

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 under § 240.14a-12

Ionis Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

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

Payment of Filing Fee (Check all boxes that apply):

- No fee required
 - Fee paid previously with preliminary materials
 - Fee computed on table in exhibit required by Item 25(b) per Exchange Act Rules 14a-6(i)(1) and 0-11
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**NOTICE OF 2022 ANNUAL MEETING OF STOCKHOLDERS
AND PROXY STATEMENT**

Dear Stockholders,

I am pleased to invite you to Ionis Pharmaceuticals, Inc.'s 2022 Annual Meeting of Stockholders to be held on June 2, 2022. The Annual Meeting will be held in a virtual meeting format only, via live webcast on the Internet, with no physical in-person meeting. You can attend and participate in the Annual Meeting online by visiting www.virtualshareholdermeeting.com/IONS2022, where you will be able to listen to the meeting live, submit questions and vote. As always, we encourage you to vote your shares prior to the Annual Meeting.

This document 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 2022 via webcast. You can find information regarding how to join the webcast on our website at ir.ionispharma.com. The Proxy Statement explains the matters we will discuss in the meeting and provides additional information about us.

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

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

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

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

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

Sincerely,

Patrick R. O'Neil
Corporate Secretary



NOTICE OF 2022 ANNUAL MEETING OF STOCKHOLDERS

- Date:** June 2, 2022
- Time:** 2:00 p.m. Pacific Time
- Place:** Online only: www.virtualshareholdermeeting.com/IONS2022
- Record Date:** April 5, 2022. If you were an Ionis stockholder of record at the close of business on April 5, 2022, you may vote at the Annual Meeting.
- Items of Business:** We are holding the Annual Meeting for the following purposes, as more fully described in the accompanying Proxy Statement:
1. To elect our nominees, Allene M. Diaz, Michael Hayden, Joseph Klein, III, and Joseph Loscalzo, to our Board of Directors to serve as Directors for a three-year term;
 2. To make an advisory vote on executive compensation; and
 3. To ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2022 fiscal year.
 4. To transact any other business that may be properly presented at the Annual Meeting.
- Virtual Meeting:** To participate in the Annual Meeting, please visit www.virtualshareholdermeeting.com/IONS2022. You will need the 16-digit control number included on your Notice of Internet Availability of Proxy Materials or your proxy card or voting instruction form that accompanied your proxy materials. Stockholders will be able to vote and submit questions during the Annual Meeting.
- Voting:** WHETHER OR NOT YOU EXPECT TO ATTEND THE MEETING, PLEASE VOTE BY TELEPHONE OR INTERNET BY FOLLOWING THE INSTRUCTIONS INCLUDED IN THIS PROXY STATEMENT AND YOUR NOTICE REGARDING THE AVAILABILITY OF PROXY MATERIALS OR PROXY CARD. ALTERNATIVELY, YOU MAY REQUEST A WRITTEN PROXY STATEMENT, AND COMPLETE, DATE, SIGN AND RETURN YOUR PROXY AS PROMPTLY AS POSSIBLE TO ENSURE YOUR REPRESENTATION AT THE MEETING. IF YOU RECEIVE YOUR PROXY MATERIALS BY MAIL, WE WILL INCLUDE A RETURN ENVELOPE (WHICH IS POSTAGE PREPAID IF MAILED IN THE UNITED STATES) FOR THAT PURPOSE. EVEN IF YOU HAVE GIVEN YOUR PROXY, YOU MAY STILL VOTE AT THE VIRTUAL MEETING VIA LIVE WEBCAST. PLEASE NOTE, HOWEVER, THAT IF YOUR SHARES ARE HELD OF RECORD BY A BROKER, BANK OR OTHER NOMINEE AND YOU WISH TO VOTE AT THE MEETING, YOU MUST OBTAIN FROM THE BROKER, BANK OR OTHER NOMINEE A PROXY ISSUED IN YOUR NAME.

By order of the Board of Directors,

Patrick R. O'Neil
Corporate Secretary

Carlsbad, California
April 20, 2022

ALL STOCKHOLDERS ARE CORDIALLY INVITED TO ATTEND THE VIRTUAL MEETING VIA LIVE WEBCAST.

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

PROXY STATEMENT
FOR THE 2022 ANNUAL MEETING OF STOCKHOLDERS

To Be Held on June 2, 2022

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 2022 Annual Meeting of Stockholders, including at any adjournments or postponements of the meeting. We are distributing our Notice of Annual Meeting and Proxy Materials (the "Notice") by mail using the Notice and Access procedures established by the United States Securities and Exchange Commission (the "SEC"). The Notice is important because it contains a control number and instructions that will allow you to access our proxy materials and vote electronically through the Internet or to request printed proxy materials so you may vote by telephone or mail. Your vote is very important. Whether or not you plan to attend the meeting, please be sure to vote your shares as soon as possible to ensure your representation at the meeting. All stockholders will have the ability to access the proxy materials on the website referred to in the Notice or request to receive a printed set of the proxy materials. You can find instructions on how to access the proxy materials over the Internet or to request a printed copy in the Notice.

We intend to mail the Notice on or before April 22, 2022 to all stockholders of record entitled to vote at the Annual Meeting.

Will I receive any other proxy materials by mail?

We may send you a proxy card, along with a second Notice, on or after May 3, 2022.

Where and when is the Annual Meeting?

The Annual Meeting will be held on Thursday, June 2, 2022, at 2:00 p.m. Pacific Time. The Annual Meeting will be held in a virtual meeting format only, via live webcast on the Internet, with no physical in-person meeting. To participate, vote or submit questions during the Annual Meeting via live webcast, please visit www.virtualshareholdermeeting.com/IONS2022.

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

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

How do I attend the Annual Meeting?

We will be hosting the Annual Meeting via live webcast on the Internet. **You will not be able to attend the Annual Meeting in person.** All stockholders at the close of business on April 5, 2022 can listen to and participate in the Annual Meeting live via the internet at www.virtualshareholdermeeting.com/IONS2022. **The webcast will begin at 2:00 p.m. Pacific Time on June 2, 2022. Stockholders may vote and submit questions while connected to the Annual Meeting on the Internet.** A summary of the information you need to attend the Annual Meeting online is provided below.

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

You will need the 16-digit control number included on your proxy card in order to be able to vote your shares or submit questions during the virtual Annual Meeting. **Instructions on how to connect and participate in the Annual Meeting via the internet, including how to demonstrate proof of stock ownership, are posted at www.virtualshareholdermeeting.com/IONS2022.**

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



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

If you encounter any difficulties accessing the live webcast of the Annual Meeting or during the Annual Meeting, please call the telephone number that is listed at www.virtualshareholdermeeting.com/IONS2022 for assistance. If you misplace the 16-digit control number that is required to enter the Annual Meeting webcast and are a stockholder of record, operators providing assistance at this telephone number will be able to provide it to you. However, if you need your 16-digit control number and hold your shares in an account at a brokerage firm, bank, dealer, or other similar organization, you must contact that organization to obtain your 16-digit control number prior to the Annual Meeting.

Who can attend and vote at the Annual Meeting?

Only stockholders at the close of business on April 5, 2022 may attend and vote at the Annual Meeting. On this record date, there were 141,753,122 shares of common stock outstanding and entitled to vote.

Stockholder of Record: Shares Registered in Your Name

If on April 5, 2022 your shares were registered directly in your name with our transfer agent, American Stock Transfer & Trust Company, then you are a stockholder of record. As a stockholder of record, you may vote online at the virtual meeting or vote by proxy over the telephone, by mail, or the Internet as instructed under the section below titled “How do I vote?” Whether or not you plan to attend the meeting, we urge you to fill out and return the proxy card or vote over the telephone or Internet to ensure your vote is counted.

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

If on April 5, 2022 you did not own shares in your name, but rather in an account at a brokerage firm, bank, dealer or other similar organization, then you are the beneficial owner of shares held in “street name” and that organization is forwarding the Notice to you. The organization holding your account is the stockholder of record for purposes of voting at the Annual Meeting. As a beneficial owner, you may direct your broker or other agent regarding how to vote the shares in your account. If your shares are registered in the name of a broker or other nominee, your nominee may be participating in a program provided through Broadridge Financial Solutions, Inc. (“Broadridge”) that also allows you to vote by telephone or through the Internet. If so, the voting form your nominee sends you will provide telephone and Internet instructions. You are also invited to attend the virtual Annual Meeting via live webcast.

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

What am I voting on?

The following matters are scheduled for a vote:

1. **Proposal 1:** elect our nominees, Allene M. Diaz, Michael Hayden, Joseph Klein, III, and Joseph Loscalzo, to our Board of Directors to serve as Directors for a three-year term;
2. **Proposal 2:** make an advisory vote on executive compensation; and
3. **Proposal 3:** ratify the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2022 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:

1. vote through the Internet by following the instructions included with your Notice or proxy card;
2. vote by telephone by following the instructions included with your proxy card if you have received proxy materials electronically or by mail;



3. vote by mail by completing, signing, dating, and returning your proxy card in the postage paid envelope provided; or
4. vote during the virtual Annual Meeting by following the instructions posted at www.virtualshareholdermeeting.com/IONS2022.

The procedures for voting are fairly simple:

For Shares Registered in Your Name:

If you are a stockholder of record, you may go to www.proxyvote.com to vote your shares through the Internet up until 11:59 p.m. Eastern Time on June 1, 2022. The votes represented by your proxy will be displayed on the computer screen and you will be prompted to submit or revise your votes as desired.

To vote your shares by telephone, you must first request that we send proxy materials to you by following the instructions included in your Notice. Once you have received your proxy materials, you may vote using a touch-tone telephone by calling 1-800-690-6903 up until 11:59 p.m. Eastern Time on June 1, 2022 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 we receive your signed proxy card before the Annual Meeting, we will vote your shares as you direct.

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

If your broker or bank holds your shares in “street name,” you will need to obtain a proxy form from the institution that holds your shares and follow the instructions included on that form regarding how to instruct your broker to vote your shares. If you do not give instructions to your broker, your broker can vote your shares with respect to “discretionary” items, but not with respect to “non-discretionary” items. Discretionary items are proposals considered routine under the rules of the New York Stock Exchange (“NYSE”) on which a broker may vote shares held in street name in the absence of your voting instructions. While Ionis is listed with the Nasdaq Stock Market (“Nasdaq”), NYSE rules affect how brokers licensed by the NYSE can vote in a director election of any company, including companies listed with Nasdaq. The proposal to ratify Ernst & Young LLP as independent auditors is a discretionary item. Proposals 1 and 2 regarding (1) the election of Directors, and (2) 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 your broker cannot vote your shares, which will result in what is commonly referred to as a “broker non-vote.” Broker non-votes will have no effect.

A number of brokers and banks are participating in a program provided by Broadridge that allows proxies to vote shares by means of the telephone and Internet. If your shares are held in an account with a broker or bank participating in the Broadridge program, you may vote your shares by telephone or through the Internet by having the voting form in hand and calling the number or going to the website indicated on the form and following the instructions.

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

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

1. “For” the election of the nominees for Director named in the Proxy Statement;
2. “For” the approval, on an advisory basis, of executive compensation; and
3. “For” the ratification of the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2022 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:

1. you may mail another proxy marked with a later date;
2. you may revoke it through the Internet;
3. 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
4. you may vote during the virtual Annual Meeting. *Attending* the meeting *will not*, by itself, revoke a proxy.

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

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

If you have a proposal that you would like us to include in our proxy materials for next year's Annual Meeting of Stockholders, you must send the proposal to us in writing by no later than December 21, 2022 and comply with all applicable requirements of Rule 14a-8 promulgated under the Securities Exchange Act of 1934, as amended ("Rule 14a-8"). Stockholders wishing to submit proposals or Director nominations that are not to be included in such proxy materials for next year's Annual Meeting of Stockholders pursuant to Rule 14a-8 must do so no later than the close of business on February 2, 2023, as required by our bylaws. Stockholders should also review our bylaws, which contain additional requirements with respect to advance notice of stockholder proposals and Director nominations.

In addition to satisfying the foregoing requirements under our bylaws, to comply with the universal proxy rules (once effective), stockholders who intend to solicit proxies in support of director nominees other than our Board's nominees must provide notice that sets forth any additional information required by Rule 14a-19 no later than April 3, 2023.

What is the quorum requirement?

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

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

How are votes counted?

Each share of our common stock you own entitles you to one vote. Your Notice and proxy card indicates the number of shares of our common stock you owned at the close of business on April 5, 2022. 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 or Proposal 3. Abstentions will count towards the vote total for Proposal 2 and 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 (1) the election of Directors, and (2) approval, on an advisory basis, of our executive compensation, are non-discretionary items.

How many votes are needed to approve each proposal?

1. **Proposal 1:** For the election of Directors in an uncontested election, a Director nominee must receive a majority of the votes cast in the election such that the number of shares voted “For” the nominee must exceed 50% of the votes cast with respect to that Director. Only “For” and “Withhold” votes will affect the outcome. Abstentions and broker non-votes, if any, will have no effect.
2. **Proposal 2:** We will consider the advisory approval of the compensation of our executive officers to be approved if it receives “For” votes from a majority of the holders of shares present or represented by proxy at the Annual Meeting and entitled to vote on the matter. If you “Abstain” from voting, it will have the same effect as an “Against” vote. Broker non-votes, if any, will have no effect.
3. **Proposal 3:** To be approved, the ratification of the selection of Ernst & Young LLP as our independent auditors for our 2022 fiscal year must receive “For” votes from a majority of the holders of shares present or represented by proxy at the Annual Meeting and entitled to vote on the matter. Abstentions, if any, will have no effect. Because brokers have discretionary authority to vote on the ratification of the selection of Ernst & Young LLP, we do not expect any broker non-votes in connection with the ratification.

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

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

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

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

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

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

List of Shareholders

A list of stockholders entitled to vote at the Annual Meeting will be available for examination at our principal executive offices at the address listed above for a period of 10 days prior to the Annual Meeting, and will be available during the virtual Annual Meeting for examination at www.virtualshareholdermeeting.com/IONS2022.



Environmental, Social and Governance Initiatives

We recognize the importance of Environmental, Social and Governance (“ESG”) initiatives as they relate to our business strategy and risk assessment. During 2020 and 2021, we took steps to formalize our corporate responsibility program. In December 2021, we issued our inaugural corporate responsibility report in which we identified the corporate responsibility initiatives that we believe are most important to our business, some of which are discussed below.

We have a relatively small environmental footprint, so our stewardship programs focus on improving eco-awareness, identifying efficiencies and integrating more sustainable practices into our daily operations. The identification of our ESG initiatives considered investor and other stakeholder interests and is aligned with the requirements of ESG ratings agencies and with leading ESG frameworks, including the Sustainability Accounting Standards Board.

Safety of Clinical Trial Participants

The safety of participants in our clinical trials is very important to us. We have standard operating procedures to govern how we conduct clinical trials. Independent ethics committees and institutional review boards and health authorities review and approve essential clinical trial documents, such as protocols and informed consent forms before they are implemented. During clinical trials, participants are treated by qualified doctors and their staff, who are trained on the administration of our investigational drugs. Our safety data review committees, and, for some studies, independent external Data and Safety Monitoring Boards, monitor safety data across all study participants to identify potential issues or concerns, which are handled in accordance with our study plans. During trials, we evaluate benefit-to-risk assessments, and share annual summary reports and post-approval safety surveillance reports with health authorities.

Drug Safety and Supply Chain Management

We rigorously monitor our products throughout the manufacturing process. Raw materials, components, utilities and products are tested at key stages against pre-defined acceptance criteria using validated or compendial methods. Testing methods are validated in line with international standards to demonstrate consistent and valid results. We use a Quality Management System (“QMS”) to provide governance oversight, control quality and monitor compliance. A Quality Management Review (“QMR”) is performed at least annually to update senior management on the compliance of the QMS against agreed metrics and external vendor performance. Processes are also in place to share learnings from projects and inspections with senior leadership through the QMR.

Access to Medicines

At the core of everything we do is a belief in the potential of our medicines to transform lives. To fulfill this potential, we need to get our medicines to those who need them most. We work closely with patient advocacy organizations and communities around the world to identify and understand the needs of people we serve. Patients are experts in living with their disease, and their perspectives inform our approach to drug development. We recently introduced initiatives to better match the demographics of our clinical trials with the demographics of patient populations, which we believe will improve access and ensure diversity.

Sharing the Benefits of Antisense Technology: The n-Lorem Foundation

The power to develop treatments for patients with extremely rare diseases is a tremendous responsibility that we take seriously. We have donated our time, knowledge, and resources to discover and develop treatments for these diseases. We are closely associated with the n-Lorem Foundation, a charitable organization established by Ionis’ founder and former CEO and Executive Chairman, Stanley T. Crooke. The mission of n-Lorem is to provide personalized antisense treatments to patients with ultra-rare diseases (afflicting fewer than 30 patients worldwide) – for free, for life. Given the rarity of the diseases in question, developing treatments is not commercially viable; however, n-Lorem’s not-for-profit model offers hope to these patients. Ionis supports n-Lorem both financially and with in-kind activities.

Employee Recruitment and Development

We are committed to fair and equitable recruitment of the best and most qualified candidates, and we cast a wide net when searching for talent. We offer internships to promising students to nurture their interest in the biotech and pharmaceutical sectors. Whether we are hiring entry-level, mid-career, or executive level candidates, we look beyond a candidate’s academic qualifications to identify valuable experience and skills. New employees enter a peer mentoring “buddy” program, and we offer comprehensive training and development plans for employees at all levels. Our training and development program supports the development of our employees as they progress through their careers. We also offer integration programs, science classes for non-scientists, a manager’s book club, soft skills training, English language skills, supervisory capabilities, and leadership development programs.



Diversity, Equity and Inclusion

We strive to create an environment that values different perspectives, where all employees are encouraged to contribute wholeheartedly and reach their full potential. Encouraging diversity has always been part of our corporate culture and we work hard to promote fairness, inclusion and equity. In 2020, we launched Employee Resource Groups (“ERGs”) to promote diversity and inclusion within our organization. The groups are employee-led and focused on a particular dimension of diversity. ERGs give colleagues the opportunity to discuss issues around diversity and inclusion, and are designed to support our business goals, diversify our leadership, build cultural awareness and promote an inclusive and supportive culture. Employee-led ERGs at Ionis include groups focused on:

ERGs give colleagues the opportunity to discuss issues around diversity and inclusion, and are designed to support our business goals, diversify our leadership, build cultural awareness and promote an inclusive and supportive culture.

- LGBTQIA+;
- women’s empowerment;
- diversity, equity and inclusion and social justice;
- new and expecting parents;
- mental health; and
- minority student outreach.

Employee Health and Safety

We strive to protect the health and safety of all employees, contractors, and visitors, and we aim to provide an injury-free workplace. We have implemented a safety management system that uses risk metrics, monitoring, auditing, and target setting to continuously improve occupational health and work safety. We provide regular safety training to all laboratory and manufacturing employees, and we routinely audit health and safety compliance.

COVID-19

As the COVID-19 outbreak developed in 2020, we were quick to implement a plan to keep our employees and patients safe and minimize disruption to the supply of medicines to our patients and clinical trials. For the safety of our workforce, we asked employees to work from home when possible. We gave essential employees in research and manufacturing the flexibility to determine on-site working hours. Working closely with our employee benefits provider, we rolled out a range of health and wellness programs to help manage the additional stress that many experienced. We also provided extra holiday time, and periodically, we delivered boxes of fresh farm produce to all employees to thank them for their dedication and hard work. We continue to offer our employees health and wellness programs and flexible work arrangements, including remote work options.

Our Employees.

Fairness and transparency guide our culture and our commitment to our employees. Our employees are our core resource. We strive to compensate our employees according to market, internal equity, and performance factors. We work hard to create a rewarding and supportive environment that empowers our employees to thrive. We are proud to have been named one of the Best Places to Work in San Diego in 2020 and one of the Top Biotech Companies in San Diego in 2021 by the San Diego Business Journal. 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. As of December 31, 2021, more than 50 employees, representing nearly 10% of our workforce, had been with us for over 20 years, and six had been with us for over 30 years. Additionally, our average employee turnover rate in 2021 was 16%, while the turnover for life sciences/medical device companies over this period was 19% according to a survey published by Radford – an Aon company. Historically our turnover rate has been even lower and we are encouraged that it is still below the average for life sciences/medical device companies given the current nationwide trend of increased employee turnover.



Thoughtful Corporate Responsibility in Everything We Do

Inaugural Corporate Responsibility Report Published in December 2021



We encourage you to view our *2021 Corporate Responsibility Report* published on our website for more detailed information regarding our ESG initiatives. Nothing in the report or on our website shall be deemed incorporated by reference into this Proxy Statement.



PROPOSAL 1

ELECTION OF DIRECTORS

Information about our Board

The Board is divided into three classes. Presently, the Board has ten members with two classes consisting of four 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 whom the Board appoints. As a result, whenever the Board appoints a new member, the Board will submit such new member's directorship for ratification or election at the next regularly scheduled Annual Meeting of Stockholders.

The Board represents the interests of our stockholders by overseeing the Chief Executive Officer and other members of senior management in our operations. 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 2022 Elections

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

Name	Commencement of Ionis Directorship
Allene M. Diaz	June 2021
Michael Hayden	September 2018
Joseph Klein, III	December 2005
Joseph Loscalzo	February 2014

Dr. Hayden, Mr. Klein and Dr. Loscalzo have each been previously re-elected by our stockholders. This is the first time Ms. Diaz is a nominee for election by our stockholders. If re-elected or elected, as applicable, Ms. Diaz, Dr. Hayden, Mr. Klein and Dr. Loscalzo will serve until the 2025 Annual Meeting or, in each case, until his or her successor is elected and has qualified, or until his or her earlier death, resignation or removal.

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

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

On March 16, 2022, the Nominating, Governance and Review Committee provided its recommendations to the Board for Director nominees to stand for election at the Annual Meeting. Following such recommendations, the Board determined it would be in the best interests of Ionis and its stockholders to nominate Ms. Diaz, Dr. Hayden, Mr. Klein, and Dr. Loscalzo to be elected as Directors at the Annual Meeting. We provide below a short biography for each nominee. Ms. Diaz, Dr. Hayden, 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 2025 Annual Meeting

Allene M. Diaz, age 57², has served as a Director of Ionis since June 2021. Since 2020 Ms. Diaz has led AMD Consulting, a new product strategy and portfolio management consulting practice based in Boston, MA. Previously, Ms. Diaz served as Senior Vice President, Research and Development Portfolio Management at GlaxoSmithKline, a global pharmaceutical company based in Brentwood, UK, from September 2019 through June 2020 and as Senior Vice President, Global Commercial Development and Program Strategy at TESARO Inc., a biotechnology company based in Waltham, MA, from May 2015 through August 2019. Prior to that she held a variety of commercial leadership roles in the Merck Serono and EMD Serono divisions of Merck KGaA. Earlier in her career, Ms. Diaz held management, operating, sales, and medical affairs roles at various biopharmaceutical companies, including Pfizer, Parke-Davis, Biogen, and Amylin Pharmaceuticals. She has contributed to the global development, launch or commercialization of multiple transformative products across several therapeutic areas. Ms. Diaz has served on the boards of directors of Mersana Therapeutics since March 2021, Allena Pharmaceuticals since April 2019 and BCLS Acquisition Corporation since October 2020. Ms. Diaz served on the board of directors of Erytech Pharma SA from September 2016 to September 2019.

The Board believes Ms. Diaz is uniquely suited to serve on the Board primarily because of her deep expertise in product development, commercial strategy, market access, and portfolio management.

Michael Hayden, CM, OBC, MB, ChB, Ph.D., FRCP(C), FRSC, age 70, has served as a Director of Ionis since September 2018. Dr. Hayden has been Chief Executive Officer of Prilenia Therapeutics, a private clinical stage biotech company, since September 2018. Dr. Hayden is also a Killam Professor at the University of British Columbia, the highest honor UBC can confer on any faculty member. In addition, he is an accomplished scientist and physician. He was the President of Global R&D and Chief Scientific Officer at Teva Pharmaceuticals from 2012 to 2017. During this time approximately 35 new products were approved in major markets with many for diseases of the central nervous system. In 2015 Teva R&D was recognized as one of the 100 most exciting innovators in the pharmaceutical industry by IDEA Pharma and in 2017 Teva R&D ranked top of the industry for central nervous system development and clinical trial success rate by Pharma Intelligence. Dr. Hayden has founded three biotechnology companies and has been the recipient of numerous prestigious honors and awards, including being inducted into the Canadian Medical Hall of Fame and receiving the July 2012 Diamond Jubilee Medal on behalf of HRH Queen Elisabeth II. He has also received the Canada Gairdner Wightman award. Dr. Hayden was awarded the Order of Canada, the Order of British Columbia, named Canada's Health Researcher of the Year by Canadian Institutes of Health Research, and received the Prix Galien Award in 2007.

Dr. Hayden served on the board of Aurinia Pharmaceuticals, Inc. until August 2021, and currently serves on the boards of Xenon Pharmaceuticals, 89Bio, AbCellera Biologics and Oxford Biomedica. Although Dr. Hayden serves on these public company boards in addition to that of Ionis, Dr. Hayden attended 75% or more of the aggregate number of meetings of the boards and the committees on which he served during 2021. In addition, we expect that Dr. Hayden will only serve on the boards of a total of four publicly traded companies (including Ionis) starting in June 2022.

The Board believes Dr. Hayden is uniquely suited to serve on the Board because he has significant expertise in pharmaceutical research and development, both in academia and in commercial settings. In addition, Dr. Hayden has made substantial research contributions to advance treatments for brain diseases, which is particularly valuable as we grow our neurologic disease franchise, a key focus of ours. Dr. Hayden also serves as the Chair of our Science/Medical Committee, providing invaluable guidance on the key scientific and development issues facing our technology and medicines in development.

Joseph Klein, III, age 60, has served as a Director of Ionis since December 2005 and is Chairman of the Audit Committee. Mr. Klein is currently Managing Director of Gauss Capital Advisors, LLC, a financial consulting and investment advisory firm focused on biopharmaceuticals, which he founded in March 1998. From September 2003 to December 2008, Mr. Klein also served as a Venture Partner of Red Abbey Venture Partners, L.P., a life science private equity fund. From September 2001 to September 2002, Mr. Klein was a Venture Partner of MPM Capital, a healthcare venture capital firm. From June 1999 to September 2000 when it merged with WebMD Corporation, Mr. Klein served as Vice President, Strategy, for Medical Manager Corporation, a leading developer of physician office management information systems. For over nine years from 1989 to 1998, Mr. Klein was a health care investment analyst at T. Rowe Price Associates, Inc., where he was the founding portfolio manager of the T. Rowe Price Health Sciences Fund. Mr. Klein has served on the boards of directors of The Prospector Funds, Inc., an SEC Registered Investment Company that manages two no-load mutual funds, since September 2007, and Akcea Therapeutics, Inc., from September 2019 until the completion of the Company's merger with Akcea Therapeutics, Inc. in October 2020 (the "Akcea Merger"). Mr. Klein also serves on the boards of private and non-profit entities.

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

Joseph Loscalzo, M.D., Ph.D., age 70, has served as a Director of Ionis since February 2014 and as Chairman of the Board since June 2021. Dr. Loscalzo is Hersey Professor of the Theory and Practice of Medicine at Harvard Medical School and Chairman of the Department of Medicine and Physician-in-Chief at Brigham and Women's Hospital. Dr. Loscalzo is also a co-founder and member of the Scientific Advisory Board of Scipher Medicine, a private network medicine-based company matching patients with their most effective therapy. Dr. Loscalzo received his A.B. degree, *summa cum laude*, his Ph.D. in biochemistry, and his M.D. from the University of Pennsylvania. He completed his clinical training at Brigham and Women's Hospital and Harvard Medical School, where he served as Resident and Chief Resident in medicine and Fellow in cardiovascular medicine. Post-training, Dr. Loscalzo joined the Harvard faculty and staff at Brigham and Women's Hospital in 1984. He rose to the rank of Associate Professor of Medicine, Chief of Cardiology at the West Roxbury Veterans Administration Medical Center, and Director of the Center for Research in Thrombolysis at Brigham and Women's Hospital. He joined the faculty of Boston University in 1994, first as Chief of Cardiology and, in 1997, Wade Professor and Chair of Medicine, Professor of Biochemistry, and Director of the Whitaker Cardiovascular Institute. He returned to Harvard and Brigham and Women's Hospital in 2005. Since January 2016, Dr. Loscalzo has served on the board of directors of Leap Therapeutics, Inc., a public biopharmaceutical company.

² The ages of all our Directors are as of March 1, 2022.

The Board believes Dr. Loscalzo is uniquely suited to serve on the Board and as our Chairman primarily because of his extensive scientific expertise, including 31 years of research in the areas of vascular biology, thrombosis, and atherosclerosis, and practical knowledge as a practicing physician. Dr. Loscalzo's expertise and role as a leading cardiologist is particularly valuable as we advance and grow our cardiovascular franchise.

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

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

Spencer R. Berthelsen, M.D., age 69, has served as a Director of Ionis since May 2002. Dr. Berthelsen practiced Internal Medicine with the Kelsey Seybold Clinic, a 400-physician medical group based in the Texas Medical Center in Houston, until March 2017. Dr. Berthelsen began at Kelsey Seybold in 1980 and served in various senior leadership positions throughout his nearly four-decade career at the clinic, including Chairman of the Department of Internal Medicine, Medical Director and Managing Director. He also served as Chairman of its board of directors from October 2001 through April 2016. He has served as Clinical Professor of Medicine at both Baylor College of Medicine and The University of Texas Health Science Center. Previously, Dr. Berthelsen served on the boards of the Texas Academy of Internal Medicine and the Caremark National Pharmacy and Therapeutics Committee from 1999 through 2005.

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

Joan E. Herman, age 68, has served as a Director of Ionis since June 2019. Since 2008, Ms. Herman has served as President and Chief Executive Officer of Herman & Associates, a management consulting firm that specializes in advising private equity firms investing in healthcare. She has experience leading healthcare and payor companies, serving in several executive positions at Anthem (formerly WellPoint), including as President and Chief Executive Officer of several different business units. Ms. Herman also served as a Senior Vice President of Phoenix Life Insurance Company. Since January 2013, Ms. Herman has served on the board of directors of Encompass Health (formerly HealthSouth). She previously served on the boards of both Convergys and AARP Services, Inc.

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

B. Lynne Parshall, age 67, has served as a Director of Ionis since September 2000 and as a Senior Strategic Advisor to Ionis since January 2018. Previously she served as our Chief Operating Officer from December 2007 through January 2018 and as our Chief Financial Officer from June 1994 through December 2012. She also served as our Corporate Secretary through 2014 and has served with the Company in various executive roles since November 1991. Prior to joining Ionis, Ms. Parshall practiced law at Cooley LLP, outside counsel to Ionis, where she was a partner from 1986 to 1991. Ms. Parshall is a member of the American and California bar associations. Ms. Parshall has served on the boards of directors of Cytokinetics, Inc., a public biopharmaceutical company, since February 2013, and Akcea Therapeutics, Inc., from January 2015 until the completion of the Akcea Merger.

The Board believes Ms. Parshall is uniquely suited to serve on the Board primarily because, as the former Chief Operating Officer and former executive of the Company for over 26 years, she has valuable Company-specific experience and expertise. In addition, Ms. Parshall has over 35 years of experience structuring and negotiating strategic licensing and financing transactions in the life sciences field.

Joseph H. Wender, age 77, has served as a Director of Ionis since January 1994 and our Independent Lead Director since December 2020. Mr. Wender began with Goldman, Sachs & Co. in 1971 and became a General Partner of that firm in 1982, where he headed the Financial Institutions Group for over a decade. Since January 2022 he has been a Senior Consultant to Goldman Sachs & Co., from January 2019 to December 2021 he was an Advisory Director to Goldman Sachs & Co. and from January 2008 to December 2018 was a Senior Consultant to Goldman Sachs & Co. He is a former Independent Trustee of the Schwab Family of Funds and Director of Grandpoint Capital, a bank holding company. Mr. Wender also is co-CEO and partner of Colgin Cellars. Since March 2014, Mr. Wender has been a Director of Outfront Media, a lessor of advertising space on out-of-home advertising structures, and has served as its Lead Independent Director since 2016.



The Board believes Mr. Wender is uniquely suited to serve on the Board and as our Independent Lead Director primarily because, with over 50 years of experience as an investment banker with Goldman, Sachs & Co., he provides Ionis important advice regarding our financial reporting, corporate finance, strategic transactions, and compensation matters.

Biographies of the Directors Whose Terms Expire at the 2024 Annual Meeting

Brett P. Monia, Ph.D., age 60, has served as a Director of Ionis since March 2019. Dr. Monia was promoted to Chief Executive Officer in January 2020. From January 2018 to December 2019, Dr. Monia served as our Chief Operating Officer, from January 2012 to January 2018, as our Senior Vice President, Drug Discovery, from February 2009 to January 2012, as our Vice President, Drug Discovery, and from October 2000 to February 2009, as our Vice President, Preclinical Drug Discovery. From October 1989 to October 2000, he held various positions within our Molecular Pharmacology department. Following the Akcea Merger, Dr. Monia became the President of Akcea. Dr. Monia has served on the board of directors of Cognition Therapeutics, Inc., a public clinical stage neuroscience company, since October 2020.

The Board believes Dr. Monia is uniquely suited to serve on the Board primarily because, as an executive officer of the Company since 2012 and a founder of Ionis, he has dedicated more than 32 years to discovering and developing antisense-based drugs. Dr. Monia is the inventor on over 100 issued patents and has directly supervised programs resulting in the clinical development of more than 40 antisense-based drugs across a broad range of therapeutic areas.

Frederick T. Muto, age 68, has served as a Director of Ionis since March 2001. Mr. Muto is now retired, but previously worked at the law firm of Cooley LLP, outside counsel to Ionis, which he joined in 1980. In 1986, Mr. Muto became a partner of Cooley LLP, and in 2018, began serving as senior counsel to Cooley LLP. He is a founder of Cooley LLP's San Diego office and was chair of the firm's Business Department for a number of years.

The Board believes Mr. Muto is uniquely suited to serve on the Board primarily because, with over 40 years of experience at one of the country's leading law firms focused on life sciences and technology companies, he provides us important advice regarding our strategic transactions, corporate governance and compensation matters.

Biographies of Former Directors Who Served in 2021

Breaux B. Castleman, age 81, served as a Director of Ionis from June 2013 to June 2021. Since August 2001, Mr. Castleman has been President and Chief Executive Officer of Syntiro Healthcare Services, Inc., a healthcare investment company, which sold its operations as a service provider of integrated care management and disease management. Since January 2008, Mr. Castleman has been a Senior Advisor of McNally Capital, LLC, a private equity and merchant banking firm focused on investments in private equity, both direct to companies and through private equity partnerships. Mr. Castleman was a director of USMD Holdings, Inc., a physician-led integrated healthcare system, from August 2010 until September 2016.

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

Stanley T. Crooke, M.D., Ph.D., age 76, is a founder of Ionis and was the Executive Chairman of our Board from January 2020 until June 2021. Dr. Crooke is also founder, Chairman and Chief Executive Officer of n-Lorem, a nonprofit foundation focused on providing treatments for patients with nano-rare diseases (1 to 30 patients worldwide), which he initiated in January 2020. Dr. Crooke was a Director of the Company beginning in January 1989 and Chairman of the Board from February 1991 until January 2020. He served as our Chief Executive Officer from February 1989 until January 2020. Prior to founding Ionis, from 1980 until January 1989, Dr. Crooke worked for SmithKline Beckman Corporation, a pharmaceutical company, where his titles included President of Research and Development of SmithKline and French Laboratories. Dr. Crooke served on the board of directors of Akcea Therapeutics, Inc. from January 2015 through October 2018.

In June 2021, Dr. Crooke stepped down from the Board and began serving as a Strategic Advisor to the Company, providing strategic advice and continuing to participate in the Company's scientific activities. Ionis thanks Dr. Crooke for his 32 years of service to the Company as its founder, former Chief Executive Officer and Executive Chairman of the Board.



Peter N. Reikes, age 61, served as a Director of Ionis from September 2018 until November 2021. Since November 2021, Mr. Reikes has served as Senior Advisor to the U.S. Food and Drug Administration. From July 2021 to November 2021, Mr. Reikes served as Senior Advisor to Stifel, Nicolaus & Company, Inc. and from December 2010 until July 2021 as Vice Chairman in the Investment Banking Division at Stifel. Prior to joining Stifel, he spent 11 years at Cowen and Company, LLC, where he was Vice Chairman and Head of Healthcare Investment Banking, and over 14 years at PaineWebber Incorporated, where he was a Managing Director and Head of Healthcare Investment Banking and began his career in 1985. Over the course of his extensive career in investment banking, Mr. Reikes has completed a wide range of financing and merger and acquisition transactions for companies in the life sciences, medical technology, and healthcare services sectors. Mr. Reikes is also a director of the Heart & Soul Foundation, an organization that supports a range of community service programs in the greater New York City area. Mr. Reikes is a former director of Ricerca Biosciences, LLC, Biocompatibles, Ltd., and the affiliated partnership boards of Alkermes, Inc., Cephalon, Inc., Gensia, Inc., Genzyme Corporation and Repligen Corporation, as well as the Institute for Quality Improvement of the Accreditation Association for Ambulatory Health Care. Mr. Reikes received his B.A. in Economics from the University of California at Los Angeles and his M.B.A. in Finance from The Wharton School at the University of Pennsylvania.

In November 2021, Mr. Reikes resigned as a Director of Ionis because he accepted a position with the U.S. Food and Drug Administration that required him to step off the Company's Board to avoid a perception of a conflict of interest. The Company thanks Mr. Reikes for his advice and leadership as a member of the Company's Board and wishes Mr. Reikes success in his new endeavor.



Independence of the Board of Directors

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

Consistent with these considerations, after review of all relevant transactions or relationships between each Director, or any of his or her family members, and Ionis, its senior management and its independent auditors, the Board affirmatively has determined that all of our Directors are independent Directors within the meaning of the applicable Nasdaq listing standards and SEC rules and regulations, except for Ms. Parshall and Dr. Monia, our former Chief Operating Officer, and current Chief Executive Officer, respectively. In making this determination, the Board found that none of these independent Directors has a material or other disqualifying relationship with us. Notably, Mr. Muto has retired from Cooley LLP, Ionis' outside counsel. Also, although the Company does business with Goldman Sachs & Co. and Brigham and Women's Hospital, neither Mr. Wender nor Dr. Lozcalzo, respectively, receives any personal compensation directly from revenue received from Ionis.

Information Regarding the Board and its Committees

Leadership Structure

Until January 2020, our Chief Executive Officer was the Chairman of the Board. In January 2020, Dr. Monia assumed the position of Chief Executive Officer and Dr. Crooke transitioned to Executive Chairman of the Board. Following the 2021 Annual Meeting of Stockholders, Dr. Crooke stepped down from the Board and began serving as a Strategic Advisor to the Company, providing strategic advice and continuing to participate in the Company's scientific activities. In June 2021, Dr. Loscalzo was appointed Chairman of the Board.

In December 2020, the Board appointed Mr. Wender as the Independent Lead Director of the Board. The Board believes that the appointment of an Independent Lead Director and the separated roles of Chairman of the Board and Chief Executive Officer reinforce the independence of the Board in its oversight of the business and affairs of the Company.

Risk Oversight

Our Board administers its risk oversight function directly and through all of its current committees. We provide a complete description of each committee and its respective roles and responsibilities on pages 20 through 24 of this Proxy Statement. While each of these committees is responsible for evaluating certain risks and overseeing how we manage risk, these committees inform the entire Board about such risks through committee reports.

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

The Nominating, Governance and Review Committee manages risks associated with the independence of the Board and potential conflicts of interests at the Board level, and periodically reviews our policies and procedures and makes recommendations when appropriate. The Compensation Committee reviews risks to the Company related to our executive compensation program and our general compensation philosophies. The Finance Committee evaluates risks to the Company associated with our corporate finance matters. The Science/Medical Committee identifies risks to the Company related to our technology platform. The Compliance Committee is responsible for evaluating risks to the Company in connection with the commercialization of our medicines and good practice guidelines and regulations.

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



Board Committees

The Board had six committees as of December 31, 2021: an Audit Committee, a Compensation Committee, a Nominating, Governance and Review Committee, a Science/Medical Committee, a Finance Committee, and a Compliance Committee. On March 26, 2021, the Board dissolved the Agenda Committee and formed the Compliance Committee. Below is a description of each committee of our Board. Each of the committees has authority to engage legal counsel or other experts or consultants as it deems appropriate to carry out its responsibilities. The Board has determined that each member of our Audit Committee, Compensation Committee, and Nominating, Governance and Review Committee:

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

Meetings and Attendance; Committee Members

The Board met six times in 2021. Each Director serving as of December 31, 2021 attended 75% or more of the aggregate number of meetings of the Board and the committees on which such Director served during 2021. 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 each of the Board committees in 2021.

Name	Agenda ⁽¹⁾	Audit	Compensation	Nominating, Governance and Review	Compliance ⁽²⁾	Science/ Medical**	Finance	Attended 2021 Annual Meeting
Dr. Spencer R. Berthelsen	--	--	X*	X	--	X	--	--
Breaux B. Castleman ⁽³⁾	--	X	--	--	--	--	--	--
Stanley T. Croke ⁽⁴⁾	X*	--	--	--	--	--	--	--
Ms. Allene M. Diaz ⁽⁵⁾	--	--	--	--	X	--	--	X
Dr. Michael Hayden	--	--	--	--	--	X*	--	--
Ms. Joan E. Herman	--	X	--	--	X	--	--	X
Mr. Joseph Klein, III	--	X*	--	--	--	--	--	X
Dr. Joseph Loscalzo	X	--	--	X	--	X	--	X
Dr. Brett P. Monia	X	--	--	--	--	--	--	X
Mr. Frederick T. Muto	--	X	X	X	--	--	X	--
Ms. B. Lynne Parshall	X	--	--	--	X*	--	X	--
Mr. Peter Reikes ⁽⁶⁾	X	--	--	--	--	--	X	--
Mr. Joseph H. Wender	--	--	X	X*	--	--	X*	--
Total meetings in fiscal year 2021	1	8	9	1	3	3	5	

* Committee Chairperson

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

- (1) The Agenda Committee was dissolved in March 2021.
- (2) The Compliance Committee was formed in March 2021.
- (3) Mr. Castleman did not stand for re-election at the 2021 Annual Meeting of Stockholders.
- (4) Dr. Croke resigned from the Board in June 2021.
- (5) Ms. Diaz was appointed to the Board in June 2021.
- (6) Mr. Reikes resigned from the Board in November 2021.



Audit Committee

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

The Audit Committee:

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

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

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

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

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

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

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

The Audit Committee typically meets twice each quarter: once face-to-face in connection with quarterly Board of Director meetings, and once by teleconference to review quarterly financial results and Form 10-Q or annual financial results and Form 10-K. In 2021, the Audit Committee met eight 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.

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.

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 33 through 59 of this Proxy Statement. The charter of the Compensation Committee grants the Compensation Committee full access to all of our books, records, facilities and personnel, and authority to obtain, at our expense, advice and assistance from internal and external legal, accounting or other advisors and consultants and other external resources that the Compensation Committee considers necessary or appropriate in the performance of its duties. In particular, the Compensation Committee has the sole authority to retain independent compensation consultants to help the Compensation Committee evaluate executive and Director compensation, including the authority to approve the consultants' reasonable fees and other retention terms.

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

The Compensation Committee met nine times in 2021. The Compensation Committee acted by unanimous written consent ("UWC") 22 times, which increased in 2021 due to separate UWCs for grants made pursuant to our 2020 Equity Incentive Plan for legacy Akcea employees. The Board has adopted a written Compensation Committee charter, which you can find on our corporate website at www.ionispharma.com.⁴

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

Compensation Committee Interlocks and Insider Participation

As noted above, during the fiscal year ended December 31, 2021, our Compensation Committee was composed of Dr. Berthelsen, Mr. Wender and Mr. Muto. In each case, none of the members of the Compensation Committee has ever been an employee or officer of Ionis. None of our executive officers serves as a member of the board of directors or compensation committee of any other entity that has one or more executive officers serving as a member of our Board or Compensation Committee.

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 and executive 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 one time during 2021. You can find our Nominating, Governance and Review Committee charter on our corporate website at www.ionispharma.com.⁵

Director Nominations - Approach to Board Composition

The Nominating, Governance and Review Committee believes that candidates for Director should have certain minimum qualifications. As a result, the Board adopted membership standards (that may be revised from time to time) 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;

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.

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

- members must demonstrate high personal integrity and ethics;
- members cannot serve as a director on the boards of more than five total publicly traded companies (including Ionis);
- members cannot serve more than ten consecutive three-year terms on the Board; and
- members cannot run for re-election to 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;
- being committed to vigorously representing the long-term interests of our stockholders; and
- contributing to the diversity of the Board.

Director Nominations - Diversity

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 four large categories: (1) investment banking, financial accounting, and corporate governance experience; (2) medical and scientific expertise; (3) experience with the commercialization of pharmaceutical products, and (4) employee versus non-employee Directors. By selecting individuals who have investment banking, financial accounting, and corporate governance backgrounds, we gain valuable experience that ensures we are managing our financial resources appropriately, reporting our financial results fairly and accurately, and generally running our business consistent with current good corporate practices. As a cutting-edge drug discovery and development company, we also greatly benefit from Board members who themselves are scientists and medical doctors and can help set and adjust our strategy and objectives based on the results we generate from our research and development efforts. In addition, as we advance our vision of becoming a leading fully integrated biotechnology company, we will benefit from Board members with backgrounds in the commercialization of pharmaceutical products. In different ways, these first three categories allow us to effectively manage our cash and make prudent investments in our technology to achieve the greatest likelihood of success. We have historically tried to evenly balance the Board members across the first two categories and are increasing our focus on the third category as we work towards our goal of becoming a leading fully integrated biotechnology company.

Regarding the fourth category, we believe that employee Directors can provide the Board valuable insight regarding our day-to-day operations, which can offer the Board a different perspective and help the Board make important management and compensation decisions. Our non-employee Directors can compare the opportunities and challenges presented to Ionis against the facts and circumstances they are experiencing outside Ionis. We have more non-employee Directors than employee Directors and believe that the current mix in this respect provides consistent leadership balanced with appropriate independent oversight. Additionally, the non-employee Directors regularly meet in executive session without employee Directors present.

We also value diversity on our Board and do not discriminate against nominees on the basis of gender, race, religion, national origin, sexual orientation, disability, or any other basis. Recognizing the importance of diversity on our Board, in December 2020, the Nominating, Governance and Review Committee approved authorizing the Company to begin a search for qualified Director candidates who are diverse and have commercial experience. As a result of such search, Ms. Allene Diaz, who self-identifies as a member of several underrepresented communities and has extensive experience with product development, commercial strategy, market access, and portfolio management, joined our Board in June 2021. We will continue to strive to add Directors to our Board who will provide relevant and valuable expertise while contributing to its diversity.



Board Diversity Matrix (as of February 8, 2022)				
Total Number of Directors	10			
	Female	Male	Non-Binary	Did Not Disclose Gender
Part I: Gender Identity	3	6	0	1
Part II: Demographic Self-Identification				
African American or Black	--	--	--	--
Alaskan Native or Native American	--	--	--	--
Asian	--	--	--	--
Hispanic or Latinx	1	--	--	--
Native Hawaiian or Pacific Islander	--	--	--	--
White	3	6	--	--
Two or More Races/Ethnicities	1	--	--	--
LGBTQ+	--	--	--	--
Did not disclose demographic background	--	--	--	1

Director Nominations - Process

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

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

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

Stockholder Recommendations for Directors

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

- the name, age, business address and residence address of the nominee;
- the principal occupation or employment of the nominee;
- the stock ownership in Ionis of the nominee;



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

In addition, the nominee will need to complete a written questionnaire regarding the background and qualifications of the nominee, and the background of any other person or entity on whose behalf the nomination is being made. The nominee must also agree to comply with all of our applicable publicly disclosed corporate governance, conflict of interest, confidentiality and stock ownership and trading policies and guidelines. The description of the requirements for Director nomination set forth above is qualified in its entirety by reference to our full and complete bylaws, which is an exhibit to our Current Report on Form 8-K filed with the SEC on March 29, 2021, a copy of which is available by contacting our corporate secretary. To date, the Board has not received or rejected a timely Director nominee for election at the upcoming stockholder meeting from a stockholder or stockholders holding more than 5% of our voting stock.

Agenda Committee

The primary function of the Agenda Committee of the Board was to determine the matters to be considered by the Board at each of its meetings and prepare an agenda accordingly. We dissolved the Agenda Committee as of March 26, 2021, as our Chief Executive Officer now meets with our Board Chair and Independent Lead Director to set the agendas for Board meetings. The Agenda Committee discussed in advance and set the agenda for one regularly scheduled Board meeting held in 2021 prior to its dissolution in March 2021.

Science/Medical Committee

The primary functions of the Science/Medical Committee of the Board are to focus on the key scientific and development issues facing our technology and medicines in development and help set our strategy in such areas. The Science/Medical Committee met three times in 2021.

Finance Committee

The primary function of the Finance Committee of the Board is to advise the Board on certain corporate finance matters for the Company and its subsidiaries, including capital structures, financings, investments, and share repurchase activities. The Finance Committee met five times in 2021.

Compliance Committee

The Compliance Committee was formed in March 2021 and met three times in 2021. The Compliance Committee is primarily responsible for overseeing and reviewing the Company’s healthcare compliance program and the status of the Company’s compliance with laws, regulations (including good practice guidelines and regulations), industry standards, and internal procedures. The primary function of the Committee is to oversee the development and implementation of compliance and ethics policies and practices at the Company; however, management is responsible to design and implement such policies and practices.

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, California 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 appropriate committee of the Board. One or more of our employees designated by the Board will review these communications and will determine whether to present the materials to the Board. The purpose of this screening is to allow the Board to avoid having to consider irrelevant or inappropriate communications, such as advertisements, commercial solicitations, and hostile communications. In accordance with our Code of Ethics and Business Conduct, all communications that relate to questionable accounting or auditing matters involving Ionis will be promptly and directly forwarded to the Audit Committee. Other than the processes described above, our Board has not adopted a formal written process for stockholder communications with the Board. We believe our Board’s responsiveness to stockholder communications has been excellent.



Code of Ethics and Business Conduct

We have adopted a Code of Ethics and Business Conduct that applies to all officers, Directors, and employees. We have posted our Code of Ethics and Business Conduct on our website. If we make any substantive amendments to the Code of Ethics and Business Conduct or grant any waiver from a provision of the Code of Ethics and Business Conduct to any executive officer or Director, we will promptly disclose the nature of the amendment or waiver via an 8-K filing with the SEC or on our website at www.ionispharma.com.⁶

Corporate Governance Guidelines

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

Anti-Hedging Policy and Anti-Pledging Policy

All Directors and employees, including our named executive officers, are prohibited from taking a "short" position in our stock and otherwise hedging their position in our stock against a future drop in our stock price including short sales and derivatives such as put or call options, swaps, forwards, and futures, or other inherently speculative transactions with respect to Ionis' securities at any time. In addition, we also prohibit all Directors and employees, including our named executive officers, from pledging our stock as collateral.

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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, 2021), called our “named executive officers” as disclosed in this Proxy Statement in accordance with Section 14A of the Exchange Act.

We are asking our stockholders to indicate their support for our named executive officers’ compensation as described in this Proxy Statement. This Proposal 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 2022 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 33 through 59. 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.

Unless the Board decides to modify its policy regarding the frequency of soliciting advisory votes on the compensation of our named executives, the next scheduled “say on pay” vote will be at the 2023 Annual Meeting of Stockholders. Our stockholders will be able to indicate by advisory vote at the 2023 Annual Meeting of Stockholders any change in their preference as to the frequency of future advisory votes.



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, and those that we choose not to implement as we believe they are counter to our vision and long-term stockholder value:

<p>✓ General compensation principles</p>	<p>We design our compensation structure to drive the creation of long-term shareholder value and mitigate unnecessary or imprudent business risk taking. Specifically, we:</p> <ul style="list-style-type: none"> • Use a combination of compensation vehicles that provide a balanced mix of fixed and variable cash incentives, and long-term stock incentives; • Require a 12-month minimum vesting period for equity awards; • Set explicit and demanding objectives at the beginning of each year from which we measure performance for the year; • Set a strict budget for equity awards and salary increases; • Do <i>not</i> provide perquisites for any employees; and • Do <i>not</i> provide “gross-up” payments, other than for relocation.
<p>✓ Align executive compensation with Company performance</p>	<p>We tie a significant portion of our executive officers’ compensation to Company performance. For example, we:</p> <ul style="list-style-type: none"> • Allocate over 60% of our Chief Executive Officer’s compensation in the form of performance-based compensation, which we consider to consist of cash bonuses, stock options and PRSUs; • Place a maximum limit on cash bonuses and do not guarantee a cash bonus – cash bonuses can be, and have been, zero; and • Empower our Compensation Committee with the ability to exercise downward discretion with respect to the Company Performance Factor (used to determine cash bonuses) for our executive officers based on Company performance. <ul style="list-style-type: none"> o For 2021 performance, the Compensation Committee awarded our Company’s executive officers a Company Performance Factor of 95%, and all other employees a Company Performance Factor of 110%, due to a few key Company disappointments during the year.
<p>✓ Stock ownership and holding guidelines</p>	<p>We maintain stock ownership and holding guidelines that require our executive officers and non-employee Directors to hold shares received from their RSU and PRSU grants until such officers and Directors meet certain ownership thresholds or no longer serve the Company. We increased such ownership requirements in 2021.</p>
<p>✓ Clawback policy</p>	<p>We use an executive “clawback” policy that applies to all Section 16 officers.</p>
<p>✓ Disallow hedging and pledging</p>	<p>We do not allow pledging, shorting, or hedging against our stock by Directors or employees.</p>
<p>✓ No option re-pricing or cash buyouts</p>	<p>We do not reprice or “cash-out” stock options without stockholder approval.</p>
<p>✓ Engage an independent compensation consultant</p>	<p>The Compensation Committee has retained a compensation consultant whose relationship with the Company was confirmed to be independent for 2021.</p> <p>The compensation consultant, among other things, assists us in selecting an appropriate peer group and reviewing our compensation compared to the 25th, 50th and 75th percentiles of our peer group.</p>
<p>✓ Use a “double trigger” for change of control for our executive officers</p>	<p>We use a “double trigger” for cash payments and equity acceleration for change of control for our executive officers.</p>



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.



PROPOSAL 3

RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

The Audit Committee has selected Ernst & Young LLP as our independent registered public accounting firm for our 2022 fiscal year and has requested management to ask for stockholder ratification at the Annual Meeting. Ernst & Young LLP has audited our financial statements since we were founded in 1989. Representatives of Ernst & Young LLP will be at the virtual Annual Meeting to answer any questions and make a statement should they desire to do so.

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

The affirmative vote of the holders of a majority of the shares present or represented by proxy at the Annual Meeting and entitled to vote on the matter will be required to ratify the selection of Ernst & Young LLP. Abstentions and broker non-votes will have no effect on this Proposal 3.

Independent Auditors' Fees; Pre-Approval Policies and Procedures

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

Audit Fees

For the fiscal years ended December 31, 2021 and 2020, Ernst & Young LLP billed us approximately \$1.7 million and \$2.0 million, respectively, primarily related to the integrated audit of our financial statements and reviews of our interim financial statements. In addition, Ernst & Young LLP billed us approximately \$400,000 and approximately \$90,000 in 2021 and 2020, respectively, related to corporate transactions, of which approximately \$10,000 was billed to Akcea in 2020. Additionally, for the fiscal year ended December 31, 2020, Ernst & Young LLP billed us approximately \$415,000 related to the audit of the financial statements of Akcea.

Audit Related Fees

For the fiscal years ended December 31, 2021 and 2020, there were no audit related fees billed by Ernst & Young LLP.

Tax Fees

For the fiscal years ended December 31, 2021 and 2020, Ernst & Young LLP billed us approximately \$365,000 and \$640,000 for each year, respectively, primarily related to professional services on tax projects, of which approximately \$46,000 and \$195,000 in 2021 and 2020, respectively, was related to the Akcea Merger.

All Other Fees

During the fiscal years ended December 31, 2021 and 2020, all other fees billed by Ernst & Young LLP were approximately \$4,000 and \$6,000 for each year, respectively. These fees were for a subscription to an online accounting and tax information service. The Audit Committee has determined that the rendering of all non-audit services by Ernst & Young LLP is compatible with maintaining the auditor's independence. During the fiscal year ended December 31, 2021, none of the total hours expended on our financial audit by Ernst & Young LLP were provided by persons other than Ernst & Young LLP's employees.

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



SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of March 1, 2022 by:

- each Director and nominee for Director;
- each named executive officer;
- all Directors and executive officers as a group; and
- every entity that we know beneficially owns more than five percent of our common stock.

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

Beneficial Owner	Beneficial Ownership ⁽¹⁾	
	Number of Shares	Percent of Total ⁽²⁾
FMR LLC ⁽³⁾ 245 Summer Street Boston, MA 02210	21,181,502	14.95%
T. Rowe Price Associates, Inc. ⁽⁴⁾ 100 E. Pratt Street Baltimore, MD 21202	12,490,280	8.82%
The Vanguard Group ⁽⁵⁾ 100 Vanguard Boulevard Malvern, PA 19355	12,007,076	8.47%
BB Biotech AG ⁽⁶⁾ Schwertstrasse 6 CH-8200, Schaffhausen Switzerland	10,232,973	7.22%
BlackRock, Inc. ⁽⁷⁾ 55 East 52 nd Street New York, NY 10055	8,539,282	6.03%
Spencer R. Berthelsen ⁽⁸⁾	228,219	*
Allene M. Diaz	--	--
Michael Hayden ⁽⁹⁾	58,222	*
Joan Herman ⁽¹⁰⁾	52,000	*
Joseph Klein, III ⁽¹¹⁾	94,227	*
Joseph Loscalzo ⁽¹²⁾	144,474	*
Frederick T. Muto ⁽¹³⁾	152,349	*
B. Lynne Parshall ⁽¹⁴⁾	438,242	*
Joseph H. Wender ⁽¹⁵⁾	192,971	*
Joseph Baroldi ⁽¹⁶⁾	3,935	*
Frank Bennett ⁽¹⁷⁾	273,336	*
Onaiza Cadoret-Manier ⁽¹⁸⁾	54,105	*
Richard Geary ⁽¹⁹⁾	267,611	*
Elizabeth L. Hougen ⁽²⁰⁾	289,899	*
Brett Monia ⁽²¹⁾	477,329	*
Patrick R. O'Neil ⁽²²⁾	206,042	*
Eugene Schneider ⁽²³⁾	142,213	*
Eric Swayze ⁽²⁴⁾	148,869	*
All Directors and executive officers as a group (eighteen persons) ⁽²⁵⁾	3,346,015	2.36%



*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 141,692,055 shares of common stock outstanding on March 1, 2022, adjusted as required by rules promulgated by the SEC.
- (3) FMR LLC has sole voting power to direct the vote of 8,799,662 shares and sole power to dispose or direct the disposition of 21,181,502 shares. The Fidelity Growth Company Commingled Pool holds the interest of 8,795,680 shares of our common stock, which amounts to 6.21% of our total outstanding as of March 1, 2022.

Abigail P. Johnson is a Director, the Chairman, and the Chief Executive Officer of FMR LLC. Members of the Johnson family, including Abigail P. Johnson, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders' voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders' voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC.

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

- (4) T. Rowe Price Associates, Inc. has sole voting power to direct the vote of 4,094,894 shares and sole power to dispose or direct the disposition of 12,490,280 shares.
- (5) The Vanguard Group has shared voting power to direct the vote of 79,445 shares, sole power to dispose or direct the disposition of 11,806,525 shares, and shared dispositive power for 200,551 shares.
- (6) BB Biotech AG shares voting and dispositive powers for its shares with Biotech Invest N.V.
- (7) BlackRock, Inc. is a parent holding company and various persons have the right to receive or the power to direct the receipt of dividends from, or the proceeds from the sale of shares of our common stock. BlackRock has sole voting power to direct the vote of 8,147,677 shares and sole power to dispose or direct the disposition of 8,539,282 shares.
- (8) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 118,500 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before April 30, 2022.
- (9) Includes 44,000 shares of common stock issuable upon exercise of options held by Dr. Hayden that are exercisable on or before April 30, 2022.
- (10) Includes 36,000 shares of common stock issuable upon exercise of options held by Ms. Herman that are exercisable on or before April 30, 2022.
- (11) Includes 100 shares of common stock beneficially owned by Mr. Klein's son, 6,000 shares held in trusts for the benefit of Mr. Klein's three children, and 76,000 shares of common stock issuable upon exercise of options held in trusts for the benefit of Mr. Klein's three children that are exercisable on or before April 30, 2022.
- (12) Includes 118,500 shares of common stock issuable upon exercise of options held by Dr. Loscalzo that are exercisable on or before April 30, 2022.
- (13) Includes 1,500 shares of common stock beneficially owned through the Cooley LLP Salary Deferral and Profit Sharing Plan and 110,500 shares of common stock issuable upon exercise of options held by Mr. Muto that are exercisable on or April 30, 2022.
- (14) Includes 360,762 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 30, 2022.
- (15) Includes 96,971 shares of common stock held by Mr. Wender in a trust, and 96,000 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 30, 2022.



- (16) No shares of common stock are issuable upon exercise of options held by Mr. Baroldi that are exercisable on or before April 30, 2022.
- (17) Includes 218,103 shares of common stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before April 30, 2022.
- (18) Includes 45,723 shares of common stock issuable upon exercise of options held by Ms. Cadoret-Manier that are exercisable on or before April 30, 2022.
- (19) Includes 211,238 shares of common stock issuable upon exercise of options held by Dr. Geary that are exercisable on or before April 30, 2022.
- (20) Includes 231,540 shares of common stock issuable upon exercise of options held by Ms. Hougen that are exercisable on or before April 30, 2022.
- (21) Includes 388,312 shares of common stock issuable upon exercise of options held by Dr. Monia that are exercisable on or before April 30, 2022.
- (22) Includes 164,714 shares of common stock issuable upon exercise of options held by Mr. O’Neil that are exercisable on or before April 30, 2022.
- (23) Includes 128,453 shares of common stock issuable upon exercise of options held by Mr. Schneider that are exercisable on or before April 30, 2022.
- (24) Includes 128,138 shares of common stock issuable upon exercise of options held by Dr. Swayze that are exercisable on or before April 30, 2022.
- (25) Includes an aggregate of 2,476,483 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, 2022.

Delinquent Section 16(a) Reports

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

To our knowledge, based on a review of Section 16 reports submitted on EDGAR and written representations from the reporting persons that no Form 5s were required, during the fiscal year ended December 31, 2021, our officers, Directors and greater than ten percent beneficial owners complied with all applicable Section 16(a) filing requirements.

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, 2021:

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options	Weighted Average Exercise Price of Outstanding Options	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders ⁽¹⁾	14,088,816	\$ 54.04	11,102,267 ⁽²⁾
Equity compensation plans not approved by stockholders	--	--	--
Total	14,088,816	\$ 54.04	11,102,267 ⁽²⁾

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

(2) Of these shares, 588,529 remained available for purchase under the ESPP as of December 31, 2021.



Compensation Discussion and Analysis

2021 NEOs, 2021 “Say on Pay” Vote and Summary of Recent Compensation and Governance Changes

Named Executive Officers. At December 31, 2021, our Chief Executive Officer, Chief Financial Officer, and our three other most highly compensated executive officers, called our “named executive officers” were as follows:

Name	Title
Brett P. Monia	Chief Executive Officer
Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer
Patrick R. O’Neil	Executive Vice President, Chief Legal Officer and General Counsel
Onaiza Cadoret-Manier	Executive Vice President, Chief Global Product Strategy and Operations Officer ⁸
Eric E. Swayze	Executive Vice President, Research

“Say on Pay” Vote. In June 2021, we held a stockholder advisory vote on the compensation of our named executive officers. Our stockholders overwhelmingly approved, on an advisory basis, the compensation of our named executive officers, with approximately 90% of stockholder votes cast in favor of our “say on pay” resolution. In evaluating our general compensation practices during fiscal 2021 and in early 2022, we were mindful of the strong support our stockholders expressed for our compensation philosophies and practices; however, we remain committed to considering stockholder feedback on an ongoing basis and ensuring that our compensation practices align with market trends. As a result, the Compensation Committee retained our general approach to executive compensation as in the prior fiscal year, but to more directly tie executive compensation with stock price performance, the Compensation Committee increased the allocation of PRSU awards from 20% to 33% of our CEO’s total equity awards and implemented PRSU awards for our other Section 16 officers beginning in 2022. The Compensation Committee will continue to consider stockholder feedback in the future.

Recent Compensation and Governance Changes. We have recently made several notable compensation and governance-related changes that we believe appropriately address feedback we have received or continue to align the Company with peer companies and incentivize management to enhance long-term stockholder value. Specifically, as discussed in greater detail in the pages that follow, we:

- implemented performance-based equity awards for our CEO in 2020, and in 2022, increased the allocation of such awards from 20% to 33% of his total equity awards;
- implemented performance-based equity awards for our other executive officers in 2022, accounting for 20% of their total equity awards;
- increased the ownership requirements in our stock ownership and holding guidelines applicable to our executive officers and non-employee Directors;
- expanded our executive clawback policy to apply to all Section 16 officers;
- codified compensation for non-employee Directors in a written compensation policy;
- reduced the size of the annual equity awards for non-employee Directors, and had our shareholders approve such reduced equity awards as part of the amended and restated Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors’ Stock Option Plan; and
- adopted a policy for equity awards granted to non-employee Directors whereby the Compensation Committee, with input from its independent compensation consultant, may reduce the number of shares to be automatically issued on a grant date for each such award so that the awards granted have an aggregate grant date fair value that is aligned with the set of peer companies the Compensation Committee uses to evaluate compensation.

⁸ Prior to March 6, 2022, Ms. Cadoret-Manier’s title was Executive Vice President, Chief Corporate Development and Commercial Officer.

Overview. We are a leader in RNA-targeted therapeutics. We believe our medicines, which are based on our novel antisense technology, have the potential to pioneer new markets, change standards of care and transform the lives of people with devastating diseases.

Our Focus. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming a leading, fully integrated biotechnology company. To achieve our vision, we are focused on building the Ionis commercial pipeline, expanding and diversifying our technology and delivering an abundance of new medicines to the market.

Our Medicines and Technology. Ionis was created with the belief that we could find a better way to design and develop medicines to address diseases that traditional pharmaceutical approaches could not address. This belief, and our unwavering commitment to the scientific process, has enabled us to discover and develop medicines that we believe will fundamentally change the standards of care across a wide range of disease.

We currently have three marketed medicines - SPINRAZA, TEGSEDI and WAYLIVRA. We also have a rich mid- and late-stage pipeline of medicines, primarily focused on our cardiovascular and neurology franchises. In 2021, we continued to advance and expand our Phase 3 pipeline with the achievement of key enrollment milestones for eplontersen and pelacarsen, and the addition of two new Phase 3 programs for olezarsen and donidalorsen, bringing us to six medicines in Phase 3 development addressing eight indications. Our mid-stage pipeline also continued to perform well, with positive data readouts from several medicines, including donidalorsen, IONIS-MAPT_{RX} and IONIS-AGT-L_{RX}. We also continued to invest in advancing and expanding the reach of our technology to ensure we remain innovative and competitive. For example, in 2021 we obtained exclusive rights to Bicycle Therapeutic's peptide technology to expand the capabilities of our Ligand Conjugated Antisense ("LICA") technology.

Our Commercial Vision. Our commercial vision is centered on maximizing the value of our innovative medicines. As a result, we are focused on commercializing medicines primarily within our cardiovascular and neurologic disease franchises. We also plan to commercialize medicines from our emerging specialty rare pipeline that address underserved medical needs and provide an attractive market opportunity. Today, we have three near-term commercial opportunities, eplontersen, olezarsen and donidalorsen, which we are advancing towards the market. In 2021, we entered into an agreement with AstraZeneca to jointly develop and commercialize eplontersen, which we believe positions eplontersen to maximize value for patients and shareholders while also enabling us to bolster our commercial organization and accelerate our preparations for our near-term product launches. We are focused on go-to-market execution in the U.S. for our near-term commercial opportunities. As a result, we have begun building our commercial capabilities, including through the merger of Akcea Therapeutics.

Our Financial Strength. Our financial strength has been an enduring quality of Ionis for many years. Our multiple sources of revenue and our strong balance sheet enable us to invest in our strategic priorities to build our commercial pipeline, expand and diversify our technology and deliver new medicines to the market. By continuing to focus on these priorities, we believe we are well positioned to drive future growth and to deliver increasing value for patients and shareholders.

We are a leader in RNA-targeted therapeutics. We believe our medicines, which are based on our novel antisense technology, have the potential to pioneer new markets, change standards of care and transform the lives of people with devastating diseases.

Our multiple sources of revenue and strong balance sheet enable us to invest in our strategic priorities, which we believe will position us to drive future growth and deliver increasing value for patients and shareholders.



Our accomplishments last year led us to exceed our 2021 financial guidance, achieve revenues of \$810 million and end the year with \$2.1 billion in cash. For the sixth year in a row, Ionis was profitable on a non-GAAP⁹ basis.

\$810 million in revenue

Numerous diverse sources

\$116 million in net income*

Continued financial strength

\$695 million in operating expenses*

Investments in advancing our medicines and our technology

\$2.1 billion of cash

Enabling accelerating investments in 2022

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

⁹ We use “non-GAAP” in place of “pro-forma” when discussing our financial results that exclude non-cash compensation expense related to equity awards, costs related to the Akcea Merger, and costs related to our restructured commercial operations and the related tax effects because we believe that non-GAAP financial results better represent the economics of our business and how we manage our business. For a detailed reconciliation of non-GAAP and GAAP measures, see our earnings release reporting fourth quarter and full year 2021 financial results available [here](#).



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, and those we choose not to implement as we believe they are counter to our vision and building long-term stockholder value.

<p>✓ General compensation principles</p>	<p>We design our compensation structure to drive the creation of long-term shareholder value and mitigate unnecessary or imprudent business risk taking. Specifically, we:</p> <ul style="list-style-type: none"> • Use a combination of compensation vehicles that provide a balanced mix of fixed and variable cash incentives, and long-term stock incentives; • Require a 12-month minimum vesting period for equity awards; • Set explicit and demanding objectives at the beginning of each year from which we measure performance for the year; • Set a strict budget for equity awards and salary increases; • Do <u>not</u> provide perquisites for any employees; and • Do <u>not</u> provide “gross-up” payments, other than for relocation.
<p>✓ Align executive compensation with Company performance</p>	<p>We tie a significant portion of our executive officers’ compensation to Company performance. For example, we:</p> <ul style="list-style-type: none"> • Allocate over 60% of our Chief Executive Officer’s compensation in the form of performance-based compensation, which we consider to consist of cash bonuses, stock options and PRSUs; • Place a maximum limit on cash bonuses and do not guarantee a cash bonus – cash bonuses can be, and have been, zero; and • Empower our Compensation Committee with the ability to exercise downward discretion with respect to the Company Performance Factor (used to determine cash bonuses) for our executive officers based on Company performance. <ul style="list-style-type: none"> o For 2021 performance, the Compensation Committee awarded our Company’s executive officers a Company Performance Factor of 95%, and all other employees a Company Performance Factor of 110%, due to a few key Company disappointments during the year.
<p>✓ Stock ownership and holding guidelines</p>	<p>We maintain stock ownership and holding guidelines that require our executive officers and non-employee Directors to hold shares received from their RSU and PRSU grants until such officers and Directors meet certain ownership thresholds or no longer serve the Company. We increased such ownership requirements in 2021.</p>
<p>✓ Clawback policy</p>	<p>We use an executive “clawback” policy that applies to all Section 16 officers.</p>
<p>✓ Disallow hedging and pledging</p>	<p>We do not allow pledging, shorting, or hedging against our stock by Directors or employees.</p>
<p>✓ No option re-pricing or cash buyouts</p>	<p>We do not reprice or “cash-out” stock options without stockholder approval.</p>
<p>✓ Engage an independent compensation consultant</p>	<p>The Compensation Committee has retained a compensation consultant whose relationship with the Company was confirmed to be independent for 2021.</p> <p>The compensation consultant, among other things, assists us in selecting an appropriate peer group and reviewing our compensation compared to the 25th, 50th and 75th percentiles of our peer group.</p>
<p>✓ Use a “double trigger” for change of control for our executive officers</p>	<p>We use a “double trigger” for cash payments and equity acceleration for change of control for our executive officers.</p>



Compensation Overview and the Role of the Compensation Committee

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

The Compensation Committee's responsibilities include:

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

Independent Compensation Consultant

The Compensation Committee has the authority and budget to hire an independent compensation consultant as it deems necessary. The Compensation Committee has retained Aon's Human Capital Solutions practice, a division of Aon plc (formerly known as Radford) ("Aon") as its independent compensation consultant. For 2021, Aon primarily provided the Compensation Committee advice in the following areas:

- assessing Board of Directors compensation;
- selecting the 2021 Executive Peer Group;
- reviewing the mix of stock options and RSUs for all employees;
- assessing the bonus plan for employees below director level;
- evaluating the pay and equity mix for our executive officers;
- assessing executive officer compensation;
- evaluating our named executive officers' equity awards;
- performing the valuation calculations for our CEO's PRSU awards that vested and paid out in 2021; and
- reviewing our executive stock ownership guidelines.

Compensation Consultant Fees

As described above, the Compensation Committee has engaged Aon to provide the committee with peer company and industry compensation data and advice regarding executive officers' compensation. In 2021, we paid Aon approximately \$115,000 for Aon's consulting services directly related to Compensation Committee support.



In addition, management of the Company engaged affiliates of Aon for other services in 2021 that were not related to Aon's Compensation Committee consulting services. Our human resources department obtained general benchmarking survey data from an affiliate of Aon, for which we paid approximately \$23,000 in 2021. Additionally, our Finance department engaged an affiliate of Aon for insurance brokerage services, for which we paid approximately \$590,000 in 2021. Although the Compensation Committee was aware of the nature of these additional services, the committee did not review and approve such services, insurance premiums or policies, as those were reviewed and approved by management in the ordinary course of business.

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

Compensation Philosophy

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



Pay for Performance. We incorporate a number of features into our compensation structure to mitigate the risk that our compensation policies and practices could encourage unnecessary or imprudent business risk taking. We use a combination of compensation vehicles that provide a balanced mix of fixed and variable cash incentives, and long-term stock incentives. Our Performance Management By Objective (“MBO”) awards are not guaranteed (i.e., are 100% at risk) and include a multiplier, or performance factor, based on Ionis’ and the employee’s performance (respectively, the “Company Performance Factor” and the “Individual Performance Factor”). Therefore, if *either* Ionis or the employee performs poorly, the Performance MBO can be, and has been, zero. For example, for 2021 performance, the Compensation Committee exercised downward discretion with respect to the Company Performance Factor for our executive officers based on Company performance and awarded our Company’s executive officers a Company Performance Factor of 95%, and all other employees a Company Performance Factor of 110%, due to a few key Company disappointments during the year.



Based on stockholder feedback, beginning in 2020, we added performance-based restricted stock unit (“PRSU”) awards to our Chief Executive Officer’s compensation, and increased the proportion of such awards for our CEO’s total equity awards beginning in 2022. Additionally, in 2022, we added PRSU awards to the compensation of our other executive officers. These PRSU awards provide our executive officers the opportunity to earn a defined number of shares of our common stock if we achieve pre-determined performance goals. Beginning in 2022, at target level of achievement, the PRSU awards represent 33% of our CEO’s total equity awards and 20% of each other executive officer’s total equity awards. We believe these PRSU awards provide a challenging incentive to the executive officers to significantly grow the Company.

Beginning in 2022, at target level of achievement, the PRSU awards represent 33% of our CEO’s total equity awards and 20% of each other executive officer’s total equity awards.

One third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (*i.e.*, the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant; the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant; and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on the Company’s relative total shareholder return (“TSR”) as compared to a peer group of companies and as measured, in each case, at the end of the applicable performance period. The key elements of the PRSUs are as follows:

- No number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 150% of the target number depending on the Company’s relative TSR;
- If the Company’s TSR is negative over the applicable performance period, the payout will not exceed 100% of the target number for that performance period; and
- Performance below the threshold level results in a payout of zero shares, performance at the threshold level (25th percentile) results in a payout of 50% of target shares, performance at the target level (50th percentile) results in a payout of 100% of target shares, and performance at the maximum level (75th percentile) results in a payout of 150% of target shares.

No number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 150% of the target number depending on the Company’s relative TSR.

For the second performance period of the PRSU award that was granted to Dr. Monia in January 2020, Ionis’ TSR was -47.56%, which ranked 54 out of the 186 companies in the peer group under the PRSU award, or approximately the 29th percentile. Based on performance at approximately the 29th percentile as of January 15, 2022, the final number of units earned for the second performance period of the PRSU award granted to Dr. Monia in January 2020 was below target at 58.06% of the target number for the performance period.

For the first performance period of the PRSU award that was granted to Dr. Monia in January 2021, Ionis’ TSR was -47.82%, which ranked 107 out of the 263 companies in the peer group under the PRSU award, or approximately the 41st percentile. Based on performance at approximately the 41st percentile as of January 15, 2022, the final number of units earned for the first performance period of the PRSU award granted to Dr. Monia in January 2021 was below target at 81.37% of the target number for the performance period.

As mentioned above, we previously considered stockholder feedback regarding the need to include performance awards that directly align the executive officer’s interests with those of our shareholders and implemented PRSU awards for our executive officers. We structured the PRSU awards to pay out based on relative TSR, which we believe is the best way to directly tie performance that positively impacts shareholders with the payout that the executive officers receive at the end of the performance period. Since relative TSR awards are subject to a different form of valuation under ASC Topic 718, and often that accounting fair value is higher due to capturing the potential upside of the award on the grant date rather than the vesting date, the value of these awards will fluctuate year-over-year depending on the economic inputs included in these valuations.

Since relative TSR awards are subject to a different form of valuation under ASC Topic 718, and often that accounting fair value is higher due to capturing the potential upside of the award on the grant date rather than vesting, the value of these awards will fluctuate year-over-year depending on the economic inputs included in these valuations.

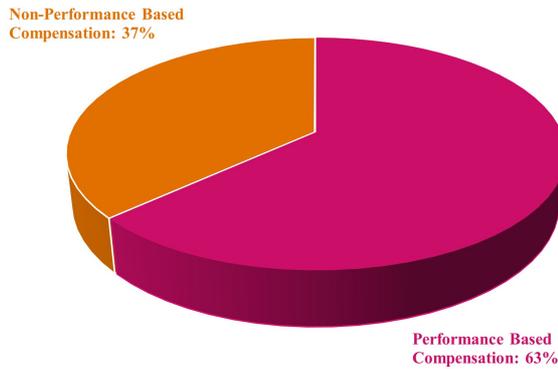


2021 NEO Compensation: Performance Based vs. Non-Performance Based

We are committed to ensuring that a significant portion of our NEOs' compensation is tied to Company performance. The charts below illustrate the proportion of our CEO's and average NEOs' (excluding the CEO) 2021 total compensation that was allocated among performance based compensation and non-performance based compensation. We consider cash bonuses, stock options and PRSUs to be performance based compensation, as the realization of the amount of such bonuses, and value of such options and PRSUs, are directly related to one or more measures of Company performance.

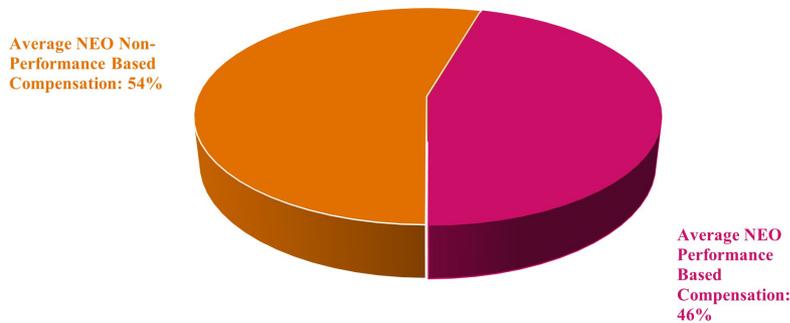
2021 CEO Compensation: Performance Based vs. Non-Performance Based

The performance based compensation reflected below includes the CEO's cash bonus for 2021 performance (\$469,300), fair value of stock options granted in 2021 (\$3,919,810) and fair value of PRSU awards granted in 2021 (\$3,984,360). The non-performance based compensation reflected below includes the CEO's 2021 base salary (\$800,000) and fair value of RSU awards granted in 2021 (\$4,081,860).



2021 Average NEO Compensation: Performance Based vs. Non-Performance Based

The performance based compensation reflected below includes the NEOs' (excluding the CEO) average cash bonus for 2021 performance (\$236,219) and average fair value of stock options granted in 2021 (\$1,488,850). The non-performance based compensation reflected below includes the NEOs' (excluding the CEO) average 2021 base salary (\$509,362) and fair value of RSU awards granted in 2021 (\$1,550,399). Beginning in 2022, the NEOs (excluding the CEO) receive 20% of their total equity awards in the form of PRSUs.



Internal Pay Equity

We are committed to paying our employees fairly, regardless of their gender, race, or other personal characteristics. To achieve this commitment, we benchmark and evaluate pay based on market data and consider factors such as an employee's role and experience, an employee's performance and internal equity. We also regularly review our compensation practices, both in terms of our overall workforce and individual employees, to ensure our pay is fair and equitable. In 2021, we engaged an independent third-party expert to perform a pay equity analysis that reviewed pay equity by gender, race and age. We plan to continue to engage a third-party expert to review pay equity every two to three years, as we determine necessary.

In 2021, we engaged an independent third-party expert to perform a pay equity analysis that reviewed pay equity by gender, race and age.

An executive officer's salary plus bonus represents the officer's total cash compensation. Our philosophy has been to have the CEO's total cash compensation be between 20-30 times the lowest levels of compensation received by an employee. Historically, the total cash compensation of our CEO over a rolling three-year period has been on average approximately 30 times that of the average cash compensation for our lowest level employees, and two to three times greater than the average of that of our other executive officers. Our CEO's total cash compensation over the last three years was on average approximately 22 times greater than the average cash compensation for our lowest level employees, and 1.76 times greater than the average of that of our other executive officers.

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



Overview of Our Compensation Program

Drug discovery and development across a portfolio of many medicines 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.

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

We structure our corporate objectives so they are results driven rather than task driven. We have historically included a number of objectives that are based on achieving positive data in the clinic, and as our strategy to commercialize medicines from our wholly owned pipeline has evolved, we have added objectives that are based on achieving sales or revenue targets. For example, in 2021 we had a key corporate objective to achieve certain pipeline goals with measures to (i) keep several medicines on track for scheduled data readouts, (ii) advance two medicines into Phase 3 clinical trials, (iii) achieve at least five positive Phase 2 proof of concept outcomes, and (iv) initiate at least four Phase 2 clinical trials. We also had a key corporate objective in 2021 to meet our financial goals with a measure being to achieve a specified revenue target for our commercial medicines. Results driven objectives only reward our employees if the data are positive or the sales efforts are successful – we do this to encourage the prudent spending of stockholder money on development and commercialization decisions. In other words, we want to structure our objectives to reward success based on judgment, rather than the making of “bad bets.”

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

Importance of Tenure; Our Investment in Knowledge-Rich Employees

It takes a significant period of time and a substantial investment to recruit and develop employees who possess the experience and talent necessary to lead at Ionis given our transformative technology, deep drug development pipeline and emerging commercial business. 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. The principles below outline our general approach to achieving this objective:

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

- Long tenure among a dedicated and highly skilled workforce, combined with the highest performance standards, contributes to our leadership in the industry and serves the interests of stockholders.
- Our focus on retention is coupled with a strong belief that executive talent most often should be developed and promoted from within Ionis.
 - The long tenure of high-performing executive officers reflects this strategy at all levels of the organization. Our executive officers who served as of December 31, 2021 have on average approximately 21 years and individually as much as over 32 years of tenure at Ionis.
- The Company has carefully evaluated and selected each of our executive officers through a rigorous performance assessment process over a long career. In their current assignments, they remain subject to a challenging annual performance assessment in which they must continue to meet the highest standards or be reassigned or separated from the Company.

To recognize our employees, including our named executive officers, who deliver long-term productivity to the Company, Ionis has implemented two awards. In 2019, we implemented the “Lifetime Achievement Award” (which we renamed to “Career Achievement Award” in 2022) to recognize our distinguished, long-tenured, senior-level contributors, including Board members, who made extraordinary contributions that helped determine the Company’s future, with a \$50,000 cash award. In 2018, we implemented the “Commitment to Ionis Award” to thank employees for their commitment to the Company. The amount of the Commitment to Ionis Award correlates to the employee’s length of service with the Company and is paid on the employee’s milestone anniversary. The table below shows the Commitment to Ionis award for each corresponding milestone anniversary. In 2021, we added 15-year and 25-year milestone anniversaries for which Commitment to Ionis Awards will be awarded. When we implemented this award in 2018, every employee with five or more years of service who was not scheduled to receive a Commitment to Ionis Award in 2018 or 2019 received a one-time “catch-up” award for one-half of the amount of the milestone award immediately preceding his or her actual length of service. Similarly, when we added the 15-year and 25-year milestone anniversaries, every employee who had a 15-year or 25-year service anniversary between 2018 and 2021 received a one-time “catch-up” award in 2022 for one-half of the amount of the applicable milestone award. In 2021, Mr. O’Neil was awarded a Commitment to Ionis Award to recognize his 20 years of service to Ionis.

Years of Service	Award
5	\$5,000
10	\$10,000
15	\$15,000
20	\$20,000
25	\$25,000
30	\$30,000
35	\$35,000
40	\$40,000

Elements of Executive Compensation

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

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

Our executive officers’ total compensation consists of four elements:

- (1) base salary;
- (2) Performance MBO – performance-based, at-risk cash compensation, *no portion of which is guaranteed*;
- (3) stock-based compensation, including performance-based restricted stock unit awards, **which are granted annually in each January following the performance year for which such grants are awarded**; and
- (4) the same benefits, including 401(k) matching, that we provide to all employees.

The PRSU awards are the only element that do not apply to all employees.

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

- Company-wide performance, including achievement of pre-established corporate objectives;
- the Compensation Committee’s assessment of our CEO’s and executive officers’ individual performance;
- competitive compensation practices;
- increased efficiencies and process improvements;

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

- 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.

Executive Peer Group

The Compensation Committee considers relevant market pay practices when setting executive compensation to ensure our ability to recruit and retain high performing talent. As such, the Compensation Committee compares the compensation opportunity for our executive officers to similarly situated executives at the 25th, 50th and 75th percentiles of the Executive Peer Group as a "market check" to ensure, in its judgment, that the executive officers' compensation remains appropriate. While the Compensation Committee uses these data to inform and shape decision-making, it does not strictly adhere to quantitative benchmarks. The Executive Peer Group data is just one factor considered in the annual compensation approval process, in addition to the factors described above under "Elements of Executive Compensation."

The Compensation Committee, in consultation with its independent compensation consultant, evaluated and selected a peer group of 18 life science companies for evaluating Ionis' 2021 compensation (the "Executive Peer Group"). The Compensation Committee reviews the compensation of our named executive officers against the Executive Peer Group's executive compensation to ensure that our compensation is competitive and to inform and shape its decision-making when setting compensation.

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

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

The Executive Peer Group generally does not include companies headquartered outside the United States (because compensation and benefit practices are generally different outside the United States, the comparable compensation data for the named executive officers is not available and cost of living is different) or companies in industries whose compensation programs are not comparable to our programs, such as non-life science companies. Although BeiGene is headquartered in China, it is suitable to include in our Executive Peer Group because its leadership team is located in the United States and the company maintains a traditional American compensation program.

In June 2021, the Compensation Committee reviewed the Executive Peer Group using the criteria listed above and publicly available data as of May 2021. The Compensation Committee noted Ionis' market capitalization was approximately \$6 billion and trailing 12-month revenue was approximately \$729 million. As part of this process, the Compensation Committee looked at companies in Ionis' industry with an emphasis on companies with market capitalizations of between \$2 billion and \$20 billion, and revenue between \$375 million and \$2 billion. The Compensation Committee also looked at companies that identified Ionis as a peer, so called "reverse peers." Based on this evaluation, the Compensation Committee added PTC Therapeutics and Ultragenyx Pharmaceutical to the Executive Peer Group, as both of these companies fell within the target market capitalization and revenue ranges, were in Ionis' sector, and were identified as "reverse peers." Additionally, the Compensation Committee removed Intercept Pharmaceuticals because it fell below the target market capitalization and revenue ranges and Seagen because it fell above such ranges.

The following table lists the companies in the 2021 Executive Peer Group, along with Ionis' rankings among these companies, based on market capitalization and financial data reported by each company at the time the Compensation Committee selected the Executive Peer Group in June 2021.



Company (ticker)	Annual Revenues (in millions) ⁽¹⁾	Market Capitalization (in millions) ⁽²⁾	Stage of Lead Drug
Acadia Pharmaceuticals (ACAD)	\$441.8	\$3,411.0	Market
Agios Pharmaceuticals (AGIO)	\$203.2	\$3,782.9	Phase 3
Alkermes (ALKS)	\$1,044.0	\$3,212.2	Market
Alnylam Pharmaceuticals (ALNY)	\$570.9	\$16,370.5	Market
BeiGene (BGNE)	\$308.9	\$29,363.2	Market
BioMarin Pharmaceuticals (BMRN)	\$1,844.4	\$14,333.6	Market
bluebird bio (BLUE)	\$250.7	\$1,964.6	Market (EU)
Exact Sciences Corp (EXAS)	\$1,491.4	\$22,183.3	Market
Exelixis (EXEL)	\$987.5	\$7,477.5	Market
Horizon Therapeutics (HZNP)	\$2,200.4	\$20,711.0	Market
Incyte Corporation (INCY)	\$2,666.7	\$18,274.4	Market
Jazz Pharmaceuticals (JAZZ)	\$2,363.6	\$9,325.1	Market
Nektar Therapeutics (NKTR)	\$152.9	\$3,566.1	Phase 3
Neurocrine Biosciences (NBIX)	\$1,045.9	\$9,028.2	Market
PTC Therapeutics (PTCT)	\$380.8	\$3,295.5	Market
Sarepta Therapeutics (SRPT)	\$540.1	\$5,725.1	Market
Ultragenyx Pharmaceutical (RARE)	\$271.0	\$7,323.7	Market
United Therapeutics (UTHR)	\$1,483.3	\$8,930.0	Market
Ionis Pharmaceuticals, Inc. (IONS)	\$729.3	\$6,037.3	Market
Ionis' Percentile Rank	49%	36%	N/A

(1) Trailing 12-month revenue.

(2) 30-day average market cap.

Our Productivity vs. Industry Peers

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

Even for established pharmaceutical companies for which the comparator group is obvious, comparisons of productivity are challenging. While revenues and profits per employee may be good measures for a portion of the equation, they provide little insight into potential for topline sales growth and no insight into innovation, which is the foundation for long-term sustainable growth. To provide insight into these attributes, measures of the size, maturity and potential value of the drug pipeline as well as the number of issued patents are useful and, viewed in the context of the company's financial performance, they help show a comprehensive picture of the company's productivity and strength. We have historically been, and continue to be, competitive in all of these measures, all while advancing an efficient and robust drug pipeline and effectively managing expenses and headcount.

In 2021, a number of achievements demonstrated our productivity and strength, even with the continued challenges created by the ongoing COVID-19 pandemic:

- We earned \$810 million in revenue, exceeded our 2021 financial guidance and ended the year with \$2.1 billion in cash.
- We achieved these financial successes while continuing to advance and expand our Phase 3 pipeline with the achievement of key enrollment milestones for eplontersen and pelacarsen, and the addition of two new Phase 3 programs for olezarsen and

In 2021, we earned \$810 million in revenue, exceeded our financial guidance and ended the year with \$2.1 billion in cash.



- We advanced our commercial strategy and go-to-market plans for our near-term commercial opportunities, eplontersen, olezarsen and donidalorsen.

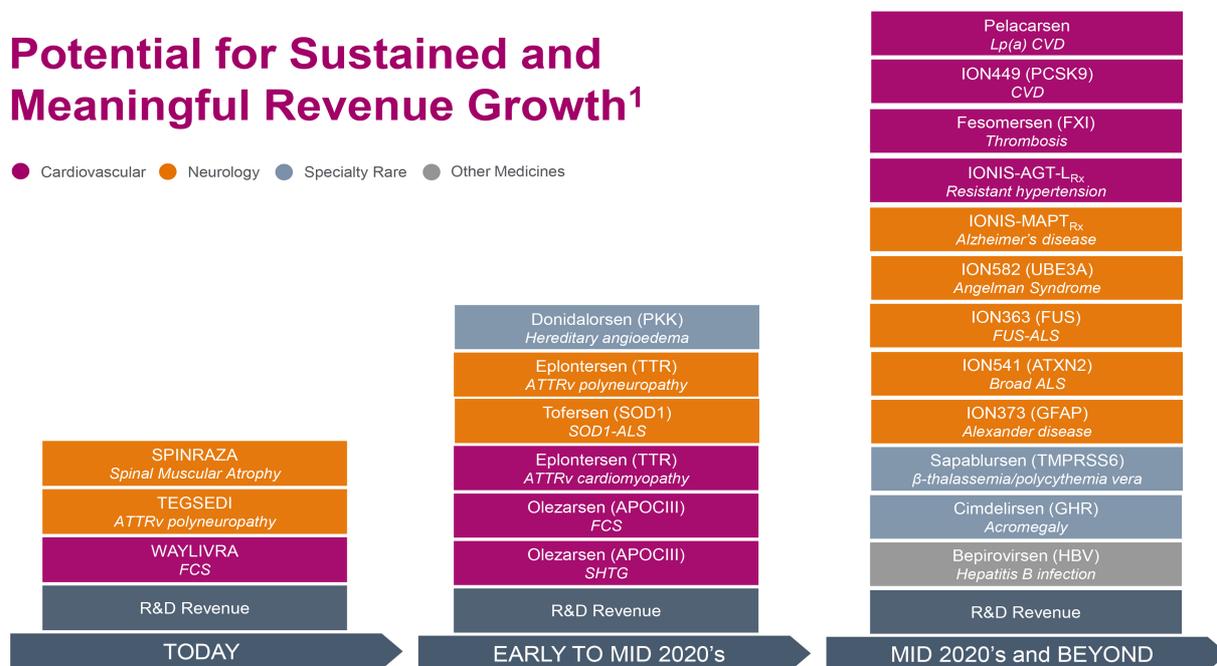
Our efficient platform and the dedication of our employees enabled us to accomplish these robust results and set us apart from our peers.

Advancing Our Pipeline

We now have six Phase 3 studies underway addressing eight indications. We also have a prolific mid-stage pipeline of medicines advancing towards Phase 3 development, many of which are expected to reach pivotal trials in the near term. Based on our anticipated near- and mid-term catalysts, we are well positioned to drive increasing and meaningful value for patients and shareholders.

Potential for Sustained and Meaningful Revenue Growth¹

● Cardiovascular ● Neurology ● Specialty Rare ● Other Medicines



1. Market opportunity and timing expectations are based on current assumptions and are subject to change.

Compensation Allocation/Pay Mix

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

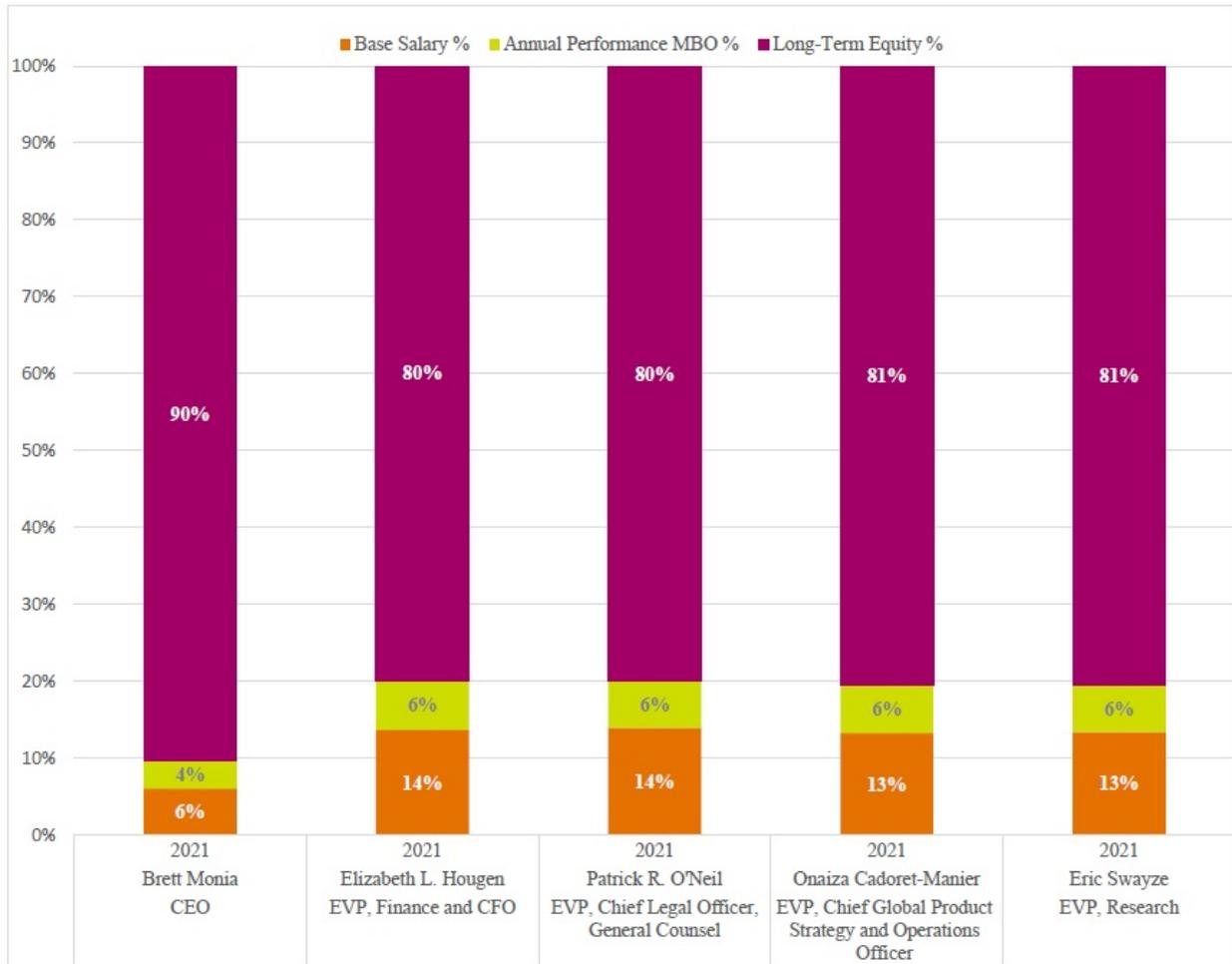
- ***A significant portion of cash compensation is at risk.*** The Compensation Committee structures cash compensation such that a significant proportion of our CEO's and other executive officers' cash compensation is at risk;
- ***More of total compensation is long-term equity.*** The Compensation Committee structures the total pay mix for our CEO and other executive officers such that more of their compensation is in the form of long-term equity compensation; and
- ***Less of total compensation is salary.*** The Compensation Committee strives to structure the total pay mix for our CEO and other executive officers such that less of their compensation is in the form of salary.

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 executive officers is a result of the compensation targets that emphasize long-term compensation versus short-term compensation. Actual salary levels, annual Performance MBO awards and long-term incentive awards vary based on one or more of the following: an individual's responsibilities, tenure in a particular position, experience, individual performance, and company performance.



Pay Mix Chart

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 2021:



Name	Year	% of Total Direct Compensation					
		Base Salary	Annual Performance MBO	Long-Term Equity	Base Salary %	Annual Performance MBO %	Long-Term Equity %
Brett Monia CEO	2021	\$800,000	\$469,300	\$11,986,030	6%	4%	90%
Elizabeth L. Hougen EVP, Finance and CFO	2021	\$557,541	\$262,713	\$3,258,953	14%	6%	80%
Patrick O'Neil EVP, Chief Legal Officer, General Counsel	2021	\$521,463	\$237,787	\$3,107,453	14%	6%	80%
Onaiza Cadoret-Manier EVP, Chief Global Product Strategy and Operations Officer	2021	\$482,000	\$227,118	\$2,910,446	13%	6%	81%
Eric Swayze EVP, Research	2021	\$476,442	\$217,258	\$2,880,147	13%	6%	81%



2020 CEO Transition

After 30 years as Ionis' Chief Executive Officer, in January 2020, Dr. Crooke, our founder, transitioned to Executive Chairman of the Board and was responsible for the activities of the Board. Following the 2021 Annual Meeting of Stockholders, Dr. Crooke stepped down from the Board and now serves as a Strategic Advisor to the Company, providing strategic advice and continuing to participate in the Company's scientific activities. Dr. Loscalzo now serves as Chairman of our Board. Dr. Monia, who was our Chief Operating Officer and a member of the Ionis team since our founding, assumed the position of Chief Executive Officer in January 2020.

The historical information contained in this Proxy Statement for the period preceding 2020 provides compensation data for Dr. Crooke and Dr. Monia with respect to each of their former roles.



CEO Compensation vs. Total Return (Over Five Years)

Ionis ended 2021 in a very strong financial position with \$2.1 billion in cash and revenues of \$810 million for the year. The graph below shows the relationship of our CEO’s compensation (\$ in thousands) compared to the TSR on \$100 invested on December 31, 2017 in our common stock through December 31, 2021. In the graph below, we present the fair value of equity awards granted to the CEO in the years in which the awards were earned, not in the years in which the awards were granted; for example, in January 2022 we granted equity awards for 2021 performance. Although we have historically calculated our CEO’s total annual compensation for this graph using the fair value of equity awards granted during such year for the prior year’s performance instead of the fair value of equity awards granted for the most recent performance year¹⁰, we believe using the fair value of equity awards granted for the most recent performance year is more meaningful for two reasons. First, we believe that it presents a more accurate depiction of how our Compensation Committee sets our CEO’s compensation for the year. Second, given that December 31 is the relevant measurement date for the stock price in this graph, using the fair value of equity awards granted shortly thereafter, rather than one year prior, more directly compares our CEO’s total compensation with stock price performance for that year. While stock price is only one of the measures of performance we use to set executive compensation, including for our CEO, over the past five-year period, our CEO’s compensation has generally aligned with our stock performance. Over this period, TSR has generally increased year over year, with the exceptions of 2020 and 2021.

As shown in the graph below, our CEO’s compensation aligned with TSR for 2017, 2018 and 2019¹¹. While our CEO’s compensation did not align with TSR for 2020, such misalignment was primarily due to additional equity awards granted to our CEO in 2020 in connection with his promotion to CEO and an increase in the allocation of PRSUs awarded to our CEO for 2020 performance. As discussed above, as a result of stockholder feedback and consideration of market trends, we implemented PRSU awards for our CEO in 2020. Due to an increase in the allocation of PRSUs awarded to Dr. Monia for 2020 performance and the higher grant date fair value assigned to such PRSUs as a result of using a monte carlo simulation¹², our CEO’s reported total compensation increased in 2020.



¹⁰ If we had calculated our CEO’s total annual compensation for this graph using the fair value of equity awards granted during such year for the prior year’s performance, it would have resulted in the following: for 2017, CEO compensation of \$7,314,652 with TSR of \$100; for 2018, CEO compensation of \$7,625,579 with TSR of \$107; for 2019, CEO compensation of \$9,598,830 with TSR of \$120; for 2020, CEO compensation of \$10,963,040 with TSR of \$112; and for 2021, CEO compensation of \$13,305,673 with TSR of \$60.

¹¹ This graph is not “soliciting material,” is not deemed “filed” with the SEC, is not subject to the liabilities of Section 18 of the Exchange Act and is not to be incorporated by reference in any of our filings under the Securities Act of 1933, as amended (the “Securities Act”) or the Exchange Act, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

¹² For performance awards based on relative TSR, a monte carlo simulation is required under ASC Topic 718, which incorporates the following factors: (i) three-year historical volatility of 43.63%; (ii) three-year historical correlation with the NASDAQ Composite index of 0.60; (iii) a risk-free-rate of 0.20%; and (iv) average three-year historical volatility and correlation for the constituents of the NASDAQ Composite Index of 77.48% and 0.44, respectively. Since the potential for a maximum payout is captured in the monte carlo simulation, the fair value for this award is often higher than the stock price on the date of grant.



2021 Compensation Decisions and Results

Base Salary

The fixed component of our compensation structure is base salary. We do not have salary ranges, and therefore we do not set salary minimums or maximums. 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 1,300 life sciences companies. The Compensation Committee uses these data to inform and shape its decision-making but does not strictly adhere to quantitative benchmarks. In addition, we assess whether the scope of job responsibilities and internal equity warrant a given base salary.

For all of our named executive officers, salary represents less than 15% of total compensation, and for our executive officers as a group, less than 20% of total compensation.

Each year all of 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, the Company-wide merit budget for increases effective in January 2021 was 3.3%, with a potential range of individual merit award increases of 0% to 10%. However, regardless of individual employee variances, we do not exceed the Company-wide approved merit budget.

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

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

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

2021 Base Salary Calculations

The table below reflects the 2021 base salary calculations effective December 27, 2020, which were based on 2020 performance, for our named executive officers. The Compensation Committee approved merit increases to the salaries of the named executive officers of 3.9% on average, which was consistent with the budget for merit increases approved by the Compensation Committee. The Compensation Committee noted its desired target mix of compensation that is less weighted on salary.

When reviewing salaries in December 2020, the Compensation Committee noted that the salaries of our named executive officers were within the competitive range of the Executive Peer Group, with the exceptions of Dr. Monia, Ms. Hougen, and Ms. Cadoret-Manier, whose salaries were below the competitive range. To address Dr. Monia's, Ms. Hougen's and Ms. Cadoret-Manier's lower salary positions to the market, the Compensation Committee approved a market adjustment for each as reflected in the table below.



Name	2020 Base Salary	Merit Increase for 2021	Market Adjustment	2021 Base Salary
Brett P. Monia	\$700,000	3.3%	\$76,900	\$800,000
Elizabeth L. Hougen	\$499,555	4.3%	\$35,000	\$557,541
Patrick R. O'Neil	\$500,925	4.1%	--	\$521,463
Onaiza Cadoret-Manier	\$430,000	4.0%	\$10,000	\$456,896 ⁽¹⁾
Eric E. Swayze	\$459,000	3.8%	--	\$476,442

(1) Ms. Cadoret-Manier received a salary increase in April 2021 from \$456,896 to \$482,000 to further address her lower salary position to the market.

2022 Base Salary Calculations

The table below reflects the 2022 base salary calculations effective December 26, 2021, which were based on 2021 performance, for our named executive officers. The Compensation Committee approved merit increases to the salaries of the named executive officers of 3.6% on average, which was consistent with the budget for merit increases approved by the Compensation Committee. The Compensation Committee noted its desired target mix of compensation that is less weighted on salary.

When reviewing salaries in December 2021, the Compensation Committee noted that the salaries of our named executive officers were within the competitive range of the Executive Peer Group, with the exceptions of Dr. Monia, Ms. Hougen and Ms. Cadoret-Manier, whose salaries were below the competitive range. Despite Dr. Monia's lower salary position to the market, the Compensation Committee decided not to increase Dr. Monia's salary for 2022 due to the Company's stock price performance in 2021. To address Ms. Hougen's and Ms. Cadoret-Manier's lower salary positions to the market, the Compensation Committee approved a market adjustment for each as reflected in the table below.

Name	2021 Base Salary	Merit Increase for 2022	Market Adjustment	2022 Base Salary
Brett P. Monia	\$800,000	3.1%	--	\$824,800
Elizabeth L. Hougen	\$557,541	3.9%	\$5,000	\$584,480
Patrick R. O'Neil	\$521,463	3.6%	--	\$540,236
Onaiza Cadoret-Manier	\$482,000	3.9%	\$29,000	\$530,929
Eric E. Swayze	\$476,442	3.5%	--	\$493,117

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

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

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

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

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

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

Performance MBO awards have a maximum amount.

For 2021 performance, the Compensation Committee awarded the Company's executive officers a Company Performance Factor of 95%, and all other employees a Company Performance Factor of 110%, due to a few key Company disappointments during the year. In a prior year, we did not pay Performance MBOs to executive officers due to the failures we faced at the time. Conversely, in successful years, we reward our executive officers consistent with Ionis' success.



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

- We have a maximum Company Performance Factor of 200% and a maximum Individual Performance Factor of 160%. This range represents the boundary conditions for our Performance Factors and ensures we reward our employees consistent with Ionis’ success.
- We base Target Performance MBO percentages on position levels within Ionis. The Target Performance MBO percentage for 2021 for Executive Vice Presidents was 40% and for CEO was 65%.

An individual’s Target Performance MBO percentage does not change unless the individual changes position level or the Compensation Committee sets a new target for that level. The table below summarizes the minimum and maximum Performance MBO for 2021 as a percentage of salary:

Name	Minimum Performance MBO Percentage of Salary	Maximum Performance MBO Percentage of Salary
Brett P. Monia	0%	208%
Elizabeth L. Hougen	0%	128%
Patrick R. O’Neil	0%	128%
Onaiza Cadoret-Manier	0%	128%
Eric E. Swayze	0%	128%

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

- At the end of each year, the Compensation Committee meets to evaluate Ionis’ overall performance for the year. As described below in the chart called “Evaluation of Key 2021 Corporate Objectives,” the Compensation Committee measures Ionis’ performance based upon the achievement of goals set at the beginning of the year with objective measures and agreed upon by our Board and senior management.
- In addition, the Compensation Committee considers our one-, three- and five-year TSRs, and based on these returns has *negative discretion to reduce the Company Performance Factor and Individual Performance Factors for our executive officers, which occurred for 2021 performance.*
- The Compensation Committee then reviews the Company Performance Factor history from the prior ten years to form a comparison for our current year’s successes and/or failures.
- Finally, the Compensation Committee approves each executive officer’s Individual Performance Factor based on the individual’s performance.

Based on our one-, three- and five-year TSRs, the Compensation Committee has negative discretion to reduce the Company Performance Factor and Individual Performance Factors for our executive officers, which occurred for 2021 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 2021 Key Corporate Objectives. On December 15, 2021, the Compensation Committee completed its evaluation of the Company’s performance against the 2021 Key Corporate Objectives.

As mentioned above, the Compensation Committee set two different Company Performance Factors for the 2021 Performance MBO: 95% for the executive officers and 110% for the rest of our employees. This was in recognition of a year full of many accomplishments across drug discovery, development, corporate development, and financial performance, especially given the ongoing challenges of the COVID-19 pandemic, balanced against a few key setbacks, such as disappointing clinical trial results and poor stock price performance. Despite these setbacks, we achieved the following successes in 2021 because of the dedication of our employees and strength of our technology and our business:

- We earned \$810 million in revenue, exceeded our 2021 financial guidance and ended the year with \$2.1 billion in cash.



- We achieved these financial successes while continuing to advance and expand our Phase 3 pipeline with the achievement of key enrollment milestones for eplontersen and pelacarsen, and the addition of two new Phase 3 programs for olezarsen and donidalorsen, bringing us to six medicines in Phase 3 development addressing eight indications.
- We advanced our commercial strategy and go-to-market plans for our near-term commercial opportunities, eplontersen, olezarsen and donidalorsen.

The Compensation Committee evaluates performance based on the achievement of goals (*including objective measures*) that the Board and management set at the beginning of each year. The table below provides a detailed evaluation of each key objective and the related achievements for 2021, as well as a description of notable unplanned accomplishments that the Compensation Committee considered in evaluating the Company's performance. The Company Performance Factor of 95% for executive officers in 2021 reflects a decrease from 115% for 2020, which was primarily due to our failure to meet the key corporate objectives to achieve positive results for the tofersen study and to increase our stock price performance.

Evaluation of 2021 Key Corporate Objectives		
	Objective & Pre-Approved Objective Measures	Evaluation
1	Meet financial goals: <ul style="list-style-type: none"> • Meet budget • Meet financial guidance • Commercial revenue \geq a specified target • R&D revenue \geq a specified target 	Ionis <i>exceeded</i> this objective: <ul style="list-style-type: none"> • We ended the year under our operation expense budget and exceeded our revenue and net income budgets • We exceeded our financial guidance • We exceeded our commercial revenue target • We exceeded our R&D revenue target
2	Complete key business development transactions: <ul style="list-style-type: none"> • Complete distribution agreement for TEGSEDI in North America • Complete partnering transaction for eplontersen • Complete one additional licensing transaction • Complete partnership for certain of our oncology medicines 	Ionis <i>substantially met</i> this objective: <ul style="list-style-type: none"> • We expanded our distribution agreement with Sobi to include TEGSEDI in North America • We completed a co-development, co-commercialization transaction for eplontersen with AstraZeneca • Did not complete; however, revenue from such additional licensing transaction was not needed for our business development team to hit its financial goals for the year • Completed partnering transaction with Flamingo Therapeutics for certain of our oncology medicines
3	Achieve key pipeline goals: <ul style="list-style-type: none"> • Keep pelacarsen on track for scheduled Phase 3 data readout • Keep tominersen on track for scheduled Phase 3 data readout • Achieve positive results for the Phase 3 study of tofersen 	Ionis <i>partially met</i> this objective: <ul style="list-style-type: none"> • Kept pelacarsen on track for scheduled Phase 3 data readout by completing 50% enrollment • Roche discontinued dosing in the Phase 3 study in March 2021; however, in January 2022, Roche announced plans to initiate a new Phase 2 study of tominersen in patients with Huntington's disease based on new findings from a post hoc analysis from the Phase 3 GENERATION HD1 study of tominersen • Biogen reported that while the Phase 3 VALOR study of tofersen in patients with SOD-ALS did not meet the primary endpoint, signs of reduced disease progression across multiple secondary and exploratory endpoints were observed. Biogen is actively engaged with regulators to determine the next steps for tofersen



	<ul style="list-style-type: none"> Complete enrollment for eplontersen and keep study on track File follow-on IND for SPINRAZA Initiate two new Phase 3/pivotal clinical trials Achieve \geq five positive Phase 2 proof of concept outcomes Initiate \geq four new Phase 2 clinical trials Initiate \geq four new first in human in human clinical trials 	<ul style="list-style-type: none"> We achieved full enrollment for the NEURO-TTRtransform study ahead of schedule; enrollment for the CARDIO-TTRtransform study is still underway Did not file the follow-on IND; however, Biogen exercised its option to license ION306 (BIIB115), the follow on for SPINRAZA, for the treatment of SMA with the potential for extended dosing intervals We initiated five new Phase 3/pivotal clinical trials We achieved seven positive Phase 2 proof of concept outcomes We initiated six new Phase 2 clinical trials We initiated five new first in human clinical trials
4	<p>Successfully complete Akcea Merger:</p> <ul style="list-style-type: none"> Complete planned synergies and integrations Achieve \geq a specified dollar amount in savings (excluding severance and retention costs) as a result of planned synergies and integrations Effectively transition TEGSEDI and WAYLIVRA to Sobi 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> We completed our planned synergies and integrations following the Akcea Merger We achieved the specified dollar amount in savings as a result of planned synergies and integrations following the Akcea Merger We effectively transitioned the distribution of TEGSEDI and WAYLIVRA to Sobi
5	<p>Finalize asset level commercial strategies for Ionis-owned portfolio:</p> <ul style="list-style-type: none"> Prioritize Ionis-owned assets based on Board approved strategy Buildout strategic and operational capabilities Prepare markets for prioritized disease areas 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> We prioritized our Ionis-owned assets based on a strategy approved by the Board We have made progress building out our strategic and operational capabilities We have made progress preparing markets for prioritized disease areas
6	<p>Progress research technology advancements into development:</p> <ul style="list-style-type: none"> Advance muscle LICA into development Complete oral GLP tox for Ionis owned program so that it is on track for first in human clinical trial in 2022 	<p>Ionis <u>partially met</u> this objective:</p> <ul style="list-style-type: none"> We advanced muscle LICA into development Toxicology will be completed in 2022
7	<p>Establish long-range space plan with budget:</p> <ul style="list-style-type: none"> Implement 5-10 year manufacturing plan Establish long-term office/lab space plan 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> We began implementation of our 5-10 year manufacturing plan We established a long-term office/lab space plan
8	<p>Increase stock price performance by a specified target percentage greater than or equal to median of the companies listed in the Nasdaq Biotechnology Index</p>	<p>Ionis <u>did not meet</u> this objective</p>
Unplanned Accomplishments for 2021		
9	Successfully refinanced our convertible debt	
10	Successfully managed through year two of the COVID-19 pandemic	



Once the Compensation Committee establishes the Company Performance Factor, the committee next reviews each executive officer's individual performance and contribution towards the key corporate objectives and other accomplishments set forth above and sets each executive officer's MBO award accordingly. The following table illustrates the Performance MBO awards approved for 2021 performance:

Name	2021 Base Salary	Target Performance MBO %	Company Performance Factor	Individual Performance Factor ⁽¹⁾	Resulting Performance MBO	Results Considered When Setting Individual Performance Factor ⁽¹⁾
Brett P. Monia	\$800,000	65%	95%	95%	\$469,300	1-10
Elizabeth L. Hougen	\$557,541	40%	95%	124%	\$262,713	1, 2, 4 & 7-10
Patrick R. O'Neil	\$521,463	40%	95%	120%	\$237,787	1-4, & 8-10
Onaiza Cadoret-Manier	\$482,000	40%	95%	124%	\$227,118	1-2, 4-5, 8 & 10
Eric E. Swayze	\$476,442	40%	95%	120%	\$217,258	1, 3, 6, 8 & 10

(1) The numbers correspond to the enumerated key objectives in the table entitled "Evaluation of Key 2021 Corporate Objectives" on pages 53 through 54. The Compensation Committee reviews the individual's contribution towards the key corporate objectives and other accomplishments set forth above when determining the Individual Performance Factors.

Notably, our CEO's MBO bonus for 2021 performance was below target, in recognition of a few key Company disappointments during the year. This resulted in a year-over-year decrease in our CEO's performance MBO bonus of 22%.

Since our CEO is ultimately responsible for the Company's performance, his Individual Performance Factor is usually the same as the Company Performance Factor, up to an Individual Performance Factor maximum of 160%. Notably, our CEO's MBO bonus for 2021 performance was below target, in recognition of a few key Company disappointments during the year. This resulted in a year-over-year decrease in our CEO's performance MBO bonus of 22%.

Stock Compensation

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

We grant existing employees new stock options and RSUs annually to provide a continuing incentive in Ionis' long-term success. Each year, the Compensation Committee sets a budget of option equivalents for our executive officers and a budget of option equivalents for all other employees. From these budgets, we set a target number of option equivalents for each employee level in the Company. The actual award for each employee can be higher or lower than the target for their level depending on individual performance, but the total awards cannot exceed the budget set by the Compensation Committee. Beginning in January 2019, we allocated option equivalents among stock options and RSUs as follows: 60% of option equivalents was allocated to stock options and 40% of option equivalents was allocated to RSUs. In 2022, we began allocating 50% of option equivalents to stock options and 50% to RSUs. For our executive officers, we allocate 33% (for our CEO) or 20% (for all of our other executive officers) of their total equity awards in the form of PRSUs, with the remaining option equivalents allocated 50% to stock options and 50% to RSUs.

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 do not use Black-Scholes grant date valuation calculations to set the size of our equity awards. Instead, once we identify the number of stock options and RSUs to be awarded from the option equivalent budget for our executive officers, we calculate the Black-Scholes value of the stock option awards. As a market check, we then compare the resulting values to the Black-Scholes value of awards granted by the companies in the Executive Peer Group and make adjustments to the size of the awards when appropriate. When our stock price is high, the Black-Scholes value of the awards is also high. Unlike other companies, when our stock price is low, we do not increase the equity awards to achieve a pre-defined Black-Scholes value of the stock options and RSUs to be awarded. For example, stock options granted in 2021 for 2020 performance had a fair value of \$56.78, while stock options granted in 2022 for 2021 performance had a fair value of \$32.60, and we did not increase the awards granted in 2022 such that the aggregate Black-Scholes value would be consistent with that of the prior year.

Performance-Based Stock Awards

In response to stockholder feedback, beginning in 2020, we implemented PRSU awards for our CEO's compensation, and increased the proportion of such awards for our CEO's total equity awards beginning in 2022. Additionally, in 2022, we implemented PRSU awards for our other executive officers. These PRSU awards provide our executive officers the opportunity to earn a defined number of shares of our common stock if we achieve pre-determined performance goals. At target level of achievement, the PRSU awards represent 33% of our CEO's total equity awards and 20% of each of our other executive officer's total equity awards. The PRSU awards pay out based on our relative stock price performance compared to a peer group. Measuring our stock performance relative to peers mitigates the impact of macroeconomic factors, both positive and negative, that affect the industry and stock price performance and are beyond the control of management, and provides rewards that are more directly aligned with performance through different economic cycles. We believe these PRSU awards provide a challenging incentive to the executive officers to significantly grow the Company.

Measuring our stock performance relative to peers mitigates the impact of macroeconomic factors, both positive and negative, that affect the industry and stock price performance and are beyond the control of management, and provides rewards that are more directly aligned with performance through different economic cycles.

One third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (*i.e.*, the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant; the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant; and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on the Company's relative TSR as compared to a peer group of companies, and as measured, in each case, at the end of the applicable performance period. The key features of the PRSUs are as follows:

- No number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 150% of the target number depending on the Company's relative total shareholder return;
- If the Company's TSR is negative over the applicable performance period, the payout will not exceed 100% of the target number for that performance period; and
- Performance below the threshold level results in a payout of zero shares, performance at the threshold level (25th percentile) results in a payout of 50% of target shares, performance at the target level (50th percentile) results in a payout of 100% of target shares, and performance at the maximum level (75th percentile) results in a payout of 150% of target shares.

If the Company's TSR is negative over the applicable performance period, the payout will not exceed 100% of the target number for that performance period.

In connection with his promotion to CEO, in January 2020, Dr. Monia received 40,822 time-vested stock options, 18,143 time-vested RSUs and 17,009 PRSUs (target payout of 11,339, multiplied by 150% to account for potential upside). For 2020 performance, in January 2021, Dr. Monia received 149,872 time-vested stock options, 66,610 time-vested RSUs and 77,447 PRSUs (target payout of 51,631, multiplied by 150% to account for potential upside). For 2021 performance, in January 2022, Dr. Monia received 101,489 time-vested stock options, 50,745 time-vested RSUs and 76,117 PRSUs (target payout of 50,745, multiplied by 150% to account for potential upside).



Vesting of Stock Awards

Vesting schedules reward long-term performance and incentivize long-term stock appreciation and increased stockholder returns. For each stock option and RSU granted (except PRSUs), the Compensation Committee sets a vesting schedule over four years, with no vesting during the first year. Therefore, the stock options and RSUs granted to our executive officers directly align the interests of our executive officers with the interests of our stockholders and Ionis' long-term success. The actual economic value of stock option awards depends directly on the performance of our stock price over the period during which the awards vest and the period during which the stock options may be exercised. In other words, our executive officers will only realize economic value when our stock price, and consequently stockholder value, increases, which aligns pay with performance and fosters accountability for Ionis' long-term success. Conversely, the stock options are not worth anything if our stock price does not increase above the exercise price. For example, a total of 173,954 stock options expired underwater for our executive officers in the first quarter of 2022.

Similarly, in the same way our stockholder returns increase and decrease based on our stock's performance, the value to our employees of the RSUs increases and decreases based on our stock's performance. In addition, RSUs promote retention and reinforce an ownership culture, and provide value even during periods of stock price or market underperformance.

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

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

The stock option vesting schedule is typically over a four-year period at the rate of 25% at the end of the first year and then at the rate of 2.08% per month for 36 months thereafter during the optionee's employment. The RSU vesting schedule is typically over a four-year period at the rate of 25% per year. In addition, as further described below, our executive officers must hold shares received upon vesting of their RSUs and PRSUs until they meet certain ownership thresholds or no longer serve the Company. These practices align our employee compensation with our stockholders' interests because if stockholder value declines over time, so too will the value of the equity compensation provided to all employees. We have historically had low employee turnover, particularly in our management team, and the members of our management have traditionally held their stock options for a long period of time before exercise. Our historically low turnover is indicative of our employees' commitment to Ionis and its technology and reflects our executive officers' belief in the long-term value of our stock.

Our stock compensation budget minimizes dilution. Each year the Compensation Committee approves a budget that sets the number of stock options, RSUs and PRSUs we can grant our employees for annual merit awards. We do not grant stock options, RSUs or PRSUs that exceed this budget without the Compensation Committee's approval. Over the past three years, the average merit award stock budget set by the Compensation Committee has been approximately 2.1% of our outstanding common stock on an issued and outstanding basis. This stock compensation budget, and therefore our equity compensation burn rate, is well below the Executive Peer Group average of 4.3% from 2018 through 2020. We believe this stock budget is an important tool to balance our compensation objectives with stockholder interests. For 2021 performance, the Compensation Committee set a merit stock award budget that resulted in approximately 1.6 million stock options, approximately 800,000 RSUs and a target number of approximately 100,000 PRSUs awarded to our employees, including the executive officers. Together these shares represent approximately 2% of our outstanding common stock on an issued and outstanding basis for that year. This budget, as well as each employee's position level and performance in the previous year, ultimately determines the size of the individual annual stock grants.

Over the past 3 years, the average merit award stock budget set by the Compensation Committee has been approximately 2.1% of our outstanding common stock on an issued and outstanding basis.

Corporate Governance

Stock Ownership Guidelines and Holding Periods

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

Our Compensation Committee and our Board set stock ownership and holding guidelines for our executive officers and members of the Board. These guidelines require our executive officers and non-employee Board members to hold the shares they receive under their RSU and PRSU 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 and PRSU awards are exempt from these holding requirements.



The number of shares subject to the guidelines is determined at the beginning of each calendar quarter, using the product of (i) the number of shares held by the individual on the first business day of such quarter and (ii) the average closing price of the Company's common stock over the 30 trading days immediately preceding the start of such quarter.

In 2021, we increased the stock ownership guidelines for our executive officers and non-employee Board members such that the current guidelines are as follows:

Executive Officer/Director	Stock Ownership Guideline (as a multiple of base salary/annual cash retainer)
CEO	6 times Base Salary
All other executive officers	2 times Base Salary
Non-employee Directors	4 times Base Annual Cash Retainer

As of March 31, 2022, all of our non-employee Directors, except Ms. Diaz, and all of our executive officers except Dr. Monia, Dr. Swayze, Dr. Schneider and Ms. Cadoret-Manier met these guidelines. Due to the recent increase in the stock ownership guidelines, coupled with recent appointments/transitions, Ms. Diaz, Dr. Monia, Dr. Swayze, Dr. Schneider and Ms. Cadoret-Manier do not yet hold enough shares sufficient to meet the guidelines.

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

Clawback Policy

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

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

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

Anti-Hedging Policy and Anti-Pledging Policy

We explicitly prohibit employees from "shorting" and hedging against our stock. To help avoid situations in which our employees may benefit from transactions that harm our stockholders, or that remove economic risk from their holdings of our securities, our policies specifically prohibit all employees, including our executive officers, from taking a "short" position in our stock and otherwise hedging their position in our stock against a future drop in our stock price including short sales and derivatives such as put or call options, swaps, forwards, and futures, or other inherently speculative transactions with respect to Ionis' securities at any time. In addition, we also prohibit all directors and employees, including our named executive officers, from pledging our stock as collateral.

Rule 10b5-1 Trading Program

10b5-1 plan required for executive officers and vice presidents. We have a Rule 10b5-1 trading program. Our Rule 10b5-1 trading program allows our executive officers, vice presidents and other employees to establish plans that permit prearranged future sales of the employee's 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 and PRSUs.

Perquisites

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



Retirement & Other Benefits

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

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

Retention and Change of Control Agreements

As part of our normal course of business, we engage in discussions with other biotechnology and pharmaceutical companies about possible collaborations, licensing and/or other ways in which the companies may work together to further our respective long-term objectives. In addition, many larger established pharmaceutical companies consider companies at similar stages of development to ours as potential acquisition targets. Occasionally, a transaction in the biotech/biopharmaceutical industry may start as a licensing transaction, but ultimately result in an acquisition. In certain scenarios, the potential for merger or being acquired may be in the best interests of our stockholders. As further described on page 66, we adopted a Change in Control and Severance Benefit Plan to provide certain economic benefits to our executive officers and vice presidents if their employment is terminated in certain circumstances, including as a result of a transaction that results in a change in control of the Company.

Tax and Accounting Considerations

Under Section 162(m) of the Internal Revenue Code (“Section 162(m)”), compensation paid to each of the Company’s “covered employees” that exceeds \$1 million per taxable year is generally non-deductible unless the compensation qualifies for certain grandfathered exceptions (including the “performance-based compensation” exception) for certain compensation paid pursuant to a written binding contract in effect on November 2, 2017 and not materially modified on or after such date.

Although the Compensation Committee will continue to consider tax implications as one factor in determining executive compensation, the Compensation Committee also looks at other factors in making its decisions and retains the flexibility to provide compensation for the Company’s named executive officers in a manner consistent with the goals of the Company’s executive compensation program and the best interests of the Company and its stockholders, which may include providing for compensation that is not deductible by the Company due to the deduction limit under Section 162(m). The Compensation Committee also retains the flexibility to modify compensation that was initially intended to be exempt from the deduction limit under Section 162(m) if it determines that such modifications are consistent with the Company’s business needs.

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



Compensation of Executive Officers

The following table shows for the fiscal years ended December 31, 2021, 2020, and 2019, compensation awarded to or paid to, or earned by, our named executive officers. Of particular note is that the value of Dr. Monia's stock awards increased in 2021 primarily due to an increase in PRSUs awarded to Dr. Monia in 2021 and the higher fair value assigned to such PRSUs as a result of using a monte carlo simulation (see footnote 3 below for additional information).

Summary Compensation Table

Name and Principal Position	Year	Salary (\$)	Bonus ⁽¹⁾ (\$)	Stock Awards ⁽²⁾		Option Awards ⁽⁵⁾ (\$)	All Other Compensation ⁽⁶⁾ (\$)	Total (\$)
				RSUs ⁽³⁾ (\$)	PRSUs ⁽⁴⁾ (\$)			
Brett P. Monia ⁽⁷⁾ President, Chief Executive Officer	2021	\$800,000	\$469,300	\$4,081,860	\$3,984,360	\$3,919,810	\$50,343	\$13,305,673
	2020	\$700,000	\$601,738	\$4,094,657 ⁽⁸⁾	\$1,055,547 ⁽⁸⁾	\$4,470,351 ⁽⁸⁾	\$40,747	\$10,963,040
	2019	\$527,850	\$395,888	\$2,664,113	--	\$2,806,646	\$133,466	\$6,527,963
Elizabeth L. Hougen Executive Vice President, Finance and Chief Financial Officer	2021	\$557,541	\$262,713	\$1,662,465	--	\$1,596,488	\$49,121	\$4,128,329
	2020	\$499,555	\$298,734	\$1,663,208	--	\$1,815,765	\$63,838	\$4,341,100
	2019	\$479,880	\$299,925	\$1,289,352	--	\$1,358,319	\$54,382	\$3,481,858
Patrick R. O'Neil Executive Vice President, Chief Legal Officer and General Counsel	2021	\$521,463	\$237,787	\$1,585,191	--	\$1,522,262	\$56,442	\$3,923,145
	2020	\$500,925	\$288,032	\$1,502,162	--	\$1,639,968	\$33,978	\$3,965,065
	2019	\$483,052	\$289,831	\$1,289,352	--	\$1,358,319	\$43,347	\$3,463,901
Onaiza Cadoret-Manier, Executive Vice President, Chief Global Product Strategy and Operations Officer	2021	\$482,000 ⁽⁹⁾	\$227,118	\$1,484,692	--	\$1,425,753	\$46,404	\$3,665,966
	2020	\$430,000	\$235,461	\$1,151,710	--	\$1,595,777	\$91,494	\$3,504,442
	2019	N/A ⁽¹⁰⁾	N/A ⁽¹⁰⁾	N/A ⁽¹⁰⁾	--	N/A ⁽¹⁰⁾	N/A ⁽¹⁰⁾	N/A ⁽¹⁰⁾
Eric E. Swayze, Executive Vice President, Research	2021	\$476,442	\$217,258	\$1,469,249	--	\$1,410,898	\$45,603	\$3,619,450
	2020	\$459,000	\$253,368	\$759,304	--	\$828,944	\$42,084	\$2,342,700
	2019	\$407,796	\$221,229	\$701,975	--	\$739,545	\$44,487	\$2,112,032

(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 2022 we paid bonuses for 2021 performance.

(2) We present stock awards in the years they were awarded, not in the year earned. For example, in January 2022 we granted stock awards for 2021 performance.

(3) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with ASC 718 for RSU and option awards granted to our named executive officers. 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, 2021 regarding assumptions underlying valuation of equity awards.

(4) For performance awards based on relative TSR, a monte carlo simulation is required under ASC Topic 718 based upon the then-probable outcome of the performance conditions underlying such awards, which incorporated the following factors: (i) three-year historical volatility of 43.63%; (ii) three-year historical correlation with the NASDAQ Composite index of 0.60; (iii) a risk-free-rate of 0.20%; and (iv) average three-year historical volatility and correlation for the constituents of the NASDAQ Composite Index of 77.48% and 0.44, respectively. Since the potential for a maximum payout is captured in the monte carlo simulation, the fair value for this award is often higher than the stock price 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, 2021 regarding assumptions underlying valuation of equity awards.

- (5) 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. 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, 2021 regarding assumptions underlying valuation of equity awards.



- (6) Includes AD&D, Basic Life, Medical, Dental, Vision and 401(k) matching contributions, which are available to all employees. Amount for 2021 includes a Commitment to Ionis Award for Mr. O'Neil. Amounts for 2020 include a Career Achievement Award for Dr. Geary and a Commitment to Ionis Award for Ms. Hougen. Amounts for 2019 include a Career Achievement Award and Commitment to Ionis Award for Dr. Monia.
- (7) 2020 compensation for Dr. Monia was for his role as CEO, and 2019 compensation was for his role as COO.
- (8) Includes equity awards granted to Dr. Monia in connection with his promotion to CEO in 2020.
- (9) Ms. Cadoret-Manier received a salary increase in April 2021 from \$456,896 to \$482,000 to bring her base salary closer to the competitive range for similar positions at companies in the Executive Peer Group.
- (10) Ms. Cadoret-Manier joined Ionis in January 2020; therefore, no 2019 salary information is available.



Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2021, certain information regarding grants of plan-based awards to our named executive officers:

Grants of Plan-Based Awards in Fiscal 2021

Name	Grant Date	Estimated Future Payouts Under Equity Incentive Plan Awards			All Other Stock Awards: Number of Shares of Stock or Units (#)	All Other Option Awards: Number of Securities Underlying Options (#)	Exercise or Base Price of Option Awards (\$/Sh)	Grant Date Fair Value of Stock and Option Awards ⁽¹⁾
		Threshold (#)	Target (#)	Maximum (#)				
Brett P. Monia	1/4/21	--	--	--	--	149,872	\$56.78	\$3,919,810
	1/15/21	--	--	--	66,610	--	--	\$4,081,860
	1/15/21	25,816	51,631	77,447	--	--	--	\$3,984,359
Elizabeth L. Hougen	1/4/21	--	--	--	--	61,041	\$56.78	\$1,596,488
	1/15/21	--	--	--	27,129	--	--	\$1,662,465
Patrick R. O'Neil	1/4/21	--	--	--	--	58,203	\$56.78	\$1,522,262
	1/15/21	--	--	--	25,868	--	--	\$1,585,191
Onaiza Cadoret-Manier	1/4/21	--	--	--	--	54,513	\$56.78	\$1,425,753
	1/15/21	--	--	--	24,228	--	--	\$1,484,692
Eric E. Swayze	1/4/21	--	--	--	--	53,945	\$56.78	\$1,410,898
	1/15/21	--	--	--	23,976	--	--	\$1,469,249

- (1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with ASC 718 for RSU and option awards granted to our named executive officers. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. The fair value of PRSUs is based upon the then-probable outcome of the performance conditions underlying such awards and calculated using a monte carlo simulation because the performance target is based on our relative TSR, which represents a market condition. For more information, please see Note 4, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2021 regarding assumptions underlying valuation of equity awards.

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

The Compensation Committee granted merit non-statutory stock options to the executive officers on January 4, 2021 for their 2020 performance. All of these stock options were granted out of our 2011 Plan. The options have a term of ten 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, 2021 for their 2020 performance. 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, 2022.

In 2021, Dr. Monia received twenty percent of his total equity awards in the form of PRSUs. One third of the PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant (*i.e.*, the one-year period commencing on the date of grant and ending on the first anniversary of the date of grant; the two-year period commencing on the date of grant and ending on the second anniversary of the date of grant; and the three-year period commencing on the date of grant and ending on the third anniversary of the date of grant) based on the Company's relative TSR as compared to a peer group of companies, and as measured, in each case, at the end of the applicable performance period. No number of PRSUs is guaranteed to vest and the actual number of PRSUs that will vest at the end of each performance period may be anywhere from zero to 150% of the target number depending on the Company's relative TSR. Performance below the threshold level results in a payout of 0 shares, performance at the threshold level (25th percentile) results in a payout of 50% of target shares, performance at the target level (50th percentile) results in a payout of 100% of target shares, and performance at the maximum level (75th percentile) results in a payout of 150% of target shares.

Outstanding Equity Awards at Fiscal Year-End – Executive Officers

The following table shows for the fiscal year ended December 31, 2021, 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, 2021.



Outstanding Equity Awards as of December 31, 2021

Name	Grant Date	Option Awards				Stock Awards			
		Number of Securities Underlying Unexercised Options (#) Exercisable ⁽¹⁾	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price (\$)	Option Expiration Date	Number of Shares or Units of Stock that Have Not Vested ⁽²⁾	Market Value of Shares or Units of Stock that Have Not Vested ⁽³⁾	Equity incentive plan awards: number of unearned shares, units or other rights that have not vested (#) ⁽⁴⁾	Equity incentive plan awards: market or payout value of unearned shares, units or other rights that have not vested (\$) ⁽⁵⁾
Brett P. Monia	1/2/2015	36,423	--	\$ 61.57	1/1/2022	--	--	--	--
	1/4/2016	38,240	--	\$ 61.68	1/3/2023	--	--	--	--
	1/3/2017	48,000	--	\$ 47.34	1/2/2024	--	--	--	--
	1/2/2018	56,914	1,211	\$ 49.25	1/1/2025	--	--	--	--
	1/14/2018	29,375	625	\$ 53.22	1/13/2025	--	--	--	--
	1/2/2019	75,031	27,869	\$ 53.77	1/1/2026	--	--	--	--
	1/2/2020	51,573	56,059	\$ 60.89	1/1/2027	--	--	--	--
	1/2/2020	19,561	21,261	\$ 60.89	1/1/2027	--	--	--	--
	1/4/2021	--	149,872	\$ 56.78	1/3/2028	--	--	--	--
	1/15/2018	--	--	--	--	3,229	\$ 98,258	--	--
	1/15/2018	--	--	--	--	1,666	\$ 50,696	--	--
	1/15/2019	--	--	--	--	22,864	\$ 695,752	--	--
	1/15/2020	--	--	--	--	35,877	\$ 1,091,737	--	--
	1/15/2020	--	--	--	--	13,607	\$ 414,061	--	--
	1/15/2020	--	--	--	--	--	--	3,779	\$ 114,995
1/15/2021	--	--	--	--	66,610	\$ 2,026,942	--	--	
1/15/2021	--	--	--	--	--	--	25,816	\$ 785,581	
Elizabeth L. Hougen	1/2/2015	33,112	--	\$ 61.57	1/1/2022	--	--	--	--
	1/4/2016	38,240	--	\$ 61.68	1/3/2023	--	--	--	--
	1/3/2017	45,225	--	\$ 47.34	1/2/2024	--	--	--	--
	1/2/2018	53,481	1,138	\$ 49.25	1/1/2025	--	--	--	--
	1/2/2019	36,312	13,488	\$ 53.77	1/1/2026	--	--	--	--
	1/2/2020	28,893	31,406	\$ 60.89	1/1/2027	--	--	--	--
	1/4/2021	--	61,041	\$ 56.78	1/3/2028	--	--	--	--
	1/15/2018	--	--	--	--	3,034	\$ 92,325	--	--
	1/15/2019	--	--	--	--	11,065	\$ 336,708	--	--
	1/15/2020	--	--	--	--	20,100	\$ 611,643	--	--
1/15/2021	--	--	--	--	27,129	\$ 825,535	--	--	
Patrick R. O'Neil	1/4/2016	7,967	--	\$ 61.68	1/3/2023	--	--	--	--
	1/3/2017	20,825	--	\$ 47.34	1/2/2024	--	--	--	--
	1/2/2018	45,499	1,139	\$ 49.25	1/1/2025	--	--	--	--
	1/2/2019	36,312	13,488	\$ 53.77	1/1/2026	--	--	--	--
	1/2/2020	26,096	28,365	\$ 60.89	1/1/2027	--	--	--	--
	1/4/2021	--	58,203	\$ 56.78	1/3/2028	--	--	--	--
	1/15/2018	--	--	--	--	3,035	\$ 92,355	--	--
	1/15/2019	--	--	--	--	11,065	\$ 336,708	--	--
	1/15/2020	--	--	--	--	18,153	\$ 552,396	--	--
1/15/2021	--	--	--	--	25,868	\$ 787,163	--	--	
Onaiza Cadoret-Manier	1/9/2020	24,437	26,563	\$ 63.27	1/8/2027	--	--	--	--
	1/4/2021	--	54,513	\$ 56.78	1/3/2028	--	--	--	--
	4/15/2020	--	--	--	--	17,000	\$ 517,310	--	--
	1/15/2021	--	--	--	--	24,228	\$ 737,258	--	--
Eric E. Swayze	1/2/2015	15,000	--	\$ 61.57	1/1/2022	--	--	--	--
	1/4/2016	15,266	--	\$ 61.68	1/3/2023	--	--	--	--
	1/3/2017	27,100	--	\$ 47.34	1/2/2024	--	--	--	--
	1/2/2018	30,745	655	\$ 49.25	1/1/2025	--	--	--	--
	1/2/2019	19,771	7,343	\$ 53.77	1/1/2026	--	--	--	--
	1/2/2020	10,315	11,213	\$ 60.89	1/1/2027	--	--	--	--
	1/2/2020	2,875	3,125	\$ 60.89	1/1/2027	--	--	--	--
	1/4/2021	--	53,945	\$ 56.78	1/3/2028	--	--	--	--
	1/15/2018	--	--	--	--	1,744	\$ 53,070	--	--
	1/15/2019	--	--	--	--	6,024	\$ 183,310	--	--
	1/15/2020	--	--	--	--	7,176	\$ 218,366	--	--
	1/15/2020	--	--	--	--	2,000	\$ 60,860	--	--
1/15/2021	--	--	--	--	23,976	\$ 729,590	--	--	

- (1) The options granted to our employees 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. Options granted to our employees before January 1, 2022 have a term of seven years and options granted to our employees beginning January 1, 2022 have a term of ten years.



- (2) The RSUs granted to our employees were granted out of our 2011 Plan. The RSUs vest at the rate of 25% per year over four years.
- (3) Market value of stock awards was determined by multiplying the number of unvested shares by \$30.43, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 31, 2021, the last trading day of fiscal 2021.
- (4) Represents the threshold payout of shares under the PRSU awards granted to Dr. Monia.
- (5) Market value of PRSUs was determined by multiplying the threshold payout of shares by \$30.43, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 31, 2021, the last trading day of fiscal 2021.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2021, 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 (#)	Value Realized on Exercise (\$)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting (\$)
Brett P. Monia	--	\$ --	37,457	\$2,293,811
Elizabeth L. Hougen	--	\$ --	17,151	\$1,051,013
Patrick R. O'Neil	--	\$ --	16,504	\$1,011,365
Onaiza Cadoret-Manier	--	\$ --	5,667	\$232,517
Eric E. Swayze	--	\$ --	8,944	\$548,088

Post-Employment Compensation

Pension Benefits and Nonqualified Deferred Compensation

Following the 2021 Annual Meeting of Stockholders, Dr. Crooke transitioned from our Executive Chairman of the Board to a Strategic Advisor. The Company entered into a Strategic Advisory Services Agreement with Dr. Crooke (the "Strategic Advisory Services Agreement") to reflect his new role. Pursuant to such agreement, from the end of Dr. Crooke's service on the Board through June 30, 2023, the Company will pay Dr. Crooke's COBRA premium payments, or if COBRA is not available, an amount equal to the cost of comparable health insurance coverage. See page 72 of this Proxy Statement for further information regarding the Strategic Advisory Services Agreement.

In January 2018, B. Lynne Parshall transitioned from our then Chief Operating Officer to a Senior Strategic Advisor to Ionis and she continues to be a member of the Board of Directors of Ionis. Ionis entered into a Strategic Advisory Services Agreement with Ms. Parshall, as amended on March 22, 2019, January 9, 2020, February 22, 2021, and February 22, 2022 (the "Amended Advisory Services Agreement"), to reflect her new role. Pursuant to such agreement, if in the future Ms. Parshall's board of director service for the Company ends, for 18 months following such date, the Company will pay Ms. Parshall's COBRA premium payments, or if COBRA is not available, an amount equal to the cost of comparable health insurance coverage. See page 72 of this Proxy Statement for further information regarding the Amended Advisory Services Agreement.

Our executive officers are eligible to participate in our 401(k) contributory defined contribution plan. In 2021, we contributed to each participant a matching contribution equal to 100% of the first 5% of the participant's compensation he or she contributed to the plan. In 2021, the maximum matching contribution was \$14,500. The Compensation Committee can also grant discretionary contributions under our 401(k) plan. We do not provide any nonqualified defined contribution or other deferred compensation plans.

Employment Agreements

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



Potential Payments Upon Termination or Change-of-Control

Severance and Change of Control Arrangements

On October 18, 2018, the Company implemented a Change of Control and Severance Benefit Plan, which was amended and restated on March 17, 2022 (the “Plan”) that provides for change of control and severance benefits to the Company’s executive officers, including but not limited to the Chief Executive Officer and the Chief Financial Officer, and vice presidents (each, a “Covered Employee”).

The Plan provides that if a Covered Employee is terminated without “cause” (as defined in the Plan) or resigns for “good reason” (as defined in the Plan), except in connection with a “change in control” of the Company (as defined in the Plan), the Covered Employee will generally be entitled to receive (i) a lump sum payment of the Covered Employee’s then-current monthly base salary, (ii) accelerated vesting of stock options and restricted stock units previously granted to the Covered Employee by the Compensation Committee and outstanding as of the termination date that otherwise would have vested during the periods noted below, and (iii) continued medical group health and dental plan coverage, in each case for the following durations:

- Chief Executive Officer: 18 months;
- Executive Vice Presidents: 12 months;
- Senior Vice Presidents: 9 months; and
- Vice Presidents: 6 months.

In addition, for the Chief Executive Officer only, payment of the then-current target bonus, prorated for time served during such calendar year.

The Plan also provides that if a Covered Employee’s termination or resignation occurs during the period that begins three months before and ends twelve months following a change in control, the Covered Employee will generally be entitled to receive (i) a lump sum payment of the Covered Employee’s then-current monthly base salary, (ii) payment of the then-current target bonus, (iii) accelerated vesting of all stock options and restricted stock units previously granted to the Covered Employee by the Compensation Committee and outstanding as of the termination date, and (iv) continued medical group health and dental plan coverage, in each of (i), (ii) and (iv) for the following durations:

- Chief Executive Officer: 24 months;
- Executive Vice Presidents: 18 months;
- Senior Vice Presidents: 12 months; and
- Vice Presidents: 9 months.

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

Conditions

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

Estimate of Benefits under Change of Control and Severance Benefit Plan

The following table estimates the lump sum payments and health benefits that would be required to be paid to our named executive officers under the Change of Control and Severance Benefit Plan as of December 31, 2021. This table estimates the lump sum payments based upon either a termination without cause, a resignation with good reason or a termination in connection with a change of control, assuming such event occurred on December 31, 2021. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 78 of this Proxy Statement.

Name	Total – Change of Control Event	Total – Non-Change of Control Event
Brett P. Monia	\$2,786,537	\$1,821,843
Elizabeth L. Hougén	\$1,275,931	\$616,828
Patrick R. O’Neil	\$1,168,409	\$562,845
Onaiza Cadoret-Manier	\$1,163,474	\$563,277
Eric Swayze	\$1,084,068	\$525,465

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

Director Compensation

For the fiscal year ending December 31, 2021, we paid our non-employee Directors a base cash retainer of \$60,000 with additional role-based compensation as noted below:

Role	2021 Cash Compensation
Board Member (Base)	\$60,000 ⁽¹⁾
Non-Executive Chairman of the Board	\$40,000
Independent Lead Director	\$40,000
Committee Chairs (Additional)	
Agenda	\$10,000
Audit	\$24,000
Compliance	\$20,000
Compensation	\$20,000
Finance	\$20,000
Nominating, Governance and Review	\$20,000
Science/Medical	\$20,000
Committee Member (Additional)	
Agenda	\$5,000
Audit	\$12,000
Compliance	\$10,000
Compensation	\$10,000
Finance	\$10,000
Nominating, Governance and Review	\$10,000
Science/Medical	\$10,000

- (1) Before March 31, 2024 this annual base cash retainer for each non-employee Director (not including fees for Non-Executive Chairman, Independent Lead Director, Committee Chair or Committee Member) is limited to a maximum of \$70,000 per year.

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

In 2021, each non-employee Director also received automatic stock award grants under our Non-Employee Director Plan. On July 1, 2021, under the Non-Employee Director Plan, each of our non-employee Directors serving at that time received an option to purchase 12,000 shares of our common stock, at an exercise price of \$40.05 per share, the fair market value of the common stock on the date of the grant, based on the closing sales price reported on the Nasdaq Global Select Market, and an RSU award for 5,333 shares. The options and RSUs vest on either (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier.

In March 2021, the Compensation Committee and Board adopted a policy whereby (1) the Compensation Committee, with input from its independent consultant, may reduce the number of shares to be automatically issued on a grant date for each such award so that the awards granted have an aggregate grant date fair value that is aligned with the set of peer companies the Compensation Committee uses to evaluate compensation, and (2) the initial equity awards granted upon commencement of Board service will be adjusted downward such that they are 1.5 times the annual equity awards for any given year. The Compensation Committee determined that for 2021, in order to align with the peer companies, if the annual awards to be automatically granted would have an aggregate grant date fair value that exceeds \$500,000, then the number of shares to be automatically issued will be reduced proportionately for each such award so that the awards granted have an aggregate grant date fair value not in excess of \$500,000. The grant date fair value of annual awards to be automatically granted in July 2021 did not exceed \$500,000; thus, for 2021, each non-employee Director received an annual award of 12,000 stock options and 5,333 RSUs.



The Compensation Committee has historically reviewed pay levels for non-employee Directors at least every other year, but now reviews it every year, with assistance from Aon, which prepares a comprehensive assessment of Ionis' non-employee Director compensation program. That assessment includes benchmarking of director compensation against the same peer group used for executive compensation purposes, an update on recent trends in director compensation, and a review of related corporate governance best practices. The Compensation Committee reviews these assessments prior to making recommendations to the Board regarding non-employee Director compensation. As a result of such review in 2019, the Compensation Committee and Board decided it would be in the best interest of the Company to propose a reduction in the size of initial awards granted to non-employee Directors of the Company upon commencement of Board service and automatic equity awards granted to non-employee Directors of the Company each year as follows: 24,000 stock options and 10,667 RSUs for initial grants and 12,000 stock options and 5,333 RSUs for annual grants. Such reductions were approved by the stockholders in June 2020.

The following table shows for the fiscal year ended December 31, 2021 certain information with respect to the compensation of our Directors:

Director Compensation for Fiscal 2021

Name	Cash Compensation Earned or Paid (\$)	Stock Awards (\$) ⁽¹⁾	Option Awards (\$) ⁽¹⁾	All Other Compensation (\$) ⁽²⁾	Total (\$)
Spencer R. Berthelsen	\$ 100,000	\$ 213,587	\$ 273,240	\$ --	\$ 586,827
Breaux B. Castleman ⁽³⁾	\$ 36,000	\$ --	\$ --	\$ 15,066	\$ 51,066
Stanley T. Crooke	\$ 683,630 ⁽⁴⁾	\$ 326,806 ⁽⁴⁾	\$ 313,853 ⁽⁴⁾	\$ 272,569 ⁽⁵⁾	\$ 1,596,858
Allene M. Diaz ⁽⁶⁾	\$ 35,000	\$ 285,360 ⁽⁷⁾	\$ 409,860 ⁽⁷⁾	\$ --	\$ 730,220
Michael Hayden	\$ 80,000	\$ 213,587	\$ 273,240	\$ 15,066	\$ 581,893
Joan E. Herman	\$ 79,500	\$ 213,587	\$ 273,240	\$ --	\$ 566,327
Joseph Klein, III	\$ 84,000	\$ 213,587	\$ 273,240	\$ 23,013	\$ 593,840
Joseph Loscalzo	\$ 101,250	\$ 213,587	\$ 273,240	\$ --	\$ 588,077
Frederick T. Muto	\$ 92,000	\$ 213,587	\$ 273,240	\$ --	\$ 578,827
B. Lynne Parshall	\$ 86,250	\$ 213,587	\$ 273,240	\$ 615,522 ⁽⁸⁾	\$ 1,188,599
Peter N. Reikes ⁽⁹⁾	\$ 63,641	\$ 213,587	\$ 273,240	\$ --	\$ 550,468
Joseph H. Wender	\$ 150,000	\$ 213,587	\$ 273,240	\$ --	\$ 636,827

- (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, 2021 regarding assumptions underlying valuation of equity awards.
- (2) For Mr. Castleman, Dr. Hayden, Mr. Klein, Ms. Parshall and Dr. Crooke, includes medical, dental and vision benefits, which are available to non-employee directors and all employees of the Company.
- (3) Mr. Castleman did not stand for re-election at the 2021 Annual Meeting of Stockholders.
- (4) Amounts represent cash earned and equity awards granted to Dr. Crooke in his role as Executive Chairman of the Board.
- (5) Following the 2021 Annual Meeting of Stockholders, Dr. Crooke transitioned out of his role as Executive Chairman of the Board. Thereafter, he became a Strategic Advisor to the Company and entered into the Strategic Advisory Services Agreement. As a result of this transition, Dr. Crooke's "All Other Compensation" for 2021 includes consulting fees earned under the Strategic Advisory Services Agreement.
- (6) Ms. Diaz was appointed to the Board in June 2021.

(7) Consists of initial awards of 18,000 stock options and 8,000 RSUs granted to Ms. Diaz upon joining the Board.

(8) On January 15, 2018, Ms. Parshall transitioned out of her role as Chief Operating Officer and retired from Ionis after 28 years of service. Thereafter, she became a Senior Strategic Advisor to the Company and entered into the Amended Advisory Services Agreement. As a result of this transition, Ms. Parshall's "All Other Compensation" for 2021 includes \$600,000 in consulting fees earned under the Amended Advisory Services Agreement. In 2022, Ms. Parshall will receive \$225,000 in consulting fees under the Amended Advisory Services Agreement.

(9) Mr. Reikes resigned from the Board in November 2021.

Outstanding Equity Awards at Fiscal Year-End – Directors

The following table shows for the fiscal year ended December 31, 2021, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors:

Outstanding Equity Awards as of December 31, 2021

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	11,250	--	\$12.94	7/1/2022	9,775	\$297,453
	11,250	--	\$28.47	6/30/2023		
	16,000	--	\$35.53	6/30/2024		
	16,000	--	\$57.16	6/30/2025		
	16,000	--	\$24.42	6/30/2026		
	16,000	--	\$52.22	7/2/2027		
	12,000	4,000	\$42.88	7/1/2028		
	8,000	8,000	\$64.80	6/30/2029		
12,000	--	\$60.20	6/30/2030			
	--	12,000	\$40.05	6/30/2031		
Breux B. Castleman ⁽⁵⁾	12,500	--	\$26.66	6/24/2023	--	--
	11,250	--	\$28.47	6/30/2023		
	16,000	--	\$35.53	6/30/2024		
	16,000	--	\$57.16	6/30/2025		
	16,000	--	\$24.42	6/30/2026		
	16,000	--	\$52.22	7/2/2027		
	12,000	--	\$42.88	7/1/2028		
8,000	--	\$64.80	6/30/2029			
Stanley T. Crooke ⁽⁶⁾	165,000	--	\$61.57	1/1/2022	93,218	\$2,836,624
	195,182	--	\$61.68	1/3/2023		
	163,013	--	\$47.34	1/2/2024		
	154,879	3,296	\$49.25	1/1/2025		
	104,562	38,838	\$53.77	1/1/2026		
	67,902	73,807	\$60.89	1/1/2027		
--	12,000	\$56.78	1/3/2028			
Allene M. Diaz	--	18,000	\$40.05	6/30/2031	8,000	\$243,440
Michael Hayden	24,000	8,000	\$50.80	9/18/2028	10,664	\$324,506
	8,000	8,000	\$64.80	6/30/2029		
	12,000	--	\$60.20	6/30/2030		
	--	12,000	\$40.05	6/30/2031		
Joan E. Herman	16,000	16,000	\$63.90	6/8/2029	15,997	\$486,789
	8,000	8,000	\$64.80	6/30/2029		
	12,000	--	\$60.20	6/30/2030		
	--	12,000	\$40.05	6/30/2031		
Joseph Klein, III	10,667	--	\$57.16	6/30/2025	9,775	\$297,453
	12,000	--	\$24.42	6/30/2026		
	16,000	--	\$52.22	7/2/2027		
	12,000	4,000	\$42.88	7/1/2028		
	8,000	8,000	\$64.80	6/30/2029		
	12,000	--	\$60.20	6/30/2030		
--	12,000	\$40.05	6/30/2031			
Joseph Loscalzo	22,500	--	\$49.09	2/2/2024	9,775	\$297,453
	16,000	--	\$35.53	6/30/2024		
	16,000	--	\$57.16	6/30/2025		
	16,000	--	\$24.42	6/30/2026		
	16,000	--	\$52.22	7/2/2027		
	12,000	4,000	\$42.88	7/1/2028		
8,000	8,000	\$64.80	6/30/2029			

	12,000	--	\$60.20	6/30/2030		
	--	12,000	\$40.05	6/30/2031		
Frederick T. Muto	11,250	--	\$12.94	7/1/2022	9,775	\$297,453
	11,250	--	\$28.47	6/30/2023		
	16,000	--	\$35.53	6/30/2024		
	16,000	--	\$57.16	6/30/2025		
	8,000	--	\$24.42	6/30/2026		
	16,000	--	\$52.22	7/2/2027		
	12,000	4,000	\$42.88	7/1/2028		
	8,000	8,000	\$64.80	6/20/2029		
	12,000	--	\$60.20	6/30/2030		
	--	12,000	\$40.05	6/30/2031		
B. Lynne Parshall ⁽⁷⁾	132,458	--	\$61.57	1/1/2022	15,529	\$472,547
	107,549	--	\$61.68	1/3/2023		
	117,638	--	\$47.34	1/2/2024		
	101,417	2,158	\$49.25	1/1/2025		
	12,000	4,000	\$42.88	7/1/2028		
	8,000	8,000	\$64.80	6/30/2029		
	12,000	--	\$60.20	6/30/2030		
	--	12,000	\$40.05	6/30/2031		
Peter N. Reikes ⁽⁸⁾	--	--	--	--	--	--
Joseph H. Wender	16,000	--	\$35.53	6/30/2024	9,775	\$297,453
	16,000	--	\$57.16	6/30/2025		
	16,000	--	\$24.42	6/30/2026		
	16,000	--	\$52.22	7/2/2027		
	12,000	4,000	\$42.88	7/1/2028		
	8,000	8,000	\$64.80	6/30/2029		
	12,000	--	\$60.20	6/30/2030		
	--	12,000	\$40.05	6/30/2031		



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- (1) Except for the awards Ms. Parshall received when she was an employee, the options have a term of ten years and were granted out of our Non-Employee Director Plan. Initial options granted upon commencement of Board service prior to June 4, 2020 vest at the rate of 25% per year over four years and those granted on or after June 4, 2020 vest 100% on the first anniversary of the date of grant. Annual options that were granted prior to June 4, 2020 vest equally over four years on each anniversary of the date of grant or the next regularly scheduled annual meeting of stockholders, whichever occurs earlier. Annual options that were granted on or after June 4, 2020 vest 100% on either (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier. The options Dr. Crooke and Ms. Parshall received as employees vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter.
- (2) Except for the awards Dr. Crooke and Ms. Parshall received as employees, the RSUs were granted out of our Non-Employee Director Plan. Initial RSUs granted upon commencement of Board service prior to June 4, 2020 vest at the rate of 25% per year over four years and those granted on or after June 4, 2020 vest 100% on the first anniversary of the date of grant. Annual RSUs that were granted prior to June 4, 2020 vest equally over four years on each anniversary of the date of grant or the next regularly scheduled annual meeting of stockholders, whichever occurs earlier. Annual RSUs that were granted on or after June 4, 2020 vest 100% on either (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier.



- (3) All of our non-employee Directors are subject to our Stock Holding and Ownership Guidelines for RSU Shares, which requires each non-employee Director to accumulate and maintain shares of common stock issued pursuant to RSUs until he or she has accumulated shares of common stock equal to four times such non-employee Director's base annual cash retainer for service as a Director (but not for service on a Board committee), or until his or her termination of service.
- (4) Market value of stock awards was determined by multiplying the number of unvested shares by \$30.43, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 31, 2021, the last trading day of fiscal year 2021.
- (5) Pursuant to the applicable award agreements, Mr. Castleman has 18 months following his retirement from the Board to exercise his unvested stock options.
- (6) Reflects awards received by Dr. Crooke during his tenure as an executive officer of the Company.
- (7) Includes awards received by Ms. Parshall during her tenure as an executive officer of the Company.
- (8) In December 2021, Mr. Reikes transferred his shares and vested options to a trust for which neither he nor any member of his immediate family sharing the same household are trustees or beneficiaries.

Option Exercises and Stock Vested

The following table shows for the fiscal year ended December 31, 2021, certain information regarding option exercises and stock awards vested during the last fiscal year with respect to our Directors:

Option Exercises and Stock Vested in Fiscal 2021

Name	Option Awards		Stock Awards	
	Number of Shares Acquired on Exercise (#)	Value Realized on Exercise (\$)	Number of Shares Acquired on Vesting (#)	Value Realized on Vesting (\$)
Spencer R. Berthelsen	15,000	\$ 566,100	8,666	\$ 309,116
Breaux B. Castleman	--	\$ --	8,666	\$ 309,116
Stanley T. Crooke ⁽¹⁾	--	\$ --	47,257	\$ 2,895,909
Allene M. Diaz	--	\$ --	--	\$ --
Michael Hayden	--	\$ --	8,888	\$ 316,022
Joan E. Herman	--	\$ --	10,666	\$ 389,486
Joseph Klein, III	--	\$ --	8,666	\$ 309,116
Joseph Loscalzo	--	\$ --	8,666	\$ 309,116
Frederick T. Muto	15,000	\$ 549,500	8,666	\$ 309,116
B. Lynne Parshall ⁽²⁾	--	\$ --	18,655	\$ 938,298
Peter N. Reikes	--	4 --	8,888	\$ 316,022
Joseph H. Wender	--	\$ --	8,666	\$ 309,116

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



Certain Relationships and Related Transactions

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

Until January 2020, Dr. Rosanne Crooke, the wife of Dr. Stanley Crooke, our former Executive Chairman and Chief Executive Officer, was one of our non-executive officers working part time at 30 hours per week. In January 2020, Dr. Rosanne Crooke transitioned to a Senior Strategic Advisor for the Company. The Compensation Committee approved Dr. Rosanne Crooke's compensation as an employee and Senior Strategic Advisor. As an employee, her compensation was commensurate with the compensation of other employees at the same level at Ionis. For the fiscal years ended 2021, 2020 and 2019, she received the following compensation:

Name and Principal Position	Year	Salary (\$)	Bonus ⁽³⁾ (\$)	Stock Awards ⁽⁴⁾ (\$)	Option Awards ⁽⁴⁾ ⁽⁵⁾ (\$)	All Other Compensation ⁽⁶⁾ (\$)	Total (\$)
Rosanne Crooke, Senior Strategic Advisor	2021	--	--	--	--	\$12,000 ⁽¹⁾	\$12,000
	2020	\$23,859 ⁽²⁾	--	\$344,123	\$375,716	\$195,193	\$938,891
	2019	\$252,199	\$113,490	\$310,642	\$327,305	\$45,583	\$1,049,220

- (1) Represents consulting fees earned by Dr. Rosanne Crooke as a Senior Strategic Advisor.
- (2) As of January 15, 2020, Dr. Rosanne Crooke transitioned to a Senior Strategic Advisor. The amount reflected represents Dr. Rosanne Crooke's salary as an Ionis employee prior to the commencement of her Strategic Advisory Services Agreement and the vacation pay-out upon termination of her employment with the Company.
- (3) We present bonuses in the years they were earned, not in the year paid. Bonuses represent compensation for achievements and are not necessarily paid in the year they are earned; for example, in January 2021 we paid bonuses for 2020 performance.
- (4) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with ASC 718 for stock and option awards granted to Dr. Rosanne Crooke. ASC 718 expense for the option awards is based on the fair value of the awards on the date of grant using an option-pricing model. The fair value of RSUs is based on the market price of our common stock on the date of grant. For more information, please see Note 4, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2021 regarding assumptions underlying valuation of equity awards.
- (5) These amounts represent the estimated fair values of stock option grants we recognized as share-based compensation expense. The estimated fair value amounts were determined using an option-pricing model and are not indicative of whether Dr. Rosanne Crooke will realize the estimated fair value or any financial benefits from the award. The applicable amounts represent:
- 12,000 shares at \$53.77 per share received on January 2, 2019; and
 - 12,477 shares at \$60.89 received on January 2, 2020.
- (6) For 2020, includes the fees paid to Dr. Rosanne Crooke pursuant to her Strategic Advisory Services Agreement and a \$50,000 Career Achievement Award. For 2020 and 2019, also includes AD&D, Basic Life, and 401(k) matching contributions while she was an employee of the Company, which are available to all employees of the Company.

Dr. Stanley Crooke entered into the Strategic Advisory Services Agreement with the Company effective immediately following the 2021 Annual Meeting of Stockholders to reflect his new role as a Strategic Advisor to the Company. Under the Strategic Advisory Services Agreement, Dr. Crooke provides strategic advice to the Company and continues to participate in the Company's scientific activities. Pursuant to the Strategic Advisory Services Agreement, Dr. Crooke received consulting fees of \$233,333 for services provided in 2021. The Audit Committee of the Board approved the Strategic Advisory Services Agreement, and the Compensation Committee of the Board approved Dr. Crooke's consideration under the Strategic Advisory Services Agreement.

B. Lynne Parshall, who was employed by Ionis for 28 years, became a Senior Strategic Advisor to the Company effective January 2018. Under the Amended Advisory Services Agreement, Ms. Parshall provides strategic advisory services to the Company, including in strategic planning, business development, and with the Company's important relationship with Biogen. Pursuant to the Amended Advisory Services Agreement, Ms. Parshall received consulting fees of \$600,000 for services provided in 2021. For services in 2022, Ms. Parshall will receive consulting fees of \$225,000. The Audit Committee of the Board approved the Amended Advisory Services Agreement, and the Compensation Committee of the Board approved Ms. Parshall's consideration under the Amended Advisory Services Agreement.



Ms. Parshall also serves on the Company's Board, for which she receives the same compensation as the Company provides its other non-employee Directors. If in the future Ms. Parshall ends her board of director service for the Company, for 18 months following such date, the Company will pay Ms. Parshall's COBRA premium payments, or if COBRA is not available, an amount equal to the cost of comparable health insurance coverage. The Amended Advisory Services Agreement will continue until termination by us or Ms. Parshall upon 90 days' advance written notice.

One of our Directors, Joseph Wender, is a Senior Consultant to Goldman Sachs & Co., a firm we engage from time to time for investment banking services. We paid Goldman an aggregate of approximately \$6.5 million in 2021, which amount is substantially less than 5% of Goldman's gross revenues for its 2021 fiscal year.

One of our Directors, Joseph Loscalzo, is Chairman of the Department of Medicine and Physician-in-Chief at Brigham and Women's Hospital, a not-for-profit corporation we engage from time to time for clinical research support services. We paid Brigham and Women's Hospital an aggregate of approximately \$0.4 million in 2021.

In 2021, one of our former Directors, Peter Reikes, was a Vice Chairman in the Investment Banking Division at Stifel, Nicolaus & Company, Inc., a firm we engage from time to time for investment banking services. We paid Stifel an aggregate of approximately \$4.7 million in 2021, which amount is substantially less than 5% of Stifel's gross revenues for its 2021 fiscal year.

In late 2019, the n-Lorem Foundation, a non-profit organization, was formed to provide advanced, experimental RNA-targeted medicines free of charge for life to patients living with ultra-rare diseases. The n-Lorem Foundation was established with an initial investment by our former Executive Chairman of the Board and Chief Executive Officer, Dr. Stanley Crooke, and his wife, Dr. Rosanne Crooke. The Company made a donation of \$500,000 to the n-Lorem Foundation in 2021. Several of the Company's current and former Directors, including Dr. Crooke, Ms. Parshall, Dr. Berthelsen, Dr. Hayden, and Dr. Loscalzo, also serve as Directors for the n-Lorem Foundation. Additionally, until February 2022, Mr. O'Neil, our EVP, General Counsel and Corporate Secretary, served as the Corporate Secretary for the n-Lorem Foundation and Dr. Bennett, our EVP and CSO, serves as a Director and the Chief Technical Officer for n-Lorem. None of our executive officers or Directors is compensated for his or her service to the n-Lorem Foundation.

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

Policies and Procedures Regarding Related Party Transactions

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

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

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



CEO Pay Ratio

Under SEC rules, we disclose below the annual total compensation of our median employee, and the ratio of the annual total compensation of our CEO compared to the annual total compensation of our median employee (“CEO Pay Ratio”). We identified our median employee in 2021 using the following methodology:

- We included all employees of Ionis who were employed by us on December 31, 2021.
- We identified our median employee from this employee population based on the W-2 income for 2021. We did not annualize any of these amounts.

Using this approach, we determined our median employee for 2021 and calculated the annual total compensation of this employee for 2021 in accordance with the requirements of the Summary Compensation Table.

For 2021, the median of the annual total compensation of our employees (other than our CEO) was \$226,222 and the annual total compensation of our CEO, as reported in the Summary Compensation Table included in this Proxy Statement, was \$13,305,673. Based on this information, the ratio of the annual total compensation of our CEO to the median of the annual total compensation of all employees was 58 to 1.

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

Currently, neither the Compensation Committee nor our management used the CEO Pay Ratio described above to make compensation decisions. The Compensation Committee does, however, consider the internal pay equity ratios described on page 41 of this Proxy Statement when making compensation decisions.



COMPENSATION COMMITTEE REPORT*

The Compensation Committee has:

- reviewed and discussed the Compensation Discussion and Analysis included in this Proxy Statement with management; and
- based on this review and discussion, the Compensation Committee recommended to the Board of Directors that the Compensation Discussion and Analysis be included in our Proxy Statement relating to the 2022 Annual Meeting of Stockholders.

The Compensation Committee

Spencer R. Berthelsen, *Chairman*

Frederick T. Muto

Joseph H. Wender

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



AUDIT COMMITTEE REPORT*

The Audit Committee is made up entirely of independent Directors and operates under a written charter that has been adopted by the Board of Directors and is reviewed annually. During fiscal year 2021, the Audit Committee fulfilled its duties and responsibilities as outlined in the charter. At its meetings, the Audit Committee meets as a group with members of the Company's financial management, the independent auditors, and the internal auditors (a function that was enhanced in 2019). In addition, the Audit Committee regularly holds separate, private, executive sessions with senior management, the independent auditors, and internal audit team to discuss applicable audit matters and provide oversight.

The Audit Committee oversees our financial reporting process on behalf of the Board of Directors. Management has the primary responsibility for the financial statements and the financial reporting process, including the systems of internal controls. In fulfilling its oversight responsibilities, the Audit Committee reviewed the audited consolidated financial statements and the related schedules in our Annual Report on Form 10-K for the fiscal year ended December 31, 2021 with management, including a discussion of the quality, not just the acceptability, of the accounting principles, the reasonableness of significant judgments, and the clarity of disclosures in the financial statements.

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

The Audit Committee also reviewed and discussed together with management and the independent auditors the audited consolidated financial statements for the fiscal year ended December 31, 2021, 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, 2021 for filing with the SEC. The Audit Committee and the Board have also approved, subject to stockholder ratification, the selection of Ernst & Young LLP as our independent auditors for 2022.

The Audit Committee
Joseph Klein, III, *Chair*
Joan Herman
Frederick T. Muto

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



HOUSEHOLDING OF PROXY MATERIALS

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

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

Other Matters

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

For further information about Ionis Pharmaceuticals, Inc., please request a free copy of our Annual Report on Form 10-K for the year ended December 31, 2021 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.com¹³) to view our 2021 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 20, 2022

¹³ Any information that is included on or linked to our website is not part of this Proxy Statement or any registration statement or report that incorporates this Proxy Statement by reference.



Special Note Regarding Forward-Looking Statements

This Proxy Statement and the information incorporated herein by reference includes forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen), eplontersen, olezarsen, donidalorsen, ION363, pelacarsen, tofersen, and our technologies and products in development. Any statement describing our goals, expectations, financial or other projections, intentions or beliefs, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning our programs are described in additional detail in our Annual Report on Form 10-K for the year ended December 31, 2021, which is on file with the SEC. Copies of the 10-K and other documents are available from the Company.

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

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



FOR THE SHAREHOLDERS OF, INC.
 2055 GAZELLE COURT
 DUBLINO, CALIFORNIA 94568
 ATTN: CORPORATE SECRETARY



SCAN TO
 VIEW MATERIALS & VOTE



VOTE BY INTERNET - www.proxyvote.com or scan the QR Barcode above
 Use the Internet to transmit your voting instructions and for electronic delivery of information up until 11:59 P.M. Eastern Time the day before the meeting date. Have your proxy card in hand when you access the web site and follow the instructions to obtain your records and to create an electronic voting instruction form.

During The Meeting - Go to www.proxyvote.com/holdertesting.com/00MS2022
 You may attend the meeting via the Internet and vote during the meeting. Have the information that is printed in the box marked by the arrow available and follow the instructions.

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

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

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

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

THIS PROXY CARD IS VALID ONLY WHEN SIGNED AND DATED.

<p>The Board of Directors recommends you vote FOR the following nominees to be elected for a term expiring in 2025:</p> <p>1. Election of Directors</p> <p>Nominees</p> <p>01) Allana M. Diaz 02) Michael Hayden 03) Joseph Klais, III 04) Joseph Loscalzo</p> <p>The Board of Directors recommends you vote FOR proposals 2 and 3.</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 2022 fiscal year.</p> <p>NOTE: Such other business as may properly come before the meeting or any adjournment thereof.</p> <p>Please sign exactly as your name(s) appear(s) hereon. When signing as attorney, executor, administrator, or other fiduciary, please give full title of such. Joint owners should each sign personally. All holders must sign. If a corporation or partnership, please sign in full corporate or partnership name by authorized officer.</p>	<p style="text-align: center;">for All Withhold for All For All Except</p> <p style="text-align: center;"> <input type="checkbox"/> <input type="checkbox"/> <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> <hr style="width: 50%; margin-left: 0;"/>
<p>Signature (PLEASE SIGN WITHIN BOX) Date</p>	<p>Signature (Joint Owners) Date</p>

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

IONIS PHARMACEUTICALS, INC.
Annual Meeting of Stockholders
June 2, 2022 2:00 PM Pacific Time
This proxy is solicited by the Board of Directors of
Ionis Pharmaceuticals, Inc.

The undersigned hereby appoints Brett Moris and Elizabeth L. Hougen, and each of them, with power to act without the other and with power of substitution, as proxies and attorneys-in-fact and hereby authorizes them to represent and vote, as provided on the reverse side, all the shares of Ionis Pharmaceuticals, Inc. Common Stock which the undersigned is entitled to vote and, in their discretion, to vote upon such other business as may properly come before the Annual Meeting of Stockholders of the Company to be held June 2, 2022 at www.virtualshareholdermeeting.com/IONS2022 or any adjournment thereof with all powers which the undersigned would possess if present at the meeting.

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

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Continued and to be signed on reverse side

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