

**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

2017 ANNUAL MEETING OF STOCKHOLDERS

Dear Stockholders,

I am pleased to invite you to Ionis Pharmaceuticals, Inc.'s 2017 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Wednesday, May 24, 2017, at 2:00 p.m. Pacific Time. 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 2017, and answer your questions. 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 meeting and prefer to vote in person, 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.

We look forward to seeing you at the meeting.

Sincerely,

Patrick R. O'Neil
Corporate Secretary

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

NOTICE OF 2017 ANNUAL MEETING OF STOCKHOLDERS

Date: Wednesday, May 24, 2017
Time: 2:00 p.m., Pacific Time
Place: Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Dear Stockholders,

At our 2017 Annual Meeting, we will ask you to:

- Proposal 1: elect Spencer R. Berthelsen, B. Lynne Parshall and Joseph H. Wender to serve as Directors for a three-year term;
- Proposal 2: approve an amendment to the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance under the 2011 Equity Incentive Plan by 5,000,000 to an aggregate of 16,000,000 shares;
- Proposal 3: make an advisory vote on executive compensation;
- Proposal 4: make an advisory vote on the frequency of future advisory votes on executive compensation; and
- Proposal 5: ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2017 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 March 31, 2017 you may vote at the Annual Meeting.

By order of the Board of Directors,

Patrick R. O'Neil
Corporate Secretary

Carlsbad, California
April 6, 2017

ALL STOCKHOLDERS ARE CORDIALLY INVITED TO ATTEND THE MEETING IN PERSON. 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 IN ORDER 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 IN PERSON IF YOU ATTEND THE MEETING. 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

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 2017 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 about April 13, 2017 to all stockholders of record entitled to vote at the Annual Meeting.

Will I receive any other proxy materials by mail?

We may choose to send you a proxy card, along with a second Notice, on or after April 24, 2017.

Where and when is the Annual Meeting and how do I attend?

We will hold the meeting on Wednesday, May 24, 2017, at 2:00 p.m. Pacific Time at our offices located at 2855 Gazelle Court, Carlsbad, California 92010. You may find directions to the Annual Meeting at www.ionispharma.com.¹ We discuss information on how to vote in person at the Annual Meeting below.

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 meeting and prefer to vote in person, you may still do so even if you have already returned your proxy.

Who can vote at the Annual Meeting?

Only stockholders of record at the close of business on March 31, 2017 may vote at the Annual Meeting. On this record date, there were 123,880,559 shares of common stock outstanding and entitled to vote.

Stockholder of Record: Shares Registered in Your Name

If on March 31, 2017 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 in person at the 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 March 31, 2017 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 Annual Meeting in person.

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.

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?

There are five matters scheduled for a vote:

- Proposal 1: elect Spencer R. Berthelsen, B. Lynne Parshall and Joseph H. Wender to serve as Directors for a three-year term;
- Proposal 2: approve an amendment to the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance under the 2011 Equity Incentive Plan by 5,000,000 to an aggregate 16,000,000 shares;
- Proposal 3: make an advisory vote on executive compensation;
- Proposal 4: make an advisory vote on the frequency of future advisory votes on executive compensation; and
- Proposal 5: ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2017 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 in person by attending the 2017 Annual Meeting.

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 May 23, 2017. 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 May 23, 2017 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 through 4 regarding (1) the election of Directors, (2) approval of an amendment to the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance, (3) approval, on an advisory basis, of our executive compensation, and (4) approval, on an advisory basis, on the frequency of future advisory votes on executive compensation, are non-discretionary items. If you do not give your broker instructions for a non-discretionary item, the inspector of elections will treat your shares as broker non-votes.

A number of brokers and banks are participating in a program provided by Broadridge which 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 to the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan;
- “For” the approval, on an advisory basis, of executive compensation;
- “For” every year as the preferred frequency of advisory votes to approve executive compensation; and
- “For” the ratification of the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2017 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 in person at the Annual Meeting. *Attendance* at the meeting *will not*, by itself, revoke a proxy.

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 2018 Annual Meeting of Stockholders, you must send the proposal to us by no later than December 14, 2017. 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 January 24, 2018. 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 are represented in person or by proxy. We will count your shares towards the quorum only if you submit a valid proxy vote 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 in person 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 March 31, 2017. 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 Proposal 1. Abstentions will count towards the vote total for Proposals 2, 3 and 5, and in each case, will have the same effect as "Against" votes. With respect to Proposal 4 regarding how often you wish us to include an advisory vote on executive compensation, the inspector of elections will count the number of votes regarding every year, every two years, and every three years, and abstentions will have no effect. 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 through 4 regarding (a) the election of Directors, (b) approval of an amendment to the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance, (c) approval, on an advisory basis, of our executive compensation, and (d) the advisory vote on the frequency of future advisory votes on 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 person or by proxy in the election such that the number of shares voted “For” the nominee must exceed 50% of the votes cast with respect to that Director. Only “For” and “Withhold” votes will affect the outcome. Abstentions and broker non-votes will have no effect.
- Proposal 2: To be approved, the amendment of our 2011 Equity Incentive Plan must receive “For” votes from the holders of a majority of shares either present in person or represented by proxy and entitled to vote. If you mark your proxy to “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes 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 the holders of a majority of shares either present in person or represented by proxy and entitled to vote. If you “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes will have no effect.
- Proposal 4: For the advisory vote on the frequency of stockholder advisory votes on executive compensation, we will consider the frequency receiving the most “For” votes from the holders of shares present in person or represented by proxy and entitled to vote as the frequency preferred by the stockholders. Abstentions and broker non-votes will have no effect.
- Proposal 5: To be approved, the ratification of the selection of Ernst & Young LLP as our independent auditors for our 2017 fiscal year, must receive “For” votes from the holders of a majority of shares present in person or by proxy and entitled to vote. If you “Abstain” from voting, it will have the same effect as an “Against” vote.

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 with a Form 8-K within four business days after the Annual Meeting, we intend to file a Form 8-K to publish preliminary results and, within four business days after we know the final results, file an additional Form 8-K to publish final results.

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

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

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

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

ELECTION OF DIRECTORS

Information about our Board

The Board is divided into three classes. Presently, the Board has eight members with two classes consisting of three Directors each and one class consisting of two 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 who 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.

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 2017 Elections

The Board has nominated three individuals for election at the 2017 Annual Meeting. Each of the nominees currently serves as one of our Directors. Dr. Berthelsen, Ms. Parshall and Mr. Wender have served as a Director since May 2002, September 2000 and January 1994, respectively. Dr. Berthelsen, Ms. Parshall and Mr. Wender have been re-elected by our stockholders each successive term. If re-elected, Dr. Berthelsen, Ms. Parshall and Mr. Wender will serve until the 2020 Annual Meeting or, in each case, until his or her successor is elected and has qualified, or until his or her earlier death, resignation or removal.

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

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

The Nominating, Governance and Review Committee delivered its report to the Board on March 3, 2017. Following that report, the Board determined it would be in the best interests of Ionis and its stockholders to nominate Dr. Berthelsen, Ms. Parshall and Mr. Wender to be elected as Directors at the Annual Meeting. We provide below a short biography for each nominee. Dr. Berthelsen, Ms. Parshall and Mr. Wender 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 2020 Annual Meeting

Spencer R. Berthelsen, M.D., age 64², has served as a Director of Ionis since May 2002. Since 1980, he has practiced Internal Medicine with the Kelsey Seybold Clinic, a 400 physician medical group based in the Texas Medical Center in Houston. Dr. Berthelsen has served in various senior leadership positions at Kelsey Seybold, including Chairman of the Department of Internal Medicine, Medical Director and Managing Director. He served as Chairman of their Board of Directors from October 2001 through April 2016. He has served as a Clinical Professor of Medicine at Baylor College of Medicine and the University of Texas Health Science Center of Houston. 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 multi-specialty group practice and 36 years of experience as a practicing physician.

B. Lynne Parshall, age 62, has served as a Director of Ionis since September 2000. She has been our Chief Operating Officer since December 2007 and previously served 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, California and San Diego bar associations. Ms. Parshall serves on the board of directors of Cytokinetics Inc., a biopharmaceutical company. Within the last five years, Ms. Parshall formerly served as a Director of Regulus Therapeutics, Inc.

The Board believes Ms. Parshall is uniquely suited to serve on the Board primarily because, as the Chief Operating Officer and an executive of the Company for over 20 years, she has valuable Company-specific experience and expertise. In addition, Ms. Parshall has over 30 years of experience structuring and negotiating strategic licensing and financing transactions in the life sciences field.

Joseph H. Wender, age 72, has served as a Director of Ionis since January 1994. Mr. Wender began with Goldman, Sachs & Co. in 1971 and became a General Partner of that firm in 1982, where he headed the Financial Institutions Group for over a decade. Since January 2008, he has been a Senior Consultant to Goldman Sachs & Co. He is also an Independent Trustee of the Schwab Family of Funds and Director of Grandpoint Capital, a bank holding company. Mr. Wender also is a managing partner and owns, with his wife, Colgin Cellars. Since March 2014, Mr. Wender has been a director of Outfront Media, lessors of advertising space on out-of-home advertising structures.

The Board believes Mr. Wender is uniquely suited to serve on the Board primarily because, with over 40 years of experience as an investment banker with Goldman, Sachs & Co., he provides Ionis important advice regarding our financial reporting, corporate finance matters, strategic transactions, and compensation matters. Mr. Wender is also highly qualified to serve on the Audit Committee.

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

Biographies of the Directors Whose Terms Expire at the 2018 Annual Meeting

Frederick T. Muto, age 63, 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 and became a partner in 1986. He is a founding partner of Cooley LLP’s San Diego office and was Chair of the firm’s Business Department.

The Board believes Mr. Muto is uniquely suited to serve on the Board primarily because, with over 36 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.

Breaux B. Castleman, age 76, has served as a Director of Ionis since June 2013. Since August 2001, Mr. Castleman has been president and chief executive officer of Syntiro Healthcare Services, Inc., a healthcare investment company, which sold its operations as a service provider of integrated care management and disease management. Mr. Castleman was a director of USMD Holdings, Inc., a physician-led integrated healthcare system, from September 2009 until October 2016 and was a director of MELA Sciences, Inc., a medical device company, from 2003 until 2011.

² All ages of our Directors provided under this Proposal 1 are as of March 1, 2017.

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

Biographies of the Directors Whose Terms Expire at the 2019 Annual Meeting

Stanley T. Crooke, M.D., Ph.D., age 71, is a founder of Ionis and has been Chief Executive Officer and a Director since January 1989. He was elected Chairman of the Board in 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.

The Board believes Dr. Crooke is uniquely suited to serve on the Board primarily because, as the Chief Executive Officer and founder of Ionis, he has dedicated nearly 30 years to discovering and developing antisense, our technology platform. He is the named inventor on some of the key patents in the field of RNA-targeted therapeutics, and has over 31 years of drug discovery and development experience.

Joseph Klein, III, age 55, has served as a Director of Ionis since December 2005. Mr. Klein is currently Managing Director of Gauss Capital Advisors, LLC, a financial consulting and investment advisory firm focused on biopharmaceuticals, which he founded in March 1998. From September 2003 to December 2008, Mr. Klein also served as a Venture Partner of Red Abbey Venture Partners, L.P., a life science private equity fund. From September 2001 to September 2002, Mr. Klein was a Venture Partner of MPM Capital, a healthcare venture capital firm. From June 1999 to September 2000 when it merged with WebMD Corporation, Mr. Klein served as Vice President, Strategy, for Medical Manager Corporation, a leading developer of physician office management information systems. For over nine years from 1989 to 1998, Mr. Klein was a health care investment analyst at T. Rowe Price Associates, Inc., where he was the founding portfolio manager of the T. Rowe Price Health Sciences Fund, Inc. Mr. Klein serves on the board of directors of The Prospector Funds, Inc., an SEC Registered Investment Company that manages two no-load mutual funds. Mr. Klein also serves on the boards of private and non-profit entities.

The Board believes that Mr. Klein is uniquely suited to serve on the Board and 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, age 65, 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. His clinical training was completed 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. He currently serves on the board of directors of Leap Therapeutics, Inc., a publicly held biopharmaceutical company.

The Board believes Dr. Loscalzo is uniquely suited to serve on the Board primarily because of his extensive scientific expertise, including 26 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.

Independence of the Board

As required under NASDAQ listing standards, a majority of the members of a listed company’s board of directors must qualify as “independent,” as affirmatively determined by our Nominating, Governance and Review Committee. 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 and Ms. Parshall, our Chief Executive Officer and Chief Operating Officer, respectively. In making this determination, the Board found that none of these Directors has a material or other disqualifying relationship with us. With respect to Mr. Muto who is a partner of Cooley LLP, our outside legal counsel, he is independent for purposes other than serving on the Audit Committee or Compensation Committee, each of which he is not a member.

Information Regarding the Board and its Committees

Leadership Structure

Our Chief Executive Officer is the Chairman of the Board. The Board believes that Ionis’ CEO is best suited to serve as Chairman because he has served as CEO since Ionis was formed 28 years ago and he is the Director most familiar with our science, business and industry. Because of that experience, he is the Director most capable of effectively identifying strategic priorities and leading the discussion and execution of strategy. Our independent Directors bring experience, oversight and expertise from outside Ionis and our industry, while the CEO brings Company-specific experience and expertise. The Board believes the combined role of Chairman and CEO promotes strategy development and execution, and facilitates information flow between management and the Board, which are essential to effective governance.

One of the key responsibilities of the Board is to develop strategic direction and hold management accountable for executing the established strategy. As part of each Board meeting, our independent Directors meet in an executive session without the presence of our employee Directors. We do not have a single “lead independent director.” Instead, the Chairpersons of the Audit Committee, the Compensation Committee, and the Nominating, Governance and Review Committee preside over the executive sessions on a rotating basis. This rotating approach provides diversity to the process, thereby ensuring healthy discussion since the same individual does not continuously lead each executive session. In addition, Dr. Loscalzo and Mr. Muto, who are both independent Board members, are members of the Agenda Committee, which sets the agenda for each Board meeting. The Board believes the combined role of Chairman and CEO, together with the executive sessions and agenda setting described above, is in the best interest of stockholders because it provides the appropriate balance between developing strategy and independently overseeing management.

Risk Oversight

Our Board administers its risk oversight function directly and through both its Audit Committee and its Nominating, Governance and Review Committee. The Audit Committee oversees management of financial risks and related party transactions. The Nominating, Governance and Review Committee manages risks associated with the independence of the Board and potential conflicts of interests at the Board level, and periodically reviews our policies and procedures and makes recommendations when appropriate. We provide a complete description of each of these committees and its respective roles and responsibilities on pages 10 through 15 of this Proxy Statement. While each of these committees is responsible for evaluating certain risks and overseeing how we manage risk, these committees regularly inform the entire Board about such risks through committee reports.

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

Board Committees

The Board has five committees: an Audit Committee, a Compensation Committee, a Nominating, Governance and Review Committee, an Agenda Committee and a Scientific/Medical 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 individual exercise of independent judgment with regard to Ionis.

Meetings and Attendance; Committee Members

The Board met five times in 2016. During 2016, each Director attended 75% or more of the aggregate number of meetings of the Board and the committees on which such Director served. We encourage each member of the Board to attend the Annual Meeting of Stockholders.

Board Committee Members

The table below provides membership and meeting information for fiscal 2016 for each of the Board committees and identifies our current Board and committee members.

Name	Audit	Compensation	Nominating, Governance and Review	Agenda	Science/ Medical	Attended 2016 Annual Meeting
Dr. Spencer R. Berthelsen	--	X*	X*	--	X	X
Mr. Breaux B. Castleman	X	--	--	--	--	X
Dr. Stanley T. Crooke	--	--	--	X*	X*	X
Mr. Joseph Klein, III	X	--	--	--	--	X
Dr. Joseph Loscalzo	--	--	X	X	X	--
Mr. Frederick T. Muto ⁽¹⁾	--	--	--	X	--	X
Ms. B. Lynne Parshall	--	--	--	X	--	X
Mr. Joseph H. Wender	X*	X	X	--	--	--
Total meetings in fiscal year 2016	5	3 ⁽²⁾	2	3	1	

* Committee Chairperson

- (1) Mr. Muto serves as an advisor, in a non-voting capacity, to the Nominating, Governance and Review Committee, and to the Compensation Committee.
- (2) The Compensation Committee also acted by written consent 12 times. Our Compensation Committee typically acts by unanimous written consent each month to confirm stock options and RSUs granted in connection with new hires and promotions.

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 and oversees the annual and quarterly financial reporting processes, including sessions with the 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:

- reviewing our annual budget with management and, if acceptable, recommending the budget to the Board for approval;
- setting and approving changes to our investment policy;
- 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; and
- pre-approving all audit and non-audit services provided by our independent auditors that are not prohibited by law.

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. Wender based on, among other things, his over 40 years of experience as an investment banker and consultant with Goldman, Sachs & Co. We provide the Audit Committee with the funding it needs to perform its duties.

In 2016, the Audit Committee met five times. The Board has adopted a written Audit Committee charter, which you can find on our corporate website at www.ionispharma.com. 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 35 through 54 of this Proxy Statement. The charter of the Compensation Committee grants the Compensation Committee full access to all of our books, records, facilities and personnel, and authority to obtain, at our expense, advice and assistance from internal and external legal, accounting or other advisors and consultants and other external resources that the Compensation Committee considers necessary or appropriate in the performance of its duties. In particular, the Compensation Committee has the sole authority to retain independent compensation consultants to help the Compensation Committee evaluate executive and Director compensation, including the authority to approve the consultants' reasonable fees and other retention terms.

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

The Compensation Committee met three times in 2016 and acted by unanimous written consent 12 times. The Board has adopted a written Compensation Committee charter, which you can find on our corporate website at www.ionispharma.com.³

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, 2016, our Compensation Committee was composed of Dr. Berthelsen and Mr. Wender. 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.

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 two times during 2016. You can find our Nominating, Governance and Review Committee charter on our corporate website at www.ionispharma.com.⁴

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.

Director Nominations - Quality Standards

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

The minimum membership requirements are as follows:

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

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

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

Director Nominations - Diversity Discussion

In considering Director nominations, the Nominating, Governance and Review Committee considers the total mix of competencies represented on the Board as a whole, as well as the competencies each member, or nominee brings to the Board. In general, our Board members' experience falls into three large categories: (1) investment banking, financial accounting and corporate governance experience; (2) medical and scientific expertise; and (3) employee versus non-employee Directors. By selecting individuals who have investment banking, financial accounting and corporate governance backgrounds, we gain valuable experience that ensures we are managing our financial resources appropriately, reporting our financial results fairly and accurately, and generally running our business consistent with current good corporate practices. As a cutting edge drug discovery and development company, we also greatly benefit from Board members who themselves are scientists and medical doctors. This way we can 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.

Regarding the third category, a mix of employee and non-employee Directors offers different perspectives for the Board to consider when making decisions. Employee Directors can provide the Board valuable insight regarding our day-to-day operations, which can help the Board make important management and compensation decisions. Non-employee Directors can compare the opportunities and challenges presented to Ionis against the facts and circumstances these Directors are experiencing outside Ionis. We have a significantly higher number of non-employee Directors vs. employee Directors. Finally, we do not discriminate against nominees on the basis of gender, race, religion, national origin, sexual orientation, disability or any other basis prohibited by applicable law.

Director Nominations - Process

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

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

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

Stockholder Recommendations for Directors

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

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

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

Agenda Committee

The primary function of the Agenda Committee of the Board is to determine the matters to be considered by the Board at each of its meetings and prepare an agenda accordingly. The Agenda Committee discussed in advance and set the agenda for each Board meeting held in 2016.

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 drugs in development, and help set our strategy in such areas. The Science/Medical Committee met once in 2016.

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. All communications directed to the Audit Committee in accordance with our Code of Ethics policy 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 that applies to all officers, Directors and employees. We have posted our Code of Ethics on our website. If we make any substantive amendments to the Code of Ethics or grant any waiver from a provision of the Code of Ethics to any executive officer or Director, we will promptly disclose the nature of the amendment or waiver on our website at www.ionispharma.com.⁵

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.⁶

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.

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PROPOSAL 2

APPROVAL OF AN AMENDMENT TO 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 2011 Plan on June 16, 2011. In March 2015, the Compensation Committee of the Board, and the Board, 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 5,500,000 to an aggregate of 11,000,000, and the stockholders approved such amendment on June 30, 2015. In this Proposal 2, we are requesting stockholders to approve an amendment to the 2011 Plan to increase the aggregate number of shares of common stock authorized for issuance under the 2011 Plan by 5,000,000 to an aggregate of 16,000,000 shares.

Our management, Board and Compensation Committee believe that stock options and restricted stock units (“RSUs”) 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. The Board, upon the recommendation of the Compensation Committee, has approved an increase in the aggregate number of shares of common stock authorized for issuance under the 2011 Plan by 5,000,000 to an aggregate of 16,000,000 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 and RSUs to employees at appropriate levels as determined by the Compensation Committee. If the stockholders do not approve Proposal 2, and as a consequence, we cannot continue to grant options and RSUs at competitive levels, we believe that it will negatively affect our ability to recruit and retain highly qualified 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.

The 2011 Plan was adopted to ultimately replace the Ionis Pharmaceuticals, Inc. 1989 Stock Option Plan (the “89 Plan”). There are only approximately 27,000 shares available as of March 31, 2017 for grant under the 89 Plan. The 2011 Plan is our primary means of offering stock options and RSUs to our employees. There are only approximately 900,000 shares available as of March 31, 2017 for grant under the 2011 Plan.

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

Employee Equity Incentive Plans (as of March 31, 2017)		
	2011 Plan	89 Plan
Total number of shares of common stock subject to outstanding stock options	8,182,975	2,491,410
Weighted-average exercise price of outstanding stock options	\$ 52.02	\$ 13.12
Weighted-average remaining term in years of outstanding stock options	5.5	2.3
Total number of shares of common stock subject to outstanding full value awards	831,831	--
Total number of shares of common stock available for grant under the plan	910,051	27,427
Total number of shares of common stock available for grant to non-employee Directors under the Non-Employee Director Plan ⁽¹⁾		747,869
Total number of shares of common stock available for grant under other equity incentive plans		--
Total number of shares of common stock outstanding		123,880,559
Per-share closing price of common stock as reported on NASDAQ Capital Market		\$ 40.20

(1) This amount reflects the number of shares of common stock available as of March 31, 2017 for grant under our 2002 Amended and Restated Non-Employee Directors’ Stock Option Plan (the “Non-Employee Director Plan”) which is used 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 603,312, the weighted-average exercise price of outstanding stock options is \$22.37, the weighted-average remaining term in years of outstanding stock options is 6.1, the total number of shares of common stock subject to outstanding full value awards is 40,214, and the total number of shares of common stock available for grant under the Non-Employee Director Plan is 747,869. We have no equity incentive plans other than the 2011 Plan, the 89 Plan and the Non-Employee Director Plan.

We expect to use the 2011 Plan as our primary means of offering stock options and RSUs to our employees. 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.

Required Vote and Board of Directors Recommendation

Approval of Proposal 2 requires the affirmative vote of a majority of the shares present or represented by proxy and entitled to vote at the Annual Meeting. 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 this proposal.

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 IONIS PHARMACEUTICALS, INC. 2011 EQUITY INCENTIVE PLAN

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

The 2011 Plan:

- is administered by our Compensation Committee, which is composed entirely of independent Directors;
- has a term ending on June 15, 2021;
- prohibits the repricing of any option or stock appreciation rights (SARs) outstanding under the 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, performance stock awards, and performance cash awards;
- requires that each newly granted option and SAR not become fully vested until a date at least two years after the date of grant, except in the case of death, disability, retirement, or change of control;
- requires that nearly all newly granted restricted stock awards and RSUs granted to employees that vest on the basis of continuous service not become fully vested until a date at least three years after the date of grant, except in the case of death, disability, retirement or change of control;
- requires that nearly all newly granted restricted stock awards and RSUs granted to employees that vest on the basis of performance goals not become fully vested until a date at least one year after the date of grant, except in the case of death, disability, retirement or change of control;
- limits our ability to accelerate vesting only in case of death, disability, retirement or change of control; and
- requires all options and SARs outstanding under the 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 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 2016, we granted our employees a combination of stock options and RSUs under our 89 Plan and 2011 Plan, where we allocated 75% of the grant date dollar value to stock options and allocated 25% of the value to RSUs; and assumed that each share subject to an RSU was worth two shares subject to a stock option.

Background

The terms of the 2011 Plan provide for the grant of stock options, SARs, restricted stock awards, RSUs, performance stock 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 16,000,000 shares of our common stock authorized for issuance under the 2011 Plan.

The following table summarizes the equity awards granted over the last three years, and through March 31, 2017, 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⁾				
	2014	2015	2016	2017 (through March 31)
Shares subject to equity awards granted	2,167,085	2,786,643	2,662,125	2,828,336
Shares subject to equity awards canceled	(130,530)	(253,579)	(346,001)	(78,724)
Net shares subject to equity awards ⁽²⁾	2,036,555	2,533,064	2,316,124	2,749,612

- (1) Amounts shown reflect grants under our 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 or expire 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 in such year.

If, under the 2011 Plan, a stock option or RSU is cancelled or terminated, then any unexercised shares subject to such cancelled or terminated stock options or unissued shares subject to such cancelled or terminated RSUs will become available for issuance under the 2011 Plan. In addition, if we issue common stock pursuant to a stock award and the common stock is later forfeited, then the forfeited shares will again become available for issuance under the 2011 Plan. Any shares we reacquire pursuant to our withholding obligations in connection with a restricted stock award, RSU, performance stock award or other stock award will again become available for issuance under the 2011 Plan. Any shares we reacquire pursuant to our withholding obligations in connection with a stock option or stock appreciation right or as consideration for the exercise of a stock option or stock appreciation right will become available for issuance under the 2011 Plan.

Eligibility

All of our employees in the United States, numbering 412 for Ionis and 26 for Akcea as of March 31, 2017, and our Directors and consultants are eligible to participate in the 2011 Plan and may receive all types of awards available under the 2011 Plan.

Administration

Our Board administers the 2011 Plan. The Board may delegate authority to administer the 2011 Plan to a committee, but may retain the authority to concurrently administer the 2011 Plan with the committee and may, at any time, revert in itself some or all of the powers previously delegated to the committee. Our Board has delegated administration of the 2011 Plan to the Compensation Committee. Subject to the terms of the 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 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”) or solely of two or more “outside directors” within the meaning of Section 162(m) of the Internal Revenue Code of 1986, as amended (the “Code”). 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. Crooke. As used herein, except as explicitly stated otherwise, with respect to the 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 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 2011 Plan, no option or SAR granted to an employee or member of the Board will become 100% vested in a period of less than two years after the grant of such option, *except that* the vesting of an option or SAR may accelerate (or may be accelerated by the Board or Compensation Committee) in the case of death, disability, retirement, corporate sale or change of control.

Under the 2011 Plan, no restricted stock award or RSU award granted to an employee or discretionary restricted stock award or RSU award granted to a member of the Board will vest more rapidly than:

- ratably over a three-year period for awards that vest based on continuous service; and
- one year for awards that vest upon the achievement of performance goals;

except that the vesting of a restricted stock award or RSU may accelerate (or may be accelerated by the Board or Compensation Committee) in the case of death, disability, retirement, corporate sale or change of control; and Ionis may grant up to 200,000 shares worth of restricted stock awards and RSUs that vest earlier than the minimum periods described above.

No Evergreen

The 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 2011 Plan pursuant to stock option agreements. The 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, 2017, the closing price of our common stock as reported on the NASDAQ Global Select Market was \$40.20 per share.

Vesting

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

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

Under the 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 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 optionholder 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 optionholder may designate a beneficiary who may exercise the stock option following the optionholder's death.

Restricted Stock Unit Awards

RSUs are granted under the 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. 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 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. 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 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 2011 Plan.

Performance Awards

The 2011 Plan provides for the grant of two types of performance awards: performance stock 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. The maximum amount covered by a performance award that may be granted to any individual in a calendar year (whether the grant, vesting or exercise is contingent upon the attainment during a performance period of the performance goals) may not exceed 750,000 shares of our common stock in the case of performance stock awards, or \$2,000,000 in the case of performance cash awards.

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. Within the time period prescribed by Section 162(m) of the Code, at a time when the achievement of the performance goals remains substantially uncertain and before the earlier of the 90th day of a performance period or the date on which twenty-five percent of the performance period has elapsed, the Compensation Committee will establish the performance goals, based upon one or more criteria, called performance criteria enumerated in the 2011 Plan and described below. As soon as administratively practicable following the end of the performance period, the Compensation Committee will certify (in writing) whether the performance goals have been satisfied.

The Board will determine performance goals under the 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)	· operating income
· operating income after taxes	· pre-tax profit
· operating cash flow	· sales or revenue targets
· increases in revenue or product revenue	· expenses and cost reduction goals
· improvement in or attainment of working capital levels	· economic value added (or an equivalent metric)
· market share	· cash flow
· cash flow per share	· share price performance
· debt reduction	· stockholders' equity
· customer satisfaction	· debt levels
· capital expenditures	· workforce diversity
· operating profit or net operating profit	· billings
· to the extent that an Award is not intended to comply with Section 162(m) of the Code, other measures of performance selected by the Board	· implementation or completion of projects or processes (including, but not limited to, development and regulatory milestones)
· 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 any "extraordinary items" as determined under generally accepted accounting principles; and
- to exclude accounting expenses relating to share-based compensation.

Compensation attributable to performance-based awards under the 2011 Plan will qualify as performance-based compensation, provided that:

- the award is granted by a compensation committee comprised solely of "outside directors;"
- the award is granted (or exercisable) only upon the achievement of an objective performance goal established in writing by the compensation committee while the outcome is substantially uncertain and before the earlier of the 90th day of the performance period and the date on which twenty-five percent of the performance period has elapsed; and
- the compensation committee certifies in writing prior to the granting, payment or exercisability of the award that the performance goal has been satisfied.

Changes to Capital Structure

In the event of certain capitalization adjustments, the Board will appropriately adjust:

- the class(es) and maximum number of securities subject to the 2011 Plan;
- the class(es) and maximum number of securities that may be awarded to any person pursuant to Section 162(m) limits; and
- the class(es) and number of securities and price per share of stock subject to outstanding stock awards.

Corporate Transactions

In the event of certain significant corporate transactions, the Board has the discretion to take one or more of the following actions with respect to outstanding stock awards under the 2011 Plan:

- arrange for assumption, continuation, or substitution of a stock award by a surviving or acquiring entity (or its parent company);
- arrange for the assignment of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award to the surviving or acquiring corporation (or its parent company);
- accelerate the vesting and exercisability of a stock award followed by the termination of the stock award;
- arrange for the lapse of any reacquisition or repurchase rights applicable to any shares of our common stock issued pursuant to a stock award;
- cancel or arrange for the cancellation of a stock award, to the extent not vested or not exercised prior to the effective date of the corporate transaction, in exchange for cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; and
- arrange for the surrender of a stock award in exchange for a payment equal to the excess of (a) the value of the property the holder of the stock award would have received upon the exercise of the stock award, over (b) any exercise price payable by such holder in connection with such exercise.

The Board need not take the same action for each stock award.

For purposes of the 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 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 may be subject to additional acceleration of vesting and exercisability upon or after specified change in control transactions (as defined in the 2011 Plan), as provided in the stock award agreement or in any other written agreement between us or any affiliate and the participant, but in the absence of such provision, no acceleration will occur.

The acceleration of vesting of an award in the event of a change in control event under the 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 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 2011 Plan as required by applicable law and listing requirements. Ionis 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 2011 Plan will automatically terminate on June 15, 2021.

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 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, the provisions of Section 162(m) of the Code 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 optionholder will recognize ordinary income equal to the excess, if any, of the fair market value on the date of exercise of the stock over the exercise price. If the optionholder is employed by us or one of our affiliates, that income will be subject to withholding taxes. The optionholder’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 optionholder’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 a tax reporting obligation, we will generally be entitled to a tax deduction equal to the taxable ordinary income realized by the optionholder.

Restricted Stock Unit Awards

Generally, the recipient of a stock unit structured to conform to the requirements of Section 409A of the Code or an exception to Section 409A of the Code will recognize ordinary income at the time the stock is delivered equal to the excess, if any, of the fair market value of the shares of our common stock received over any amount paid by the recipient in exchange for the shares of our common stock. To conform to the requirements of Section 409A of the Code, the shares of our common stock subject to a stock unit award may generally 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 stock units otherwise comply with or qualify for an exception to the requirements of Section 409A of the Code, in addition to the tax treatment described above, the recipient will owe an additional 20% federal tax and interest on any taxes owed.

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

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

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 stock awards 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 a tax reporting obligation, we will generally be entitled to a tax deduction equal to the taxable ordinary income realized by the recipient of the stock award.

Stock Appreciation Rights

We may grant under the 2011 Plan SARs separate from any other award or together with other awards under the 2011 Plan.

Where the SARs are granted with a strike 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 a tax reporting obligation, we will generally be entitled to a tax deduction equal to the taxable ordinary income realized by the recipient of the stock appreciation right.

Section 162 Limitations

Compensation of persons who are "covered employees" of the Company is subject to the tax deduction limits of Section 162(m) of the Code. Awards that qualify as "performance-based compensation" are exempt from Section 162(m), thereby permitting us to claim the full federal tax deduction otherwise allowed for such compensation. The 2011 Plan is intended to enable the Compensation Committee to make awards, including cash performance awards, that will be exempt from the deduction limits of Section 162(m). Under Section 162(m), compensation attributable to stock options and SARs will qualify as performance-based compensation if (i) such awards are approved by a compensation committee composed solely of "outside directors," (ii) the plan contains a per-employee limitation on the number of shares for which such awards may be granted during a specified period, (iii) the per-employee limitation is approved by the stockholders, and (iv) the exercise or strike price of the award is no less than the fair market value of the stock on the date of grant. Compensation attributable to restricted stock awards, RSUs and performance awards and other stock-based awards will qualify as performance-based compensation, provided that (a) the award is approved by a compensation committee composed solely of "outside directors," (b) the award is granted, becomes vested or is settled, as applicable, only upon the achievement of an objective performance goal established in writing by the compensation committee while the outcome is substantially uncertain and before the earlier of the 90th day of the performance period and the date on which twenty-five percent of the performance period has lapsed, (c) a committee of outside directors certifies in writing prior to the granting (or vesting or settlement) of the award that the performance goal has been satisfied, and (d) prior to the granting (or vesting or settlement) of the award, the stockholders have approved the material terms of the award (including the class of employees eligible for such award, the business criteria on which the performance goal is based, and the maximum amount, or formula used to calculate the maximum amount, payable upon attainment of the performance goal).

New Plan Benefits

The following table presents certain information with respect to stock options and RSUs granted in January 2017 for the recipient's 2016 performance to (a) each executive officer named in the Summary Compensation Table under "Executive Compensation--Compensation of Executive Officers", (b) all executive officers as a group, (c) all non-employee Directors as a group and (d) all non-executive officer employees as a group. This information regarding such grants is for illustration only and may not be indicative of grants that are made in the future under the 2011 Plan.

NEW PLAN BENEFITS 2011 PLAN

<u>Name and Position</u>	<u>Number of Shares Underlying RSUs</u>	<u>Number of Shares Underlying Stock Options</u>
Stanley T. Crooke Chairman, Chief Executive Officer and President	27,168	163,013
Elizabeth L. Hougen Senior Vice President, Finance and Chief Financial Officer	7,537	45,225
B. Lynne Parshall Director, Chief Operating Officer	19,606	117,638
Brett Monia Senior Vice President, Drug Discovery	8,000	48,000
Patrick R. O'Neil Senior Vice President, Legal, General Counsel and Chief Compliance Officer	7,537	45,225
All Executive Officers as a Group	92,459	554,776
All Non-Employee Directors as a Group	--	--
All Non-Executive Officer Employees as a Group	229,649	1,384,543

Please see page 34 for information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of December 31, 2016.

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, 2016), called our “named executive officers” as disclosed in this Proxy Statement in accordance with the SEC’s rules.

We are asking our stockholders to indicate their support for our named executive officer 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 2017 Annual Meeting of Stockholders pursuant to the compensation disclosure rules of the Securities and Exchange Commission.”

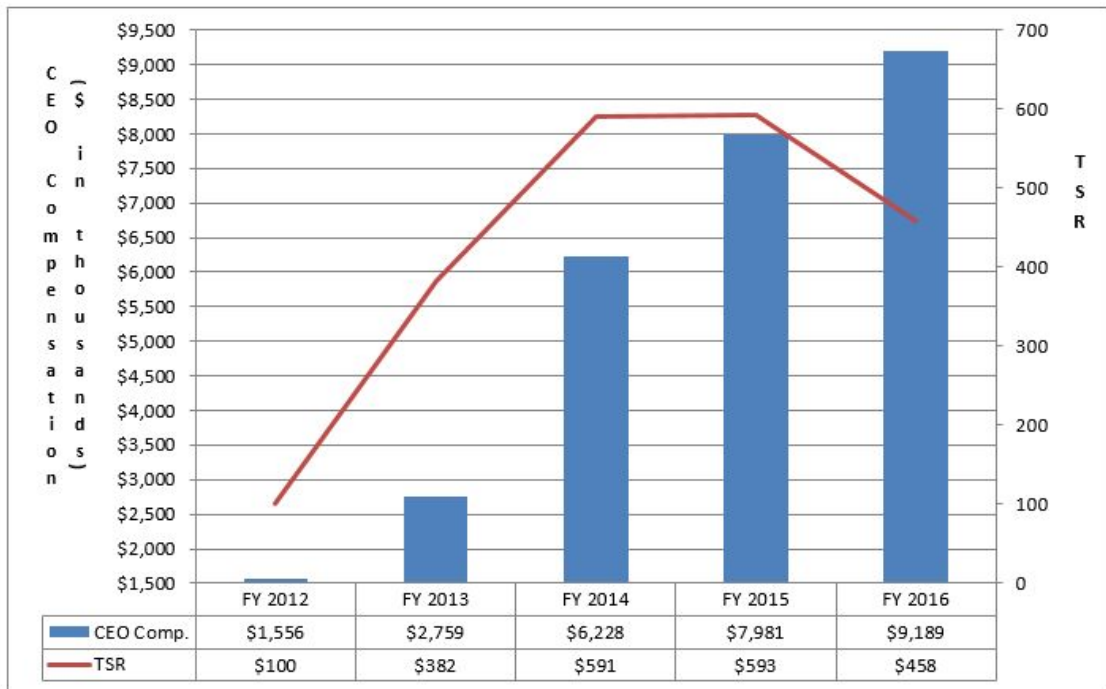
We recommend you carefully review the EXECUTIVE COMPENSATION section of this Proxy Statement located on pages 35 through 54. Below is a high-level summary of some of our compensation practices. This summary is qualified by the detailed disclosure contained in the EXECUTIVE COMPENSATION section of this 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
✓ Demand more of every employee: more commitment, more knowledge, more intensity, more innovation, more productivity	✗ Do not guarantee a cash bonus – cash bonuses can, and have been, zero
✓ Reward productivity and performance	✗ Do not provide perquisites for any employees
✓ Recognize the value of long-term employees and low turnover	✗ Do not provide “gross-up” payments, other than for relocation
✓ Use a balanced mix of fixed and variable cash incentives and long-term equity incentives	✗ Do not allow pledging, shorting or hedging against our stock
✓ Evaluate compensation compared to the 50 th percentile of our peer group	✗ Do not reprice or “cash-out” stock options without stockholder approval
✓ 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 MBOs	
✓ 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 named 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 an executive “claw-back” policy	
✓ Use an independent compensation consultant engaged by the Compensation Committee	

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

The following graphs show the relationship of our Chief Executive Officer’s compensation (\$ in thousands) as calculated pursuant to SEC rules compared to the total return (TSR) on \$100 invested on December 31, 2012 in our common stock through December 31, 2016. Although stock price is only one of the measures of Ionis’ performance we use to set the compensation for our executive officers, including our CEO, as illustrated below, our CEO’s compensation is generally in alignment with our stock performance over the period shown.⁷



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.

⁷ 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.

PROPOSAL 4

ADVISORY VOTE ON THE FREQUENCY OF THE VOTE ON EXECUTIVE COMPENSATION

Ionis is presenting this proposal, commonly known as a “say-on-frequency vote,” which gives you as a stockholder the opportunity to inform us regarding how often you wish us to include a “say-on-pay” proposal, similar to Proposal 3, in our Proxy Statement. Please note that as a stockholder you have the choice to vote for one of the following choices, as indicated on the proxy card: to hold the advisory vote on executive compensation every year, every two years, every three years, or to abstain from voting.

Board Recommendation

The Board of Directors values constructive dialogue on executive compensation and other important governance topics with our stockholders. The Board believes an advisory vote every year will provide an effective way to obtain information on stockholder sentiment about our executive compensation program.

Required Vote of Stockholders

We will consider the frequency with the highest number of votes from the holders of shares present in person or represented by proxy and entitled to vote at the Annual Meeting as the frequency preferred by the stockholders. While this say on frequency vote is advisory in nature and therefore will not bind us to adopt any particular frequency, our Board of Directors intends to carefully consider the stockholder vote resulting from the proposal in determining how frequently we will hold “say-on-pay” votes.

THE BOARD OF DIRECTORS RECOMMENDS THAT STOCKHOLDERS VOTE FOR “EVERY YEAR”

RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

The Audit Committee of the Board has selected Ernst & Young LLP as our independent registered public accounting firm for our 2017 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 2017 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 of the Board 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 of the Board will reconsider whether to keep the firm. However, even if the stockholders ratify the selection, the Audit Committee of the Board 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 in person or represented by proxy and entitled to vote at the 2017 Annual Meeting will be required to ratify the selection of Ernst & Young LLP. If you indicate on your proxy to "Abstain" from voting, it will have the same effect as an "Against" vote for this Proposal 5.

As of December 31, 2016, none of our finance or accounting employees had been employed by Ernst & Young LLP during the past five years.

Independent Auditors' Fees

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 fees described below.

Audit Fees

For the fiscal years ended December 31, 2016 and 2015, Ernst & Young LLP billed us approximately \$700,000 for each year, 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 \$100,000 and approximately \$300,000 in 2016 and 2015, respectively, related to corporate transactions. Additionally, for the fiscal year ended December 31, 2016, Ernst & Young LLP billed us approximately \$1.0 million related to the audit of the financial statements of Akcea Therapeutics, Inc. ("Akcea"), our wholly owned subsidiary, and professional services rendered in connection with the initial public offering of Akcea.

Audit Related Fees

For the fiscal years ended December 31, 2016 and 2015, there were no audit related fees billed by Ernst & Young LLP.

Tax Fees

For the fiscal year ended December 31, 2016, Ernst & Young LLP billed us approximately \$200,000 for professional services rendered for international tax planning for Akcea and state and local tax consulting projects. For the fiscal year ended December 31, 2015, Ernst & Young LLP billed us approximately \$100,000 for professional services rendered for international tax planning for Akcea and state and local tax consulting projects.

All Other Fees

During the fiscal years ended December 31, 2016 and 2015, all other fees billed by Ernst & Young LLP were approximately \$2,000 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, 2016, none of the total hours expended on our financial audit by Ernst & Young LLP were provided by persons other than Ernst & Young LLP's employees.

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

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of March 1, 2017 by:

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

Beneficial Owner	Beneficial Ownership ⁽¹⁾	
	Number of Shares	Percent of Total ⁽²⁾
FMR LLC ⁽³⁾ 245 Summer Street Boston, MA 02210	18,180,445	14.69%
ClearBridge Investments, LLC ⁽⁴⁾ 620 8 th Avenue New York, NY 10018	12,052,583	9.74%
The Vanguard Group ⁽⁵⁾ 100 Vanguard Boulevard Malvern, PA 19355	9,052,966	7.31%
Baillie Gifford & Co ⁽⁶⁾ Calton Square 1 Greenside Row Edinburgh EH1 3AN Scotland UK	8,415,156	6.80%
BB Biotech AG ⁽⁷⁾ Schwertstrasse 6 CH-8200 Schaffhausen, Switzerland	6,913,172	5.58%
BlackRock, Inc. ⁽⁸⁾ 55 East 52 nd Street New York, NY 10055	6,457,810	5.22%
Spencer R. Berthelsen ⁽⁹⁾	180,716	*
Breaux B. Castleman ⁽¹⁰⁾	43,534	*
Stanley T. Croke ⁽¹¹⁾	1,308,562	1.04%
Joseph Klein, III ⁽¹²⁾	31,008	*
Joseph Loscalzo ⁽¹³⁾	33,689	*
Frederick T. Muto ⁽¹⁴⁾	110,346	*
B. Lynne Parshall ⁽¹⁵⁾	208,584	*
Joseph H. Wender ⁽¹⁶⁾	110,468	*
Elizabeth Hougen ⁽¹⁷⁾	126,688	*
Brett Monia ⁽¹⁸⁾	131,265	*
Patrick R. O’Neil ⁽¹⁹⁾	72,001	*
All Directors and executive officers as a group (fourteen persons) ⁽²⁰⁾	2,673,412	2.13%

*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 123,797,841 shares of common stock outstanding on March 1, 2017, adjusted as required by rules promulgated by the SEC.
- (3) Abigail P. Johnson is a Director, the Vice Chairman, the Chief Executive Officer and the President of FMR LLC. Members of the Johnson family, including Abigail P. Johnson, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders' voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders' voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC.

Neither FMR LLC nor Abigail P. Johnson has the sole power to vote or direct the voting of the shares owned directly by the various investment companies registered under the Investment Company Act ("Fidelity Funds") advised by Fidelity Management & Research Company ("FMR Co"), a wholly owned subsidiary of FMR LLC, which power resides with the Fidelity Funds' Boards of Trustees. Fidelity Management & Research Company carries out the voting of the shares under written guidelines established by the Fidelity Funds' Boards of Trustees.

- (4) ClearBridge Investments, LLC is an investment adviser registered under the Investment Advisers Act. ClearBridge Investments has sole voting power to direct the vote of 11,650,493 shares and sole power to dispose or direct the disposition of 12,052,583 shares.
- (5) The Vanguard Group has sole voting power to direct the vote of 70,792 shares, shared voting power to direct the vote of 14,190 shares, sole power to dispose or direct the disposition of 8,974,484 shares, and shared dispositive power for 78,482 shares. Vanguard Fiduciary Trust Company, a wholly owned subsidiary of The Vanguard Group, Inc., is the beneficial owner of 64,292 shares of the Common Stock outstanding of Ionis as a result of its serving as investment manager of collective trust accounts. Vanguard Investments Australia, Ltd., a wholly owned subsidiary of The Vanguard Group, Inc., is the beneficial owner of 20,690 shares of Ionis' Common Stock outstanding as a result of its serving as investment manager of Australian investment offerings.
- (6) Baillie Gifford & Co is an investment advisor registered under the Investment Advisors Act. Baillie Gifford has sole voting power to direct the vote of 4,612,936 shares and sole power to dispose or direct the disposition of 8,415,156 shares.
- (7) BB Biotech AG shares voting and dispositive powers for its shares with Biotech Target N.V.
- (8) BlackRock, Inc. is a parent holding company and various persons of BlackRock, Inc. 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.
- (9) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 91,688 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before April 30, 2017.
- (10) Includes 37,313 shares of common stock issuable upon exercise of options held by Mr. Castleman that are exercisable on or before April 30, 2017.
- (11) Includes shares of common stock held by Dr. Crooke and 503,792 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 30, 2017. Also includes 38,303 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, 2017. Dr. Crooke disclaims beneficial ownership of the shares of common stock owned and issuable upon exercise of options held by his wife.
- (12) Includes 100 shares of common stock beneficially owned by Mr. Klein's son and 23,250 shares of common stock issuable upon exercise of options held by Mr. Klein that are exercisable on or before April 30, 2017.
- (13) Includes 28,875 shares of common stock issuable upon exercise of options held by Mr. Loscalzo that are exercisable on or before April 30, 2017.
- (14) Includes 1,500 shares of common stock beneficially owned through the Cooley LLP Salary Deferral and Profit Sharing Plan and 104,188 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before April 30, 2017.
- (15) Includes 182,933 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 30, 2017.

- (16) Includes 76,688 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 30, 2017.
- (17) Includes 116,400 shares of common stock issuable upon exercise of options held by Ms. Hougen that are exercisable on or before April 30, 2017.
- (18) Includes 119,493 shares of common stock issuable upon exercise of options held by Dr. Monia that are exercisable on or before April 30, 2017.
- (19) Includes 60,552 shares of common stock issuable upon exercise of options held by Mr. O’Neil that are exercisable on or before April 30, 2017.
- (20) Includes an aggregate of 1,667,024 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, 2017.

Section 16(a) Beneficial Ownership Reporting Compliance

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 solely on a review of the copies of such reports furnished to us and written representations that no other reports were required, during the fiscal year ended December 31, 2016, all Section 16(a) filing requirements applicable to our officers, Directors and greater than ten percent beneficial owners were complied with.

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 December 31, 2016.

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⁾	9,177,979	\$ 40.48	⁽²⁾ 4,434,959
Total	9,177,979	\$ 40.48	4,434,959

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

(2) Of these shares, 585,713 remained available for purchase under the ESPP as of December 31, 2016. The ESPP incorporates an evergreen formula pursuant to which on January 1 of each year, we automatically increase the aggregate number of shares reserved for issuance under the plan by 150,000 shares.

Compensation Discussion and Analysis

Since inception, the Ionis mission has been to create a new, more efficient technology for drug discovery and development – antisense technology – and exploit that technology to create a pipeline of first-in-class and/or best-in-class medicines to treat a wide range of diseases. Today, thanks to the innovation and perseverance of Ionis, we believe antisense technology is taking its place as the third platform for drug discovery alongside small molecules and protein therapeutics.

Ionis is focused on innovation. Ionis has implemented a unique business strategy intended to support long-term innovation based on the efficiency of antisense technology. Ionis has created a unique 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.

Antisense technology exists today primarily because of the innovation at Ionis. We have more than 1,100 issued patents that provide substantial control of key elements of the technology for many years to come. This intellectual property has been critical in the completion of partnerships that have resulted in over \$1.9 billion in cash since 2007 and the development of a consortium of companies who advance the technology alongside us, and thereby increase our reach. We should continue to realize the value of our partnerships, and our consortium of companies, for many years to come in the form of license fees, milestone payments and royalties. Ionis has been recognized as one of the top ten most innovative companies in the biotechnology industry, based on number of granted patents, scientific strength, industry impact, technology strength and research intensity. Our over 1,100 issued patents are all the more remarkable given that Ionis has just over 400 employees. This means Ionis has produced over three issued patents per employee.

A key component of our business and organizational strategy is to maintain an optimal size to foster innovation. We believe the optimal size is approximately 400-450 employees. To maintain this optimal size we license our medicines at key value inflection points during development, thus avoiding the need to build the large, complex, inefficient organizations associated with fully integrated pharmaceutical companies. We also demand more of every employee at Ionis and do not tolerate mediocrity. We have been remarkably successful in achieving these goals. Today we have 39 new medicines in development; one medicine in development per 11 employees. And we believe this productivity is sustainable. We plan to add three to five new medicines to the pipeline every year without significant increases in the number of employees.

By design, Ionis demands more of every employee, particularly the middle and senior level leaders. This requires us to design our compensation system to recruit, motivate and retain outstanding individuals. Here too, we have been successful. Our average employee turnover rate over the last five years (reflected as of 3rd quarter each year) has averaged 7% per year, while the average turnover in the San Diego/La Jolla area for biotech/pharmaceutical companies over this period was 15% according to a survey published by Radford – an Aon Hewitt Company. Given the uniqueness and complexity of our technology, it is critical to retain the knowledge and experience of outstanding long service employees. The experience and seniority of our employees is as critical to our future success as it has been to the success we have enjoyed to date.

In summary, at Ionis, our vision is clear and designed to promote long-term creation of value through innovation, and bring benefit to generations of patients with many diseases. Our vision is to:

- create and constantly advance a new, more efficient drug discovery platform - antisense technology;
- create a unique business model and culture committed to creating long-term value through innovation;
- broaden, deepen and advance our pipeline of antisense drugs;
- 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.

Through the efficiency of our technology platform and business strategy we have built a pipeline of 39 drugs in development with approximately 400 employees, representing a ratio of 1 medicine: 11 employees.

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
✓ Demand more of every employee: more commitment, more knowledge, more intensity, more innovation, more productivity	✗ Do not guarantee a cash bonus – cash bonuses can, and have been, zero
✓ Reward productivity and performance	✗ Do not provide perquisites for any employees
✓ Recognize the value of long-term employees and low turnover	✗ Do not provide “gross-up” payments, other than for relocation
✓ Use a balanced mix of fixed and variable cash incentives and long-term equity incentives	✗ Do not allow pledging, shorting or hedging against our stock
✓ Evaluate compensation compared to the 50 th percentile of our peer group	✗ Do not reprice or “cash-out” stock options without stockholder approval
✓ 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 MBOs	
✓ 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 named 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 an executive “claw-back” policy	
✓ Use an independent compensation consultant engaged by the Compensation Committee	

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 executives 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 approves the Compensation Committee’s recommendations regarding the compensation of executive officers.

The Compensation Committee's responsibilities include:

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

As the SEC continues to adopt the final rules implementing and defining the Dodd-Frank legislation, Ionis' management and the Compensation Committee will:

- monitor the SEC's adoption of the final rules and definitions; and
- adjust Ionis' compensation policies as necessary to satisfy the new rules.

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 Barney & Barney LLC as its independent compensation consultant. Barney & Barney LLC primarily provided the Compensation Committee advice in the following areas:

- selecting the 2016 Executive Peer Group;
- evaluating the pay mix for our named executive officers;
- evaluating short-term and long-term incentives for our executive officers;
- evaluating Board compensation; and
- evaluating our equity utilization.

In addition, Akcea Therapeutics, Inc., or Akcea, our subsidiary that we formed in December 2014 to develop and commercialize drugs addressing cardiometabolic disorders, engaged Barney & Barney LLC to provide advice regarding compensation for its independent board of directors. Akcea paid Barney & Barney LLC approximately \$7,500 for these services.

Barney & Barney LLC did not provide any additional services to us or our affiliates.

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 MBOs are not guaranteed (i.e., are 100% at risk) and include a multiplier, or performance factor, based on Ionis' and the employee's performance. Therefore, if either Ionis or the employee performs poorly, the Performance MBO can be, and has been, zero.

CEO Pay Ratio. An executive officer's salary plus bonus represents the officer's total cash compensation. Our philosophy has been to have the CEO's total cash compensation be between 20-30 times the lowest levels of compensation received by an employee. Dr. Crooke's total cash compensation, over the last three years, was on average 29.05 times that of the average cash compensation for our lowest level employees and 2.16 times greater than the average of our other executive officers. We cover the specific elements of our compensation structure in more detail below.

Business Objectives

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

- create and constantly advance a new, more efficient drug discovery platform – antisense technology;
- create a unique business model and culture committed to creating long-term value through innovation;
- broaden, deepen and advance our pipeline of antisense drugs;
- 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.

Drug discovery and development across a portfolio of many drugs (currently 39 for Ionis) 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 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, we currently do not use financial-based metrics as objectives, such as earnings per share, because financial metrics typically overly emphasize two or three annual business metrics and ignore the complexity of the tasks we are undertaking. By taking this approach, we avoid the temptation to deviate from creating fundamental long-term value to meet a short-term metric.

We structure our corporate objectives so they are results driven rather than task driven. We typically include a number of objectives that are based on achieving positive data in the clinic. For example, in 2016 we had a corporate objective to advance our pipeline with one of the measures being to achieve positive data from five Phase 2 studies. This type of objective only rewards our executives if the data are positive - we do this to encourage the prudent spending of stockholder money on development decisions. In other words, we want to structure our objectives to reward success based on judgment, rather than the making of “bad bets.”

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

- Long tenure among a dedicated and highly skilled workforce, combined with the highest performance standards, contributes to our leadership in the industry and serves the interests of stockholders.
- Our focus on retention is coupled to 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.
 - o Our named executive officers, or NEOs, who served in 2016 have on average 22 years and as much as 27 years of tenure at Ionis.
 - o Our other officers who served in 2016 have on average over 20 years of tenure at Ionis.
- Each of our executive officers has been carefully evaluated and selected 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.

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) MBO – Performance Based – At Risk Cash Compensation, no portion of which is guaranteed,
- (3) stock-based compensation, and
- (4) the same benefits, including 401(k) matching, that we provide to all employees.

The MBO – Performance Based – At Risk Cash Compensation is the only element that does not apply to all employees. Employees at the director level and above are eligible to receive Performance MBOs.

We consider many factors in determining the amounts we grant to our executives for each of the first three compensation elements listed above. These factors include:

- company-wide performance, including achievement of 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.

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.

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.

As part of setting the 2016 compensation, the Compensation Committee, in consultation with its independent compensation consultant, evaluated and selected a peer group of 21 life science companies for evaluating Ionis' compensation (the "Executive Peer Group"). The Compensation Committee reviews the compensation of our NEOs 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. However, the Compensation Committee 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, and stage of development;
- 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 2016, the Compensation Committee reviewed the Executive Peer Group using the criteria listed above and publicly available data as of April 2016. The Compensation Committee noted Ionis' market capitalization was approximately \$5.0 billion. As part of this process, the Compensation Committee looked at companies in Ionis' industry with market capitalizations of between \$2 billion and \$10 billion, including looking at companies that identified Ionis as a peer, so called "reverse peers". Based on this evaluation, the Compensation Committee added Anacor Pharmaceuticals, Ligand Pharmaceuticals and OpkoHealth to the Executive Peer Group, as these companies fell within the market capitalization range, and were in Ionis' sector. Ligand was also a reverse peer. Additionally, the Compensation Committee removed Incyte Corporation because its market capitalization exceeded the market capitalization range, removed Arena Pharmaceuticals and Momenta Pharmaceuticals because these companies fell well below the market capitalization range, and removed Receptos because another company acquired it.

The following table lists the companies in the 2016 Executive Peer Group, along with Ionis' rankings among these companies, based on market capitalization, and financial data reported by each company for the most recently-reported fiscal year at the time the Compensation Committee selected the Executive Peer Group in June 2016.

Company (ticker)	Annual Revenues (in millions)	Market Capitalization (in millions)	Stage of Lead Drug
Acorda Therapeutics (ACOR)	\$ 466.1	\$ 1,239.3	Market
Akorn (AKRX)	\$ 593.1	\$ 2,686.9	Market
Alkermes (ALKS)	\$ 628.3	\$ 5,377.0	Market
Alnylam Pharmaceuticals (ALNY)	\$ 41.1	\$ 5,516.1	Phase III
Anacor Pharmaceuticals (ANAC)	\$ 82.4	\$ 2,560.5	Market
Ariad Pharmaceuticals (ARIA)	\$ 118.8	\$ 1,201.9	Market
Clovis Oncology (CLVS)	\$ 0.0	\$ 743.0	Phase III
Halozyme Therapeutics (HALO)	\$ 135.1	\$ 1,258.7	Market
Innoviva (Theravance) (INVA)	\$ 53.9	\$ 1,460.7	Market
Intercept Pharmaceuticals (ICPT)	\$ 2.8	\$ 3,191.3	Phase III
Jazz Pharmaceuticals (JAZZ)	\$ 1,324.8	\$ 8,192.0	Market
Ligand Pharmaceuticals (LGND)	\$ 71.9	\$ 2,303.0	Market
MannKind (MNKD)	\$ 0.0	\$ 681.6	Market
Medivation (MDVN)	\$ 943.3	\$ 7,585.9	Market
Nektar Therapeutics (NKTR)	\$ 230.8	\$ 1,963.0	Market
Neurocrine Biosciences (NBIX)	\$ 19.8	\$ 3,591.3	Phase III
Opko Health (OPK)	\$ 491.7	\$ 5,682.2	Market
Pacira Pharmaceuticals (PCRX)	\$ 249.0	\$ 2,013.5	Market
Seattle Genetics (SGEN)	\$ 336.8	\$ 5,058.6	Market
The Medicines Company (MDCO)	\$ 309.0	\$ 2,224.2	Market
United Therapeutics (UTHR)	\$ 1,465.8	\$ 5,121.7	Market
Ionis Pharmaceuticals, Inc. (IONIS)	\$ 283.7	\$ 4,883.1	Market
Ionis' Ranking	10	8	NA
Ionis' Percentile Rank	58 %	69 %	NA

The table below compares total cash compensation and the total direct compensation of our NEO's against that of the 50th percentile of the Executive Peer Group.

Name	2016 Total Cash Compensation (in thousands)		2016 Total Direct Compensation (in thousands)	
	NEO	50 th Percentile of Executive Peer Group	NEO	50 th Percentile of Executive Peer Group
Stanley T. Crooke CEO	\$ 2,030	\$ 1,359	\$ 9,163	\$ 4,715
Elizabeth L. Hougen CFO	\$ 710	\$ 632	\$ 2,108	\$ 2,080
B. Lynne Parshall COO	\$ 1,514	\$ 800	\$ 5,445	\$ 3,202
Brett Monia SVP Drug Discovery	\$ 760	*	\$ 2,158	*
Patrick O'Neil SVP Legal	\$ 758	\$ 652	\$ 2,156	\$ 1,880

*Due to the unique and complex nature of Dr. Monia's position at Ionis, the outside compensation consultant advised the Compensation Committee that there were no appropriate comparable positions within the Executive Peer Group.

The independent compensation consultant advised our Compensation Committee that the competitive range for each element of compensation is within +/- 20% of the 50th percentile for the Executive Peer Group. Total cash compensation and total direct compensation in 2016 for our CFO were within the competitive range. Total cash compensation and total direct compensation in 2016 for our CEO were above the competitive range. The Compensation Committee believed paying the CEO above the range was appropriate given the strong performance for the year as further described under "Evaluation of 2016 Corporate Objectives on pages 48 through 50 below.

Our Productivity vs. Executive Peer Group

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

Even for established R&D based pharmaceutical companies for which the comparator group is obvious, comparisons of productivity are challenging. While revenues and profits per employee may be good measures for a portion of the equation, they are inadequate because 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 are necessary. Additionally, measures of innovation such as numbers of issued patents can be used.

Because biotechnology companies' business models vary, ranging from companies repurposing a single in-licensed commercial drug, to companies developing in-licensed novel drugs, to true research-based companies and a few companies pioneering broad new technology platforms, comparisons of productivity within the biotechnology industry are even more challenging. Such comparisons are even more difficult for development stage pre-commercial companies.

Nevertheless, it is as important to develop productivity metrics and compare productivity for biotechnology companies as it is for any other industry. As Ionis matures and achieves revenues from the commercial sale of its products, we will use revenue and profit per employee as metrics, supplemented by metrics that measure the value of our drug pipeline and innovation. We analyze our productivity against the Executive Peer Group and other leaders in drug development using, among other measures, number of drugs in clinical development per employee and number of patents per employee.

The table below measures Ionis on these productivity metrics against the median for the Executive Peer Group, and the leading company in the peer group for each productivity metric (based on information available in the most recent Annual Report of the companies):

	Drugs in Clinical Development per Employee	Patents per Employee
Ionis' Ranking	2 nd	2 nd
Executive Peer Group Median	1 drug for every 91 employees	1 patent per employee
Peer Leader for Drugs in Clinical Development per Employee (Ligand)	1 drug for every 1 employee	NA
Peer Leader for Patents per Employee (Innoviva)	NA	7 patents per employee
Ionis Pharmaceuticals, Inc. (IONS)	1 drug for every 11 employees	3 patents per employee

As illustrated, Ionis' innovative culture and business strategy have made Ionis incredibly productive in terms of the number of drugs in development per employee and patents per employee.

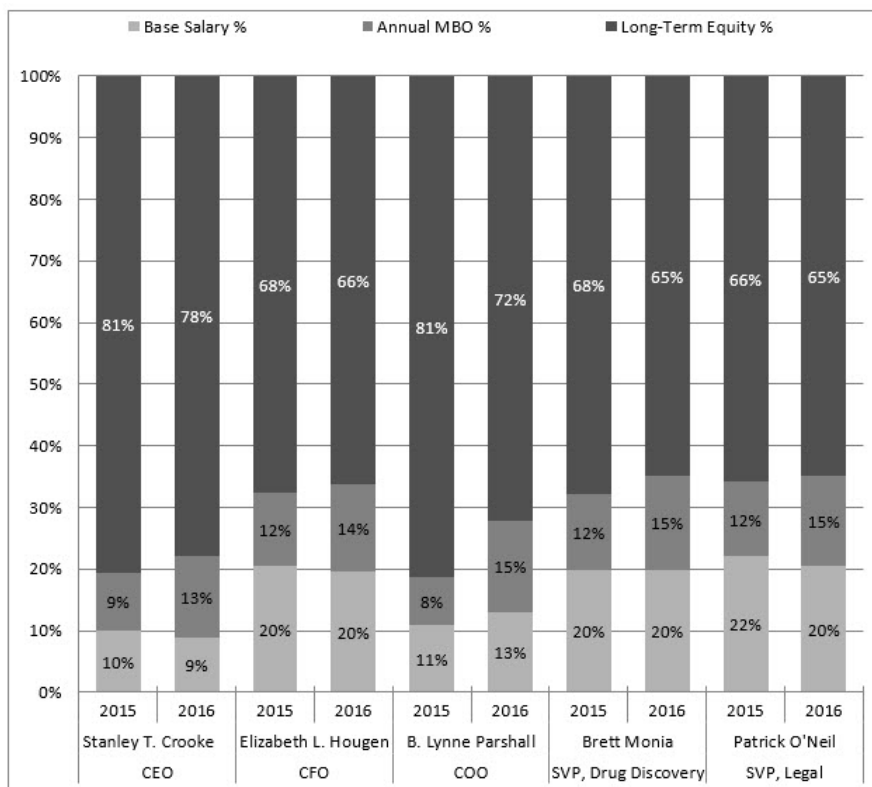
Compensation Allocation/Pay Mix

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, COO's and other NEO's 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 NEOs such that more of their compensation is in the form of long-term equity compensation; and
- *Less of total compensation is salary.* The Compensation Committee strives to have the total pay mix for our CEO and other NEOs such that less of their compensation is in the form of salary. For example, the Compensation Committee did not increase salaries for the CEO and most of our NEOs for each of 2011, 2012 and 2013 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 NEOs is a result of the compensation targets which 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.

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 2015 and 2016:



Name	Year	% of Total Direct Compensation					
		Base Salary	Annual Performance MBO	Long-Term Equity	Base Salary %	Annual Performance MBO %	Long-Term Equity %
Stanley T. Crooke CEO	2015	\$ 800	\$ 749	\$ 6,411	10%	9%	81%
	2016	\$ 825	\$ 1,206	\$ 7,133	9%	13%	78%
Elizabeth L. Hougen CFO	2015	\$ 392	\$ 226	\$ 1,286	20%	12%	68%
	2016	\$ 413	\$ 297	\$ 1,397	20%	14%	66%
B. Lynne Parshall COO	2015	\$ 692	\$ 498	\$ 5,146	11%	8%	81%
	2016	\$ 713	\$ 802	\$ 3,930	13%	15%	72%
Brett Monia SVP, Drug Discovery	2015	\$ 413	\$ 258	\$ 1,415	20%	12%	68%
	2016	\$ 427	\$ 333	\$ 1,397	20%	15%	65%
Patrick O'Neil SVP, Legal	2015	\$ 410	\$ 226	\$ 1,222	22%	12%	66%
	2016	\$ 441	\$ 317	\$ 1,397	20%	15%	65%

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 ten 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 which exceed those of someone in a higher job level. We have chosen not to have salary ranges because years of experience have shown that this approach often creates unnecessary bureaucracy and a loss of talented individuals. Our aim is to attract and retain the most highly qualified employees in an extremely competitive market.

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

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

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

Each year our employees are eligible to receive an appropriate merit salary increase. The Compensation Committee sets a Company-wide merit increase budget percentage based on Ionis' performance and external factors such as the average merit budget of comparable companies. The actual merit increase award for each employee, including our executive officers, will vary depending upon the respective employee's contributions to Ionis. For example, for 2016 performance the Company-wide merit increase budget was 3.0%, with a range of individual merit award increases of 0% to 4.5%. However, regardless of individual employee variances, we do not exceed the Company-wide approved merit budget.

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

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

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

Performance MBOs can be, and have in the past been, zero.

Performance MBOs have a maximum limit.

For example, Dr. Crooke's 2017 salary of \$849,271 was calculated as follows:

<u>2016 Base Salary</u>	(x)	<u>Merit Increase</u>	=	<u>Increase to Base Salary</u>
\$824,535	(x)	3.0%	=	\$24,736
<u>Current Base Salary</u>	(+)	<u>Increase to Base Salary</u>	=	<u>New Base Salary in 2017</u>
\$824,535	(+)	24,736	=	\$849,271

When reviewing salaries, the Compensation Committee noted that our CEO's salary, and the salary of most of our other NEOs, was within the competitive range of the Executive Peer Group. The Compensation Committee also noted (i) its desired target mix of compensation that is less weighted on salary, and (ii) historically the committee did not increase base salaries for the CEO, COO and most of the other NEOs for 2011-2013 to help adjust total pay mix so that it was weighted less heavily on fixed cash compensation. Given Ionis' outstanding 2016 performance, and given that Ionis had previously fixed executive salaries for a number of years, the Compensation Committee approved merit increases to each of the NEO's salaries for 2016.

MBO-Performance Based-At Risk Cash Compensation (Performance MBO)

The next component of an executive officer's compensation, as well as the compensation of our employees at the director level and above, is a performance based cash payment through our Performance MBO program. Our Performance MBO program rewards employees for reaching specific objectives and for the judgment they use in making decisions, while an employee's base salary compensates the employee for his or her continued service and performance. We do not guarantee a Performance MBO as compensation. It is totally at risk. As such, a Performance MBO 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 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 based on the following formula:

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

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

For example, in 1999 we did not pay Performance MBOs to executive officers due to the failures we faced at the time. In 2004 our CEO's Performance MBO was 64% of the Performance MBO he received in 2003 because of disappointing clinical trial results; the Company Performance Factor was 50% that year. Conversely, in 2007 Ionis had a seminal year and we rewarded 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 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 MBO Percentages on position levels within Ionis. The Target MBO percentages for 2016 were: Directors 20%; Executive Directors 25%; Vice Presidents 30% or 35%; Senior Vice Presidents 40%, COO 50%; and CEO 65%.

An individual's Target 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 MBO for 2016 as a percentage of salary:

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

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

- Ionis' achievement of the approved corporate objectives for the year. At the end of each year, the Compensation Committee meets to evaluate Ionis' overall performance. As described below in the chart called "Evaluation of 2016 Corporate Objectives" the Compensation Committee measures Ionis' performance based upon the achievement of goals that were set at the beginning of the year and agreed upon by our Board and upper management.
- In addition, the Compensation Committee considers our one-, three- and five-year total stockholder returns, and based on these returns may reduce the 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.

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 2016 Corporate Objectives. On January 4, 2017, the Compensation Committee completed its evaluation of the Company’s performance against the 2016 Corporate Objectives.

The Compensation Committee set the Company Performance Factor for the 2016 MBO at 150%. Even though Ionis’ stock price declined for the year, the Compensation Committee felt the 150% Company Performance Factor was appropriate due to our strong achievements for the year across drug discovery, development and corporate development, particularly given:

- Ionis and Biogen achieved FDA approval of SPINRAZA for the treatment of SMA in pediatric and adult patients. Achieving this approval so quickly for the broad patient population was an extraordinary achievement and exceeded expectations for the year;
- Ionis and Akcea formed a strategic collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx};
- Ionis significantly improved upon its financial guidance for the year; and
- Ionis’ stock outperformed *both* the median of the Nasdaq Biotechnology Index and the median of the Executive Peer Group.

The table below provides a detailed evaluation of each objective and the related achievements:

Evaluation of 2016 Corporate Objectives		
	Objective & Pre-Approved Measures	Evaluation
1	<p>Prepare for Filing/Approval:</p> <ul style="list-style-type: none"> · File NDA and MAA for SPINRAZA (filing accepted), achieve Biogen Licensing Fee · Pass regulatory inspections post filing (GMP and GCP) · NDA/MAA sections complete and reviewed for volanesorsen, except Phase 3 data · Complete all pre-clinical and clinical study reports for IONIS-TTR_{Rx} except for the ongoing Neuro-TTR study · Complete summary shells and CMC sections for the IONIS-TTR_{Rx} NDA to the extent possible · Complete position pieces on key issues · Manage process with GSK to enable a smooth transfer for NDA filing for IONIS-TTR_{Rx} should GSK exercise its option · Ensure smooth transitioning of API site and process changes to GSK/CMO to enable a successful launch for IONIS-TTR_{Rx} 	<p>Ionis <i>exceeded</i> this objective:</p> <ul style="list-style-type: none"> · Biogen filed the NDA and MAA for SPINRAZA; and paid Ionis the \$75 million license fee. Ionis and Biogen achieved FDA approval of SPINRAZA in 3 months under Priority Review for the treatment of SMA in pediatric and adult patients · The regulatory inspections supported approval for SPINRAZA · Ionis and Akcea completed the NDA/MAA sections for volanesorsen, except Phase 3 data · Ionis completed the Pre-Clinical and Clinical study reports for IONIS-TTR_{Rx} other than the ongoing Neuro-TTR study · Ionis substantially completed the summary shells and CMC sections for the IONIS-TTR_{Rx} NDA · Ionis substantially completed the position pieces for key issues · Ionis implemented a process to transfer NDA filing for IONIS-TTR_{Rx} should GSK exercise its option · Ionis worked with GSK to transition API manufacturing for IONIS-TTR_{Rx} to enable a successful launch for IONIS-TTR_{Rx}
2	<p>Advance Pipeline:</p> <ul style="list-style-type: none"> · Screening closed in volanesorsen FPL Phase 3 study 	<p>Ionis <i>met</i> this objective:</p> <ul style="list-style-type: none"> · Due to improved study designs, closing for screening in the volanesorsen FPL Phase 3 Study is planned for 2017

	<ul style="list-style-type: none"> · Positive data for IONIS-DMPK-2.5_{Rx} and Biogen agreement to advance program · Positive data for IONIS-FXI_{Rx} and Bayer agreement to advance program (milestone payment) · Solidify most rapid route leading to regulatory success and commercialization for IONIS-APO(a)-L_{Rx} (finalized plan). · Initiate first Phase 2/3 Clinical Trials on ≥3 drugs · Positive Phase 2 Clinical data on ≥5 drugs · Initiate Phase 1 Clinical Trials on ≥4 drugs · ≥4 new drugs into the pipeline 	<ul style="list-style-type: none"> · Ionis completed this study, observed encouraging biomarker trends and learned more about the disease. However, Ionis did not achieve the desired potency in muscle · Ionis reported positive data from the Phase 2 study of IONIS-FXI_{Rx} in patients with end-stage renal disease on hemodialysis. Bayer, plans to advance IONIS-FXI_{Rx} and expanded the collaboration by licensing the follow-on LICA drug, IONIS-FXI-L_{Rx} · Ionis and Akcea formed a strategic collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, which allows Ionis and Akcea to move more rapidly to Phase 3 cardiovascular outcomes studies with both therapies than their original development plans · Ionis initiated Phase 2 clinical trials for three drugs · Ionis reported positive Phase 2 data for six studies · Ionis initiated Phase 1 clinical trials on two drugs · Ionis added five new drugs to its development pipeline
3	<p>Make Biogen Idec relationship successful:</p> <ul style="list-style-type: none"> · Positive data for IONIS-DMPK-2.5_{Rx} and Biogen agreement to advance program · Initiate Phase 1 clinical trial for IONIS-BIIB4_{Rx} · Identify ≥1 development candidate and two new target sanctions · Achieve ≥\$100 million in revenue across all Biogen collaborations 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> · Ionis completed this study, observed encouraging biomarker trends and learned more about the disease. However, Ionis did not achieve the desired potency in muscle · Ionis advanced the program but the Phase 1 clinical trial for IONIS-BIIB4_{Rx} did not initiate until the first half of 2017 · Ionis achieved two target sanctions, and made significant progress towards identifying a development candidate · Ionis exceeded this measure by generating nearly \$210 million in revenue across all Biogen collaborations
4	<p>Make AstraZeneca relationship successful:</p> <ul style="list-style-type: none"> · Successful outcome of STAT3-PDL1 Phase 1/2 study · Achieve development candidate approval for IONIS-AZ4-2.5-L_{Rx} · Successfully complete IONIS-KRAS-2.5_{Rx} nonclinical study and achieve \$15 million milestone · Advance two new programs to target sanction 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> · Although the study progressed in 2016, we do not expect the study to complete until 2017 · Ionis achieved development candidate approval for IONIS-AZ4-2.5-L_{Rx} and received a \$25 million milestone · Ionis complete the IONIS-KRAS-2.5_{Rx} nonclinical study and received a \$15 million milestone · Ionis advanced two new programs to target sanction
5	<p>Demonstrate the value of technology advancements in the clinic:</p> <ul style="list-style-type: none"> · Advance ≥3 LICA drugs through Phase 1 with ED50 ≤20 mg/wk 	<p>Ionis <u>partially met</u> this objective:</p> <ul style="list-style-type: none"> · Ionis advanced three LICA drugs into Phase 1 and achieved an ED50 ≤20 mg/wk

	<ul style="list-style-type: none"> · ≥4 new Gen 2.5 drugs into development · uORF and TSE approaches fully enabled for drug discovery activities 	<ul style="list-style-type: none"> · Ionis advanced two new Gen 2.5 drugs into development · Ionis fully enabled drug discovery for uORF and TSE
6	Meet budget and financial projections for the year	<p>Ionis <u>exceeded</u> this objective:</p> <ul style="list-style-type: none"> · Ionis significantly improved upon its financial guidance for the year · Ionis met its budget
7	Stock price performance by a percentage greater than or equal to median of the companies listed in the NASDAQ Biotechnology Index; or if SPINRAZA filing successful 110%	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> · Ionis' stock price outperformed the median stock price change for companies listed in the NASDAQ Biotechnology Index
8	Successful Akcea IPO (at prespecified valuation target) assuming reasonable market conditions	<p>Ionis <u>partially met</u> this objective:</p> <ul style="list-style-type: none"> · We made substantial progress preparing for Akcea's IPO
9	Partner IONIS-APO(a)-L _{Rx} or alternative successful Akcea transaction	<p>Ionis <u>exceeded</u> this objective:</p> <ul style="list-style-type: none"> · Ionis and Akcea formed a strategic collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} for the treatment of lipid disorder
10	Complete one additional partnership either by expanding or adding a new partner	<p>Ionis <u>exceeded</u> this objective:</p> <ul style="list-style-type: none"> · The Novartis transaction noted in item 9 above also included AKCEA-APOCIII-L_{Rx}
11	Pre-commercial activity for volanesorsen on track for early 2018 launch: <ul style="list-style-type: none"> · Initial US and EU Commercial infrastructure in place 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> · Akcea made significant progress regarding its pre-commercial activity for volanesorsen for planned early 2018 launch

Unplanned Accomplishments for 2016

12	The FDA approved SPINRAZA in record time
13	Biogen reported positive data from an end of study analysis of the ENDEAR Phase 3 study in patients with infantile-onset (consistent with type 1) SMA at the British Pediatric Neurology Association. annual conference. Ionis previously reported data from an interim analysis of ENDEAR, which along with several other studies, formed the basis for the marketing application for SPINRAZA in the U.S.
14	Ionis and Biogen reported positive data from an interim analysis of the Phase 3 CHERISH study in patients with later-onset (consistent with Type 2) SMA
15	Ionis and Akcea reported that the Phase 3 COMPASS study for volanesorsen met its primary endpoint
16	Ionis sold the global rights to develop and commercialize KYNAMRO to Kastle Therapeutics and earned a \$15 million upfront payment
17	Ionis and MD Anderson Cancer Center formed a strategic alliance to advance novel cancer therapies
18	Ionis completed a satellite company transaction with Dynacure to discover, develop and commercialize drugs to treat neuromuscular diseases
19	Ionis received funding from Cystic Fibrosis Foundation for Ionis' program targeting ENAC for treating cystic fibrosis
20	Ionis settled its dispute with OncoGenex on favorable terms

Once the Committee establishes the Company Performance Factor, the Committee next reviews individual performance and sets each Executive Officer's Performance MBO payout. The following table illustrates the Performance MBOs approved for 2016 performance:

Name	Base Salary	Target MBO %	Company Performance Factor	Individual Performance Factor	Resulting Performance MBO	Results Considered When Setting Individual Performance Factor ⁽¹⁾
Stanley T. Crooke ⁽²⁾	\$ 824,535	65%	150%	150%	\$ 1,205,882	1-20
Elizabeth L. Hougen	\$ 412,839	40%	150%	120%	\$ 297,244	6-10
B. Lynne Parshall ⁽²⁾	\$ 712,676	50%	150%	150%	\$ 801,761	1-20
Brett Monia	\$ 427,245	40%	150%	130%	\$ 333,251	1, 4-7, & 17-19
Patrick O'Neil	\$ 440,777	40%	150%	120%	\$ 317,359	2, 6-10, & 16-20

- (1) The numbers correspond to the enumerated objectives in the table entitled "Evaluation of 2016 Corporate Objectives" on pages 48 through 50. The Compensation Committee reviews the individual's contribution towards the corporate objective when setting the Individual Performance Factor.
- (2) Since our CEO and COO are ultimately responsible for the Company's performance, their Individual Performance Factors are usually the same as the Company Performance Factor.

The Company Performance Factor reflects an increase of 30 percentage points from the 2015 Company Performance Factor of 120% given the very strong year of performance. As noted earlier, the corporate objectives are set and approved by our Board at the beginning of each year. We ensure these objectives are aggressive and we define excellent performance as a year in which we have met most of the objectives.

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 option awards.

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

Some of our largest institutional stockholders agree our stock options are performance-based and the best vehicle for our long-term compensation. Our independent compensation consultant did not recommend we change our equity vehicles. Over the past several years we discussed our use of time-vested stock options and RSU awards with our institutional stockholders. The results of this process were that one of our largest institutional stockholders agreed that time-vested options are the best long-term incentive compensation vehicle for a biopharmaceutical company at our stage, and others agreed that our time-vested stock options are performance-based compensation. Our independent compensation consultant also believes time-vested stock options are performance-based compensation and an appropriate equity vehicle for Ionis. Also we would be disadvantaged if we did not offer time-vested equity awards since most companies we compete with for talent (including most companies in the Executive Peer Group) do not use event-based vesting for equity compensation.

We grant existing employees new options and RSUs annually to provide a continuing financial incentive in Ionis' long-term success. We set the size of the equity awards based on individual and company performance during the previous year.

Vesting schedules reward long-term performance and incentivize long-term stock appreciation and increased stockholder returns. For each stock option and RSU granted, 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 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.

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.

The stock option vesting schedule is typically over a 4-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 4-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 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 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 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 2.1% 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 3.1% from 2013 through 2015. We believe this stock budget is an important tool to balance our compensation objectives with stockholder interests. For 2016 performance, the Compensation Committee set a merit stock award budget that resulted in approximately 2.2 million stock options and approximately 320,000 RSUs awarded to employees, including the executive officers. Together these shares represent approximately 2.1% of our outstanding common stock on an issued and outstanding basis for that year. This budget, as well as each employee’s position level and performance in the previous year, ultimately determines the size of the individual annual stock grants.

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

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

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

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

As of March 31, 2017, all of our non-employee Directors meet these guidelines and nearly all of our executive officers meet these guidelines.

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

Dr. Crooke currently holds approximately 750,000 shares of our common stock and has held most of these shares throughout his over 27-year tenure. As of December 31, 2016, Dr. Crooke’s holding represented over 40 times his Base Salary.

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

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

any profits realized from such executive's sale of Ionis' securities during that 12-month period.

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

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

We explicitly prohibit employees from "shorting" and hedging against our stock. To help avoid situations in which our employees may benefit from transactions that harm our stockholders, our policies specifically prohibit all employees, including our executive officers, from taking a "short" position in our stock and otherwise hedging their position in our stock against a future drop in our stock price. In addition, we specifically prohibit all of our employees from trading derivative instruments based on our common stock (e.g. put or call options for our stock).

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

We designed our retention agreements for our CEO and COO and the related severance compensation provisions to meet the following objectives:

Change in Control. As part of our normal course of business and as a result of our business strategy, we engage in discussions with other biotechnology and pharmaceutical companies about possible collaborations, licensing and/or other ways in which the companies may work together to further our respective long-term objectives. In addition, many larger established pharmaceutical companies consider companies at similar stages of development to ours as potential acquisition targets. Occasionally, a transaction in the biotech/biopharmaceutical industry may start as a licensing transaction, but ultimately result in an acquisition. In certain scenarios, the potential for merger or being acquired may be in the best interests of our stockholders. As further described on page 60, we provide a component of severance compensation for our CEO and COO to promote their ability to act in the best interests of our stockholders even though they could be terminated as a result of the transaction.

Termination without Cause. If we terminate the employment of our COO "without cause" we will pay her the benefits described under "Post-Employment Compensation – Retention and Change of Control Agreements." This agreement provides us with more flexibility to make a change in senior management if such a change is in our and our stockholders' best interests.

2016 Say-on-Pay Vote

We value the feedback our stockholders provide regarding executive compensation. As such, we are committed to providing our stockholders the opportunity for a “say-on-pay” vote annually.

In 2016 we asked our stockholders to provide a non-binding approval regarding our executive officer compensation for the previous year. This proposal gave our stockholders the opportunity to express their views on the compensation paid to our NEOs. At our 2016 Annual Meeting of Stockholders, we received an advisory vote in favor of our executive compensation by 97.3% of the shares voted at the meeting.

Compensation of Executive Officers

The following table shows for the fiscal years ended December 31, 2016, 2015, and 2014, 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, 2016, called our “named executive officers.”

Summary Compensation Table

Name and Principal Position	Year	Salary (\$)	Bonus ⁽¹⁾ (\$)	Stock Awards ⁽²⁾ (\$)	Option Awards ⁽²⁾ (\$)	All Other Compensation ⁽³⁾ (\$)	Total (\$)
Stanley T. Crooke Chairman, President, Chief Executive Officer	2016	\$ 824,535	\$ 1,205,882	\$ 1,427,416	\$ 5,705,552	\$ 25,366	\$ 9,188,751
	2015	\$ 800,519	\$ 749,286	\$ 1,893,100	\$ 4,517,593	\$ 20,526	\$ 7,981,025
	2014	\$ 768,252	\$ 720,236	\$ 1,489,375	\$ 3,231,294	\$ 18,986	\$ 6,228,143
Elizabeth L. Hougen Senior Vice President, Finance and Chief Financial Officer	2016	\$ 412,839	\$ 297,244	\$ 279,647	\$ 1,117,834	\$ 25,670	\$ 2,133,234
	2015	\$ 391,906	\$ 225,738	\$ 379,859	\$ 906,589	\$ 25,782	\$ 1,929,873
	2014	\$ 377,923	\$ 206,677	\$ 357,450	\$ 775,511	\$ 23,981	\$ 1,741,542
B. Lynne Parshall Director, Chief Operating Officer	2016	\$ 712,676	\$ 801,761	\$ 786,549	\$ 3,143,869	\$ 29,773	\$ 5,474,628
	2015	\$ 691,918	\$ 498,181	\$ 1,519,712	\$ 3,626,610	\$ 24,963	\$ 6,361,384
	2014	\$ 664,029	\$ 466,895	\$ 655,325	\$ 1,421,771	\$ 24,023	\$ 3,232,043
Brett Monia Senior Vice President, Drug Discovery	2016	\$ 427,245	\$ 333,251	\$ 279,647	\$ 1,117,834	\$ 26,177	\$ 2,184,154
	2015	\$ 412,797	\$ 257,585	\$ 417,859	\$ 997,237	\$ 26,542	\$ 2,112,020
	2014	\$ 396,158	\$ 233,981	\$ 357,450	\$ 775,511	\$ 24,015	\$ 1,787,115
Patrick R. O’Neil ⁽⁴⁾ Senior Vice President, Legal, General Counsel and Chief Compliance Officer	2016	\$ 440,777	\$ 317,359	\$ 279,647	\$ 1,117,834	\$ 21,573	\$ 2,177,190
	2015	\$ 409,866	\$ 226,246	\$ 360,859	\$ 861,271	\$ 20,868	\$ 1,879,110
	2014	\$ 396,006	\$ 207,903	\$ 357,450	\$ 775,511	\$ 19,234	\$ 1,756,104

(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 2017 we paid bonuses for 2016 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 of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2016 regarding assumptions underlying valuation of equity awards.

(3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) matching contributions which are available to all employees.

(4) Mr. O’Neil was not a named executive officer in 2015 or 2014.

Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2016, certain information regarding grants of plan-based awards to our named executive officers:

Grants of Plan-Based Awards in Fiscal 2016

Name	Grant Date	All Other Stock Awards: Number of Shares of Stock or Units (#)	All Other Option Awards: Number of Securities Underlying Options (#)	Exercise or Base Price of Option Awards (\$/Sh)	Grant Date Fair Value of Stock and Option Awards ⁽¹⁾ (\$)
Stanley T. Crooke	1/4/16		195,182	\$ 61.68	\$ 5,705,552
	1/15/16	32,530			\$ 1,427,416
Elizabeth L. Hougen	1/4/16		38,240	\$ 61.68	\$ 1,117,834
	1/15/16	6,373			\$ 279,647
B. Lynne Parshall	1/4/16		107,549	\$ 61.68	\$ 3,143,869
	1/15/16	17,925			\$ 786,549
Brett Monia	1/4/16		38,240	\$ 61.68	\$ 1,117,834
	1/15/16	6,373			\$ 279,647
Patrick R. O'Neil	1/4/16		38,240	\$ 61.68	\$ 1,117,834
	1/15/16	6,373			\$ 279,647

(1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with FASB Topic ASC 718 ("ASC 718") for stock and option awards granted to our named executive Officers. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 4, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2016 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 4, 2016. 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, 2016. 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, 2016.

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

The following table shows for the fiscal year ended December 31, 2016, 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, 2016.

Outstanding Equity Awards as of December 31, 2016

Name	Grant Date	Option Awards				Stock Awards	
		Number of Securities Underlying Unexercised Options (#) Exercisable (1)	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price (\$)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested(2)	Market Value of Shares or Units of Stock that Have Not Vested (3) (\$)
Stanley T. Crooke	1/3/2012	93,462	--	\$ 7.25	1/2/2019	--	--
	1/30/2013	130,405	2,775	\$ 14.69	1/29/2020	--	--
	1/2/2014	136,718	50,782	\$ 39.87	1/1/2021	--	--
	1/2/2015	79,062	85,938	\$ 61.57	1/1/2022	--	--
	1/4/2016	--	195,182	\$ 61.68	1/3/2023	--	--
	1/30/2013	--	--	--	--	5,547	\$ 265,313
	1/15/2014	--	--	--	--	15,624	\$ 747,296
	1/15/2015	--	--	--	--	20,625	\$ 986,494
	1/15/2016	--	--	--	--	32,530	\$ 1,555,910
Elizabeth L. Hougen	1/3/2011	22,000	--	\$ 10.29	1/2/2018	--	--
	1/3/2012	4,063	--	\$ 7.25	1/2/2019	--	--
	1/2/2013	15,372	328	\$ 10.82	1/1/2020	--	--
	1/2/2013	7,343	157	\$ 10.82	1/1/2020	--	--
	1/2/2014	32,812	12,188	\$ 39.87	1/1/2021	--	--
	1/2/2015	15,866	17,246	\$ 61.57	1/1/2022	--	--
	1/4/2016	--	38,240	\$ 61.68	1/3/2023	--	--
	1/15/2013	--	--	--	--	653	\$ 31,233
	1/15/2013	--	--	--	--	312	\$ 14,923
	1/15/2014	--	--	--	--	3,750	\$ 179,363
	1/15/2015	--	--	--	--	4,138	\$ 197,921
	1/15/2016	--	--	--	--	6,373	\$ 304,821
	B. Lynne Parshall	1/30/2013	11,112	1,298	\$ 14.69	1/29/2020	--
1/2/2014		60,156	22,344	\$ 39.87	1/1/2021	--	--
1/2/2015		63,470	68,988	\$ 61.57	1/1/2022	--	--
1/4/2016		--	107,549	\$ 61.68	1/3/2023	--	--
1/30/2013		--	--	--	--	2,595	\$ 124,119
1/15/2014		--	--	--	--	6,874	\$ 328,783
1/15/2015		--	--	--	--	16,557	\$ 791,921
1/15/2016		--	--	--	--	17,925	\$ 857,353
Brett Monia	1/1/2012	7,500	--	\$ 7.21	12/31/2018	--	--
	1/3/2012	8,993	--	\$ 7.25	1/2/2019	--	--
	1/30/2013	33,291	709	\$ 14.69	1/29/2020	--	--
	1/2/2014	32,812	12,188	\$ 39.87	1/1/2021	--	--
	1/2/2015	17,453	18,970	\$ 61.57	1/1/2022	--	--
	1/4/2016	--	38,240	\$ 61.68	1/3/2023	--	--
	1/30/2013	--	--	--	--	1,415	\$ 67,679
	1/15/2014	--	--	--	--	3,750	\$ 179,363
	1/15/2015	--	--	--	--	4,552	\$ 217,722
1/15/2016	--	--	--	--	6,373	\$ 304,821	
Patrick R. O'Neil	1/3/2012	1,219	--	\$ 7.25	1/2/2019	--	--
	1/2/2013	4,579	328	\$ 10.82	1/1/2020	--	--
	1/2/2013	2,187	157	\$ 10.82	1/1/2020	--	--
	1/2/2014	19,687	12,188	\$ 39.87	1/1/2021	--	--
	1/2/2015	15,073	16,384	\$ 61.57	1/1/2022	--	--
	1/4/2016	--	38,240	\$ 61.68	1/3/2023	--	--
	1/15/2013	--	--	--	--	653	\$ 31,233
	1/15/2013	--	--	--	--	312	\$ 14,923
	1/15/2014	--	--	--	--	3,750	\$ 179,363
	1/15/2015	--	--	--	--	3,931	\$ 188,020
	1/15/2016	--	--	--	--	6,373	\$ 304,821

(1) 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.

(2) The RSUs 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 \$47.83, which was the closing market price of our common stock on NASDAQ on December 30, 2016, the last trading day of fiscal 2016.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2016, certain information regarding option exercises and stock awards vesting during the last fiscal year with respect to our named executive officers:

Name	Option Awards		Stock Awards	
	Number of Shares Acquired on Exercise #(1)	Value Realized on Exercise (\$)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting (\$)
Stanley T. Crooke	6,880	\$ 226,834	23,212	\$ 1,018,543
	100	\$ 3,309		
	400	\$ 13,220		
	100	\$ 3,303		
	200	\$ 6,616		
	1,000	\$ 33,030		
	320	\$ 10,557		
	1,000	\$ 32,980		
	3,741	\$ 113,165		
	1,259	\$ 34,257		
	5,000	\$ 133,550		
	5,000	\$ 128,550		
	5,000	\$ 124,050		
	10,000	\$ 263,200		
	5,876	\$ 151,660		
	3,600	\$ 93,996		
	124	\$ 3,204		
	2,400	\$ 62,640		
	8,000	\$ 203,200		
	5,000	\$ 126,600		
5,000	\$ 126,050			
5,000	\$ 125,800			
5,000	\$ 125,750			
5,000	\$ 180,050			
5,000	\$ 178,300			
5,000	\$ 152,150			
5,000	\$ 152,300			
5,000	\$ 259,050			
10,000	\$ 507,600			
Elizabeth L. Hougen	2,500	\$ 86,950	4,762	\$ 208,957
	2,500	\$ 90,575		
	2,500	\$ 74,325		
	870	\$ 23,573		
	1,330	\$ 36,282		
	300	\$ 8,187		
B. Lynne Parshall	2,500	\$ 68,275	13,267	\$ 582,156
	2,000	\$ 52,820		
	2,000	\$ 55,820		
	3,500	\$ 100,835		
	2,500	\$ 66,525		
	3,635	\$ 55,834		
	809	\$ 37,505		
	4,500	\$ 101,520		
	4,000	\$ 90,200		
	365	\$ 8,322		
	1,000	\$ 42,750		
	1,000	\$ 42,750		
	1,000	\$ 42,750		
1,000	\$ 42,750			
Brett Monia	---	---	5,543	\$ 243,227
Patrick R. O'Neil	1,000	\$ 34,180	4,693	\$ 205,929
	806	\$ 27,549		
	194	\$ 6,631		
	848	\$ 45,665		
	350	\$ 11,963		
	1,000	\$ 34,580		
152	\$ 7,643			

(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

We do not provide pension arrangements or post-retirement health coverage for our executives or employees. Our executive officers are eligible to participate in our 401(k) contributory defined contribution plan. In 2016, we contributed to each participant a matching contribution equal to 50% of the first 6% of the participant's compensation he or she contributed to the plan. In 2016, the maximum matching contribution was \$7,950. 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

All of Ionis' employees, including our executive officers, are employees-at-will and as such do not have employment contracts with us, except in the case of severance agreements for our CEO and COO, the details of which are provided below.

Retention and Change of Control Agreements

We have severance agreements with Stanley T. Crooke and B. Lynne Parshall, which provide the following severance benefits:

- Dr. Crooke will be eligible to receive a lump sum severance payment equal to 36 months of his then-current base salary in the event his employment is terminated as a result of a change of control of Ionis; and
- Ms. Parshall will be eligible to receive a lump sum severance payment equal to:
 - o 18 months of her then-current base salary in the event that her employment is terminated without cause; and
 - o 30 months of her then-current base salary in the event that her employment is terminated as a result of a change of control of Ionis.

These agreements will remain in effect as long as each individual continues to be employed by Ionis.

In addition, the Compensation Committee has approved that in the event of a change of control, the vesting and exercisability of Dr. Crooke and Ms. Parshall's then outstanding and unvested stock options and RSUs will be accelerated in full, to the extent permitted by the applicable stock option plan.

Conditions

As a condition to receiving payments under each of the retention and change of control agreements described above, the officer is required to return all of our property and information and sign an agreement releasing Ionis from liability.

Potential Payments Upon Termination or Change-of-Control

The following table estimates the lump sum payments that would be required under the agreements described above as of December 31, 2016. This table estimates the lump sum payments based upon either a termination without cause or a termination in connection with a change of control assuming either occurred on December 31, 2016. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 68 of this Proxy Statement.

Name	Termination Event	
	Termination Without Cause	Termination in a Change of Control
Stanley T. Crooke	--	\$ 2,473,605
B. Lynne Parshall	\$ 1,069,014	\$ 1,781,690

Director Compensation

For the fiscal year ending December 31, 2016, we paid our non-employee Directors a base cash retainer of \$50,000 with additional role-based compensation as noted below. Starting in 2017, we are paying our non-employee Directors a base cash retainer of \$55,000 with additional role-based compensation as noted below:

Role	2016 Cash Compensation	2017 Cash Compensation
Board Member (Base)	\$ 50,000	\$ 55,000
Committee Chairs (Additional)		
Audit	\$ 24,000	\$ 24,000
Compensation	\$ 15,000	\$ 20,000
Nominating, Governance and Review	\$ 10,000	\$ 10,000
Agenda	\$ 10,000	\$ 10,000
Committee Member (Additional)		
Audit	\$ 10,000	\$ 12,000
Compensation	\$ 7,500	\$ 10,000
Nominating, Governance and Review	\$ 5,000	\$ 5,000
Agenda	\$ 5,000	\$ 5,000
Scientific/Medical	\$ 10,000	\$ 10,000

If the Board creates new committees, we anticipate that the non-employee members of such new committee 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 2016, each non-employee Director also received automatic stock award grants under our Directors' Plan. On July 1, 2016, under the Directors' Plan, each of our non-employee Directors serving at that time received an option to purchase 16,000 shares of our common stock, at an exercise price of \$24.42 per share, the fair market value of the common stock on the date of the grant, based on the closing sales price reported on NASDAQ Global Select Market, and an RSU for 2,667 shares. The options and RSUs vest over a four-year period in equal annual installments.

The following table shows for the fiscal year ended December 31, 2016 certain information with respect to the compensation of all our non-employee Directors:

Director Compensation for Fiscal 2016

Name	Cash Compensation Earned or Paid (\$)	Stock Awards (\$) ⁽¹⁾	Option Awards (\$) ⁽¹⁾	All Other Compensation (\$)	Total (\$)
Spencer R. Berthelsen	\$ 85,000	\$ 65,128	\$ 202,353	--	\$ 352,481
Breaux B. Castleman	\$ 60,000	\$ 65,128	\$ 202,353	--	\$ 327,481
Joseph Klein, III	\$ 60,000	\$ 65,128	\$ 202,353	--	\$ 327,481
Joseph Loscalzo	\$ 70,000	\$ 65,128	\$ 202,353	--	\$ 337,481
Frederick T. Muto	\$ 55,000	\$ 65,128	\$ 202,353	--	\$ 322,481
Joseph H. Wender	\$ 86,500	\$ 65,128	\$ 202,353	--	\$ 353,981

(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, 2016 regarding assumptions underlying valuation of equity awards.

Outstanding Equity Awards at Fiscal Year-End – Directors

The following table shows for the fiscal year ended December 31, 2016, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors:

Outstanding Equity Awards as of December 31, 2016

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	12,500	--	\$ 9.77	7/1/2017	6,468	\$ 309,364
	15,000	--	\$ 13.88	6/30/2018		
	15,000	--	\$ 16.32	6/30/2019		
	15,000	--	\$ 9.22	6/30/2020		
	15,000	--	\$ 9.30	6/30/2021		
	11,250	--	\$ 12.94	7/1/2022		
	8,438	2,812	\$ 28.47	6/30/2023		
	8,000	8,000	\$ 35.53	6/30/2024		
	4,000	12,000	\$ 57.16	6/30/2025		
--	16,000	\$ 24.42	6/30/2026			
Breaux B. Castleman	16,875	5,625	\$ 26.66	6/24/2023	7,405	\$ 354,181
	8,438	2,812	\$ 28.47	6/30/2023		
	8,000	8,000	\$ 35.53	6/30/2024		
	4,000	12,000	\$ 57.16	6/30/2025		
	--	16,000	\$ 24.42	6/30/2026		
Joseph Klein, III	2,812	--	\$ 12.94	7/1/2022	6,468	\$ 309,364
	8,438	2,812	\$ 28.47	6/30/2023		
	8,000	8,000	\$ 35.53	6/30/2024		
	4,000	12,000	\$ 57.16	6/30/2025		
	--	16,000	\$ 24.42	6/30/2026		
Joseph Loscalzo	11,250	11,250	\$ 49.09	2/2/2024	7,874	\$ 376,613
	8,000	8,000	\$ 35.53	6/30/2024		
	4,000	12,000	\$ 57.16	6/30/2025		
	--	16,000	\$ 24.42	6/30/2026		
Frederick T. Muto	12,500	--	\$ 9.77	7/1/2017	6,468	\$ 309,364
	15,000	--	\$ 13.88	6/30/2018		
	15,000	--	\$ 16.32	6/30/2019		
	15,000	--	\$ 9.22	6/30/2020		
	15,000	--	\$ 9.30	6/30/2021		
	11,250	--	\$ 12.94	7/1/2022		
	8,438	2,812	\$ 28.47	6/30/2023		
	8,000	8,000	\$ 35.53	6/30/2024		
	4,000	12,000	\$ 57.16	6/30/2025		
--	16,000	\$ 24.42	6/30/2026			
Joseph H. Wender	15,000	--	\$ 13.88	6/30/2018	6,468	\$ 309,364
	15,000	--	\$ 9.22	6/30/2020		
	15,000	--	\$ 9.30	6/30/2021		
	11,250	--	\$ 12.94	7/1/2022		
	8,438	2,812	\$ 28.47	6/30/2023		
	8,000	8,000	\$ 35.53	6/30/2024		
	4,000	12,000	\$ 57.16	6/30/2025		
	--	16,000	\$ 24.42	6/30/2026		

(1) The options were granted out of our Directors' Plan and have a term of ten years and vest at the rate of 25% per year over four years.

- (2) The RSUs were granted out of our Directors' Plan and vest at the rate of 25% per year over four years.
- (3) All of our non-employee Directors are subject to our Stock Holding and Ownership Guidelines for RSU Shares, which requires each non-employee Director to accumulate and maintain shares of Common Stock issued pursuant to RSUs until he 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 termination of service.
- (4) Market value of stock awards was determined by multiplying the number of unvested shares by \$47.83, which was the closing market price of our common stock on the NASDAQ Global Select Market on December 30, 2016, the last trading day of fiscal 2016.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2016, 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 2016

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 ⁽¹⁾	12,500	\$ 388,375	2,115	\$ 51,648
Breaux B. Castleman	--	--	2,740	\$ 66,911
Joseph Klein, III	--	--	2,115	\$ 51,648
Joseph Loscalzo	--	--	2,272	\$ 65,866
Frederick T. Muto ⁽¹⁾	12,500	\$ 204,775	2,115	\$ 51,648
Joseph H. Wender ⁽¹⁾	--	--	2,115	\$ 51,648

(1) Dr. Berthelsen and Mr. Muto exercised options that would have expired on July 2, 2016.

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.

Dr. Rosanne Crooke, the wife of Dr. Stanley Crooke, our Chairman and Chief Executive Officer, is one of our non-executive officers working part time at 30 hours per week. The Compensation Committee approves Dr. Rosanne Crooke's compensation. Her compensation is commensurate with the compensation of other employees at the same level at Ionis. For the fiscal years ended 2016, 2015 and 2014, she received the following compensation:

Name and Principal Position	Year	Salary (\$)	Bonus ⁽¹⁾ (\$)	Stock Awards ⁽²⁾ (\$)	Option Awards ⁽²⁾⁽⁴⁾ (\$)	All Other Compensation ⁽³⁾ (\$)	Total (\$)
Rosanne Crooke Vice President, Cardiovascular Diseases Drug Discovery Research	2016	\$ 227,031	\$ 132,813	\$ 58,492	\$ 233,859	\$ 7,936	\$ 660,131
	2015	\$ 218,720	\$ 102,361	\$ 99,818	\$ 238,204	\$ 7,554	\$ 666,657
	2014	\$ 210,814	\$ 82,349	\$ 67,487	\$ 146,488	\$ 5,912	\$ 513,050

(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 2017 we paid bonuses for 2016 performance.

- (2) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with ASC 718 for stock and option awards granted to Dr. 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, 2016 regarding assumptions underlying valuation of equity awards.
- (3) Includes AD&D, Basic Life, Medical, Dental, Vision, and 401(k) matching contributions which are available to all employees.
- (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:
- 8,500 shares at \$39.87 per share received on January 2, 2014;
 - 8,700 shares at \$61.57 per share received on January 2, 2015; and
 - 8,000 shares at \$61.68 per share received on January 4, 2016.

One of our Directors, Mr. Muto, who was elected to the Board in March 2001, is a partner at Cooley LLP, our outside legal counsel. We paid Cooley LLP an aggregate of approximately \$595,000 in fees in 2016 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2016 fiscal year.

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 of the Board approves all compensation we pay to employees that may qualify as a related person and the Audit Committee approves all other related party transactions, as specified in its charter. The committees only approve related-party transactions at committee meetings, or by unanimous written consent in lieu of a meeting, and record the approvals in the minutes of the committee.

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

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

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 2017 Annual Meeting of Stockholders.

The Compensation Committee

Spencer R. Berthelsen, *Chairman*

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 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, 2016 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 auditors, who are responsible for expressing an opinion on the conformity of our audited consolidated financial statements and related schedules with 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 generally accepted auditing standards. In addition, the Audit Committee has discussed with the independent auditors, the auditors' independence from management and Ionis, including the matters in the written disclosures required by PCAOB Rule 3526. The Audit Committee received from Ernst & Young LLP written disclosure and the letter regarding its independence as required by applicable requirements of the Public Company Accounting Oversight Board regarding Ernst & Young LLP's communications with the Audit Committee concerning independence. The Audit Committee also discussed with our independent auditors the matters required by the Statement on Auditing Standards No. 16.

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, 2016, 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, 2016 for filing with the SEC. The Audit Committee and the Board have also recommended, subject to stockholder approval, the selection of Ernst & Young LLP as our independent auditors for 2017.

The Audit Committee

Joseph H. Wender, *Chairman*

Breaux B. Castleman

Joseph Klein, III

* 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, 2016 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)⁸ to view our 2016 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 6, 2017

⁸ 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 includes forward-looking statements regarding Ionis' business, the business of Akcea Therapeutics, Inc., a subsidiary of Ionis, and the therapeutic and commercial potential of SPINRAZA (nusinersen), volanesorsen and IONIS-TTR_{Rx} and other of Ionis' drugs in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' Annual Report on Form 10-K for the year ended December 31, 2016 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 PharmaceuticalsTM is a trademark of Ionis Pharmaceuticals, Inc. Akcea TherapeuticsTM is a trademark of Ionis Pharmaceuticals, Inc. SPINRAZATM is a trademark of Biogen Inc.

**Amendment to
IONIS PHARMACEUTICALS, INC.
2011 EQUITY INCENTIVE PLAN
Adopted by the Board of Directors March 3, 2017**

SUBJECT TO APPROVAL BY STOCKHOLDERS

This Amendment to the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan (the “**Amendment**”), is effective as of May 24, 2017.

- A. WHEREAS, the Board of Directors of Ionis approved an amendment to the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan (the “**Plan**”), as more fully described below.

NOW THEREFORE, the Plan is hereby amended as follows:

All capitalized terms not otherwise defined herein, will have the meanings ascribed to them in the Plan.

ARTICLE 1. AMENDMENT

- 1.1 Amendment and Restatement of Section 3(a). Section 3(a) of the Plan is hereby amended, restated and replaced in its entirety by the following language:

“(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 16,000,000 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.”

- 1.2 Except as specifically provided in this Amendment, all other terms and conditions of the Plan will remain in full force and effect.

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, 2021

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

AMENDMENT SUBJECT TO STOCKHOLDER APPROVAL: Amendment approved by Board on March 20, 2015

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) Stock 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 Award 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 (A) Section 162(m) of the Code regarding the exclusion of performance-based compensation from the limit on corporate deductibility of compensation paid to Covered Employees, or (B) 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 re-vest 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, re-vest in the Board some or all of the powers previously delegated.

(ii) **Section 162(m) and Rule 16b-3 Compliance.** The Committee may consist solely of two or more Outside Directors, in accordance with Section 162(m) of the Code, or solely of two or more Non-Employee Directors, in accordance with Rule 16b-3.

(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(w) 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.

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 5,500,000 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.

(b) **Reversion of Shares to the Share Reserve.** If 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, then the shares that are forfeited shall revert to and again become available for issuance under the Plan. Any shares reacquired by the Company pursuant to Section 8(f) or as consideration for the exercise of an Option shall again become available for issuance under the Plan.

(c) **Section 162(m) Limitation on Annual Grants.** Subject to the provisions of Section 9(a) relating to Capitalization Adjustments, at such time as the Company may be subject to the applicable provisions of Section 162(m) of the Code, a maximum of 2,000,000 shares of Common Stock subject to Options or Stock Appreciation Rights (in each case whose value is determined by reference to an increase over an exercise or strike price of at least 100% of the Fair Market Value on the date any such Stock Award is granted) may be granted to any Participant during any calendar year. Notwithstanding the foregoing, if any additional Options or Stock Appreciation Rights are granted to any Participant during any calendar year (in each case whose value is determined by reference to an increase over an exercise or strike price of at least 100% of the Fair Market Value on the date of the Stock Award), compensation attributable to the exercise of such additional Stock Awards shall not satisfy the requirements to be considered “qualified performance-based compensation” under Section 162(m) of the Code unless such additional Stock Award is approved by the Company’s stockholders.

(d) **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.** 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. The vesting provisions of individual Options or SARs may vary; *provided, however*, that no Option or SAR granted to an employee or member of the Company’s Board of Director will become 100% vested in a period of less than 2 years after the grant of such Option or SAR *except that* the vesting of an Option or SAR may accelerate (or may be accelerated by the Board or Committee) (i) as provided in Section 9(c); (ii) in the event of the Participant’s death or Disability, (iii) upon a Corporate Transaction in which such Stock Award is not assumed or continued, (iv) upon a Change in Control, or (v) upon the Participant’s retirement (as such term may be defined in the Participant’s Award Agreement or in another applicable agreement). The provisions of this Section 5(f) are subject to any Option or SAR provisions governing the minimum number of shares of Common Stock as to which an Option or SAR may be exercised.

(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.

(v) Dividends. A Restricted Stock Award Agreement may provide that any dividends paid on Restricted Stock will be subject to the same vesting and forfeiture restrictions as apply to the shares subject to the Restricted Stock Award to which they relate.

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

(vi) **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 maximum number of shares covered by an Award that may be granted to any Participant in a calendar year attributable to Stock Awards described in this Section 6(c)(i) (whether the grant, vesting or exercise is contingent upon the attainment during a Performance Period of the Performance Goals) shall not exceed 750,000 shares of Common Stock. 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. In any calendar year, the Committee may not grant a Performance Cash Award that has a maximum value that may be paid to any Participant in excess of \$2,000,000. 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.

(iv) **Section 162(m) Compliance.** Unless otherwise permitted in compliance with the requirements of Section 162(m) of the Code with respect to an Award intended to qualify as "performance-based compensation" thereunder, the Committee shall establish the Performance Goals applicable to, and the formula for calculating the amount payable under, the Award no later than the earlier of (a) the date 90 days after the commencement of the applicable Performance Period, or (b) the date on which 25% of the Performance Period has elapsed, and in either event at a time when the achievement of the applicable Performance Goals remains substantially uncertain. Prior to the payment of any compensation under an Award intended to qualify as "performance-based compensation" under Section 162(m) of the Code, the Committee shall certify the extent to which any Performance Goals and any other material terms under such Award have been satisfied (other than in cases where such relate solely to the increase in the value of the Common Stock). Notwithstanding satisfaction of any completion of any Performance Goals, to the extent specified at the time of grant of an Award to "covered employees" within the meaning of Section 162(m) of the Code, the number of shares of Common Stock, Options, cash or other benefits granted, issued, retainable and/or vested under an Award on account of satisfaction of such Performance Goals may be reduced by the Committee on the basis of such further considerations as the Committee, in its sole discretion, shall determine.

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.** After the Effective Date of the Plan, except for Awards granted to Non-Employee Directors as non-discretionary initial or annual grants, generally (i) no Restricted Stock Award, or Restricted Stock Unit Award that vests on the basis of the Participant’s Continuous Service with the Company shall vest at a rate that is any more rapid than ratably over a three-year period and (ii) no Restricted Stock Award or Restricted Stock Unit Award that vests based on the satisfaction of Performance Goals shall provide for a Performance Period of less than 12 months; *provided, however*, that, the vesting of a Restricted Stock Award or Restricted Stock Unit Award may accelerate (or may be accelerated by the Board or Committee) in the event of the Participant’s death or Disability, upon a Corporate Transaction in which such Stock Award is not assumed or continued, upon a Change in Control, or upon the Participant’s retirement (as such term may be defined in the Participant’s Award Agreement or in another applicable agreement). Notwithstanding the foregoing, Stock Awards granted after the Effective Date that do not meet these vesting guidelines shall be limited to 10% of the total number of shares reserved for issuance under the Plan.

(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), (ii) the class(es) and maximum number of securities that may be awarded to any person pursuant to Sections 3(c) and 6(c)(i), and (iii) 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 following provisions shall 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 (validly executed by an authorized Executive Officer of the Company or such Affiliate) and the Participant or unless otherwise expressly provided by the Board at the time of grant of a Stock Award. In the event of a Corporate Transaction, then, notwithstanding any other provision of the Plan, the Board shall take one or more of the following actions with respect to Stock Awards, contingent upon the closing or completion of the Corporate Transaction:

(i) arrange for the surviving corporation or acquiring corporation (or the surviving or acquiring corporation's parent company) to assume or continue the Stock Award or to substitute a similar stock award for the Stock Award (including, but not limited to, an award to acquire the same consideration paid to the stockholders of the Company pursuant to the Corporate Transaction);

(ii) arrange for the assignment of any reacquisition or repurchase rights held by the Company in respect of Common Stock issued pursuant to the Stock Award to the surviving corporation or acquiring corporation (or the surviving or acquiring corporation's parent company);

(iii) accelerate the vesting, in whole or in part, of the Stock Award (and, if applicable, the time at which the Stock Award may be exercised) to a date prior to the effective time of such Corporate Transaction as the Board shall determine (or, if the Board shall not determine such a date, to the date that is five days prior to the effective date of the Corporate Transaction), with such Stock Award terminating if not exercised (if applicable) at or prior to the effective time of the Corporate Transaction;

(iv) arrange for the lapse of any reacquisition or repurchase rights held by the Company with respect to the Stock Award;

(v) cancel or arrange for the cancellation of the Stock Award, to the extent not vested or not exercised prior to the effective time of the Corporate Transaction, in exchange for such cash consideration, if any, as the Board, in its sole discretion, may consider appropriate; or

(vi) make a payment, in such form as may be determined by the Board equal to the excess, if any, of (A) the value of the property the Participant would have received upon the exercise of the Stock Award, over (B) any exercise price payable by such holder in connection with such exercise.

The Board need not take the same action or actions with respect to all Stock Awards or portions thereof or with respect to all Participants.

(d) **Change in Control.** A Stock Award may be subject to additional acceleration of vesting and exercisability upon or after a Change in Control as may be provided in the Stock Award Agreement for such Stock Award or as may be provided in any other written agreement between the Company or any Affiliate (validly executed by an authorized Executive Officer of the Company or such Affiliate) and the Participant, but in the absence of such provision, no such acceleration shall occur.

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 the day before the tenth anniversary of the date the Plan is approved by the stockholders of the Company. 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) “**Covered Employee**” shall have the meaning provided in Section 162(m)(3) of the Code.

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

- (p) **“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.
- (q) **“Effective Date”** has the meaning set forth in Section 11 of the Plan.
- (r) **“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.
- (s) **“Entity”** means a corporation, partnership, limited liability company or other entity.
- (t) **“Exchange Act”** means the Securities Exchange Act of 1934, as amended, and the rules and regulations promulgated thereunder.
- (u) **“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.
- (v) **“Executive Officer”** means a person who is an officer of the Company within the meaning of Section 16 of the Exchange Act.
- (w) **“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.
- (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) **“Outside Director”** means a Director who either (i) is not a current employee of the Company or an “affiliated corporation” (within the meaning of Treasury Regulations promulgated under Section 162(m) of the Code), is not a former employee of the Company or an “affiliated corporation” who receives compensation for prior services (other than benefits under a tax-qualified retirement plan) during the taxable year, has not been an officer of the Company or an “affiliated corporation,” and does not receive remuneration from the Company or an “affiliated corporation,” either directly or indirectly, in any capacity other than as a Director, or (ii) is otherwise considered an “outside director” for purposes of Section 162(m) of the Code.

(cc) **“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.

(dd) **“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.

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

(ff) **“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) to the extent that an Award is not intended to comply with Section 162(m) of the Code, other measures of performance selected by the Board.

(gg) **“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 any “extraordinary items” as determined under generally accepted accounting principles; and (6) to exclude accounting expenses relating to share-based compensation.

(hh) **“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.

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

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

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

(ll) **“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.

- (mm) “**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).
- (nn) “**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.
- (oo) “**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.
- (pp) “**Securities Act**” means the Securities Act of 1933, as amended.
- (qq) “**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.
- (rr) “**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.
- (ss) “**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.
- (tt) “**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.
- (uu) “**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 cut-off date or meeting date. Have your proxy card in hand when you access the web site and follow the instructions to obtain your records and to create an electronic voting instruction form.

ELECTRONIC DELIVERY OF FUTURE PROXY MATERIALS

If you would like to reduce the costs incurred by our company in mailing proxy materials, you can consent to receiving all future proxy statements, proxy cards and annual reports electronically via e-mail or the Internet. To sign up for electronic delivery, please follow the instructions above to vote using the Internet and, when prompted, indicate that you agree to receive or access proxy materials electronically in future years.

VOTE BY PHONE - 1-800-690-6903

Use any touch-tone telephone to transmit your voting instructions up until 11:59 P.M. Eastern Time the day before the cut-off date or meeting date. Have your proxy card in hand when you call and then follow the instructions.

VOTE BY MAIL

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

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

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

THIS PROXY CARD IS VALID ONLY WHEN SIGNED AND DATED.

<p>The Board of Directors recommends you vote FOR the following nominees to be elected for a term expiring in 2020:</p>		For All	Withhold All	For All Except	<p>To withhold authority to vote for any individual nominee(s), mark "For All Except" and write the number(s) of the nominee(s) on the line below.</p>						
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____						
<p>1. Election of Directors</p> <p>Nominees</p> <p>01 Spencer R. Berthelsen 02 B. Lynne Parshall 03 Joseph H. Wender</p>											
<p>The Board of Directors recommends you vote FOR Proposals 2 and 3:</p>		For	Against	Abstain	<p>The Board of Directors recommends you vote FOR Proposal 5:</p>			For	Against	Abstain	
<p>2. Approve an amendment to the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance under the 2011 Equity Incentive Plan by 5,000,000 to an aggregate of 16,000,000 shares.</p>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>5. Ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for the 2017 fiscal year.</p>			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>3. To approve, by non-binding vote, executive compensation.</p>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>NOTE: Such other business as may properly come before the meeting or any adjournment thereof.</p>						
<p>The Board of Directors recommends you vote 1 YEAR with respect to Proposal 4:</p>		1 year	2 years	3 years	Abstain						
<p>4. To recommend, by non-binding vote, the frequency of executive compensation votes.</p>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>						
<p>Please sign exactly as your name(s) appear(s) hereon. When signing as attorney, executor, administrator, or other fiduciary, please give full title as such. Joint owners should each sign personally. All holders must sign. If a corporation or partnership, please sign in full corporate or partnership name by authorized officer.</p>											
<p>Signature [PLEASE SIGN WITHIN BOX]</p>				<p>Date</p>		<p>Signature (Joint Owners)</p>				<p>Date</p>	

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**IONIS PHARMACEUTICALS, INC.
Annual Meeting of Stockholders
May 24, 2017 2:00 PM Pacific Time**
This proxy is solicited by the Board of Directors of Ionis
Pharmaceuticals, Inc.

The undersigned hereby appoints B. Lynne Parshall and Stanley T. Crooke, and each of them, with power to act without the other and with power of substitution, as proxies and attorneys-in-fact and hereby authorizes them to represent and vote, as provided on the other side, all the shares of Ionis Pharmaceuticals, Inc. Common Stock which the undersigned is entitled to vote and, in their discretion, to vote upon such other business as may properly come before the Annual Meeting of Stockholders of the Company to be held May 24, 2017 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 Proposals 2 and 3, for ONE YEAR with respect to Proposal 4, FOR Proposal 5, and in the discretion of the proxies with respect to such other business as may properly come before the meeting.

Continued and to be signed on reverse side