

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)

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

NOTICE OF

2016 ANNUAL MEETING OF STOCKHOLDERS

Dear Stockholders,

I am pleased to invite you to Ionis Pharmaceuticals, Inc.'s 2016 Annual Meeting of Stockholders. We will host the meeting at our offices in Carlsbad, California on Friday, June 3, 2016, 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 2016, 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 2016 ANNUAL MEETING OF STOCKHOLDERS

Date: Friday, June 3, 2016
Time: 2:00 p.m., Pacific Time
Place: Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

Dear Stockholders,

At our 2016 Annual Meeting, we will ask you to:

- Proposal 1: elect Stanley T. Croke, Joseph Klein, III and Joseph Loscalzo to serve as Directors for a three-year term;
- Proposal 2: make an advisory vote on executive compensation; and
- Proposal 3: ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2016 fiscal year.
- Transact any other business that may be properly presented at the Annual Meeting.

The foregoing items of business are more fully described in the enclosed Proxy Statement. If you were an Ionis stockholder of record at the close of business on April 4, 2016 you may vote at the Annual Meeting.

By order of the Board of Directors,

Patrick R. O'Neil
Corporate Secretary

Carlsbad, California
April 15, 2016

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 2016 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"). This 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 20, 2016 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 30, 2016.

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

We will hold the meeting on Friday, June 3, 2016, 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 April 4, 2016 may vote at the Annual Meeting. On this record date, there were 120,729,810 shares of common stock outstanding and entitled to vote.

Stockholder of Record: Shares Registered in Your Name

If on April 4, 2016 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 April 4, 2016 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 three matters scheduled for a vote:

- Proposal 1: elect Stanley T. Crooke, Joseph Klein, III and Joseph Loscalzo to serve as Directors for a three-year term;
- Proposal 2: make an advisory vote on executive compensation; and
- Proposal 3: ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2016 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 2016 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 June 2, 2016. The votes represented by your proxy will be displayed on the computer screen and you will be prompted to submit or revise your votes as desired.

To vote your shares by telephone, you must first request that we send proxy materials to you by following the instructions included in your Notice. Once you have received your proxy materials, you may vote using a touch-tone telephone by calling 1-800-690-6903 up until 11:59 P.M. Eastern Time on June 2, 2016 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.

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 and 2 regarding the election of Directors and approval, on an advisory basis, of our executive compensation are non-discretionary items. If you do not give your broker instructions for a non-discretionary item, the inspector of elections will treat your shares as broker non-votes.

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, on an advisory basis, of executive compensation; and
- “For” the ratification of the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2016 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 or Director nomination that you would like us to include in our Proxy Statement and form of proxy for, or to present at the 2017 Annual Meeting of Stockholders, you must send the proposal to us by no later than December 21, 2016. Stockholders wishing to submit proposals or Director nominations that are not to be included in such Proxy Statement and form of proxy must do so no later than the close of business on February 3, 2017. 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 April 4, 2016. 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 and 3 and, in each case, will have the same effect as "Against" votes. Broker non-votes have no effect and the inspector of elections will not count them towards the vote total for any proposal.

What are "broker non-votes"?

Broker non-votes occur when a beneficial owner of shares held in "street name" does not give instructions to the broker or nominee holding the shares as to how to vote on matters deemed "non-routine." If your broker holds your shares in "street name," and you do not give instructions to your broker, your broker can vote your shares with respect to "discretionary" items, but not with respect to "non-discretionary" items. The proposal to ratify Ernst & Young LLP as independent auditors is a discretionary item. Proposals 1 and 2 regarding the election of Directors and approval, on an advisory basis, of our executive compensation, are non-discretionary items. If you do not give your broker instructions for a non-discretionary item, the inspector of elections will treat your unvoted shares as broker non-votes.

How many votes are needed to approve each proposal?

- Proposal 1: For the election of Directors in an uncontested election, a Director nominee must receive a majority of the votes cast in 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: 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 3: To be approved, the ratification of the selection of Ernst & Young LLP as our independent auditors for our 2016 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 2016 Elections

The Board has nominated three individuals for election at the 2016 Annual Meeting. Each of the nominees currently serves as one of our Directors. Dr. Crooke, Mr. Klein and Dr. Loscalzo have served as a Director since January 1989, December 2005 and February 2014, respectively. Dr. Crooke and Mr. Klein have been re-elected by our stockholders each successive term. Our stockholders ratified Dr. Loscalzo's appointment at our 2014 Annual Meeting of Stockholders. If re-elected, Dr. Crooke, Mr. Klein and Dr. Loscalzo will serve until the 2019 Annual Meeting or, in each case, until his successor is elected and has qualified, or until his earlier death, resignation or removal.

Our bylaws provide a majority vote standard for the election of directors in uncontested elections. In an uncontested election, the majority vote standard means that to be elected, a director nominee must receive a majority of the votes cast in the election such that the number of shares voted "For" the nominee must exceed 50% of the votes cast with respect to that Director. The number of votes cast with respect to a Director's election excludes abstentions and broker non-votes. In contested elections where the number of nominees exceeds the number of Directors to be elected, the vote standard will be a plurality of the shares present 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 16, 2016. Following that report, the Board determined it would be in the best interests of Ionis and its stockholders to nominate Dr. Crooke, Mr. Klein and Dr. Loscalzo to be elected as Directors at the Annual Meeting. We provide below a short biography for each nominee. Dr. Crooke, Mr. Klein and Dr. Loscalzo 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 2019 Annual Meeting

Stanley T. Crooke, M.D., Ph.D., age 70², 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 over 26 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 30 years of drug discovery and development experience.

Joseph Klein, III, age 54, 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. Within the last five years, Mr. Klein formerly served on the board of directors of five publicly held biotechnology companies: BioMarin Pharmaceutical Inc., NPS Pharmaceuticals, Inc., OSI Pharmaceuticals, Inc., PDL BioPharma, Inc. and Savient Pharmaceuticals, Inc.

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.

Joseph Loscalzo, age 64, 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.

The Board believes Dr. Loscalzo is uniquely suited to serve on the Board primarily because of his extensive scientific expertise, including 25 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 mature and grow our cardiovascular franchise.

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

Biographies of the Directors Whose Terms Expire at the 2017 Annual Meeting

Spencer R. Berthelsen, M.D., age 63, 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 has been Chairman of their Board of Directors since October 2001. 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.

² All ages of our Directors provided under this Proposal 1 are as of March 1, 2016.

The Board believes Dr. Berthelsen is uniquely suited to serve on the Board because of his current position managing a large multi-specialty group practice and 35 years of experience as a practicing physician.

B. Lynne Parshall, age 61, 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 31, 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 Cytokinetcs 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 71, 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.

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

Frederick T. Muto, age 62, 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 Chair of the firm's Business Department and a founding partner of Cooley LLP's San Diego office.

The Board believes Mr. Muto is uniquely suited to serve on the Board primarily because, with over 35 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 75, 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 has been a director of USMD Holdings, Inc., a physician-led integrated healthcare system, since September 2009 and was a director of MELA Sciences, Inc., a medical device company, from 2003 until 2011.

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.

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. Crooke 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 27 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 14 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 2015. During 2015, all Directors attended 100% of the meetings of the Board. 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 2015 for each of the Board committees.

Name	Audit	Compensation	Nominating, Governance and Review	Agenda	Science/ Medical	Attended 2015 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	--	--
Mr. Joseph H. Wender	X*	X	X	--	--	--
Total meetings in fiscal year 2015	4	3 ⁽²⁾	2	4	3	

* 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.

The table below provides membership information for fiscal 2016 for each of the Board committees.

Name	Audit	Compensation	Nominating, Governance and Review	Agenda	Science/ Medical
Dr. Spencer R. Berthelsen	--	X*	X*	--	X
Mr. Breaux B. Castleman	X	--	--	--	--
Dr. Stanley T. Croke	--	--	--	X*	X*
Mr. Joseph Klein, III	X	--	--	--	--
Dr. Joseph Loscalzo	--	--	X	X	X
Mr. Frederick T. Muto ⁽¹⁾	--	--	--	X	--
Ms. B. Lynne Parshall	--	--	--	X	--
Mr. Joseph H. Wender	X*	X	X	--	--

* 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.

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 2015, the Audit Committee met four times. The Board has adopted a written Audit Committee charter, which you can find on our corporate website at www.ionispharma.com.³ Each member meets the membership criteria set forth in the Audit Committee charter and as stated above.

Compensation Committee

The primary function of the Compensation Committee of the Board is to review, modify (as needed) and approve our overall compensation strategy and policies and approve the compensation and other terms of employment of our executive officers, including our Chief Executive Officer. We include a full list of the Compensation Committee’s responsibilities as part of the Compensation Discussion and Analysis (“CD&A”) set forth on pages 24 through 41 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 2015 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, 2015, 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 2015. You can find our Nominating, Governance and Review Committee charter on our corporate website at www.ionispharma.com.³

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.

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 and be included in our Proxy Statement for our 2017 Annual Meeting of Stockholders may do so by delivering a written recommendation to Ionis' corporate secretary at the following address: 2855 Gazelle Court, Carlsbad, CA 92010, by December 21, 2016. 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 2015.

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 three times in 2015.

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.⁴

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.⁴

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.

PROPOSAL 2

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, 2015), 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 2, 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 2016 Annual Meeting of Stockholders pursuant to the compensation disclosure rules of the Securities and Exchange Commission.”

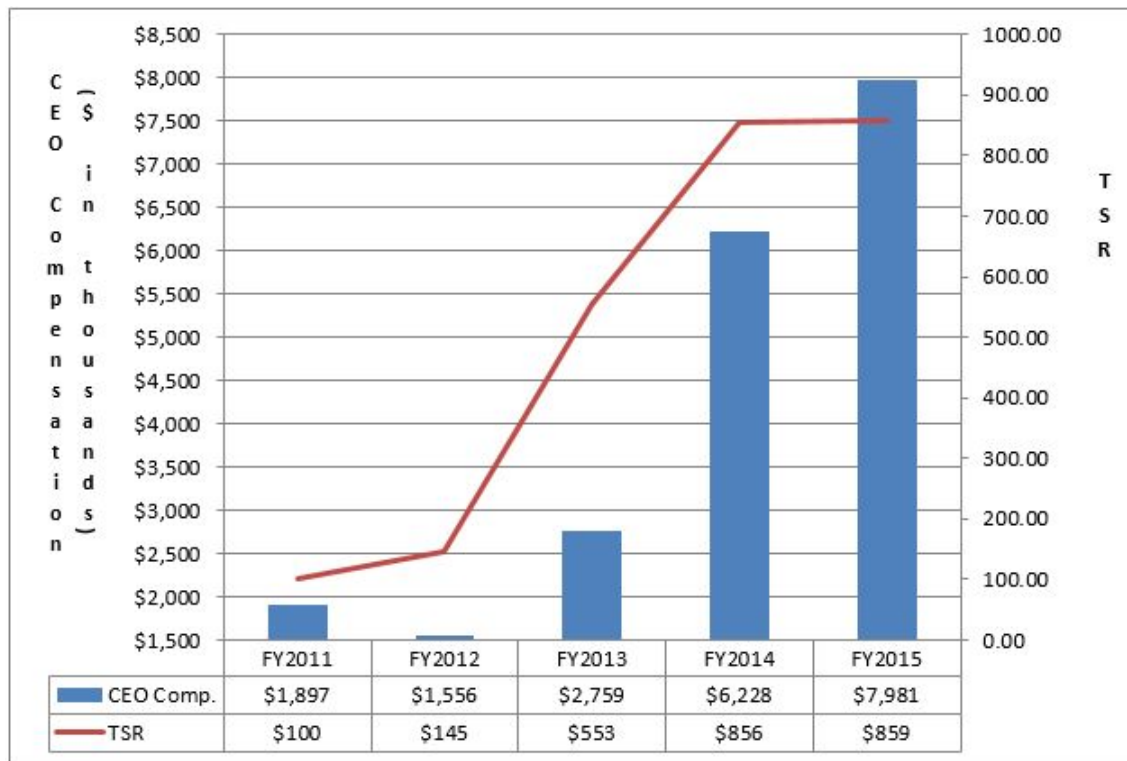
We recommend you carefully review the EXECUTIVE COMPENSATION section of this Proxy Statement located on pages 24 through 46. Below is a high-level summary of some of our compensation practices. This summary is qualified by the detailed disclosure contained in the EXECUTIVE COMPENSATION section of this 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	û Do not guarantee a cash bonus – cash bonuses can, and have been, zero
✓ Reward productivity and performance	û Do not provide perquisites for any employees
✓ Recognize the value of long-term employees and low turnover	û 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	û Do not allow pledging, shorting or hedging against our stock
✓ Evaluate compensation compared to the 50 th percentile of our peer group	û 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, 2011 in our common stock through December 31, 2015. 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.⁵



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 2. Brokers do not have discretion to vote uninstructed shares with respect to this Proposal 2. 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 2.

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 2.

⁵ 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.

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 2016 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 2016 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 2016 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 3.

As of December 31, 2015, 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. As an additional measure to ensure auditor independence, we do not use Ernst & Young LLP as our primary tax advisor. The Audit Committee pre-approved all of the fees described below.

Audit Fees

For the fiscal years ended December 31, 2015 and 2014, Ernst & Young LLP billed us \$0.7 million and \$0.6 million, respectively, 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 \$0.2 million and \$0.1 million in 2015 and 2014, respectively, related to corporate transactions.

Audit Related Fees

For the fiscal years ended December 31, 2015 and 2014, there were no audit related fees billed by Ernst & Young LLP.

Tax Fees

For the fiscal year ended December 31, 2015, Ernst & Young LLP billed us \$60,000 for professional services rendered for international tax planning for Akcea and state and local tax consulting projects. For the fiscal year ended December 31, 2014, there were no tax fees billed by Ernst & Young LLP for tax related matters that were not part of the integrated audit fees.

All Other Fees

During the fiscal years ended December 31, 2015 and 2014, 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, 2015, 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.

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of March 1, 2016 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	18,071,779	14.98%
ClearBridge Investments, LLC ⁽⁴⁾ 620 8 th Avenue New York, NY 10018	9,474,704	7.85%
The Vanguard Group ⁽⁵⁾ 100 Vanguard Boulevard Malvern, PA 19355	8,250,750	6.84%
BlackRock, Inc. ⁽⁶⁾ 55 East 52 nd Street New York, NY 10055	8,182,073	6.78%
Baillie Gifford & Co ⁽⁷⁾ Carlton Square 1 Greenside Row Edinburgh EH1 3AN Scotland UK	8,078,158	6.69%
BB Biotech AG ⁽⁸⁾ Schwertstrasse 6, CH-8200 Schaffhausen, Switzerland	6,529,838	5.41%
Spencer R. Berthelsen ⁽⁹⁾	164,977	*
Breaux B. Castleman ⁽¹⁰⁾	24,357	*
Stanley T. Crooke ⁽¹¹⁾	1,253,818	1.03%
Joseph Klein, III ⁽¹²⁾	15,269	*
Joseph Loscalzo ⁽¹³⁾	17,793	*
Frederick T. Muto ⁽¹⁴⁾	107,107	*
B. Lynne Parshall ⁽¹⁵⁾	133,821	*
Joseph H. Wender ⁽¹⁶⁾	94,729	*
Sarah Boyce ⁽¹⁷⁾	18,141	*
Elizabeth L. Hougen ⁽¹⁸⁾	96,902	*
Brett Monia ⁽¹⁹⁾	88,505	*
All Directors and executive officers as a group (fourteen persons) ⁽²⁰⁾	2,269,881	1.86%

*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 120,662,818 shares of common stock outstanding on March 1, 2016, 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 Advisors, LLC is an investment adviser registered under the Investment Advisers Act. ClearBridge Advisors has sole voting power to direct the vote of 9,248,743 shares and sole power to dispose or direct the disposition of 9,474,704 shares.
- (5) The Vanguard Group has sole voting power to direct the vote of 120,253 shares, shared voting power to direct the vote of 12,100 shares, sole power to dispose or direct the disposition of 8,118,897 shares, and shared dispositive power for 131,853 shares. Vanguard Fiduciary Trust Company, a wholly owned subsidiary of The Vanguard Group, Inc., is the beneficial owner of 80,853 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 90,400 shares of Ionis' Common Stock outstanding as a result of its serving as investment manager of Australian investment offerings.
- (6) 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.
- (7) Baillie Gifford & Co is an investment advisor registered under the Investment Advisers Act. Baillie Gifford has sole voting power to direct the vote of 4,491,060 shares and sole power to dispose or direct the disposition of 8,078,158 shares.
- (8) BB Biotech AG shares voting and dispositive powers for its shares with Biotech Target N.V.
- (9) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 90,564 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before April 30, 2016.
- (10) Includes 20,876 shares of common stock issuable upon exercise of options held by Mr. Castleman that are exercisable on or before April 30, 2016.
- (11) Includes shares of common stock held by Dr. Crooke and 458,700 shares of common stock issuable upon exercise of options held by Dr. Crooke that are exercisable on or before April 30, 2016. Also includes 42,528 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, 2016. 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 9,626 shares of common stock issuable upon exercise of options held by Mr. Klein that are exercisable on or before April 30, 2016.
- (13) Includes 15,250 shares of common stock issuable upon exercise of options held by Mr. Loscalzo that are exercisable on or before April 30, 2016.
- (14) Includes 1,500 shares of common stock beneficially owned through the Cooley LLP Salary Deferral and Profit Sharing Plan and 103,064 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or before April 30, 2016.
- (15) Includes 117,531 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 30, 2016.

- (16) Includes 63,064 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 30, 2016.
- (17) Includes 16,406 shares of common stock issuable upon exercise of options held by Ms. Boyce that are exercisable on or before April 30, 2016.
- (18) Includes 90,571 shares of common stock issuable upon exercise of options held by Ms. Hougen that are exercisable on or before April 30, 2016.
- (19) Includes 80,812 shares of common stock issuable upon exercise of options held by Dr. Monia that are exercisable on or before April 30, 2016.
- (20) Includes an aggregate of 1,335,386 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, 2016.

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, 2015, 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, 2015.

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⁾	7,996,753	\$ 33.31	⁽³⁾ 6,863,085
Equity compensation plans not approved by stockholders ⁽²⁾	44,025	\$ 14.66	--
Total	8,040,778	\$ 33.21	6,863,085

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

(2) Consists of the 2000 Broad-Based Equity Incentive Plan, more fully described below. The 2000 Broad-Based Equity Incentive Plan expired on January 5, 2010.

(3) Of these shares, 481,764 remained available for purchase under the ESPP as of December 31, 2015. 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.

Description of 2000 Broad-Based Equity Incentive Plan

We adopted the 2000 Broad-Based Equity Incentive Plan, or the 2000 Plan, to provide our employees, officers, directors and consultants an opportunity to benefit from increases in the value of our common stock through the granting of non-statutory stock options, stock bonuses and rights to purchase restricted stock. At the time we adopted the 2000 Plan, we were not required to seek the approval of our stockholders. The Board has delegated administration of the 2000 Plan to the Compensation Committee. The Board has the power to construe and interpret the 2000 Plan.

As of December 31, 2015, the 2000 Plan had 5,990,000 shares authorized for issuance, options to purchase an aggregate of 44,025 shares were granted and outstanding under the 2000 Plan, option holders had exercised options to purchase an aggregate of 5,492,172 shares under the 2000 Plan, and no shares remained available for grant thereunder. The 2000 Plan expired on January 5, 2010, so we may no longer grant new options under the 2000 Plan.

Options granted under the 2000 Plan generally have a term of seven or ten years, have an exercise price equal to the fair market value at the time of grant, can only be exercised with a cash payment and vest at the rate of 25 percent per year after the first year and then at the rate of 2.08 percent per month thereafter during the option holder's employment or service as a consultant, employee or director. If any change is made in the common stock subject to the 2000 Plan, or subject to any stock award, without the receipt of consideration by us (through merger, consolidation, reorganization, recapitalization, reincorporation, stock dividend, dividend in property other than cash, stock split, liquidating dividend, combination of shares, exchange of shares, change in corporate structure or other transaction not involving the receipt of consideration by us), we will adjust the outstanding stock awards appropriately in the class(es) and number of securities and price per share of common stock subject to such outstanding stock awards. Our board of directors will make such adjustments, and its determination will be final, binding and conclusive. We will not treat the conversion of any of our convertible securities as a transaction without receipt of consideration.

In the event of our dissolution or liquidation, all outstanding stock awards will terminate immediately prior to such event.

In the event of:

- a sale, lease or other disposition of all or substantially all of our assets;
- a merger or consolidation in which we are not the surviving corporation; or
- reverse merger in which we are the surviving corporation but the shares of common stock outstanding immediately preceding the merger are converted by virtue of the merger into other property, whether in the form of securities, cash or otherwise;

then any surviving corporation or acquiring corporation will assume any stock awards outstanding under the 2000 Plan or will substitute similar stock awards (including an award to acquire the same consideration paid to the stockholders in the transaction for those outstanding under the 2000 Plan). In the event any surviving corporation or acquiring corporation refuses to assume such stock awards or to substitute similar stock awards for those outstanding under the 2000 Plan, then with respect to stock awards held by participants whose continuous service has not terminated, we will accelerate the vesting of such stock awards in full and the stock awards will terminate if not exercised (if applicable) at or prior to such event.

Compensation Discussion and Analysis

Overview

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.

Through the efficiency of our technology platform and business strategy we have built a pipeline of 38 drugs in development with approximately 400 employees, representing a ratio of 1 drug: 11 employees.

Antisense technology exists today primarily because of the innovation at Ionis. We have more than 1,350 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 \$1.7 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 1,350 issued patents and applications are all the more remarkable given that Ionis has a little more than 400 employees. This means Ionis has produced over three issued patents and applications 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 38 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 16% 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.

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	û Do not guarantee a cash bonus – cash bonuses can, and have been, zero
✓ Reward productivity and performance	û Do not provide perquisites for any employees
✓ Recognize the value of long-term employees and low turnover	û 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	û Do not allow pledging, shorting or hedging against our stock
✓ Evaluate compensation compared to the 50 th percentile of our peer group	û 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 2015 Executive Peer Group;
- evaluating the pay mix for our named executive officers;
- evaluating short-term and long-term incentives for our executive officers; and
- evaluating our equity utilization.

In addition, Akcea Therapeutics, Inc., or Akcea, our wholly-owned 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 \$20,000 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 26.13 times that of the average cash compensation for our lowest level employees and 2.03 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 38 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 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 2015 we had a corporate objective to advance our pipeline with one of the measures being to achieve positive data from four 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 2015 have on average 18.6 years and as much as 27 years of tenure at Ionis.
 - o Our other officers who served in 2015 have on average 20.4 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 2015 compensation, the Compensation Committee, in consultation with its independent compensation consultant, evaluated and selected a peer group of 22 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 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 2015, the Compensation Committee reviewed the Executive Peer Group using the criteria listed above and publically available data as of April 2015. The Compensation Committee noted Ionis' market capitalization was approximately \$8.0 billion and had increased approximately 60% since the Compensation Committee last set the Executive Peer Group. As part of this process, the Compensation Committee looked at companies in Ionis' industry with market capitalizations of between \$2 billion and \$16 billion, including looking at companies that identified Ionis as a peer, so called "reverse peers". Based on this evaluation, the Compensation Committee added Clovis Oncology, Intercept Pharmaceuticals, Neurocrine Biosciences and Receptos to the Executive Peer Group, as these companies fell within the market capitalization range, and were in Ionis' sector. Additionally, the Compensation Committee removed Exelixis, Immunogen and Lexicon because these companies fell below the market capitalization range, and removed Auxilium, InterMune, NPS Pharmaceuticals and Pharmacyclis because another company acquired them.

The following table lists the companies in the 2015 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 2015.

Company (ticker)	Annual Revenues (in millions)	Market Capitalization (in millions)	Stage of Lead Drug
Acorda Therapeutics (ACOR)	\$ 401.5	\$ 1,299.6	Market
Akorn (AKRX)	\$ 593.1	\$ 5,292.5	Market
Alkermes (ALKS)	\$ 618.8	\$ 8,966.9	Market
Alnylam Pharmaceuticals (ALNY)	\$ 50.6	\$ 11,058.7	Phase III
Arena Pharmaceuticals (ARNA)	\$ 37.0	\$ 999.6	Market
Ariad Pharmaceuticals (ARIA)	\$ 105.4	\$ 1,682.0	Market
Clovis Oncology (CLVS)	\$ 13.6	\$ 2,963.6	Phase III
Halozyne Therapeutics (HALO)	\$ 75.3	\$ 2,275.4	Market
Incyte Corporation (INCY)	\$ 511.5	\$ 19,637.4	Market
Intercept Pharmaceuticals (ICPT)	\$ 1.7	\$ 6,205.6	NDA Filing
Jazz Pharmaceuticals (JAZZ)	\$ 1,172.9	\$ 10,959.7	Market
MannKind (MNKD)	\$ 0.0	\$ 2,113.4	Market
Medivation (MDVN)	\$ 710.5	\$ 10,098.8	Market
Momenta Pharmaceuticals (MNTA)	\$ 52.3	\$ 1,253.6	Market
Nektar Therapeutics (NKTR)	\$ 200.7	\$ 1,509.9	Market
Neurocrine Biosciences (NBIX)	\$ 0.0	\$ 3,568.8	Phase III
Pacira (PCRX)	\$ 197.7	\$ 2,908.9	Market
Receptos (RCPT)	\$ 5.9	\$ 5,098.1	Phase III
Seattle Genetics (SGEN)	\$ 286.8	\$ 5,418.8	Market
The Medicines Company (MDCO)	\$ 724.4	\$ 1,860.4	Market
Theravance (THRAX) (now Innoviva)	\$ 8.4	\$ 1,981.0	Market
United Therapeutics (UTHR)	\$ 1,288.5	\$ 8,428.3	Market
Ionis Pharmaceuticals, Inc. (IONIS)	\$ 214.2	\$ 8,013.6	Market
Ionis' Ranking	14	17	NA
Ionis' Percentile Rank	58 %	75 %	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	2015 Total Cash Compensation (in thousands)		2015 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	\$ 1,549,805	\$ 1,395,000	\$ 7,960,498	\$ 6,619,300
Elizabeth L. Hougen CFO	\$ 617,644	\$ 600,500	\$ 1,904,092	\$ 2,254,400
B. Lynne Parshall COO	\$ 1,190,099	\$ 1,131,100	\$ 6,336,421	\$ 2,763,300
Sarah Boyce CBO	\$ 601,600	\$ 492,100	\$ 2,645,337	\$ 1,317,500
Brett Monia SVP Drug Discovery	\$ 670,382	*	\$ 2,085,478	*

*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 2015 for our CEO and CFO were within the competitive range. A significant portion of total direct compensation was due to the high price of Ionis' stock on the date our NEOs received their stock awards in 2015. Our CBO's total direct compensation was higher since she received equity awards when we hired her that were larger than our typical annual equity awards for her level.

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 at the time the Compensation Committee selected the Executive Peer Group in June 2015):

	Drugs in Clinical Development per Employee	Patents per Employee
Ionis' Ranking	1 st	3 rd
Executive Peer Group Median	1 drug for every 36 employees	1 patent per employee
Peer Leader for Drugs in Clinical Development per Employee (Innoviva fka Theravance)	1 drug for every 20 employees	NA
Peer Leader for Patents per Employee (Innoviva fka Theravance)	NA	6.0 patents per employee
Ionis Pharmaceuticals, Inc. (IONS)	1 drug for every 11 employees	3.2 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.

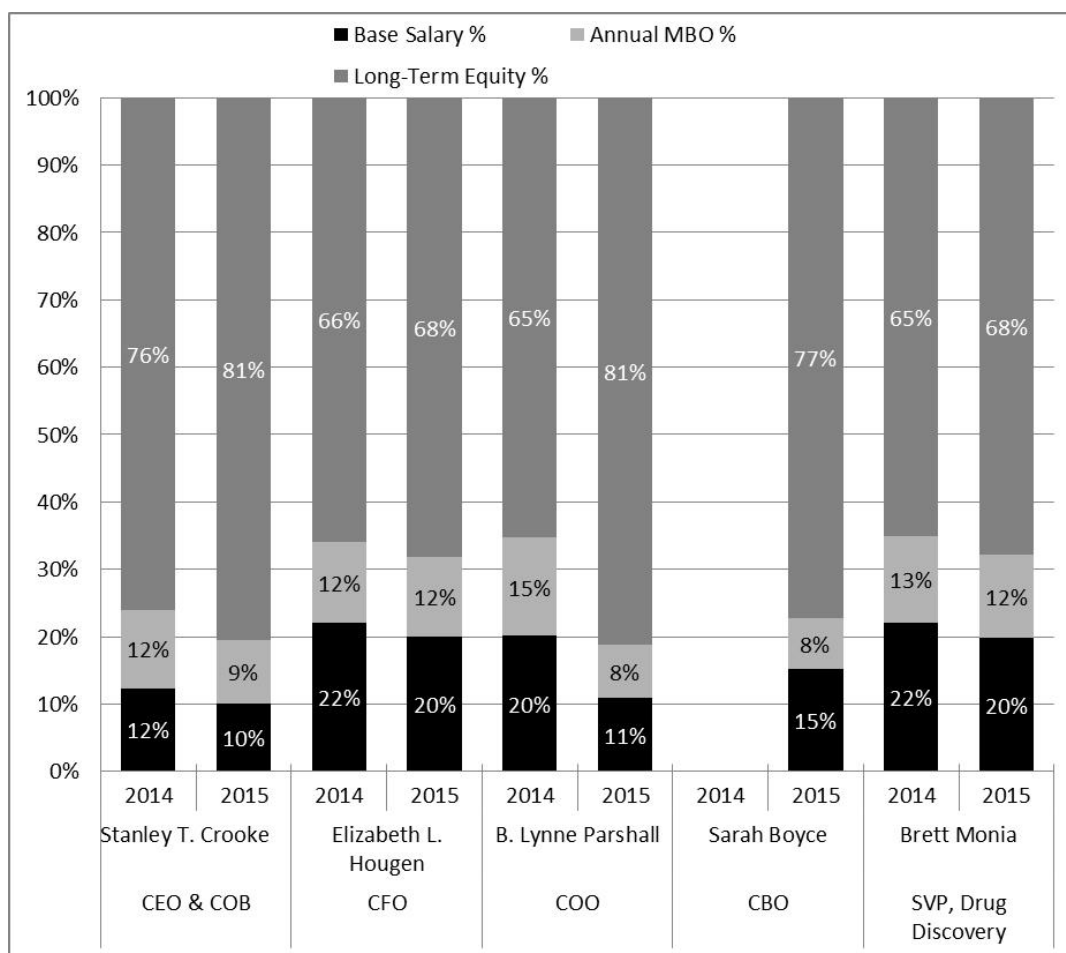
Compensation Allocation/Pay Mix

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 implemented the following:

- Salaries were frozen for most NEOs from 2011-2013. 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;
- 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; and
- More of total compensation is long-term equity. The Compensation Committee adjusted 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.

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 2014 and 2015:



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 & COB	2014	\$ 768,252	\$ 720,236	\$ 4,720,669	12 %	12 %	76 %
	2015	\$ 800,519	\$ 749,286	\$ 6,410,693	10 %	9 %	81 %
Elizabeth L. Hougen CFO	2014	\$ 377,923	\$ 206,677	\$ 1,132,961	22 %	12 %	66 %
	2015	\$ 391,906	\$ 225,738	\$ 1,286,448	20 %	12 %	68 %
B. Lynne Parshall COO	2014	\$ 664,029	\$ 466,895	\$ 2,077,096	20 %	15 %	65 %
	2015	\$ 691,918	\$ 498,181	\$ 5,146,322	11 %	8 %	81 %
Sarah Boyce CBO	2014	*	*	*	*	*	*
	2015	\$ 400,000	\$ 201,600	\$ 2,043,737	15 %	8 %	77 %
Brett Monia SVP, Drug Discovery	2014	\$ 396,158	\$ 233,981	\$ 1,132,961	22 %	13 %	65 %
	2015	\$ 412,797	\$ 257,585	\$ 1,415,096	20 %	12 %	68 %

*Sarah Boyce, our CBO, joined Ionis in January 2015.

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.

Base salaries for CEO and COO were frozen for 2011-2013.

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 2015 performance the Company-wide merit increase budget was 3.2%, with a range of individual merit award increases of 0% to 5.0%. 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 2016 salary of \$824,535 was calculated as follows:

<u>2015 Base Salary</u>	(x)	<u>Merit Increase</u>	=	<u>Increase to Base Salary</u>
\$800,519	(x)	3.0%	=	\$24,016
<u>Current Base Salary</u>	(+)	<u>Increase to Base Salary</u>	=	<u>New Base Salary in 2016</u>
\$800,519	(+)	\$24,016	=	\$824,535

When reviewing salaries, the Compensation Committee noted that our CEO’s salary, and the salary of our other NEOs, was within or below the competitive range of the Executive Peer Group. The Compensation Committee also noted its desired target mix of compensation that is less weighted on salary and historically 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 2015 performance, and given that most salaries were fixed for three years, the Compensation Committee approved merit increases to each of the NEO’s salaries for 2015. In addition, the Compensation Committee noted our CFO’s salary was below the competitive range, and therefore approved an additional salary increase for our CFO to bring her salary within the competitive range resulting in a 2016 base salary of \$412,839.

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 2015 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 2015 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%
Sarah Boyce	0%	128%
Brett Monia	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 2015 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 2015 Corporate Objectives. On December 16, 2015, the Compensation Committee completed its evaluation of the Company's performance against the 2015 Corporate Objectives.

The Compensation Committee set the Company Performance Factor for the 2015 MBO at 120% due to our strong achievements for the year across drug discovery, development and corporate development, including completing target enrollment in the first pivotal Phase 3 study for each of nusinersen, volanesorsen and IONIS-TTR_{Rx}, partnering IONIS-FXI_{Rx} with Bayer, expanding our collaboration with AstraZeneca, and significantly improving upon Ionis' financial guidance for the year. The table below provides a detailed evaluation of each objective and the related achievements:

Evaluation of 2015 Corporate Objectives		
	Objective & Pre-Approved Measures	Evaluation
1	<p>Advance Pipeline:</p> <ul style="list-style-type: none"> · Finalize regulatory plan for nusinersen with Biogen to achieve approval of nusinersen as early as possible · Initiate Phase 3 study for IONIS-TTR_{Rx} for FAC · Enroll a target number of patients for the Phase 3 Study of IONIS-TTR_{Rx} for patients with FAP · Enroll a target number of patients for the Phase 3 Study of nusinersen in infants with Spinal Muscular Atrophy, ENDEAR · Enroll a target number of patients for the Phase 3 Study of nusinersen in children with Spinal Muscular Atrophy, CHERISH · Enroll a target number of patients for the Phase 3 Study of volanesorsen in patients with FCS, APPROACH · Initiate volanesorsen lipodystrophy study (measured by enrolling a target number of patients, with a target number of study sites opened by the third quarter of 2015) · Positive Phase 2 clinical data for four or more drugs · Initiate Phase 2 clinical trials for six or more drugs 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> · Ionis finalized the regulatory plan for nusinersen with Biogen to achieve approval of nusinersen as early as possible · Ionis and GSK made substantial progress towards initiating the Phase 3 study for IONIS-TTR_{Rx} for FAC · Ionis completed target enrollment for the Phase 3 Study of IONIS-TTR_{Rx} for patients with FAP · Ionis enrolled the target number of patients for the Phase 3 Study of nusinersen in infants with Spinal Muscular Atrophy, ENDEAR · Ionis completed target enrollment for the Phase 3 Study of nusinersen in children with Spinal Muscular Atrophy, CHERISH · Ionis exceeded its target enrollment for the Phase 3 Study of volanesorsen in patients with FCS, APPROACH · Ionis initiated the volanesorsen lipodystrophy study meeting the enrollment and site targets by the third quarter of 2015 · Ionis reported positive Phase 2 data from three drugs · Ionis initiated phase 2 clinical studies for five drugs

	<ul style="list-style-type: none"> · Advance IONIS-FXIRx dialysis study to remain on track for target completion date · Initiate Phase 1 clinical trials for four or more drugs · Add at least four new drugs to development pipeline 	<ul style="list-style-type: none"> · Ionis advanced the IONIS-FXIRx dialysis study such that it was on track within one quarter of the target completion date · Ionis initiated Phase 1 studies for four drugs · Ionis exceeded this measure by adding eleven new drugs to its development pipeline
2	Stock price increase by a percentage greater than or equal to median of the companies listed in the NASDAQ Biotechnology Index	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> · Ionis' stock price slightly <i>increased</i> for the year while the median stock price change for companies listed in the NASDAQ Biotechnology Index <i>decreased</i> by 5.69%
3	Meet budget and financial projections for the year	<p>Ionis <u>exceeded</u> this objective:</p> <ul style="list-style-type: none"> · Ionis significantly exceeded its financial guidance for the year · Ionis met its budget
4	<p>Make Biogen Idec relationship successful:</p> <ul style="list-style-type: none"> · Achieve target sanction for at least two targets under its Biogen collaborations · Initiate Phase 1 clinical trial for IONIS-BIIB4Rx · Identify two collaboration targets in specific therapeutic area · Identify two additional development candidates · Generate at least \$80 million in revenue across all Biogen collaborations 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> · Ionis achieved target sanction for two targets under its Biogen collaborations · Ionis advanced the program but did not initiate the Phase 1 clinical trial for IONIS-BIIB4Rx · Ionis identified two collaboration targets in the specific therapeutic area · Ionis exceeded this measure by identifying four additional development candidates · Ionis exceeded this measure by generating over \$100 million in revenue across all Biogen collaborations
5	Advance at least two LICA development candidate through Phase 1	<p>Ionis <u>partially met</u> this objective:</p> <ul style="list-style-type: none"> · Ionis advanced one LICA development candidate through Phase 1 and made significant progress on others
6	Create and staff Akcea and ensure integration	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> · Ionis completed Akcea's formation and Akcea hired targeted key employees
7	Partner IONIS-FXIRx	<p>Ionis <u>exceeded</u> this objective:</p> <ul style="list-style-type: none"> · Ionis licensed IONIS-FXIRx to Bayer, a global leader in developing and commercializing treatments for thrombosis
8	Complete two partnerships by expanding an existing relationship or adding a new partner	<p>Ionis <u>partially met</u> this objective:</p> <ul style="list-style-type: none"> · Ionis and AstraZeneca formed a strategic collaboration to discover and develop antisense therapies for treating cardiovascular and metabolic diseases, primarily focused on targets in the kidney, and renal diseases.
9	Make chief business officer effective	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> · Ionis' chief business officer contributed meaningfully to Ionis' success in 2015

Unplanned Accomplishments for 2015

10	Achieved GSK's plan to initiate a Phase 3 outcome study, CARDIO-TTR, in all forms of TTR amyloid cardiomyopathy, including both FAC and wt-TTR amyloidosis, and a small Phase 3 study in Japan in patients with FAP to support Japanese regulatory filings
11	Data from the ongoing open-label extension study of NEURO-TTR in which patients with FAP treated with IONIS-TTR _{Rx} for at least three months experienced reductions in TTR protein of up to 92 percent with a mean maximum (nadir) reduction of 76 percent compared to baseline. Phase 2 data from an ongoing open-label, investigator-initiated study in patients with FAC and patients with wt-TTR treated with IONIS-TTR _{Rx} for 12 months preliminarily evidencing disease stabilization and sustained TTR reductions.
12	Phase 2 data from two ongoing open-label studies in which infants and children with SMA treated with nusinersen experienced increases in muscle function scores. Additionally, there were no events of death or permanent ventilation reported in 2015 in nusinersen-treated infants in the ongoing Phase 2 clinical study.
13	Phase 1 study of IONIS-APO(a)-L _{Rx} demonstrated a greater than 30-fold increase in potency in humans as compared to the non-LICA IONIS-APO(a) _{Rx} .

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 2015 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⁾	\$ 800,519	65 %	120 %	120 %	\$ 749,286	1-13
Elizabeth L. Hougen	\$ 391,906	40 %	120 %	120 %	\$ 225,738	2-4 & 6-9
B. Lynne Parshall ⁽²⁾	\$ 691,918	50 %	120 %	120 %	\$ 498,181	1-13
Sarah Boyce	\$ 400,000	40 %	120 %	105 %	\$ 201,600	2-4 & 6-10
Brett Monia	\$ 412,797	40 %	120 %	130 %	\$ 257,585	1-11 & 13

- (1) The numbers correspond to the enumerated objectives in the table entitled "Evaluation of 2015 Corporate Objectives" on pages 36 through 38. 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 a decrease of 5 percentage points from the 2014 Company Performance Factor of 125%, but reflects a 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 1.5% 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 3.2% from 2012 through 2014. We believe this stock budget is an important tool to balance our compensation objectives with stockholder interests. For 2015 performance, the Compensation Committee set a merit stock award budget that resulted in 1.6 million stock options and approximately 250,000 RSUs awarded to employees, including the executive officers. Together these shares represent approximately 1.5% 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 grant.

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 ⁽¹⁾	3 times Base Salary
COO	2 times Base Salary
All other executive officers	1 times Base Salary
Non-employee Directors ⁽²⁾	4 times Base Annual Cash Retainer

(1) Dr. Crooke currently meets these ownership guidelines.

(2) Dr. Berthelsen, Mr. Klein and Mr. Wender currently meet these ownership 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 26-year tenure. As of December 31, 2015, Dr. Crooke's holding represented over 55 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/WorkLife, 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 46, 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.

2015 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 2015 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 2015 Annual Meeting of Stockholders, we received an advisory vote in favor of our executive compensation by 98% of the shares voted at the meeting.

Compensation of Executive Officers

The following table shows for the fiscal years ended December 31, 2015, 2014, and 2013, 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, 2015, called our “named executive officers.”

Summary Compensation Table

Name and Principal Position	Year	Salary (\$)	Bonus ⁽¹⁾ (\$)	Stock Awards ⁽²⁾ (\$)	Option Awards (\$)	All Other Compensation ⁽³⁾ (\$)	Total (\$)
Stanley T. Croke Chairman, President, Chief Executive Officer	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
	2013	\$ 735,169	\$ 803,907	\$ 325,971	\$ 877,737	\$ 15,752	\$ 2,758,536
Elizabeth L. Hougen Senior Vice President, Finance and Chief Financial Officer	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
	2013	\$ 365,496	\$ 215,871	\$ 54,419	\$ 113,461	\$ 20,619	\$ 769,865
B. Lynne Parshall Director, Chief Operating Officer	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
	2013	\$ 641,574	\$ 526,171	\$ 152,482	\$ 410,463	\$ 20,636	\$ 1,751,326
Sarah Boyce Chief Business Officer	2015	\$ 400,000	\$ 201,600	⁽⁴⁾ \$602,350	⁽⁴⁾ \$1,441,387	⁽⁵⁾ \$261,202	\$ 2,906,539
Brett Monia ⁽⁶⁾ Senior Vice President, Drug Discovery	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
	2013	\$ 381,288	\$ 142,983	\$ 83,145	\$ 224,081	\$ 22,834	\$ 854,331

- (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 2016 we paid bonuses for 2015 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, 2015 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) We hired Ms. Boyce as the Chief Business Officer in January 2015 and granted her Stock and Option Awards as part of her hire. New-hire awards are generally larger than annual merit awards.
- (5) Ms. Boyce received (i) AD&D, Basic Life, Medical, Dental, Vision, and 401(k) matching contributions totaling \$25,799; and (ii) relocation assistance in the amount of \$235,403 in connection with her move to Carlsbad, CA.
- (6) Mr. Monia was not a named executive officer in 2013.

Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2015, certain information regarding grants of plan-based awards to our named executive officers:

Grants of Plan-Based Awards in Fiscal 2015

Name	Grant Date	All Other Stock Awards: Number of Shares of Stock or Units (#)	All Other Option Awards: Number of Securities Underlying Options (#)	Exercise or Base Price of Option Awards (\$/Sh)	Grant Date Fair Value of Stock and Option Awards ⁽¹⁾ (\$)
Stanley T. Crooke	1/2/15		165,000	\$ 61.57	\$ 4,517,593
	1/15/15	27,500			\$ 1,893,100
Elizabeth L. Hougen	1/2/15		33,112	\$ 61.57	\$ 906,589
	1/15/15	5,518			\$ 379,859
B. Lynne Parshall	1/2/15		132,458	\$ 61.57	\$ 3,626,610
	1/15/15	22,076			\$ 1,519,712
Brett Monia	1/2/15		36,423	\$ 61.57	\$ 997,237
	1/15/15	6,070			\$ 417,859
Sarah Boyce ⁽²⁾	1/1/15		52,500	\$ 61.74	\$ 1,441,387
	1/15/15	8,750			\$ 602,350

(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, 2015 regarding assumptions underlying valuation of equity awards.

(2) Ms. Boyce received an option to purchase 52,500 shares of our common stock and an RSU for 8,750 shares of our common stock when she joined the Company in January 2015. New-hire awards are generally larger than annual merit awards.

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

The Compensation Committee granted merit non-statutory stock options to the executive officers on January 2, 2015, except Ms. Boyce, who received a stock option when she joined the Company. 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, 2015, except Ms. Boyce who received an RSU when she joined the Company. 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, 2015.

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

The following table shows for the fiscal year ended December 31, 2015, 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, 2015.

Outstanding Equity Awards as of December 31, 2015

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	1/3/2011	101,259	--	\$ 10.29	1/2/2018	--	--
	1/3/2012	104,969	2,234	\$ 7.25	1/2/2019	--	--
	1/30/2013	97,110	36,070	\$ 14.69	1/29/2020	--	--
	1/2/2014	89,843	97,657	\$ 39.87	1/1/2021	--	--
	1/2/2015	--	165,000	\$ 61.57	1/1/2022	--	--
	1/15/2012	--	--	--	--	2,997	\$ 185,604
	1/30/2013	--	--	--	--	11,094	\$ 687,051
	1/15/2014	--	--	--	--	23,437	\$ 1,451,453
	1/15/2015	--	--	--	--	27,500	\$ 1,703,075
Elizabeth L. Hougen	1/4/2010	10,000	--	\$ 11.27	1/3/2017	--	--
	1/3/2011	22,000	--	\$ 10.29	1/2/2018	--	--
	1/3/2012	3,656	407	\$ 7.25	1/2/2019	--	--
	1/2/2013	11,447	4,253	\$ 10.82	1/1/2020	--	--
	1/2/2013	5,468	2,032	\$ 10.82	1/1/2020	--	--
	1/2/2014	21,562	23,438	\$ 39.87	1/1/2021	--	--
	1/2/2015	--	33,112	\$ 61.57	1/1/2022	--	--
	1/15/2012	--	--	--	--	541	\$ 33,504
	1/15/2013	--	--	--	--	624	\$ 38,644
	1/15/2013	--	--	--	--	1,307	\$ 80,943
	1/15/2014	--	--	--	--	5,625	\$ 348,356
1/15/2015	--	--	--	--	5,518	341,730	
B. Lynne Parshall	1/3/2012	7,578	1,287	\$ 7.25	1/2/2019	--	--
	1/30/2013	12,486	16,868	\$ 14.69	1/29/2020	--	--
	1/2/2014	39,531	42,969	\$ 39.87	1/1/2021	--	--
	1/2/2015	--	132,458	\$ 61.57	1/1/2022	--	--
	1/15/2012	--	--	--	--	1,715	\$ 106,210
	1/30/2013	--	--	--	--	5,190	\$ 321,417
	1/30/2014	--	--	--	--	10,312	\$ 638,622
	1/15/2015	--	--	--	--	22,076	\$ 1,367,167
Brett Monia	1/1/2012	7,343	157	\$ 7.21	12/31/2018	--	--
	1/3/2012	8,597	396	\$ 7.25	1/2/2019	--	--
	1/30/2013	24,791	9,209	\$ 14.69	1/29/2020	--	--
	1/2/2014	21,562	23,438	\$ 39.87	1/1/2021	--	--
	1/2/2015	--	36,423	\$ 61.57	1/1/2022	--	--
	1/15/2012	--	--	--	--	527	\$ 65,074
	1/15/2012	--	--	--	--	208	\$ 25,684
	1/30/2013	--	--	--	--	2,830	\$ 262,086
	1/15/2014	--	--	--	--	5,625	\$ 463,050
	1/15/2015	--	--	--	--	6,070	\$ 375,915
Sarah Boyce	1/1/2015	--	52,500	\$ 61.74	12/31/2021	--	--
	1/15/2015	--	--	--	--	8,750	\$ 541,888

(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 \$61.93, which was the closing market price of our common stock on NASDAQ on December 31, 2015, the last trading day of fiscal 2015.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2015, 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	3,000	\$ 95,790	16,338	\$ 1,124,708
	5,000	\$ 228,685		
	10,000	\$ 547,680		
	10,000	\$ 567,780		
	10,000	\$ 623,000		
	10,000	\$ 616,560		
	5,000	\$ 231,455		
	3,000	\$ 95,190		
	3,000	\$ 96,390		
	4,163	\$ 135,839		
	3,000	\$ 93,990		
	3,000	\$ 94,590		
	19,657	\$ 995,864		
	20,343	\$ 1,053,788		
	5,000	\$ 172,050		
	5,000	\$ 168,550		
5,000	\$ 175,050			
837	\$ 28,132			
5,000	\$ 169,050			
Elizabeth L. Hougen	8,000	\$ 515,344	3,383	\$ 232,886
	7,437	\$ 476,459		
	10,000	\$ 620,560		
	12,657	\$ 723,955		
B. Lynne Parshall	5,565	\$ 269,240	7,748	\$ 533,373
	1,000	\$ 27,310		
	2,000	\$ 50,820		
	1,000	\$ 26,060		
	11,200	\$ 531,160		
	1,436	\$ 40,222		
	1,838	\$ 46,795		
	1,000	\$ 27,660		
	5,377	\$ 254,021		
	162	\$ 5,329		
	4,843	\$ 240,973		
	2,000	\$ 65,200		
	500	\$ 16,275		
	500	\$ 16,305		
	1,000	\$ 33,050		
1,375	\$ 64,236			
6,218	\$ 293,931			
Brett Monia	7,600	\$ 425,076	4,025	\$ 277,081
Sarah Boyce	--	--	--	--

(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 2015, 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 2015, the maximum matching contribution was \$7,950. 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, 2015. 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, 2015. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 54 of this Proxy Statement.

Name	Termination Event	
	Termination Without Cause	Termination in a Change of Control
Stanley T. Crooke	--	\$ 2,401,554
B. Lynne Parshall	\$ 1,037,877	\$ 1,729,795

Director Compensation

We pay our non-employee Directors a base fee of \$50,000 with additional role-based compensation as noted below:

Role	2015 Cash Compensation
Board Member (Base)	\$ 50,000
Committee Chairs (Additional)	
Audit	\$ 24,000
Compensation	\$ 15,000
Nominating & Gov.	\$ 10,000
Agenda	\$ 10,000
Committee Member (Additional)	
Audit	\$ 10,000
Compensation	\$ 7,500
Nominating & Gov.	\$ 5,000
Agenda	\$ 5,000
Scientific/Medical	\$ 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 2015, each non-employee Director also received automatic stock award grants under our Directors' Plan. On July 1, 2015, 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 \$57.16 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, 2015 certain information with respect to the compensation of all our non-employee Directors:

Director Compensation for Fiscal 2015

Name	Fees Earned or Paid in Cash (\$)	Stock Awards (\$)(1)	Option Awards (\$)(1)	All Other Compensation (\$)	Total (\$)
Spencer R. Berthelsen	\$ 85,000	\$ 152,446	\$ 494,904	--	\$ 732,350
Breaux B. Castleman	\$ 60,000	\$ 152,446	\$ 494,904	--	\$ 707,350
Joseph Klein, III	\$ 60,000	\$ 152,446	\$ 494,904	--	\$ 707,350
Joseph Loscalzo	\$ 68,750	\$ 152,446	\$ 494,904	--	\$ 716,150
Frederick T. Muto	\$ 55,000	\$ 152,446	\$ 494,904	--	\$ 702,350
Joseph H. Wender	\$ 86,500	\$ 152,446	\$ 494,904	--	\$ 733,850

(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, 2015 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, 2015, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors:

Outstanding Equity Awards as of December 31, 2015

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	0	\$ 5.93	7/2/16	5,916	\$ 366,378
	12,500	0	\$ 9.77	7/1/17		
	15,000	0	\$ 13.88	6/30/18		
	15,000	0	\$ 16.32	6/30/19		
	15,000	0	\$ 9.22	6/30/20		
	15,000	0	\$ 9.30	6/30/21		
	8,438	2,812	\$ 12.94	7/1/22		
	5,626	5,624	\$ 28.47	6/30/23		
	4,000	12,000	\$ 35.53	6/30/24		
0	16,000	\$ 57.16	6/30/25			
Breaux B. Castleman	11,250	11,250	\$ 26.66	6/24/23	7,478	\$ 829,490
	5,626	5,624	\$ 28.47	6/30/23		
	4,000	12,000	\$ 35.53	6/30/24		
	0	16,000	\$ 57.16	6/30/25		
Joseph Klein, III	0	2,812	\$ 12.94	7/1/22	5,916	\$ 366,378
	5,626	5,624	\$ 28.47	6/30/23		
	4,000	12,000	\$ 35.53	6/30/24		
	0	16,000	\$ 57.16	6/30/25		
Joseph Loscalzo	5,625	16,875	\$ 49.09	2/2/24	7,479	\$ 463,174
	4,000	12,000	\$ 35.53	6/30/24		
	0	16,000	\$ 57.16	6/30/25		
Frederick T. Muto	12,500	0	\$ 5.93	7/2/16	5,916	\$ 366,378
	12,500	0	\$ 9.77	7/1/17		
	15,000	0	\$ 13.88	6/30/18		
	15,000	0	\$ 16.32	6/30/19		
	15,000	0	\$ 9.22	6/30/20		
	15,000	0	\$ 9.30	6/30/21		
	8,438	2,812	\$ 12.94	7/1/22		
	5,626	5,624	\$ 28.47	6/30/23		
	4,000	12,000	\$ 35.53	6/30/24		
0	16,000	\$ 57.16	6/30/25			
Joseph H. Wender	15,000	0	\$ 13.88	6/30/18	5,916	\$ 366,378
	15,000	0	\$ 9.22	6/30/20		
	15,000	0	\$ 9.30	6/30/21		
	8,438	2,812	\$ 12.94	7/1/22		
	5,626	5,624	\$ 28.47	6/30/23		
	4,000	12,000	\$ 35.53	6/30/24		
	0	16,000	\$ 57.16	6/30/25		

(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 \$61.93, which was the closing market price of our common stock on the NASDAQ Global Select Market on December 31, 2015, the last trading day of fiscal 2015.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2015, 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 2015

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⁾	10,000	\$ 613,800	1,448	\$ 82,446
Breaux B. Castleman	--	--	2,074	\$ 118,550
Joseph Klein, III	16,875	\$ 981,722	1,448	\$ 82,446
Joseph Loscalzo	--	--	1,605	98,814
Frederick T. Muto ⁽¹⁾	10,000	\$ 629,610	1,448	\$ 82,446
Joseph H. Wender ⁽¹⁾	35,000	\$ 2,173,361	1,448	\$ 82,446

- (1) Dr. Berthelsen, Mr. Muto and Mr. Wender exercised options that would have expired on June 30, 2015.

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 2015, 2014 and 2013, 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	2015	\$ 218,720	\$ 102,361	\$ 99,818	\$ 238,204	\$ 7,554	\$ 666,657
Vice President, Cardiovascular Diseases Drug Discovery Research	2014	\$ 210,814	\$ 82,349	\$ 67,487	\$ 146,488	\$ 5,912	\$ 513,050
	2013	\$ 203,685	\$ 89,367	\$ 23,457	\$ 48,906	\$ 3,777	\$ 369,192

- (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 2016 we paid bonuses for 2015 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, 2015 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 the Black-Scholes option-valuation 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:
- 10,000 shares at \$10.82 per share received on January 2, 2013;
 - 8,500 shares at \$39.87 per share received on January 2, 2014; and
 - 8,700 shares at \$61.57 per share received on January 2, 2015.

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 \$639,287 in fees in 2015 for legal services, which amount is substantially less than five percent of Cooley's gross revenues for its 2015 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 2016 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, 2015 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, 2015, 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, 2015 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 2016.

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, 2015 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)⁶ to view our 2015 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 15, 2016

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

Special Note Regarding Forward-Looking Statements

This Proxy Statement includes forward-looking statements regarding Ionis Pharmaceuticals' business, the financial position and outlook for Ionis and the therapeutic and commercial potential of our technologies and products 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, 2015 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 and its subsidiaries.

Ionis Pharmaceuticals[™] is a trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics[™] is a trademark of Ionis Pharmaceuticals, Inc. Regulus Therapeutics[®] is a registered trademark of Regulus Therapeutics Inc.

IONIS PHARMACEUTICALS, INC.
2855 GAZELLE COURT
CARLSBAD, CA 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>IONIS PHARMACEUTICALS, INC.</p> <p>The Board of Directors recommends you vote FOR the following nominees to be elected for a term expiring in 2019.</p> <p>1. Election of Directors</p> <p>Nominees:</p> <p>01) Stanley T. Crooke 02) Joseph Klein, III 03) Joseph Loscalzo</p>	<p>For All</p> <p><input type="checkbox"/></p>	<p>Withhold All</p> <p><input type="checkbox"/></p>	<p>For All Except</p> <p><input type="checkbox"/></p>	<p>To withhold authority to vote for any individual nominee(s), mark "For All Except" and write the number(s) of the nominee(s) on the line below.</p> <p>_____</p>									
<p>The Board of Directors recommends you vote FOR the following proposals:</p> <p>2. To approve, by non-binding vote, executive compensation.</p> <p>3. Ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for the 2016 fiscal year.</p> <p>NOTE: Such other business as may properly come before the meeting or any adjournment thereof.</p>	<table style="width: 100%; border: none;"> <tr> <td style="text-align: center;">For</td> <td style="text-align: center;">Against</td> <td style="text-align: center;">Abstain</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>				For	Against	Abstain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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<p>Please sign exactly as your name(s) appear(s) hereon. When signing as attorney, executor, administrator, or other fiduciary, please give full title as such. Joint owners should each sign personally. All holders must sign. If a corporation or partnership, please sign in full corporate or partnership name by authorized officer.</p>													
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%; height: 20px;"></td> <td style="width: 20%; height: 20px;"></td> </tr> </table> <p>Signature [PLEASE SIGN WITHIN BOX] Date</p>			<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%; height: 20px;"></td> <td style="width: 20%; height: 20px;"></td> </tr> </table> <p>Signature (Joint Owners) Date</p>										

Important Notice Regarding the Availability of Proxy Materials for the Annual Meeting:

The Notice & Proxy Statement and Form 10-K are available at www.proxyvote.com.

IONIS PHARMACEUTICALS, INC.

Annual Meeting of Stockholders

June 3, 2016 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 June 3, 2016 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 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
