines on the market in 2026.

Our Compensation System. By design, Ionis demands a great deal from 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 in 2020 was 11.5%, excluding reductions related to the Akcea Acquisition, while the turnover for life sciences/medical device companies over this period was 21% according to a survey published by Radford – an Aon 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;
- maximize the value of each medicine in our wholly owned portfolio;
- 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.

Equity and Diversity

Pay Equity

We are committed to paying our employees fairly, regardless of their gender, race, or other personal characteristics. To ensure we are achieving our commitment, we benchmark and evaluate pay based on market data and consider factors such as an employee's role and experience, an employee's performance, and internal equity. We also regularly review our compensation practices, both in terms of our overall workforce and individual employees, to ensure our pay is fair and equitable. We periodically engage a third-party expert to review pay equity and will continue to do so as we determine necessary.

We are committed to paying our employees fairly, regardless of their gender, race, or other personal characteristics.

Diversity, Equity, and Inclusion

At Ionis, we encourage diversity in our workforce. Prejudicial barriers to human potential and productivity are foreign to our values. We recognize that to realize the full potential of our workforce, we must cultivate an inclusive culture where all employees feel empowered to contribute fully in an environment that values different perspectives, leading to better ideas and increased innovation.

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
✓ In 2020 we began allocating 20% of our Chief Executive Officer’s equity awards as performance-based restricted stock units	✗ Do not guarantee a cash bonus – cash bonuses can be, and have been, zero
✓ Demand more of every employee: more commitment, more knowledge, more intensity, more innovation, more productivity	✗ Do not provide perquisites for any employees
✓ Reward productivity and performance	✗ Do not provide “gross-up” payments, other than for relocation
✓ Recognize the value of long-term employees and low turnover	✗ Do not allow pledging, shorting, or hedging against our stock
✓ Use a balanced mix of fixed and variable cash incentives and long-term equity incentives	✗ Do not reprice or “cash-out” stock options without stockholder approval
✓ Review compensation compared to the 25 th , 50 th and 75 th 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 that applies to all Section 16 Officers	
✓ Use an independent compensation consultant engaged by the Compensation Committee	

In 2020, we made several notable compensation and governance-related changes. Specifically, as discussed in greater detail in the pages that follow, we:

- implemented performance-based equity awards, allocating 20% of our Chief Executive Officer's equity awards as performance-based restricted stock units;
- expanded our executive clawback policy to apply to all Section 16 Officers; and
- adopted a policy whereby the Compensation Committee, with input from its independent consultant, may reduce the number of shares to be automatically issued on a grant date for each such award so that the awards granted have an aggregate grant date fair value that is aligned with the set of peer companies the Compensation Committee uses to evaluate compensation.

We believe these changes appropriately address feedback we have received from some stockholders and our Compensation Committee and continue to align the Company with peer companies and incentivize management to enhance long-term stockholder value.

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. Following the 2021 Annual Meeting of Stockholders, Dr. Crooke will step down from the Board and will serve as a Strategic Advisor to the Company, providing strategic advice and continuing to participate in the Company's scientific activities. Dr. Monia, who was our Chief Operating Officer and a member of the Ionis team since our founding, assumed the position of Chief Executive Officer in January 2020. The historical information contained in this Proxy Statement for the period preceding 2020 provides compensation data for Dr. Crooke and Dr. Monia with respect to each of their former roles.

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 recommending approval by the Board of 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 Radford, which is part of the Rewards Solutions practice at Aon plc (“Aon”) as its independent compensation consultant. For 2020, Aon primarily provided the Compensation Committee advice in the following areas:

- selecting the 2020 Executive Peer Group;
- reviewing new hire awards and target annual equity awards for employees;
- evaluating the pay mix for our executive officers;
- assessing executive officer compensation;
- evaluating our named executive officer equity awards; and
- reviewing our non-executive equity strategy.

Compensation Consultant Fees

As described above, the Compensation Committee has engaged Aon to provide the committee with peer company and industry compensation data and advice regarding executive officers’ compensation. In 2020, we paid Aon approximately \$125,000 for Aon’s consulting services directly related to Compensation Committee support.

In addition, management of the Company engaged affiliates of Aon for other services in 2020 that were not related to Aon’s Compensation Committee consulting services. Our human resources department obtained general benchmarking survey data and benefits data from an affiliate of Aon, for which we paid approximately \$14,000, and \$3,500, respectively, in 2020. Additionally, our Finance department engaged an affiliate of Aon for insurance brokerage services, for which we paid approximately \$770,000 in 2020. Although the Compensation Committee was aware of the nature of these additional services, the committee did not review and approve such services, insurance premiums or policies, as those were reviewed and approved by management in the ordinary course of business.

Aon maintains certain policies and practices to protect the independence of the executive compensation consultants engaged by the Compensation Committee. In particular, Aon provides an annual update to the Compensation Committee on the financial relationship between Aon and the Company, and provides written assurances that, within Aon, the compensation of the affiliate consultants who perform executive compensation services for the Compensation Committee is determined separately from Aon’s other lines of business and from the other services it provides to the Company. These safeguards were designed to help ensure that the Compensation Committee’s executive compensation consultants continued to fulfill their role in providing independent, objective advice.

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.

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

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 total shareholder return (“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. If the Company’s TSR is negative over the applicable performance period, the payout will not exceed 100% of the target number for that performance period.

For the first performance period of the PRSU award that was granted in January 2020, Ionis’ TSR was -3.29%, which ranked 69 out of the 198 companies in the peer group under the PRSU award, or approximately the 35th percentile. Based on performance at approximately the 35th percentile as of January 15, 2021, the final number of units earned for the first performance period of the PRSU award granted in January 2020 equaled 69.7% of the target number.

Internal Pay Equity. 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. Historically, the total cash compensation of our CEO over a rolling three-year period has been on average approximately 30 times that of the average cash compensation for our lowest level employees, and two to three times greater than the average of that of our other executive officers. Our CEO’s total cash compensation over the last three years was on average approximately 26 times greater than the average cash compensation for our lowest level employees, and 1.89 times greater than the average of that of our other executive officers. For 2020, these ratios decreased due to Dr. Monia’s transition to CEO, as the salary data used for the calculation of such ratios included the MBO bonus paid to him in 2020 for performance in 2019 as COO.

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;
- maximize the value of each medicine in our wholly owned portfolio;
- 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 30) 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, sales targets 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 have historically included a number of objectives that are based on achieving positive data in the clinic, and as our strategy to commercialize medicines from our wholly owned pipeline has evolved, we have added objectives that are based on achieving sales targets. For example, in 2020 we had corporate objectives to (i) strengthen our Phase 3 pipeline with one of the measures being to initiate at least two new Phase 3 studies and another measure being to advance four specified medicines so they are on track to reach scheduled readouts; (ii) advance our pipeline to enable additional Phase 3 studies in 2021 with the measure being to achieve positive clinical proof-of-concept on at least four medicines; and (iii) ensure the success of our commercial pipeline with the measure being to achieve specified sales targets for our commercial medicines. Results driven objectives only reward our employees if the data are positive or the sales efforts are successful – we do this to encourage the prudent spending of stockholder money on development and commercialization 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 and deep 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 have on average approximately 21 years and individually as much as over 31 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, including Board members, 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 2020, certain of our Board members and named executive officers received such awards. Mr. Wender and Dr. Geary were each awarded a Lifetime Achievement Award and Ms. Hougen was awarded a Commitment to Ionis Award to recognize her 20 years of service to Ionis.

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 18 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 2020, the Compensation Committee reviewed the Executive Peer Group using the criteria listed above and publicly available data as of May 2020. The Compensation Committee noted Ionis' market capitalization was approximately \$7.6 billion and trailing 12-month revenue was approximately \$960 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 \$2.5 billion and \$25 billion, and revenue between \$375 million and \$2.25 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 BeiGene, Horizon Therapeutics and United Therapeutics to the Executive Peer Group. These companies all fell within the market capitalization range and were in Ionis' sector. BeiGene and Horizon Therapeutics were identified as "reverse peers." Although BeiGene is headquartered in China, it was a suitable addition to our Executive Peer Group because its leadership team is located in the United States and the company maintains a traditional American compensation program. Additionally, the Compensation Committee removed Array and The Medicines Company, as they were acquired by Pfizer and Novartis, respectively, and removed Clovis Oncology, Ironwood Pharmaceuticals and Ligand Pharmaceuticals because they all fell below the market capitalization range.

The following table lists the companies in the 2020 Executive Peer Group, along with Ionis' rankings among these companies, based on market capitalization and financial data reported by each company at the time the Compensation Committee selected the Executive Peer Group in June 2020.

Company (ticker)	Annual Revenues (in millions) ⁽¹⁾	Market Capitalization (in millions) ⁽²⁾	Stage of Lead Drug
Acadia Pharmaceuticals (ACAD)	\$339.1	\$7,427.6	Market
Agios Pharmaceuticals (AGIO)	\$174.8	\$2,908.8	Market
Alkermes (ALKS)	\$1,194.1	\$2,422.9	Market
Alnylam Pharmaceuticals (ALNY)	\$285.9	\$15,158.0	Market
BeiGene (BGNE)	\$428.2	\$11,946.8	Market
BioMarin Pharmaceuticals (BMRN)	\$1,805.4	\$16,287.8	Market
bluebird bio (BLUE)	\$44.7	\$3,000.1	Market (EU)
Exact Sciences Corp (EXAS)	\$1,062.1	\$11,168.7	Market
Exelixis (EXEL)	\$979.2	\$7,123.2	Market
Horizon Therapeutics (HZNP)	\$1,375.6	\$6,633.7	Market
Incyte Corporation (INCY)	\$2,229.4	\$20,977.9	Market
Intercept Pharmaceuticals (ICPT)	\$252.0	\$2,613.4	Market
Jazz Pharmaceuticals (JAZZ)	\$2,188.3	\$6,084.3	Market
Nektar Therapeutics (NKTR)	\$114.6	\$3,428.7	NDA
Neurocrine Biosciences (NBIX)	\$886.8	\$9,181.9	Market
Sarepta Therapeutics (SRPT)	\$407.5	\$9,091.8	Market
Seattle Genetics (SGEN)	\$956.0	\$24,374.5	Market
United Therapeutics (UTHR)	\$1,442.5	\$4,676.2	Market
Ionis Pharmaceuticals, Inc. (IONS)	\$958.8	\$7,660.6	Market
Ionis' Percentile Rank	54%	54%	N/A

(1) Trailing 12-month revenue.

(2) 30-day average market cap.

Our Productivity vs. Industry Peers

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

Even for established 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 trials. With over 30 medicines in clinical trials and just 746 employees⁸, we are able to develop more medicines more efficiently, all while continuing to achieve exceptional financial results.

We achieved these financial successes while initiating multiple phase 3 studies, reporting clinical proof-of-concept results from six medicines, and making significant progress across the rest of our pipeline by advancing more than ten medicines into Phase 2 studies, four of which were wholly owned medicines.

In 2020, a number of achievements demonstrated our productivity and strength, even in the challenging COVID-19 pandemic environment:

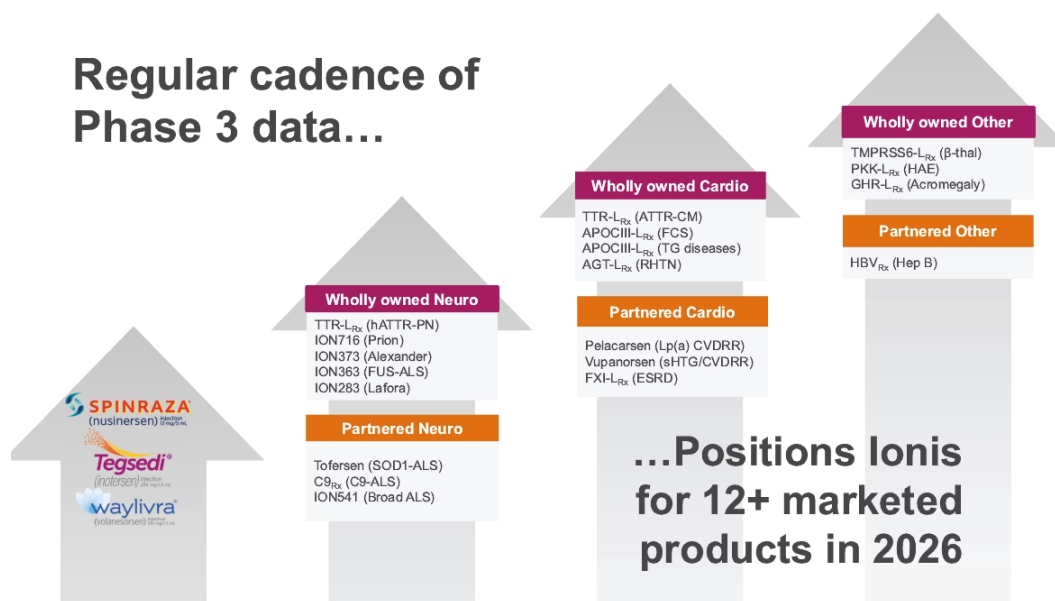
- We earned over \$700 million in revenue, met our 2020 financial guidance and ended the year with \$1.9 billion in cash.
- We achieved these financial successes while initiating multiple phase 3 studies, reporting clinical proof-of-concept results from six medicines, and making significant progress across the rest of our pipeline by advancing more than ten medicines into Phase 2 studies, four of which were wholly owned medicines.
- We broadened the scope of our antisense technology by demonstrating aerosol delivery of an antisense medicine directly to the lungs.

Our efficient platform and the dedication of our employees enabled us to accomplish these robust results and they set us apart from our peers.

⁸ As of April 5, 2021.

Advancing Our Pipeline

We now have six Phase 3 studies underway, including four studies for wholly owned medicines. We also have a prolific mid-stage pipeline of medicines advancing towards Phase 3 development, many of which are expected to reach pivotal trials in the near term. With so many programs in mid- to later stages of development, coupled with our historically high rate of clinical success, we are in a position to deliver a steady cadence of Phase 3 data readouts for many years to come.



Financial Performance

Additional evidence of our productivity and the benefit of our business strategy is reflected in our strong financial performance. Ionis ended 2020 in a very strong financial position with \$1.9 billion in cash and 2020 revenues of over \$700 million. For the fifth year in a row, Ionis was profitable on a non-GAAP⁹ basis. 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.

\$729 million in revenue

Half from commercial revenues

\$111 million of net income*

Continued financial strength



\$2 billion in sales

Continued blockbuster performance

\$1.9 billion of cash

Enabling increasing investment in three key value-driving areas

* Non-GAAP. See footnote below for additional information regarding non-GAAP financial results.

⁹ We use “non-GAAP” in place of “pro-forma” when discussing our financial results that exclude non-cash compensation expense related to equity awards, costs related to the Akcea Acquisition, and costs related to our restructured European operations, because we believe that non-GAAP financial results better represent the economics of our business and how we manage our business. For a detailed reconciliation of non-GAAP and GAAP measures, see our earnings release reporting fourth quarter and full year 2020 financial results available [here](#).

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 structure 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.

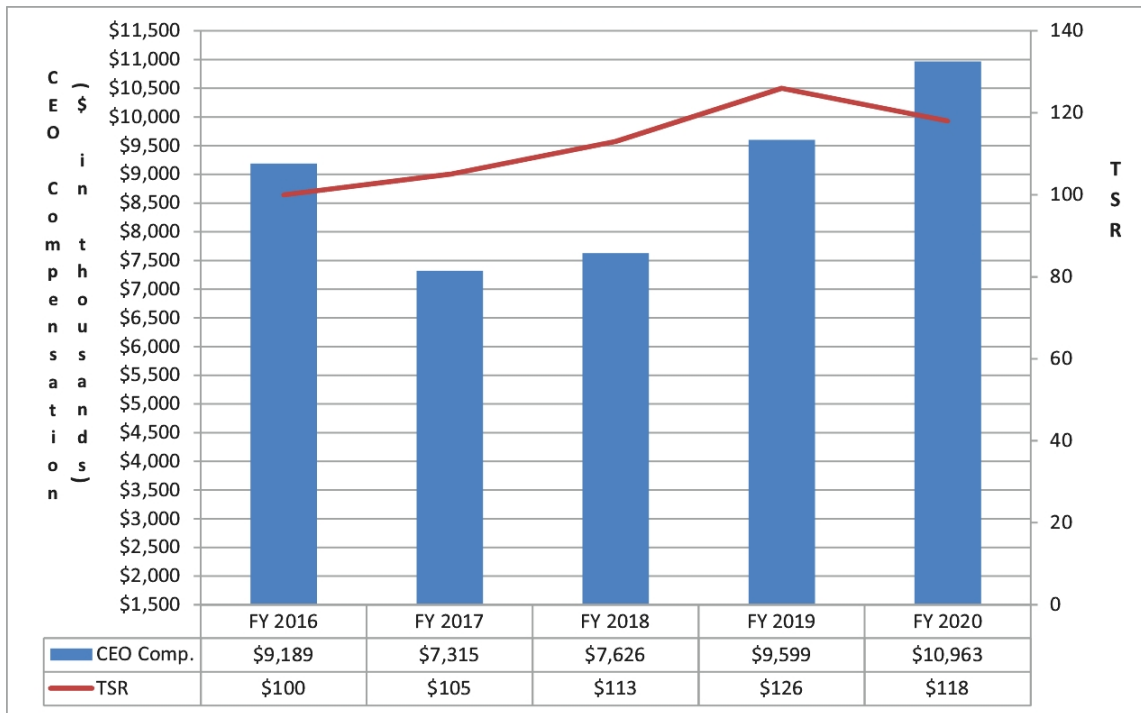
"Say on Pay" Vote

In June 2020, we held a stockholder advisory vote on the compensation of our named executive officers. Our stockholders overwhelmingly approved, on an advisory basis, the compensation of our named executive officers, with over 97% of stockholder votes cast in favor of our "say on pay" resolution. In evaluating our compensation practices during fiscal 2020 and in early 2021, we were mindful of the strong support our stockholders expressed for our compensation philosophies and practices. As a result, the Compensation Committee retained our general approach to executive compensation as in the prior fiscal year. The Compensation Committee will continue to consider stockholder feedback in the future.

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 TSR on \$100 invested on December 31, 2016 in our common stock through December 31, 2020. 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, with the exception of 2020. Historical compensation data prior to 2020 used in the graph below reflects Dr. Crooke’s compensation as CEO, and beginning in 2020, reflects Dr. Monia’s compensation as CEO.

Ionis ended 2020 in a very strong financial position, with 2020 revenues of over \$700 million. For the fifth year in a row, Ionis was profitable on a non-GAAP¹⁰ basis and ended the year with \$1.9 billion in cash. As shown in the graph below, our CEO’s compensation aligned with TSR for 2017, 2018 and 2019.¹¹ While our CEO’s compensation for 2020 did increase, such increase was due to additional equity grants awarded to Dr. Monia in connection with his promotion to CEO. Removal of the value of such additional equity awards in connection with Dr. Monia’s promotion results in total compensation of \$8,607,827 for Dr. Monia’s 2020 performance, which is approximately 10% less than Dr. Crooke’s 2019 total compensation.

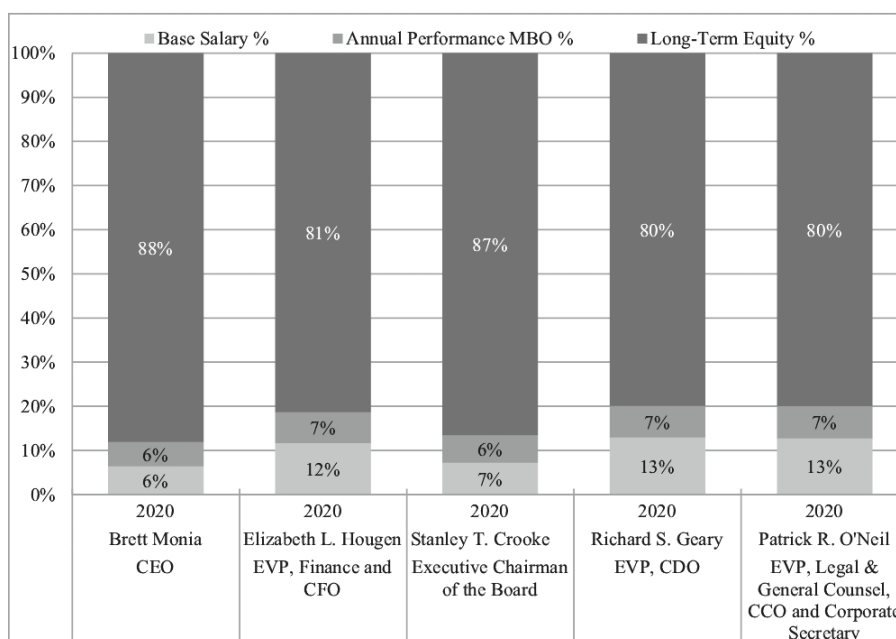


¹⁰ We use “non-GAAP” in place of “pro-forma” when discussing our financial results that exclude non-cash compensation expense related to equity awards, costs related to the Akcea Acquisition, and costs related to our restructured European operations, because we believe that non-GAAP financial results better represent the economics of our business and how we manage our business. For a detailed reconciliation of non-GAAP and GAAP measures, see our earnings release reporting fourth quarter and full year 2020 financial results available [here](#).

¹¹ 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.

2020 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 2020:



Name	Year	% of Total Direct Compensation					
		Base Salary	Annual Performance MBO	Long-Term Equity	Base Salary %	Annual Performance MBO %	Long-Term Equity %
Brett Monia CEO	2020	\$700,000	\$601,738	\$9,620,555	6%	6%	88%
Elizabeth L. Hougen EVP, Finance and CFO	2020	\$499,555	\$298,734	\$3,478,973	12%	7%	81%
Stanley T. Crooke Executive Chairman of the Board	2020	\$683,630	\$587,665	\$8,175,902	7%	6%	87%
Richard Geary EVP, CDO	2020	\$509,360	\$281,167	\$3,142,130	13%	7%	80%
Patrick O'Neil EVP, Legal & General Counsel, CCO and Corporate Secretary	2020	\$500,925	\$288,032	\$3,142,130	13%	7%	80%

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 900 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 all of our named executive officers and executive officers, salary represents less than 20% 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 2020 performance the Company-wide merit increase budget was 3.3%, with a range of individual merit award increases of 0% to 10%. 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 key corporate 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

The table below reflects the 2020 salary calculations for our named executive officers, other than Drs. Crooke and Monia:

Name	2019 Base Salary	Merit Increase for 2020	2020 Base Salary
Elizabeth L. Hougen	\$479,880	4.1%	\$499,555
Richard Geary	\$491,186	3.7%	\$509,360
Patrick O'Neil	\$483,052	3.7%	\$500,925

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 Drs. Crooke and 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 our independent compensation consultant, 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, for 2020, 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 an annual 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:

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

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 key 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 2020 were: Directors 20%; Executive Directors 25%; Vice Presidents 30% or 35%; Executive Vice Presidents 40%; CEO and Executive Chairman 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 2020 as a percentage of salary:

Name	Minimum Performance MBO Percentage of Salary	Maximum Performance MBO Percentage of Salary
Brett Monia	0%	208%

Name	Minimum Performance MBO Percentage of Salary	Maximum Performance MBO Percentage of Salary
Elizabeth L. Hougen	0%	128%
Stanley T. Crooke	0%	208%
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 Key 2020 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 2020 Key Corporate Objectives. On December 16, 2020, the Compensation Committee completed its evaluation of the Company's performance against the 2020 Key Corporate Objectives.

The Compensation Committee set the Company Performance Factor for the 2020 Performance MBO at 115% due to our strong achievements for the year across drug discovery, development, corporate development, and financial performance, especially given the challenges of the COVID-19 pandemic. Because of the dedication of our employees and strength of our technology and our business, we were able to successfully manage the evolving pandemic and achieve the following in 2020:

- We earned over \$700 million in revenue, met our 2020 financial guidance, and ended the year with \$1.9 billion in cash.
- We achieved these financial successes while initiating multiple phase 3 studies, reporting clinical proof-of-concept results from six medicines, and making significant progress across the rest of our pipeline by advancing more than ten medicines into Phase 2 studies, four of which were wholly owned medicines.
- We broadened the scope of our antisense technology by demonstrating aerosol delivery of an antisense medicine directly to the lungs.

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 key objective and the related achievements for 2020, as well as a description of notable unplanned accomplishments that the Compensation Committee considered in evaluating the Company's performance. The Company Performance Factor of 115% for 2020 reflects a decrease from 125% for 2019, which was primarily due to our failure to meet the key corporate objectives to increase our stock price performance and complete key business development transactions. For 2020, the Company reduced the total number of key corporate objectives to increase the Company's focus on objectives we considered most important for the year. We will maintain this focused approach in future years.

Evaluation of 2020 Key Corporate Objectives		
	Objective & Pre-Approved Objective Measures	Evaluation
1	<p>Meet budget projections:</p> <ul style="list-style-type: none"> Deliver pro forma net income Meet financial guidance 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> We delivered pro forma net income (non-GAAP)¹² We met our financial guidance
2	<p>Achieve successful CEO transition:</p> <ul style="list-style-type: none"> Meet corporate and additional key objectives Work successfully with Dr. Crooke and the Board of Directors Enhance investor perceptions of Ionis Reinforce and strengthen our core cultural and performance-related values Ensure successful additional senior management transitions (Dr. Swayze/EVP Research, Dr. Bennett/Chief Scientific Officer, Dr. Crooke/Executive Chairman of the Board, Ms. Cadoret-Manier/Chief Corporate Development and Commercial Officer) 	<p>Ionis <u>substantially met</u> this objective:</p> <ul style="list-style-type: none"> We met most of our corporate and additional key objectives Dr. Monia, Dr. Crooke and the Board of Directors worked together effectively We made progress in enhancing investor perceptions of Ionis and will continue working to make improvements in this area We reinforced and strengthened our core cultural and performance-related values, even with the additional challenges created by the COVID-19 pandemic Facilitated successful senior management transitions
3	<p>Ensure success of the commercial pipeline:</p> <ul style="list-style-type: none"> SPINRAZA sales \geq a specified sales target TEGSEDI sales \geq a specified sales target WAYLIVRA sales \geq a specified sales target File New Drug Application (NDA) for WAYLIVRA in the U.S. 	<p>Ionis <u>partially met</u> this objective:</p> <ul style="list-style-type: none"> We achieved an overwhelming percentage of our SPINRAZA sales target for 2020 We exceeded our TEGSEDI sales target for 2020 We achieved a substantial proportion of our WAYLIVRA sales target. Additionally, the combined product sales of TEGSEDI and WAYLIVRA increased more than 65 percent compared to that of 2019 The NDA for WAYLIVRA was not filed in 2020 due in part to delays and disruptions caused by the COVID-19 pandemic
4	<p>Strengthen late-stage (Phase 3) pipeline:</p> <ul style="list-style-type: none"> Four specified medicines on track to reach scheduled readouts Initiate \geq two new Phase 3 studies 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> We advanced four medicines so they are on track to reach scheduled readouts We initiated two Phase 3 studies (for IONIS TTR-L_{Rx} and IONIS-APOCIII-L_{Rx})
5	<p>Advance pipeline to enable additional Phase 3 studies in 2021:</p> <ul style="list-style-type: none"> Positive clinical proof-of-concept on \geq four medicines 	<p>Ionis <u>exceeded</u> this objective:</p> <ul style="list-style-type: none"> We achieved positive clinical proof-of-concept on seven medicines

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, costs related to the Akcea Acquisition, and costs related to our restructured European operations, because we believe that non-GAAP financial results better represent the economics of our business and how we manage our business. For a detailed reconciliation of non-GAAP and GAAP measures, see our earnings release reporting fourth quarter and full year 2020 financial results available [here](#).

Evaluation of 2020 Key Corporate Objectives		
	Objective & Pre-Approved Objective Measures	Evaluation
6	Complete key business development transactions	Ionis did <u>not meet</u> this objective <ul style="list-style-type: none"> While we did not complete these transactions, our business model, which relies on multiple sources of revenue, provides us with the financial strength to continue advancing these medicines and maximize their value
7	Make Akcea successful: <ul style="list-style-type: none"> Make key personnel appointments, expand pipeline, develop a strategic investment plan, and enhance intercompany communications to achieve greater efficiency 	Ionis <u>met</u> this objective: <ul style="list-style-type: none"> We met all of the measures included in this objective that continued to be applicable following the Akcea Acquisition
8	Make Biogen relationship successful: <ul style="list-style-type: none"> Full enrollment for a specified trial Initiate trials in three specified programs Achieve development candidate approval and acceptance by Biogen for specified program Achieve \geq three new target sanctions and acceptance by Biogen 	Ionis <u>substantially met</u> this objective: <ul style="list-style-type: none"> We fully enrolled the specified trial We initiated two of three specified trials and expect to initiate the third in 2021 We achieved development candidate approval and acceptance by Biogen for the specified program We achieved two new target sanctions and acceptance by Biogen
9	Establish plan and preparations to implement future commercialization strategy for wholly owned pipeline in 2021: <ul style="list-style-type: none"> Ionis-owned pipeline prioritized based on asset value, timing, and synergies Identify options and establish timing for commercialization via affiliates Establish 2021 commercial and communications plan 	Ionis <u>exceeded</u> this objective: <ul style="list-style-type: none"> We successfully prioritized our wholly owned pipeline based on asset value, timing, and synergies We achieved this objective by virtue of the Akcea Acquisition We established our commercial and communications plan for 2021
10	Increase stock price performance by a specified target percentage greater than or equal to median of the companies listed in the Nasdaq Biotechnology Index	Ionis <u>did not meet</u> this objective
Unplanned Accomplishments for 2020		
11	COVID-19 management	
12	Successful outcome for Akcea Acquisition	
13	Successfully managed Alnylam arbitration	
14	EU distribution transaction for TEGSEDI and WAYLIVRA	

Once the Committee establishes the Company Performance Factor, the Committee next reviews each executive officer's individual performance and contribution towards the key 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 2020 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⁾
Brett Monia ⁽²⁾	\$700,000	65%	115%	115%	\$601,738	1-14
Elizabeth L. Hougen	\$499,555	40%	115%	130%	\$298,734	1-3, 6-7 & 9-12
Stanley T. Crooke ⁽²⁾	\$683,630	65%	115%	115%	\$587,665	1-14
Richard Geary	\$509,360	40%	115%	120%	\$281,167	1-5 & 7-9
Patrick O'Neil	\$500,925	40%	115%	125%	\$288,032	1-2, 6-7, 9 & 12-14

(1) The numbers correspond to the enumerated key objectives in the table entitled "Evaluation of Key 2020 Corporate Objectives" on pages 60 through 61. The Compensation Committee reviews the individual's contribution towards the key corporate objectives and other accomplishments set forth above when determining the Individual Performance Factors.

(2) Since our CEO and Executive Chairman 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. Beginning 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

Some of our stockholders have requested we incorporate performance-based stock awards into our executive compensation program. Beginning in 2020, we started 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. Measuring our stock performance relative to peers mitigates the impact of macroeconomic factors, both positive and negative, that affect the industry and stock price performance and are beyond the control of management, and provides rewards that are more directly aligned with performance through different economic cycles. We believe these PRSU awards provide a challenging incentive to the CEO to significantly grow the Company.

Some of our stockholders have requested we incorporate performance-based stock awards into our executive compensation program. Beginning in 2020, we started 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.

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. In connection with his promotion to CEO, in January 2020, Dr. Monia received 40,822

time-vested stock options, 18,143 time-vested RSUs and 17,009 PRSUs (target payout of 11,339, multiplied by 150% to account for potential upside). For 2020 performance, in January 2021, Dr. Monia received 149,872 time-vested stock options, 66,610 time-vested RSUs and 77,447 PRSUs (target payout of 51,631, 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. In addition, RSUs promote retention and reinforce an ownership culture, and provide value even during periods of stock price or market underperformance.

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 4.2% from 2017 through 2019. We believe this stock budget is an important tool to balance our compensation objectives with stockholder interests. For 2020 performance, the Compensation Committee set a merit stock award budget that resulted in approximately 2.1 million stock options and approximately 955,000 RSUs awarded to Ionis 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

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.

performance in the previous year, ultimately determines the size of the individual annual stock grants. Following the Akcea Acquisition, for 2020 performance, we awarded approximately 380,000 stock options and approximately 170,000 RSUs to legacy Akcea employees.

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 at least 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 non-employee Board members:

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

As of March 31, 2021, all of our non-employee Directors, and all of our executive officers except Dr. Schneider and Ms. Cadoret-Manier met these guidelines. Due to Dr. Schneider's recent transition, 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.

Clawback Policy

We have a recoupment/“clawback” policy. Effective March 26, 2021, we adopted an executive compensation clawback policy that provides the Compensation Committee with authority to recover the following performance-based cash and equity incentive compensation of any current or former “officer” of the Company, as such term is defined under Rule 16a-1(f) of the Securities Exchange Act of 1934, as amended, and as determined by the Company, if such officer engaged in fraud or intentional misconduct that contributed to the circumstances requiring a restatement of the Company's financial statements:

- Any incentive-based compensation received by such officer during the one-year period preceding the date on which we are required to prepare a restatement of our financial statements that the Compensation Committee determines was in excess of what would have been paid to such officer under the restatement on a pre-tax basis.

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, if any, 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, or that remove economic risk from their holdings of our securities, 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, 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 71, 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 each of the Company's "covered employees" that exceeds \$1 million per taxable year is generally non-deductible unless the compensation qualifies for certain grandfathered exceptions (including the "performance-based compensation" exception) for certain compensation paid pursuant to a written binding contract in effect on November 2, 2017 and not materially modified on or after such date.

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, 2020, 2019, and 2018, 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, 2020, 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 (\$)
Brett P. Monia ⁽⁵⁾ President, Chief Executive Officer	2020	\$700,000	\$601,738	\$5,150,204 ⁽⁶⁾	\$4,470,351 ⁽⁶⁾	\$ 40,747	\$10,963,040
	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
Elizabeth L. Hougen Executive Vice President, Finance and Chief Financial Officer	2020	\$499,555	\$298,734	\$1,663,208	\$1,815,765	\$ 63,838	\$ 4,341,100
	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
Stanley T. Crooke ⁽⁵⁾ Executive Chairman	2020	\$683,630	\$587,665	\$3,908,663	\$4,267,239	\$ 39,332	\$ 9,486,529
	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
Richard S. Geary Executive Vice President, Chief Development Officer	2020	\$509,360	\$281,167	\$1,502,162	\$1,639,968	\$ 78,379	\$ 4,011,036
	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
Patrick R. O’Neil Executive Vice President, Legal, General Counsel and Corporate Secretary	2020	\$500,925	\$288,032	\$1,502,162	\$1,639,968	\$ 33,978	\$ 3,965,065
	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

- (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 2021 we paid bonuses for 2020 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 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, 2020 regarding assumptions underlying valuation of equity awards.
- (3) The grant date value of stock awards for our named executive officers increased in 2019 and 2020 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. Amounts for 2020 include a Lifetime Achievement Award for Dr. Geary and a Commitment to Ionis Award for Ms. Hougen. Amounts for 2019 include a Lifetime Achievement Award and Commitment to Ionis Award for Drs. Crooke and Monia.
- (5) 2020 compensation for Drs. Monia and Crooke was for their roles as CEO and Executive Chairman, respectively, and 2019 and 2018 compensation was for their roles as COO and CEO, respectively.
- (6) Includes equity awards granted to Dr. Monia in connection with his promotion to CEO in 2020.

Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2020, certain information regarding grants of plan-based awards to our named executive officers:

Grants of Plan-Based Awards in Fiscal 2020

Name	Grant Date	Estimated Future Payouts Under Equity Incentive Plan Awards			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⁾
		Threshold (#)	Target (#)	Maximum (#)				
Brett P. Monia	1/4/20	—	—	—	—	148,454	\$60.89	\$4,470,351
	1/15/20	—	—	—	65,979	—	—	\$4,094,657
	1/15/20	5,669	11,339	17,009	—	—	—	\$1,055,548
Elizabeth L. Hougen	1/4/20	—	—	—	—	60,299	\$60.89	\$1,815,765
	1/15/20	—	—	—	26,800	—	—	\$1,663,208
Stanley T. Crooke	1/4/20	—	—	—	—	141,709	\$60.89	\$4,267,239
	1/15/20	—	—	—	62,982	—	—	\$3,908,663
Richard Geary	1/4/20	—	—	—	—	54,461	\$60.89	\$1,639,968
	1/15/20	—	—	—	24,205	—	—	\$1,502,162
Patrick R. O'Neil	1/4/20	—	—	—	—	54,461	\$60.89	\$1,639,968
	1/15/20	—	—	—	24,205	—	—	\$1,502,162

- (1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with 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. The fair value of PRSUs is calculated using the target payout of shares under the PRSU award and is based on the market price of our common stock on the date of grant and is further adjusted to take into consideration that the award contains a market condition. 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, 2020 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, 2020. 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, 2020. 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, 2020.

The Compensation Committee granted Dr. Monia additional equity awards consisting of stock options, RSUs and PRSUs in connection with his promotion to CEO in January 2020. Twenty percent of such promotional equity awards were in the form of PRSUs. 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.

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

The following table shows for the fiscal year ended December 31, 2020, 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, 2020.

Outstanding Equity Awards as of December 31, 2020

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⁾	Equity incentive plan awards: number of unearned shares, units or other rights that have not vested (#) ⁽⁴⁾	Equity incentive plan awards: market or payout value of unearned shares, units or other rights that have not vested (\$) ⁽⁵⁾
Brett P. Monia	1/2/2015	36,423	—	\$61.57	1/1/2022	—	—	—	—
	1/4/2016	38,240	—	\$61.68	1/3/2023	—	—	—	—
	1/3/2017	47,000	1,000	\$47.34	1/2/2024	—	—	—	—
	1/2/2018	42,383	15,742	\$49.25	1/1/2025	—	—	—	—
	1/14/2018	21,875	8,125	\$53.22	1/13/2025	—	—	—	—
	1/2/2019	49,306	53,594	\$53.77	1/1/2026	—	—	—	—
	1/2/2020	—	107,632	\$60.89	1/1/2027	—	—	—	—
	1/2/2020	—	40,822	\$60.89	1/1/2027	—	—	—	—
	1/15/2017	—	—	—	—	2,000	\$ 113,080	—	—
	1/15/2018	—	—	—	—	6,458	\$ 365,135	—	—
	1/15/2018	—	—	—	—	3,333	\$ 188,448	—	—
	1/15/2019	—	—	—	—	34,296	\$1,939,096	—	—
	1/15/2020	—	—	—	—	47,836	\$2,704,647	—	—
1/15/2020	—	—	—	—	18,143	\$1,025,805	—	—	
1/15/2020	—	—	—	—	—	—	5,669	\$320,525	
Elizabeth L. Hougen	1/2/2015	33,112	—	\$61.57	1/1/2022	—	—	—	—
	1/4/2016	38,240	—	\$61.68	1/3/2023	—	—	—	—
	1/3/2017	44,282	943	\$47.34	1/2/2024	—	—	—	—
	1/2/2018	39,827	14,792	\$49.25	1/1/2025	—	—	—	—
	1/2/2019	23,862	25,938	\$53.77	1/1/2026	—	—	—	—
	1/2/2020	—	60,299	\$60.89	1/1/2027	—	—	—	—
	1/15/2017	—	—	—	—	1,884	\$ 106,521	—	—
	1/15/2018	—	—	—	—	6,068	\$ 343,085	—	—
	1/15/2019	—	—	—	—	16,598	\$ 938,451	—	—
	1/15/2020	—	—	—	—	26,800	\$1,515,272	—	—

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⁾	Equity incentive plan awards: number of unearned shares, units or other rights that have not vested ^(#) ⁽⁴⁾	Equity incentive plan awards: market or payout value of unearned shares, units or other rights that have not vested ^(\$) ⁽⁵⁾
Stanley T. Crooke	1/2/2015	165,000	—	\$61.57	1/1/2022	—	—	—	—
	1/4/2016	195,182	—	\$61.68	1/3/2023	—	—	—	—
	1/3/2017	159,616	3,397	\$47.34	1/2/2024	—	—	—	—
	1/2/2018	115,336	42,839	\$49.25	1/1/2025	—	—	—	—
	1/2/2019	68,712	74,688	\$53.77	1/1/2026	—	—	—	—
	1/2/2020	—	141,709	\$60.89	1/1/2027	—	—	—	—
	1/15/2017	—	—	—	—	6,792	\$ 384,020	—	—
	1/15/2018	—	—	—	—	17,574	\$ 993,634	—	—
	1/15/2019	—	—	—	—	47,794	\$2,702,273	—	—
1/15/2020	—	—	—	—	62,982	\$3,561,002	—	—	
Richard S. Geary	1/2/2015	33,112	—	\$61.57	1/1/2022	—	—	—	—
	1/4/2016	38,240	—	\$61.68	1/3/2023	—	—	—	—
	1/3/2017	20,282	943	\$47.34	1/2/2024	—	—	—	—
	1/2/2018	42,383	15,742	\$49.25	1/1/2025	—	—	—	—
	1/2/2019	27,743	30,157	\$53.77	1/1/2026	—	—	—	—
	1/2/2020	—	54,461	\$60.89	1/1/2027	—	—	—	—
	1/15/2017	—	—	—	—	1,884	\$ 106,521	—	—
	1/15/2018	—	—	—	—	6,458	\$ 365,135	—	—
	1/15/2019	—	—	—	—	19,297	\$1,091,052	—	—
1/15/2020	—	—	—	—	24,205	\$1,368,551	—	—	
Patrick R. O' Neil	1/4/2016	7,967	—	\$61.68	1/3/2023	—	—	—	—
	1/3/2017	19,882	943	\$47.34	1/2/2024	—	—	—	—
	1/2/2018	31,840	14,798	\$49.25	1/1/2025	—	—	—	—
	1/2/2019	23,862	25,938	\$53.77	1/1/2026	—	—	—	—
	1/2/2020	—	54,461	\$60.89	1/1/2027	—	—	—	—
	1/15/2017	—	—	—	—	1,884	\$ 106,521	—	—
	1/15/2018	—	—	—	—	6,070	\$ 343,198	—	—
	1/15/2019	—	—	—	—	16,598	\$ 938,451	—	—
1/15/2020	—	—	—	—	24,205	\$1,368,551	—	—	

- (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 \$56.54, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 31, 2020, the last trading day of fiscal 2020.
- (4) Represents the threshold payout of shares under the PRSU award granted to Dr. Monia in January 2020.
- (5) Market value of PRSUs was determined by multiplying the threshold payout of shares by \$56.54, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 31, 2020, the last trading day of fiscal 2020.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2020, 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 (\$)
Brett P. Monia	45,000	\$2,302,758	19,921	\$1,236,297
Elizabeth L. Hougen	45,000	\$2,256,814	12,044	\$ 747,451
Stanley T. Crooke	6,518	\$ 327,847	39,643	\$2,460,245
Richard Geary	25,000	\$1,253,799	13,139	\$ 815,406
Patrick R. O'Neil	—	\$ —	12,045	\$ 747,513

(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, January 9, 2020, and February 22, 2021 (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 77 of this Proxy Statement for further information regarding the Amended Advisory Services Agreement.

Following the 2021 Annual Meeting of Stockholders, Dr. Crooke will transition from our Executive Chairman of the Board to a Senior Strategic Advisor. The Company entered into a Strategic Advisory Services Agreement with Dr. Crooke on December 17, 2020 to reflect his new role. Pursuant to such agreement, from the end of Dr. Crooke's service on the Board through June 30, 2023, the Company will pay Dr. Crooke's COBRA premium payments, or if COBRA is not available, an amount equal to the cost of comparable health insurance coverage.

Our executive officers are eligible to participate in our 401(k) contributory defined contribution plan. In 2020, 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 2020, the maximum matching contribution was \$14,500. 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, 2020. 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, 2020. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 83 of this Proxy Statement.

Name	Total – Change of Control Event	Total – Non-Change of Control Event
Brett P. Monia	\$1,781,022	\$1,098,522
Elizabeth L. Hougen	\$ 732,372	\$ 532,550
Stanley T. Crooke	\$1,151,050	\$ 706,691
Richard S. Geary	\$ 736,165	\$ 532,421
Patrick R. O’Neil	\$ 724,356	\$ 523,986

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, 2020, we paid our non-employee Directors a base cash retainer of \$60,000 with additional role-based compensation as noted below:

Role	2020 Cash Compensation
Board Member (Base)	\$60,000
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 2020, each non-employee Director also received automatic stock award grants under our Non-Employee Director Plan. On July 1, 2020, under the Non-Employee Director Plan, each of our non-employee Directors serving at that time received an option to purchase 12,000 shares of our common stock, at an exercise price of \$60.20 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 5,333 shares. The options and RSUs vest on either (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier.

The Compensation Committee has historically reviewed pay levels for non-employee Directors at least every other year, but will review it every year starting in 2021, with assistance from Aon, 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 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. Such reductions were approved by the stockholders in June 2020.

In March 2021, the Compensation Committee and Board adopted a policy whereby (1) the Compensation Committee, with input from its independent consultant, may reduce the number of shares to be automatically issued on a grant date for each such award so that the awards granted have an aggregate grant date fair value that is aligned with the set of peer companies the Compensation Committee uses to evaluate compensation, and (2) the initial equity awards granted upon commencement of Board service will be adjusted downward such that they are 1.5 times the annual equity awards for any given year. The Compensation Committee determined that for 2021, in order to align with the peer companies, if the annual awards to be automatically granted would have an aggregate grant date fair value that exceeds \$500,000, then the number of shares to be automatically issued will be reduced proportionately for each such award so that the awards granted have an aggregate grant date fair value not in excess of \$500,000.

The following table shows for the fiscal year ended December 31, 2020 certain information with respect to the compensation of all our non-employee Directors:

Director Compensation for Fiscal 2020

Name	Cash Compensation Earned or Paid (\$)	Stock Awards (\$) ⁽¹⁾	Option Awards (\$) ⁽¹⁾	All Other Compensation (\$) ⁽²⁾	Total (\$)
Spencer R. Berthelsen	\$ 95,000	\$321,047	\$399,284	\$ —	\$ 815,331
Breaux B. Castleman	\$ 72,000	\$321,047	\$399,284	\$ 15,066	\$ 807,397
Michael Hayden	\$ 70,000	\$321,047	\$399,284	\$ 15,066	\$ 805,397
Joan Herman	\$ 72,000	\$321,047	\$399,284	\$ —	\$ 792,331
Joseph Klein, III	\$ 84,000	\$321,047	\$399,284	\$132,754 ⁽³⁾	\$ 937,085
Joseph Loscalzo	\$ 80,000	\$321,047	\$399,284	\$ —	\$ 800,331
Frederick T. Muto	\$ 92,000	\$321,047	\$399,284	\$ —	\$ 812,331
B. Lynne Parshall	\$ 75,000	\$321,047	\$399,284	\$959,461 ⁽³⁾⁽⁴⁾	\$1,754,792
Peter N. Reikes	\$ 75,000	\$321,047	\$399,284	\$ —	\$ 795,331
Joseph H. Wender	\$100,000	\$321,047	\$399,284	\$ 50,000 ⁽⁵⁾	\$ 870,331

(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, 2020 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 fees earned for service on Akcea's Board of Directors prior to the completion of the Akcea Acquisition and the cash-out of unvested options in connection with the Akcea Acquisition.

(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 2020 includes consulting fees earned under the Amended Advisory Services Agreement.

(5) Amount represents the Lifetime Achievement Award awarded to Mr. Wender in 2020.

Outstanding Equity Awards at Fiscal Year-End – Directors

The following table shows for the fiscal year ended December 31, 2020, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors:

Outstanding Equity Awards as of December 31, 2020

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	—	\$ 9.30	6/30/2021	13,108	\$741,126
	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		
	16,000	—	\$24.42	6/30/2026		
	12,000	4,000	\$52.22	7/2/2027		
	8,000	8,000	\$42.88	7/1/2028		
	4,000	12,000	\$64.80	6/30/2029		
—	12,000	\$60.20	7/1/2030			
Breaux B. Castleman	12,500	—	\$26.66	6/24/2023	13,108	\$741,126
	11,250	—	\$28.47	6/30/2023		
	16,000	—	\$35.53	6/30/2024		
	16,000	—	\$57.16	6/30/2025		
	16,000	—	\$24.42	6/30/2026		
	12,000	4,000	\$52.22	7/2/2027		
	8,000	8,000	\$42.88	7/1/2028		
	4,000	12,000	\$64.80	6/30/2029		
	—	12,000	\$60.20	7/1/2030		
Joseph Klein, III	16,000	—	\$57.16	6/30/2025	13,108	\$741,126
	12,000	—	\$24.42	6/30/2026		
	12,000	4,000	\$52.22	7/2/2027		
	8,000	8,000	\$42.88	7/1/2028		
	4,000	12,000	\$64.80	6/30/2029		
	—	12,000	\$60.20	7/1/2030		
Joseph Loscalzo	22,500	—	\$49.09	2/2/2024	13,108	\$741,126
	16,000	—	\$35.53	6/30/2024		
	16,000	—	\$57.16	6/30/2025		
	16,000	—	\$24.42	6/30/2026		
	12,000	4,000	\$52.22	7/3/2027		
	8,000	8,000	\$42.88	7/1/2028		
	4,000	12,000	\$64.80	6/30/2029		
	—	12,000	\$60.20	7/1/2030		
Frederick T. Muto	15,000	—	\$ 9.30	6/30/2021	13,108	\$741,126
	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		
	8,000	—	\$24.42	6/30/2026		
	12,000	4,000	\$52.22	7/2/2027		
	8,000	8,000	\$42.88	7/1/2028		
	4,000	12,000	\$64.80	6/30/2029		
	—	12,000	\$60.20	7/1/2030		

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	16,000	—	\$35.53	6/30/2024	13,108	\$ 741,126
	16,000	—	\$57.16	6/30/2025		
	16,000	—	\$24.42	6/30/2026		
	12,000	4,000	\$52.22	7/2/2027		
	8,000	8,000	\$42.88	7/1/2028		
	4,000	12,000	\$64.80	6/30/2029		
	—	12,000	\$60.20	7/1/2030		
B. Lynne Parshall ⁽⁵⁾	132,458	—	\$61.57	1/1/2022	28,851	\$1,631,236
	107,549	—	\$61.68	1/3/2023		
	115,187	2,451	\$47.34	1/2/2024		
	75,524	28,051	\$49.25	1/1/2025		
	8,000	8,000	\$42.88	7/1/2028		
	4,000	12,000	\$64.80	6/30/2029		
	—	12,000	\$60.20	7/1/2030		
Michael Hayden	16,000	16,000	\$50.80	9/18/2028	14,219	\$ 803,942
	4,000	12,000	\$64.80	6/30/2029		
	—	12,000	\$60.20	7/1/2030		
Peter N. Reikes	16,000	16,000	\$49.14	9/21/2028	14,219	\$ 803,942
	4,000	12,000	\$64.80	6/30/2029		
	—	12,000	\$60.20	7/1/2030		
Joan Herman	8,000	24,000	\$63.90	6/8/2029	21,330	\$1,205,998
	4,000	12,000	\$64.80	6/30/2029		
	—	12,000	\$60.20	7/1/2030		

- (1) Except for the awards Ms. Parshall received when she was an employee, the options have a term of ten years and were granted out of our Non-Employee Director Plan. Initial options granted upon commencement of Board service prior to June 4, 2020 vest at the rate of 25% per year over four years and those granted on or after June 4, 2020 vest 100% on the first anniversary of the date of grant. Annual options that were granted prior to June 4, 2020 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. Annual options that were granted on or after June 4, 2020 vest 100% on either (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier. 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. Initial RSUs granted upon commencement of Board service prior to June 4, 2020 vest at the rate of 25% per year over four years and those granted on or after June 4, 2020 vest 100% on the first anniversary of the date of grant. Annual RSUs that were granted prior to June 4, 2020 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. Annual RSUs that were granted on or after June 4, 2020 vest 100% on either (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier.
- (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 \$56.54, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 31, 2020, the last trading day of fiscal year 2020.
- (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, 2020, 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 2020

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	\$ 881,400	4,000	\$ 241,708
Breaux B. Castleman	\$10,000	\$ 600,000	4,000	\$ 241,708
Joseph Klein, III	—	—	4,000	\$ 241,708
Joseph Loscalzo	—	—	4,000	\$ 241,708
Frederick T. Muto	\$15,000	\$ 884,400	4,000	\$ 241,708
Joseph H. Wender	\$22,500	\$1,164,825	4,000	\$ 241,708
B. Lynne Parshall ⁽¹⁾	\$ 7,500	\$ 376,151	17,803	\$1,100,418
Michael Hayden	—	—	3,556	\$ 192,895
Peter N. Reikes	—	—	3,556	\$ 192,895
Joan Herman	—	—	5,334	\$ 315,311

(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. In January 2020, Dr. Rosanne Crooke transitioned to a Senior Strategic Advisor for the Company. The Compensation Committee approved Dr. Rosanne Crooke's compensation as an employee and Senior Strategic Advisor. As an employee, her compensation was commensurate with the compensation of other employees at the same level at Ionis. For the fiscal years ended 2020, 2019 and 2018, she received the following compensation:

Name and Principal Position	Year	Salary (\$)	Bonus ⁽²⁾ (\$)	Stock Awards ⁽³⁾ (\$)	Option Awards ⁽³⁾⁽⁴⁾ (\$)	All Other Compensation ⁽⁵⁾ (\$)	Total (\$)
Rosanne Crooke, Senior Strategic Advisor	2020	\$23,859 ⁽¹⁾	—	\$344,123	\$375,716	\$195,193	\$ 938,891
	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

- (1) As of January 15, 2020, Dr. Rosanne Crooke transitioned to a Senior Strategic Advisor. The amount reflected represents Dr. Rosanne Crooke's salary as an Ionis employee prior to the commencement of her Strategic Advisory Services Agreement and the vacation pay-out upon termination of her employment with the Company.
- (2) 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 2021 we paid bonuses for 2020 performance.
- (3) 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, 2020 regarding assumptions underlying valuation of equity awards.
- (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:
 - 17,603 shares at \$49.25 per share received on January 2, 2018;
 - 12,000 shares at \$53.77 per share received on January 2, 2019; and
 - 12,477 shares at \$60.89 received on January 2, 2020.
- (5) For 2020, includes the fees paid to Dr. Rosanne Crooke pursuant to her Strategic Advisory Services Agreement and a \$50,000 Lifetime Achievement Award. For 2020, 2019 and 2018, also includes AD&D, Basic Life, and 401(k) matching contributions while she was an employee of the Company, which are available to all employees of the Company.

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 \$1.3 million in fees in 2020 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2020 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 relationship with Biogen. Pursuant to the Amended Advisory Services Agreement, Ms. Parshall received consulting fees of \$653,750 for services provided in 2020. 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.

Ms. Parshall also serves on the Board and served on the board of directors of Akcea until the completion of the Akcea Acquisition. For her service on Akcea's board of directors in 2020 until the completion of the Akcea Acquisition, Ms. Parshall received \$237,125. Ms. Parshall also received \$53,064 for the cash-out of her unvested stock options in connection with the Akcea Acquisition. For her service on the Company's board of directors, Ms. Parshall receives the same compensation as the Company provides its 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 90 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 \$10.1 million in 2020, which amount is substantially less than 5% of Stifel's gross revenues for its 2020 fiscal year.

One of our Directors, Joseph Wender, is an Advisory Director to Goldman Sachs & Co., a firm we engage from time to time for investment banking services. We paid Goldman an aggregate of approximately \$10.6 million in 2020, which amount is substantially less than 5% of Goldman's gross revenues for its 2020 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 \$1.38 million to the n-Lorem Foundation in 2020. 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 EVP, General Counsel and Corporate Secretary, serves as the Corporate Secretary for the n-Lorem Foundation and Dr. Bennett, our EVP and CSO, serves as a Director and the Chief Technical Officer for n-Lorem. 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 Compliance 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 and 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 2020, 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 2020 in accordance with the requirements of the Summary Compensation Table.

For 2020, the median of the annual total compensation of our employees (other than our CEO) was \$352,641 and the annual total compensation of our CEO, as reported in the Summary Compensation Table included in this Proxy Statement, was \$10,963,040. 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 31 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 internal pay equity ratios described on page [47](#) 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 2021 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 2020, 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, 2020 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 PCAOB 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, 2020, 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, 2020 for filing with the SEC. The Audit Committee and the Board have also approved, subject to stockholder ratification, the selection of Ernst & Young LLP as our independent auditors for 2021.

The Audit Committee
Joseph Klein, III, *Chairman*
Breux 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, 2020 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.com)¹³ to view our 2020 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 23, 2021

¹³ 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. 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, including those related to the impact COVID-19 could have on our business, and 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, 2020, 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. 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 IONIS PHARMACEUTICALS, INC.
2011 EQUITY INCENTIVE PLAN**

**ADOPTED BY THE BOARD OF DIRECTORS: MARCH 23, 2011
APPROVED BY THE STOCKHOLDERS: JUNE 16, 2011
TERMINATION DATE: JUNE 15, 2031**

AMENDED: JUNE 25, 2013 (Amendment approved by Board on February 12, 2013 and by the Stockholders on June 25, 2013)

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

AMENDED: MAY 24, 2017 (Amendment approved by Board on March 3, 2017 and by the Stockholders on May 24, 2017)

AMENDED AND RESTATED: JUNE 6, 2019 (Amendment and Restatement approved by Board on March 22, 2019 and by the Stockholders on June 6, 2019)

Amendment approved by Board on March 26, 2021

SUBJECT TO APPROVAL BY STOCKHOLDERS

1. GENERAL.

(a) Eligible Award Recipients. The persons eligible to receive Awards are Employees, Directors and Consultants.

(b) Available Awards. The Plan provides for the grant of the following Awards: (i) Options, (ii) Stock Appreciation Rights (iii) Restricted Stock Awards, (iv) Restricted Stock Unit Awards, (v) Performance Stock Awards, and (vi) Performance Cash Awards.

(c) Purpose. The Company, by means of the Plan, seeks to secure and retain the services of the group of persons eligible to receive Awards as set forth in Section 1(a), to provide incentives for such persons to exert maximum efforts for the success of the Company and any Affiliate and to provide a means by which such eligible recipients may be given an opportunity to benefit from increases in value of the Common Stock through the granting of Awards.

2. ADMINISTRATION.

(a) Administration by Board. The Board shall administer the Plan unless and until the Board delegates administration of the Plan to a Committee or Committees, as provided in Section 2(c).

(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 from time to time (A) which of the persons eligible under the Plan shall be granted Awards; (B) when and how each Award shall be granted; (C) what type or combination of types of Awards shall be granted; (D) the provisions of each Award granted (which need not be identical), including the time or times when a person shall be permitted to receive cash or Common Stock pursuant to a Stock Award; (E) the number of shares of Common Stock with respect to which a Stock Award shall be granted to each such person; and (F) the Fair Market Value applicable to a Stock Award.

(ii) To construe and interpret the Plan and 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 Stock Award Agreement or in the written terms of a Performance Cash Award, in a manner and to the extent it shall deem necessary or expedient to make the Plan or Award fully effective.

(iii) To settle all controversies regarding the Plan and Awards granted under it.

(iv) Subject to the limitations set forth in Sections 5(f) and 8(j), to accelerate the time at which an Award may first be exercised or the time during which an Award or any part thereof will vest in accordance with the Plan, notwithstanding the provisions in the Award stating the time at which it may first be exercised or the time during which it will vest.

(v) To suspend or terminate the Plan at any time. Suspension or termination of the Plan shall not impair rights and obligations under any Award granted while the Plan is in effect except with the written consent of the affected Participant.

(vi) To amend the Plan in any respect the Board deems necessary or advisable. However, except as provided in Section 9(a) relating to Capitalization Adjustments, to the extent required by applicable law or listing requirements, stockholder approval shall be required for any amendment of the Plan that either (A) materially increases the number of shares of Common Stock available for issuance under the Plan, (B) materially expands the class of individuals eligible to receive Awards under the Plan, (C) materially increases the benefits accruing to Participants under the Plan or materially reduces the price at which shares of Common Stock may be issued or purchased under the Plan, (D) materially extends the term of the Plan, or (E) expands the types of Awards available for issuance under the Plan. Except as provided above, rights under any Award granted before amendment of the Plan shall not be impaired by any amendment of the Plan unless (1) the Company requests the consent of the affected Participant, and (2) such Participant consents in writing.

(vii) To submit any amendment to the Plan for stockholder approval, including, but not limited to, amendments to the Plan intended to satisfy the requirements of Rule 16b-3.

(viii) To approve forms of Award Agreements for use under the Plan and to amend the terms of any one or more Awards, including, but not limited to, (subject to the limitations on repricing and non-acceleration as provided in Section 2(f), 5(f), and 8(j)) amendments to provide terms more favorable to the Participant than previously provided in the Award Agreement, subject to any specified limits in the Plan that are not subject to Board discretion; *provided however*, that a Participant's rights under any Award shall not be impaired by any such amendment unless (A) the Company requests the consent of the affected Participant, and (B) such Participant consents in writing. Notwithstanding the foregoing, subject to the limitations of applicable law, if any, the Board may amend the terms of any one or more Awards without the affected Participant's consent if necessary to bring the Award into compliance with Section 409A of the Code.

(ix) 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 or Awards.

(x) To adopt such procedures and sub-plans as are necessary or appropriate to permit participation in the Plan by Employees, Directors or Consultants who are foreign nationals or employed outside the United States.

(c) Delegation to Committee.

(i) **General.** The Board may delegate some or all of the administration of the Plan to a Committee or Committees. If administration of the Plan is delegated to a Committee, the Committee shall have, in connection with the administration of the Plan, the powers theretofore possessed by the Board that have been delegated to the Committee, including the power to delegate to a subcommittee of the Committee any of the administrative powers the Committee is authorized to exercise (and references in this Plan to the Board shall thereafter be to the Committee or subcommittee), subject, however, to such resolutions, not inconsistent with the provisions of the Plan, as may be adopted from time to time by the Board. The Committee may, at any time, abolish the subcommittee and/or revest in the Committee any powers delegated to the subcommittee. The Board may retain the authority to concurrently administer the Plan with the Committee and may, at any time, revest in the Board some or all of the powers previously delegated.

(ii) **Rule 16b-3 Compliance.** The Committee may consist solely of two or more Non-Employee Directors, in accordance with Rule 16b-3 who are independent under applicable Nasdaq rules.

(d) Delegation to an Executive Officer. The Board may delegate to one or more Executive Officers of the Company the authority to do one or both of the following: (i) designate Employees who are not Executive Officers of the Company or any of its Subsidiaries to be recipients of Options and Stock Appreciation Rights (and, to the extent permitted by applicable law, other Stock Awards) and the terms thereof, and (ii) determine the number of shares of Common Stock to be subject to such Stock Awards granted to such Employees; *provided, however*, that the Board resolutions regarding such delegation shall specify the total number of shares of Common Stock that may be subject to the Stock Awards granted by such Executive Officer and that such Executive Officer may not grant a Stock Award to himself or herself or to other Executive Officers. Notwithstanding the foregoing, the Board may not delegate authority to an Executive Officer to determine the Fair Market Value pursuant to Section 13(v) below.

(e) 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.

(f) 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 or Stock Appreciation Rights under the Plan, or (ii) cancel any outstanding Options or Stock Appreciation Rights 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.

(g) Dividends and Dividend Equivalents. Dividends or dividend equivalents may be paid or credited, as applicable, with respect to any shares of Common Stock subject to a Stock Award (other than an Option or SAR), as determined by the Board and contained in the applicable Stock Award Agreement; *provided, however*, that (i) no dividends or dividend equivalents may be paid with respect to any such shares before the date such shares have vested under the terms of such Stock Award Agreement, (ii) any dividends or dividend equivalents that are credited with respect to any such shares will be subject to all of the terms and conditions applicable to such shares under the terms of such Stock Award Agreement (including, but not limited to, any vesting conditions), and (iii) any dividends or dividend equivalents that are credited with respect to any such shares will be forfeited to the Company on the date, if any, such shares are forfeited to or repurchased by the Company due to a failure to meet any vesting conditions under the terms of such Stock Award Agreement.

3. SHARES SUBJECT TO THE PLAN.

(a) Share Reserve. Subject to Section 9(a) relating to Capitalization Adjustments, the aggregate number of shares of Common Stock that may be issued pursuant to Stock Awards from and after the Effective Date shall not exceed 29,700,000 shares (the "Share Reserve"). For clarity, the Share Reserve in this Section 3(a) is a limitation on the number of shares of the Common Stock that may be issued pursuant to the Plan and does not limit the granting of Stock Awards except as provided in Section 7(a). Shares may be issued in connection with a merger or acquisition as permitted by, as applicable, NASDAQ Listing Rule 5635(c) or, if applicable, NYSE Listed Company Manual Section 303A.08, AMEX Company Guide Section 711 or other applicable rule, and such issuance shall not reduce the number of shares available for issuance under the Plan. Furthermore, if a Stock Award or any portion thereof (i) expires or otherwise terminates without all of the shares covered by such Stock Award having been issued or (ii) is settled in cash (*i.e.*, the Participant receives cash rather than stock), such expiration, termination or settlement shall not reduce (or otherwise offset) the number of shares of Common Stock that may be available for issuance under the Plan. Subject to Section 3(b), the number of shares of Common Stock available for issuance under the Plan will be reduced by: (A) one share for each share of Common Stock issued pursuant to an Option or SAR with respect to which the exercise or strike price is at least 100% of the Fair Market Value of the Common Stock subject to the Option or SAR on the date of grant; and (B) one and seven tenths (1.7) shares for each share of Common Stock issued pursuant to a Full Value Award.

(b) Reversion of Shares to the Share Reserve. If (A) any shares of Common Stock subject to a Stock Award are not issued because such Stock Award or any portion thereof expires or otherwise terminates without all of the shares covered by such Stock Award having been issued or is settled in cash (*i.e.*, the Participant receives cash rather than stock), (B) any shares of Common Stock issued pursuant to a Stock Award are forfeited back to the Company because of the failure to meet a contingency or condition required to vest such shares in the Participant, or (C) with respect to a Full Value Award, any shares of Common Stock are reacquired or withheld (or not issued) by the Company to satisfy a tax withholding obligation in connection with such Full

Value Award, such shares will again become available for issuance under the Plan (collectively, the “2011 Plan Returning Shares”). For clarity, any shares underlying an Option or a Stock Appreciation Right that are reacquired by the Company pursuant to Section 8(f) or as consideration for the exercise of an Option or a Stock Appreciation Right shall not again become available for issuance under the Plan. For each 2011 Plan Returning Share subject to a Full Value Award granted prior to June 2, 2021, the number of shares of Common Stock available for issuance under the Plan will increase by one share, and for each 2011 Plan Returning Share subject to a Full Value Award granted on or after June 2, 2021, the number of shares of Common Stock available for issuance under the Plan will increase by one and seven tenths (1.7) shares.

(c) **Source of Shares.** The stock issuable under the Plan shall be (i) shares of authorized but unissued Common Stock or (ii) shares of reacquired Common Stock, including shares repurchased by the Company on the open market or otherwise.

4. ELIGIBILITY.

(a) **Eligibility for Specific Stock Awards.** Stock Awards may be granted to Employees, Directors and Consultants; *provided, however*, Options and SARs may not be granted to Employees, Directors and Consultants who are providing Continuous Service only to any “parent” of the Company, as such term is defined in Rule 405 promulgated under the Securities Act, unless the stock underlying such Stock Awards is treated as “service recipient stock” under Section 409A of the Code because the Stock Awards are granted pursuant to a corporate transaction (such as a spin off transaction) or unless such Stock Awards comply with the distribution requirements of Section 409A of the Code.

5. PROVISIONS RELATING TO OPTIONS AND STOCK APPRECIATION RIGHTS.

Each Option or SAR shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. The provisions of separate Options or SARs need not be identical; *provided, however*, that each Option Agreement or Stock Appreciation Right Agreement shall conform to (through incorporation of provisions hereof by reference in the applicable Award Agreement or otherwise) the substance of each of the following provisions:

(a) **Term.** No Option or SAR shall be exercisable after the expiration of ten years from the date of its grant or such shorter period specified in the Award Agreement.

(b) **Exercise Price.** The exercise price (or strike price) of each Option or SAR shall be not less than 100% of the Fair Market Value of the Common Stock subject to the Option or SAR on the date the Option or SAR is granted. Notwithstanding the foregoing, an Option or SAR may be granted with an exercise price (or strike price) lower than 100% of the Fair Market Value of the Common Stock subject to the Option or SAR if such Option or SAR is granted pursuant to an assumption of or substitution for another option or stock appreciation right pursuant to a Corporate Transaction and in a manner consistent with the provisions of Sections 409A and, if applicable, 424(a) of the Code. Each SAR will be denominated in shares of Common Stock equivalents.

(c) **Purchase Price for Options.** The purchase price of Common Stock acquired pursuant to the exercise of an Option shall be paid, to the extent permitted by applicable law and as determined by the Board in its sole discretion, by any combination of the methods of payment set forth below. The Board shall have the authority to grant Options that do not permit all of the following methods of payment (or otherwise restrict the ability to use certain methods) and to grant Options that require the consent of the Company to utilize a particular method of payment. The permitted methods of payment are as follows:

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

(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;

(iii) by delivery to the Company (either by actual delivery or attestation) of shares of Common Stock; or

(iv) by a “net exercise” arrangement pursuant to which the Company will reduce the number of shares of Common Stock issuable upon exercise by the largest whole number of shares with a Fair Market

Value that does not exceed the aggregate exercise price; *provided, however*, that the Company shall accept a cash or other payment from the Participant to the extent of any remaining balance of the aggregate exercise price not satisfied by such reduction in the number of whole shares to be issued; *provided, further*, that shares of Common Stock will no longer be subject to an Option and will not be exercisable thereafter to the extent that (A) shares issuable upon exercise are reduced to pay the exercise price pursuant to the “net exercise,” (B) shares are delivered to the Participant as a result of such exercise, and (C) shares are withheld to satisfy tax withholding obligations.

(d) Exercise and Payment of a SAR. To exercise any outstanding Stock Appreciation Right, the Participant must provide written notice of exercise to the Company in compliance with the provisions of the Stock Appreciation Right Agreement evidencing such Stock Appreciation Right. The appreciation distribution payable on the exercise of a Stock Appreciation Right will be not greater than an amount equal to the excess of (A) the aggregate Fair Market Value (on the date of the exercise of the Stock Appreciation Right) of a number of shares of Common Stock equal to the number of Common Stock equivalents in which the Participant is vested under such Stock Appreciation Right, and with respect to which the Participant is exercising the Stock Appreciation Right on such date, over (B) the strike price that will be determined by the Board at the time of grant of the Stock Appreciation Right. The appreciation distribution in respect to a Stock Appreciation Right may be paid in Common Stock, in cash, in any combination of the two or in any other form of consideration, as determined by the Board and contained in the Stock Appreciation Right Agreement evidencing such Stock Appreciation Right.

(e) Transferability of Options and SARs. The Board may, in its sole discretion, impose such limitations on the transferability of Options and SARs as the Board shall determine. In the absence of such a determination by the Board to the contrary, the following restrictions on the transferability of Options and SARs shall apply:

(i) Restrictions on Transfer. An Option or SAR shall not be transferable except by will or by the laws of descent and distribution and shall be exercisable during the lifetime of the Participant only by the Participant; *provided, however*, that the Board may, in its sole discretion, permit transfer of the Option or SAR in a manner that is not prohibited by applicable tax and securities laws upon the Participant’s request. Except as explicitly provided herein, neither an Option nor a SAR may be transferred for consideration.

(ii) Domestic Relations Orders. Notwithstanding the foregoing, an Option or SAR may be transferred pursuant to a domestic relations order.

(iii) Beneficiary Designation. Notwithstanding the foregoing, the Participant may, by delivering written notice to the Company, in a form provided by or otherwise satisfactory to the Company and any broker designated by the Company to effect Option exercises, designate a third party who, in the event of the death of the Participant, shall thereafter be entitled to exercise the Option or SAR and receive the Common Stock or other consideration resulting from such exercise. In the absence of such a designation, the executor or administrator of the Participant’s estate shall be entitled to exercise the Option or SAR and receive the Common Stock or other consideration resulting from such exercise.

(f) Vesting Generally. Subject to Section 8(j), the total number of shares of Common Stock subject to an Option or SAR may vest and therefore become exercisable in periodic installments that may or may not be equal. The Option or SAR may be subject to such other terms and conditions on the time or times when it may or may not be exercised (which may be based on the satisfaction of Performance Goals or other criteria) as the Board may deem appropriate.

(g) Termination of Continuous Service. Except as otherwise provided in the applicable Award Agreement or other agreement between the Participant and the Company (validly executed by an authorized Executive Officer of the Company), if a Participant’s Continuous Service terminates (other than upon the Participant’s death or Disability), the Participant may exercise his or her Option or SAR (to the extent that the Participant was entitled to exercise such Award as of the date of termination of Continuous Service) but only within such period of time ending on the earlier of (i) the date three months following the termination of the Participant’s Continuous Service (or such longer or shorter period specified in the applicable Award Agreement), or (ii) the expiration of the term of the Option or SAR as set forth in the Award Agreement. If, after termination of Continuous Service, the Participant does not exercise his or her Option or SAR within the time specified herein or in the Award Agreement (as applicable), the Option or SAR shall terminate.

(h) Extension of Termination Date. If the exercise of an Option or SAR following the termination of the Participant's Continuous Service (other than upon the Participant'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 or SAR shall terminate on the earlier of (i) the expiration of a total period of three months (that need not be consecutive) after the termination of the Participant's Continuous Service during which the exercise of the Option or SAR would not be in violation of such registration requirements, or (ii) the expiration of the term of the Option or SAR as set forth in the applicable Award Agreement. In addition, unless otherwise provided in a Participant's Award Agreement, if the immediate sale of any Common Stock received upon exercise of an Option or SAR following the termination of the Participant's Continuous Service would violate the Company's insider trading policy, then the Option or SAR 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 Participant's Continuous Service during which the sale of Common Stock received upon exercise of the Option or SAR would not be in violation of the Company's insider trading policy, or (ii) the expiration of the term of the Option or SAR as set forth in the applicable Award Agreement.

(i) Disability of Participant. Except as otherwise provided in the applicable Award Agreement or other agreement between the Participant and the Company (validly executed by an authorized Executive Officer of the Company), if a Participant's Continuous Service terminates as a result of the Participant's Disability, the Participant may exercise his or her Option or SAR (to the extent that the Participant was entitled to exercise such Option or SAR as of the date of termination of Continuous Service), but only within such period of time ending on the earlier of (i) the date 12 months following such termination of Continuous Service (or such longer or shorter period specified in the Award Agreement), or (ii) the expiration of the term of the Option or SAR as set forth in the Award Agreement. If, after termination of Continuous Service, the Participant does not exercise his or her Option or SAR within the time specified herein or in the Award Agreement (as applicable), the Option or SAR (as applicable) shall terminate.

(j) Death of Participant. Except as otherwise provided in the applicable Award Agreement or other agreement between the Participant and the Company (validly executed by an authorized Executive Officer of the Company), if (i) a Participant's Continuous Service terminates as a result of the Participant's death, or (ii) the Participant dies within the period (if any) specified in the Award Agreement for exercisability after the termination of the Participant's Continuous Service (for a reason other than death), then the Option or SAR may be exercised (to the extent the Participant was entitled to exercise such Option or SAR as of the date of death) by the Participant's estate, by a person who acquired the right to exercise the Option or SAR by bequest or inheritance or by a person designated to exercise the Option or SAR upon the Participant's death, but only within the period ending on the earlier of (i) the date 18 months following the date of death (or such longer or shorter period specified in the Award Agreement), or (ii) the expiration of the term of such Option or SAR as set forth in the Award Agreement. If, after the Participant's death, the Option or SAR is not exercised within the time specified herein or in the Award Agreement (as applicable), the Option or SAR shall terminate.

(k) Non-Exempt Employees. Without limiting the provisions set forth in Section 5(f), no Option or SAR, whether or not vested, granted to an Employee who is a non-exempt employee for purposes of the Fair Labor Standards Act of 1938, as amended, shall be first exercisable for any shares of Common Stock until at least six months following the date of grant of the Option or SAR. Notwithstanding the foregoing, consistent with the provisions of the Worker Economic Opportunity Act, (i) in the event of the Participant's death or Disability, (ii) upon a Corporate Transaction in which such Option or SAR is not assumed, continued, or substituted, (iii) upon a Change in Control, or (iv) upon the Participant's retirement (as such term may be defined in the Participant's Award Agreement or in another applicable agreement or in accordance with the Company's then current employment policies and guidelines), any such vested Options and SARs may be exercised earlier than six months following the date of grant. The foregoing provision is intended to operate so that any income derived by a non-exempt employee in connection with the exercise or vesting of an Option or SAR will be exempt from his or her regular rate of pay.

6. PROVISIONS OF STOCK AWARDS OTHER THAN OPTIONS AND SARs.

(a) Restricted Stock Awards. Each Restricted Stock Award Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. To the extent consistent with the Company's Bylaws, at the Board's election, shares of Common Stock may be (i) held in book entry form subject to the Company's instructions until any restrictions relating to the Restricted Stock Award lapse; or (ii) evidenced

by a certificate, which certificate shall be held in such form and manner as determined by the Board. The terms and conditions of Restricted Stock Award Agreements may change from time to time, and the terms and conditions of separate Restricted Stock Award Agreements need not be identical; *provided, however*, that each Restricted Stock 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:

(i) **Consideration.** A Restricted Stock Award may be awarded in consideration for (A) cash, check, bank draft or money order payable to the Company, (B) past services to the Company or an Affiliate, or (C) any other form of legal consideration (including future services) that may be acceptable to the Board, in its sole discretion, and permissible under applicable law.

(ii) **Vesting.** Shares of Common Stock awarded under the Restricted Stock Award Agreement may be subject to forfeiture to the Company in accordance with a vesting schedule to be determined by the Board.

(iii) **Termination of Participant's Continuous Service.** If a Participant's Continuous Service terminates, the Company may receive through a forfeiture condition or a repurchase right any or all of the shares of Common Stock held by the Participant that have not vested as of the date of termination of Continuous Service under the terms of the Restricted Stock Award Agreement.

(iv) **Transferability.** Rights to acquire shares of Common Stock under the Restricted Stock Award Agreement shall be transferable by the Participant only upon such terms and conditions as are set forth in the Restricted Stock Award Agreement, as the Board shall determine in its sole discretion, so long as Common Stock awarded under the Restricted Stock Award Agreement remains subject to the terms of the Restricted Stock Award Agreement.

(b) **Restricted Stock Unit Awards.** 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:

(i) **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 Participant upon delivery of each share of Common Stock subject to the Restricted Stock Unit Award. The consideration to be paid (if any) by the Participant 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.

(ii) **Vesting.** Subject to the limitations set forth in Section 8(j), at the time of the grant of a Restricted Stock Unit Award, the Board may impose such restrictions on or conditions to the vesting of the Restricted Stock Unit Award as it, in its sole discretion, deems appropriate.

(iii) **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.

(iv) **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.

(v) **Termination of Participant'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 Participant's termination of Continuous Service.

(c) **Performance Awards.**

(i) **Performance Stock Awards.** A Performance Stock Award is a Stock Award that may vest or may be exercised contingent upon the attainment during a Performance Period of certain Performance Goals. A Performance Stock Award may, but need not, require the completion of a specified period of Continuous

Service. The length of any Performance Period, the Performance Goals to be achieved during the Performance Period, and the measure of whether and to what degree such Performance Goals have been attained shall be conclusively determined by the Committee, in its sole discretion. The Board may provide for or, subject to such terms and conditions as the Board may specify, may permit a Participant to elect for, the payment of any Performance Stock Award to be deferred to a specified date or event. In addition, to the extent permitted by applicable law and the applicable Award Agreement, the Board may determine that cash may be used in payment of Performance Stock Awards.

(ii) Performance Cash Awards. A Performance Cash Award is a cash award that may be paid contingent upon the attainment during a Performance Period of certain Performance Goals. A Performance Cash Award may also require the completion of a specified period of Continuous Service. At the time of grant of a Performance Cash Award, the length of any Performance Period, the Performance Goals to be achieved during the Performance Period, and the measure of whether and to what degree such Performance Goals have been attained shall be conclusively determined by the Committee, in its sole discretion. The Board may provide for or, subject to such terms and conditions as the Board may specify, may permit a Participant to elect for, the payment of any Performance Cash Award to be deferred to a specified date or event. The Committee may specify the form of payment of Performance Cash Awards, which may be cash or other property, or may provide for a Participant to have the option for his or her Performance Cash Award, or such portion thereof as the Board may specify, to be paid in whole or in part in cash or other property.

(iii) Board Discretion. The Board retains the discretion to reduce or eliminate the compensation or economic benefit due upon attainment of Performance Goals and to define the manner of calculating the Performance Criteria it selects to use for a Performance Period.

7. 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 reasonably 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 that 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 Participant 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 Participant 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.

8. MISCELLANEOUS.

(a) Use of Proceeds from Sales of Common Stock. Proceeds from the sale of shares of Common Stock pursuant to Stock Awards shall constitute general funds of the Company.

(b) Corporate Action Constituting Grant of Stock Awards. Corporate action constituting a grant by the Company of a Stock Award to any Participant shall be deemed completed as of the date of such corporate action, unless otherwise determined by the Board, regardless of when the instrument, certificate, or letter evidencing the Stock Award is communicated to, or actually received or accepted by, the Participant.

(c) Stockholder Rights. No Participant 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 (i) such

Participant has satisfied all requirements for exercise of the Stock Award pursuant to its terms, if applicable, and (ii) the issuance of the Common Stock subject to such Stock Award has been entered into the books and records of the Company.

(d) No Employment or Other Service Rights. Nothing in the Plan, any Stock Award Agreement or any other instrument executed thereunder or in connection with any Award granted pursuant thereto shall confer upon any Participant any right to continue to serve the Company or an Affiliate in the capacity in effect at the time the Stock Award was granted 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.

(e) Investment Assurances. The Company may require a Participant, as a condition of exercising or acquiring Common Stock under any Stock Award, (i) to give written assurances satisfactory to the Company as to the Participant'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 Participant is acquiring Common Stock subject to the Stock Award for the Participant'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 (A) the issuance of the shares 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 (B) as to any particular requirement, counsel for the Company determines 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 or the Company's insider trading policy, including, but not limited to, legends restricting the transfer of the Common Stock.

(f) Withholding Obligations. Unless prohibited by the terms of an Award Agreement, the Company may, in its sole discretion, satisfy any federal, state or local tax withholding obligation relating to an Award by any of the following means or by a combination of such means: (i) causing the Participant to tender a cash payment; (ii) withholding shares of Common Stock from the shares of Common Stock issued or otherwise issuable to the Participant in connection with the 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 lesser amount as may be necessary to avoid classification of the Stock Award as a liability for financial accounting purposes); (iii) withholding cash from an Award settled in cash; (iv) withholding payment from any amounts otherwise payable to the Participant; or (v) by such other method as may be set forth in the Award Agreement.

(g) 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 Participant has access).

(h) Deferrals. To the extent permitted by applicable law, the Board, in its sole discretion, may determine that the delivery of Common Stock or the payment of cash, upon the exercise, vesting or settlement of all or a portion of any Award may be deferred and may establish programs and procedures for deferral elections to be made by Participants. Deferrals by Participants will be made in accordance with Section 409A of the Code. Consistent with Section 409A of the Code, the Board may provide for distributions while a Participant is still an employee or otherwise providing services to the Company. The Board is authorized to make deferrals of Awards and determine when, and in what annual percentages, Participants may receive payments, including lump sum payments, following the Participant's termination of Continuous Service, and implement such other terms and conditions consistent with the provisions of the Plan and in accordance with applicable law.

(i) Compliance with Section 409A. To the extent that the Board determines that any Award granted hereunder is subject to Section 409A of the Code, the Award Agreement evidencing such Award shall incorporate the terms and conditions necessary to avoid the consequences specified in Section 409A(a)(1) of the Code. To the extent applicable, the Plan and Award Agreements shall be interpreted in accordance with Section 409A of

the Code. Notwithstanding anything to the contrary in this Plan (and unless the Award Agreement specifically provides otherwise), if the shares of Common Stock are publicly traded and a Participant holding an Award that constitutes “deferred compensation” under Section 409A of the Code is a “specified employee” for purposes of Section 409A of the Code, no distribution or payment of any amount shall be made upon a “separation from service” before a date that is six months following the date of such Participant’s “separation from service” (as defined in Section 409A of the Code without regard to alternative definitions thereunder) or, if earlier, the date of the Participant’s death.

(j) Minimum Vesting. Except as provided in Section 9, no Stock Award will vest until at least twelve (12) months following the date of grant of such Stock Award (excluding, for this purpose, any (A) Stock Award granted in assumption, substitution or exchange for previously granted awards of a company acquired by the Company or an Affiliate, and (B) Stock Awards to Non-Employee Directors that vest on the earlier of the one year anniversary of the date of grant or the next annual meeting of shareholders (provided that such vesting period may not be less than 50 weeks after grant); *provided, however*, that up to five percent (5%) of the Share Reserve (as defined in Section 3(a)) may be subject to Stock Awards that do not meet such vesting requirements; and *provided further* that for the avoidance of doubt, that the foregoing restriction does not apply to accelerated exercisability or vesting in accordance with Section 9(c) or 9(d) herein.

(k) Compliance with Insider-Trading Policy. The Company may limit or restrict a Participant’s ability to exercise options or sell stock pursuant to the Company’s then-applicable insider-trading policy (or similar policy adopted by the Company).

9. ADJUSTMENTS UPON CHANGES IN COMMON STOCK; OTHER CORPORATE EVENTS.

(a) Capitalization Adjustments. In the event of a Capitalization Adjustment, the Board shall appropriately and proportionately adjust: (i) the class(es) and maximum number of securities subject to the Plan pursuant to Section 3(a) and (ii) the class(es) and number of securities and price per share of stock subject to outstanding Stock Awards. The Board shall make such adjustments, and its determination shall be final, binding and conclusive.

(b) Dissolution or Liquidation. Except as otherwise provided in the Stock Award Agreement, in the event of a dissolution or liquidation of the Company, all outstanding Stock Awards (other than Stock Awards consisting of vested and outstanding shares of Common Stock not subject to a forfeiture condition or the Company’s right of repurchase) shall terminate immediately prior to the completion of such dissolution or liquidation, and the shares of Common Stock subject to the Company’s repurchase rights or subject to a forfeiture condition may be repurchased or reacquired by the Company notwithstanding the fact that the holder of such Stock Award is providing Continuous Service, *provided, however*, that the Board may, in its sole discretion, cause some or all Stock Awards to become fully vested, exercisable and/or no longer subject to repurchase or forfeiture (to the extent such Stock Awards have not previously expired or terminated) before the dissolution or liquidation is completed but contingent on its completion.

(c) Corporate Transaction. The provisions of this Section 9(c) will apply to Stock Awards in the event of a Corporate Transaction unless otherwise provided in the instrument evidencing the Stock Award or any other written agreement between the Company or any Affiliate and the Participant or in any director compensation policy of the Company or unless otherwise expressly provided by the Board at the time of grant of a Stock Award.

(i) Stock Awards May Be Assumed. In the event of a Corporate Transaction, any surviving corporation or acquiring corporation (or the surviving or acquiring corporation’s parent company) may assume or continue any or all Stock Awards outstanding under the Plan or may substitute similar stock awards for Stock Awards outstanding under the Plan (including but not limited to, awards to acquire the same consideration paid to the stockholders of the Company pursuant to the Corporate Transaction), and any reacquisition or repurchase rights held by the Company in respect of Common Stock issued pursuant to Stock Awards may be assigned by the Company to the successor of the Company (or the successor’s parent company, if any), in connection with such Corporate Transaction. A surviving corporation or acquiring corporation (or its parent) may choose to assume or continue only a portion of a Stock Award or substitute a similar stock award for only a portion of a Stock Award, or may choose to assume or continue the Stock Awards held by some, but not all Participants. The terms of any assumption, continuation or substitution will be set by the Board.

(ii) Stock Awards Held by Current Participants. In the event of a Corporate Transaction in which the surviving corporation or acquiring corporation (or its parent company) does not assume or continue such outstanding Stock Awards or substitute similar stock awards for such outstanding Stock Awards, then with respect to Stock Awards that have not been assumed, continued or substituted and that are held by Participants whose Continuous Service has not terminated prior to the effective time of the Corporate Transaction (referred to as the “Current Participants”), the vesting of any time-based Stock Awards (and, with respect to Options and Stock Appreciation Rights, the time when such Stock Awards may be exercised) will be accelerated in full (and the vesting of any performance-based Stock Awards shall be deemed satisfied at the greater of actual performance or target level) to a date prior to the effective time of such Corporate Transaction (contingent upon the effectiveness of the Corporate Transaction) as the Board will determine (or, if the Board does not determine such a date, to the date that is five days prior to the effective time of the Corporate Transaction), and such Stock Awards will terminate if not exercised (if applicable) at or prior to the effective time of the Corporate Transaction, and any reacquisition or repurchase rights held by the Company with respect to such Stock Awards will lapse (contingent upon the effectiveness of the Corporate Transaction).

(iii) Stock Awards Held by Persons other than Current Participants. In the event of a Corporate Transaction in which the surviving corporation or acquiring corporation (or its parent company) does not assume or continue such outstanding Stock Awards or substitute similar stock awards for such outstanding Stock Awards, then with respect to Stock Awards that have not been assumed, continued or substituted and that are held by persons other than Current Participants, such Stock Awards will terminate if not exercised (if applicable) prior to the effective time of the Corporate Transaction; provided, however, that any reacquisition or repurchase rights held by the Company with respect to such Stock Awards will not terminate and may continue to be exercised notwithstanding the Corporate Transaction.

(iv) Payment for Stock Awards in Lieu of Exercise. Notwithstanding the foregoing, in the event a Stock Award will terminate if not exercised prior to the effective time of a Corporate Transaction, the Board may provide, in its sole discretion, that the holder of such Stock Award may not exercise such Stock Award but instead will receive a payment, in such form as may be determined by the Board, equal in value to the excess, if any, of (A) the value of the property the Participant would have received upon the exercise of the Stock Award immediately prior to the effective time of the Corporate Transaction after application of the vesting acceleration described in (iii) above), over (B) any exercise price payable by such holder in connection with such exercise. For clarity, this payment may be zero if the value of the property is equal to or less than the exercise price. Payments under this provision may be delayed to the same extent that payment of consideration to the holders of the Company’s Common Stock in connection with the Corporate Transaction is delayed as a result of escrows, earn outs, holdbacks or any other contingencies.

(d) Change in Control. A Stock Award will not be subject to additional acceleration of vesting and exercisability in connection with a Change in Control, except upon certain termination events that are in connection with a Change in Control as provided in the Stock Award Agreement for such Stock Award or as otherwise may be provided in any other written agreement between the Company or any Affiliate and the Participant. In such a case, the Stock Award Agreement or other written agreement may provide that vesting (and, if applicable, exercisability) of time-based awards will be accelerated in full and performance-based Stock Awards will be deemed to have been satisfied at the greater of actual performance or target level.

10. TERMINATION OR SUSPENSION OF THE PLAN.

(a) Plan Term. The Board may suspend or terminate the Plan at any time. Unless terminated sooner by the Board, the Plan shall automatically terminate on June 15, 2031. No 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 Award granted while the Plan is in effect except with the written consent of the affected Participant.

11. EFFECTIVE DATE OF PLAN.

This Plan shall become effective on the date of the annual meeting of stockholders of the Company held in 2011 provided this Plan is approved by the Company’s stockholders at such meeting (the “Effective Date”).

12. CHOICE OF LAW.

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

13. DEFINITIONS. AS USED IN THE PLAN, THE FOLLOWING DEFINITIONS SHALL APPLY TO THE CAPITALIZED TERMS INDICATED BELOW:

(a) "**Affiliate**" means, at the time of determination, any "parent" or "subsidiary" of the Company as such terms are defined in Rule 405 promulgated under the Securities Act. The Board shall have the authority to determine the time or times at which "parent" or "subsidiary" status is determined within the foregoing definition, and such determination shall be final, binding and conclusive on all persons.

(b) "**Award**" means a Stock Award or a Performance Cash Award.

(c) "**Award Agreement**" means a written agreement between the Company and a Participant evidencing the terms and conditions of an Award.

(d) "**Board**" means the Board of Directors of the Company.

(e) "**Capitalization Adjustment**" means any change that is made in, or other events that occur with respect to, the Common Stock subject to the Plan or subject to any Stock Award after the Effective Date without the receipt of consideration by the Company through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, large nonrecurring cash dividend, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or any similar equity restructuring transaction, as that term is used in Statement of Financial Accounting Standards No. 123 (revised). Notwithstanding the foregoing, the conversion of any convertible securities of the Company shall not be treated as a Capitalization Adjustment.

(f) "**Change in Control**" means the consummation, 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. Notwithstanding the foregoing, a Change in Control shall not be deemed to occur (A) on account of the acquisition of securities of the Company directly from the Company, (B) on account of the acquisition of securities of the Company by an investor, any affiliate thereof or any other Exchange Act Person that acquires the Company's securities in a transaction or series of related transactions the primary purpose of which is to obtain financing for the Company through the issuance of equity securities, or (C) solely because the level of Ownership held by any Exchange Act Person (the "Subject Person") exceeds the designated percentage threshold 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 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 designated percentage threshold, 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, either (A) 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 (B) more than 50% of the combined outstanding voting power of the parent of the surviving Entity in such merger, consolidation or similar transaction, in each case in substantially the same proportions as their Ownership of the outstanding voting securities of the Company immediately prior to such 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, except for a liquidation into a parent corporation;

(iv) there is consummated a sale, lease, exclusive 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 outstanding voting securities of the Company immediately prior to such sale, lease, license or other disposition; or

(v) individuals who, on the date the 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, (A) the term Change in Control shall not include a sale of assets, merger or other transaction effected exclusively for the purpose of changing the domicile of the Company, and (B) the definition of Change in Control (or any analogous term) in an individual written agreement between the Company or any Affiliate and the Participant (validly executed by an authorized Executive Officer of the Company or such Affiliate) shall supersede the foregoing definition with respect to Awards subject to such agreement; *provided, 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.

(g) "**Code**" means the Internal Revenue Code of 1986, as amended, including any applicable regulations and guidance thereunder.

(h) "**Committee**" means a committee of one or more Directors to whom authority has been delegated by the Board in accordance with Section 2(c).

(i) "**Common Stock**" means the common stock of the Company.

(j) "**Company**" means Ionis Pharmaceuticals, Inc., a Delaware corporation.

(k) "**Consultant**" means any person, including an advisor, who is (i) engaged by the Company or an Affiliate to render consulting or advisory services and is compensated for such services, or (ii) serving as a member of the board of directors of an Affiliate and is compensated for such services. However, service solely as a Director, or payment of a fee for such service, shall not cause a Director to be considered a "Consultant" for purposes of the Plan. Notwithstanding the foregoing, a person is treated as a Consultant under this Plan only if a Form S-8 Registration Statement under the Securities Act is available to register either the offer or the sale of the Company's securities to such person.

(l) "**Continuous Service**" means that the Participant'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 Participant renders service to the Company or an Affiliate as an Employee, Consultant or Director or a change in the entity for which the Participant renders such service, provided that there is no interruption or termination of the Participant's service with the Company or an Affiliate, shall not terminate a Participant's Continuous Service; *provided, however*, if the Entity for which a Participant is rendering services ceases to qualify as an Affiliate, as determined by the Board, in its sole discretion, such Participant's Continuous Service shall be considered to have terminated on the date such Entity ceases to qualify as an Affiliate. To the extent permitted by law, 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 (i) any leave of absence approved by the Board or Chief Executive Officer, including sick leave, military leave or any other personal leave, or (ii) transfers between the Company, an Affiliate, or their successors. Notwithstanding the foregoing, a leave of absence shall be treated as Continuous Service for purposes of vesting in a Stock Award only to such extent as may be provided in the Company's leave of absence policy, in the written terms of any leave of absence agreement or policy applicable to the Participant, or as otherwise required by law.

(m) “**Corporate Transaction**” means the consummation, 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 sole 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.

(n) “**Director**” means a member of the Board.

(o) “**Disability**” means, with respect to a Participant, the inability of such Participant to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months, as provided in Sections 22(e)(3) and 409A(a)(2)(c)(i) of the Code, and shall be determined by the Board on the basis of such medical evidence as the Board deems warranted under the circumstances.

(p) “**Effective Date**” has the meaning set forth in Section 11 of the Plan.

(q) “**Employee**” means any person employed by the Company or an Affiliate. However, service solely as a Director, or payment of a fee for such services, shall not cause a Director to be considered an “Employee” for purposes of the Plan.

(r) “**Entity**” means a corporation, partnership, limited liability company or other entity.

(s) “**Exchange Act**” means the Securities Exchange Act of 1934, as amended, and the rules and regulations promulgated thereunder.

(t) “**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 (i) the Company or any Subsidiary of the Company, (ii) 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, (iii) an underwriter temporarily holding securities pursuant to a registered public offering of such securities, (iv) 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; or (v) any natural person, Entity or “group” (within the meaning of Section 13(d) or 14(d) of the Exchange Act) that, as of the Effective Date, is 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.

(u) “**Executive Officer**” means a person who is an officer of the Company within the meaning of Section 16 of the Exchange Act.

(v) “**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 any established market, the Fair Market Value of a share of Common Stock shall be the closing sales price for such stock as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the date of determination, as reported in a source the Board deems reliable.

(ii) Unless otherwise provided by the Board, if there is no closing sales price for the Common Stock on the date of determination, then the Fair Market Value shall be the closing selling price on the last preceding date for which such quotation exists.

(iii) In the absence of such markets for the Common Stock, the Fair Market Value shall be determined by the Board in good faith and in a manner that complies with Sections 409A and 422 of the Code.

(w) **“Full Value Award”** means a Stock Award that is not an Option or SAR with respect to which the exercise or strike price is at least 100% of the Fair Market Value of the Common Stock subject to the Option or SAR on the date of grant.

(x) **“Non-Employee Director”** means a Director who either (i) is not a current employee or officer of the Company or an Affiliate, does not receive compensation, either directly or indirectly, from the Company or an Affiliate for services rendered as a consultant or in any capacity other than as a Director (except for an amount as to which disclosure would not be required under Item 404(a) of Regulation S-K promulgated pursuant to the Securities Act (“Regulation S-K”)), does not possess an interest in any other transaction for which disclosure would be required under Item 404(a) of Regulation S-K, and is not engaged in a business relationship for which disclosure would be required pursuant to Item 404(b) of Regulation S-K; or (ii) is otherwise considered a “non-employee director” for purposes of Rule 16b-3.

(y) **“Option”** means a stock option granted pursuant to Section 5 of the Plan to purchase shares of Common Stock granted pursuant to the Plan.

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

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

(bb) **“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.

(cc) **“Participant”** means a person to whom an Award is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Stock Award.

(dd) **“Performance Cash Award”** means an award of cash granted pursuant to the terms and conditions of Section 6(c)(ii).

(ee) **“Performance Criteria”** means the one or more criteria that the Board shall select for purposes of establishing the Performance Goals for a Performance Period. The Performance Criteria that shall be used to establish such Performance Goals may be based on any one of, or combination of, the following as determined by the Board: (i) earnings (including earnings per share and net earnings); (ii) earnings before interest, taxes and depreciation; (iii) earnings before interest, taxes, depreciation and amortization; (iv) total stockholder return; (v) return on equity or average stockholder’s equity; (vi) return on assets, investment, or capital employed; (vii) stock price; (viii) margin (including gross margin); (ix) income (before or after taxes); (x) operating income; (xi) operating income after taxes; (xii) pre-tax profit; (xiii) operating cash flow; (xiv) sales or revenue targets; (xv) increases in revenue or product revenue; (xvi) expenses and cost reduction goals; (xvii) improvement in or attainment of working capital levels; (xviii) economic value added (or an equivalent metric); (xix) market share; (xx) cash flow; (xxi) cash flow per share; (xxii) share price performance; (xxiii) debt reduction; (xxiv) implementation or completion of projects or processes (including, but not limited to development and regulatory milestones); (xxv) customer satisfaction; (xxvi) stockholders’ equity; (xxvii) capital expenditures; (xxviii) debt levels; (xxix) operating profit or net operating profit; (xxx) workforce diversity; (xxxi) growth of net income or operating income; (xxxii) billings; and (xxxiii) any other measure or measures of performance selected by the Board.

(ff) **“Performance Goals”** means, for a Performance Period, the one or more goals established by the Board for the Performance Period based upon the Performance Criteria. Performance Goals may be based on a Company-wide basis, with respect to one or more business units, divisions, Affiliates, or business segments, and in either absolute terms or relative to the performance of one or more comparable companies or the performance of one or more relevant indices. Unless specified otherwise by the Board (i) in the Award Agreement at the time the Award is granted or (ii) in such other document setting forth the Performance Goals at the time the Performance Goals are established, the Board shall appropriately make adjustments in the method of calculating the attainment of Performance Goals for a Performance Period as

follows: (1) to exclude restructuring and/or other nonrecurring charges; (2) to exclude exchange rate effects, as applicable, for non-U.S. dollar denominated Performance Goals; (3) to exclude the effects of changes to generally accepted accounting principles; (4) to exclude the effects of any statutory adjustments to corporate tax rates; (5) to exclude the effects of items that are “unusual” in nature or occur “infrequently” as determined under generally accepted accounting principles; and (6) to exclude accounting expenses relating to share-based compensation.

(gg) “Performance Period” means the period of time selected by the Board over which the attainment of one or more Performance Goals will be measured for the purpose of determining a Participant’s right to and the payment of a Stock Award or a Performance Cash Award. Performance Periods may be of varying and overlapping duration, at the sole discretion of the Board.

(hh) “Performance Stock Award” means a Stock Award granted under the terms and conditions of Section 6(c)(i).

(ii) “Plan” means this Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan.

(jj) “Restricted Stock Award” means an award of shares of Common Stock which is granted pursuant to the terms and conditions of Section 6(a).

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

(ll) “Restricted Stock Unit Award” means a right to receive shares of Common Stock which is granted pursuant to the terms and conditions of Section 6(b).

(mm) “Restricted Stock Unit Award Agreement” means a written agreement between the Company and a holder of a Restricted Stock Unit Award evidencing the terms and conditions of a Restricted Stock Unit Award grant. Each Restricted Stock Unit Award Agreement shall be subject to the terms and conditions of the Plan.

(nn) “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.

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

(pp) “Stock Appreciation Right” or **“SAR”** means a right to receive the appreciation on Common Stock that is granted pursuant to the terms and conditions of Section 5.

(qq) “Stock Appreciation Right Agreement” means a written agreement between the Company and a holder of a Stock Appreciation Right evidencing the terms and conditions of a Stock Appreciation Right grant. Each Stock Appreciation Right Agreement shall be subject to the terms and conditions of the Plan.

(rr) “Stock Award” means any right to receive Common Stock granted under the Plan, including an Option, a Restricted Stock Award, a Restricted Stock Unit Award, a Stock Appreciation Right, or a Performance Stock Award.

(ss) “Stock Award Agreement” means a written agreement between the Company and a Participant evidencing the terms and conditions of a Stock Award grant. Each Stock Award Agreement shall be subject to the terms and conditions of the Plan.

(tt) “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, limited liability company or other entity 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%.

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

VOTE BY INTERNET - 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 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/IQNS2021

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 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:

 THIS PROXY CARD IS VALID ONLY WHEN SIGNED AND DATED.

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

The Board of Directors recommends you vote FOR the following nominees to be elected for a term expiring in 2024:	<table border="0"> <tr> <td style="padding-right: 10px;">For All</td> <td style="padding-right: 10px;">Withhold All</td> <td style="padding-right: 10px;">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"/>	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.	
For All	Withhold All	For All Except							
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>							

1. Election of Directors

Nominees

- 01) Brett Monia 02) Frederick Muto 03) Peter Reikes

The Board of Directors recommends you vote FOR proposals 2, 3 and 4.

- | | | | |
|--|--------------------------|--------------------------|--------------------------|
| 2. To approve an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under such plan by 6,700,000 shares to an aggregate of 29,700,000 shares and add a fungible share counting ratio. | FOR | AGAINST | ABSTAIN |
| | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 3. To approve, by non-binding vote, executive compensation. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| 4. Ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for the 2021 fiscal year. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

NOTE: Such other business as may properly come before the meeting or any adjournment thereof.

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.

Signature [PLEASE SIGN WITHIN BOX]	Date

Signature (Joint Owners)	Date

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**IONIS PHARMACEUTICALS, INC.
Annual Meeting of Stockholders
June 2, 2021 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 reverse 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 2, 2021 at www.virtualshareholdermeeting.com/IONS2021 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 and FOR Proposal 4, and in the discretion of the proxies with respect to such other business as may properly come before the meeting.

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Continued and to be signed on reverse side