

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 2023 ANNUAL MEETING OF STOCKHOLDERS
AND PROXY STATEMENT**

Dear Stockholders,

I am pleased to invite you to Ionis Pharmaceuticals, Inc.'s 2023 Annual Meeting of Stockholders to be held on June 1, 2023. 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/IONS2023, 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 2023 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



A Genetic Medicines Company

NOTICE OF 2023 ANNUAL MEETING OF STOCKHOLDERS

Date: June 1, 2023

Time: 2:00 p.m. Pacific Time

Place: Online only: www.virtualshareholdermeeting.com/IONS2023

Record Date: April 3, 2023. If you were an Ionis stockholder of record at the close of business on April 3, 2023, 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, Spencer R. Berthelsen, Joan E. Herman, B. Lynne Parshall, and Joseph H. Wender, to our Board of Directors to serve as Directors for a three-year term;
2. To make an advisory vote on executive compensation;
3. To make an advisory vote on the frequency of future advisory votes on executive compensation;
4. To approve an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance under such plan by 5,500,000 shares to an aggregate of 35,200,000 shares;
5. To ratify increasing the vesting of future initial stock option and restricted stock unit awards to new non-employee Directors from one year to three years;
6. To ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2023 fiscal year; and
7. 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/IONS2023. 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, 2023

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

PROXY STATEMENT
FOR THE 2023 ANNUAL MEETING OF STOCKHOLDERS

To Be Held on June 1, 2023

QUESTIONS AND ANSWERS ABOUT THESE PROXY MATERIALS AND VOTING

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

The Board of Directors (the “*Board*”) of Ionis Pharmaceuticals, Inc. (the “*Company*”) is soliciting your proxy to vote at the 2023 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 April 21, 2023 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, 2023.

Where and when is the Annual Meeting?

The Annual Meeting will be held on Thursday, June 1, 2023, 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/IONS2023.

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 3, 2023 can listen to and participate in the Annual Meeting live via the internet at www.virtualshareholdermeeting.com/IONS2023. **The webcast will begin at 2:00 p.m. Pacific Time on June 1, 2023. Stockholders may vote and submit questions while connected to the Annual Meeting on the Internet.** A summary of the information you need to attend the Annual Meeting online is provided below.

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



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

You will need the 16-digit control number included on your Notice of Internet Availability of Proxy Materials, proxy card or voting instruction form that accompanied your proxy materials 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/IONS2023.**

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/IONS2023 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 3, 2023 may attend and vote at the Annual Meeting. On this record date, there were 143,023,414 shares of common stock outstanding and entitled to vote.

Stockholder of Record: Shares Registered in Your Name

If on April 3, 2023 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 3, 2023 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, Spencer R. Berthelsen, Joan E. Herman, B. Lynne Parshall, and Joseph H. Wender, to our Board of Directors to serve as Directors for a three-year term;
2. **Proposal 2:** make an advisory vote on executive compensation;
3. **Proposal 3:** make an advisory vote on the frequency of future advisory votes on executive compensation;
4. **Proposal 4:** approve an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance under such plan by 5,500,000 shares to an aggregate of 35,200,000 shares;



5. **Proposal 5:** ratify increasing the vesting of future initial stock option and restricted stock unit awards to new non-employee Directors from one year to three years; and
6. **Proposal 6:** ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for our 2023 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/IONS2023.

The procedures for voting are fairly simple:

For Shares Registered in Your Name:

If you are a stockholder of record, you may go to www.proxyvote.com to vote your shares through the Internet up until 11:59 p.m. Eastern Time on May 31, 2023. The votes represented by your proxy will be displayed on the computer screen and you will be prompted to submit or revise your votes as desired.

To vote your shares by telephone, you must first request that we send proxy materials to you by following the instructions included in your Notice. Once you have received your proxy materials, you may vote using a touch-tone telephone by calling 1-800-690-6903 up until 11:59 p.m. Eastern Time on May 31, 2023 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 through 5 regarding (1) the election of Directors, (2) approval, on an advisory basis, of our executive compensation, (3) approval, on an advisory basis, of the frequency of future advisory votes on executive compensation, (4) approval of an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance under such plan by 5,500,000 shares to an aggregate of 35,200,000 shares, and (5) ratification of increasing the vesting of future initial stock option and restricted stock unit awards to new non-employee Directors from one year to three years 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;
3. “For” every year as the preferred frequency of future advisory votes on executive compensation;
4. “For” the approval of an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance under such plan by 5,500,000 shares to an aggregate of 35,200,000 shares;
5. “For” ratification of increasing the vesting of future initial stock option and restricted stock unit awards to new non-employee Directors from one year to three years; and
6. “For” the ratification of the Audit Committee’s selection of Ernst & Young LLP as independent auditors for our 2023 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 22, 2023 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, 2024, 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, stockholders who intend to solicit proxies in support of director nominees other than the Company's nominees must also comply with the additional requirements of Rule 14a-19(b).

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 3, 2023. 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, Proposal 4, Proposal 5 and Proposal 6 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 through 5 regarding (1) the election of Directors, (2) approval, on an advisory basis, of our executive compensation, (3) the advisory vote on the frequency of future advisory votes on executive compensation, (4) approval of an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance under such plan by 5,500,000 shares to an aggregate of 35,200,000 shares, and (5) ratification of increasing the vesting of future initial stock option and restricted stock unit awards to new non-employee Directors from one year to three years, are all 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 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:** For the advisory vote on the frequency of stockholder advisory votes on executive compensation, we will consider the frequency receiving the most “For” votes from the holders of shares present or represented by proxy and entitled to vote as the frequency preferred by the stockholders. Abstentions and broker non-votes, if any, will have no effect.
4. **Proposal 4:** To be approved, the amendment of the 2011 Equity Incentive Plan must receive “For” votes from the holders of a majority of shares present or represented by proxy 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 will have no effect.
5. **Proposal 5:** To be approved, ratification of increasing the vesting of future initial stock option and restricted stock unit awards to new non-employee Directors from one year to three years must receive “For” votes from a majority of shares present or represented by proxy 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 will have no effect.
6. **Proposal 6:** To be approved, the ratification of the selection of Ernst & Young LLP as our independent auditors for our 2023 fiscal year must receive “For” votes from a majority of the holders of shares present or represented by proxy and entitled to vote on the matter. If you “Abstain” from voting, it will have the same effect as an “Against” vote. 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/IONS2023.



Environmental, Social and Governance Initiatives

At Ionis, we work with a sense of urgency to discover, develop and deliver breakthrough medicines to create a better future for people with devastating diseases. We believe operating responsibly and sustainably creates value for the Company and our stakeholders. We consider the long-term impact we can make across five key areas:

	PATIENTS	At the core of everything we do is the belief in the potential of our medicines to transform lives.
	INNOVATION	We are a science-centric organization dedicated to the perseverance and rigor that the scientific approach demands.
	EMPLOYEES	We offer a rewarding and supportive environment that empowers our employees to thrive.
	COMMUNITIES	We are proud of the work we do to support and uplift our communities.
	ENVIRONMENT	We believe we have a responsibility to help create a better, more sustainable future.

We continue to build our corporate responsibility program and environmental, social and governance (“ESG”) framework to support our ongoing commitment to operate our business responsibly and sustainably. In 2022, we established a formal Corporate Responsibility Steering Committee (the “*Steering Committee*”) to guide us as we develop the right programs and policies to continue to integrate ESG across our organization. Our corporate responsibility initiatives, policies and programs are reviewed on a regular basis by the Steering Committee and its recommendations are key to driving efforts to advance our corporate responsibility strategy to support our growth. The Steering Committee reports to our Chief Executive Officer (“CEO” or “PEO”) and consists of senior leaders in key functions across the Company, including legal, finance, human resources and corporate affairs.

Product Quality and Safety

Our senior management is focused on proactively managing risks associated with quality and safety. The Ionis Quality Steering Committee oversees our quality programs including our formal Quality Management System (“QMS”). In addition, our team of researchers and developers receive training according to internationally recognized current Good Laboratory Practice (“GLP”), Good Clinical Practice (“GCP”), Good Manufacturing Practice (“GMP”), Good Distribution Practice (“GDP”) and Good Pharmacovigilance Practice (“GVP”) standards.

Safety of Clinical Trial Participants

Clinical research is a key component of developing safe and effective new medicines to treat diseases where no other therapeutic approaches have proven effective. We require adherence to GCP guidance and regional laws and regulations for designing and conducting clinical trials and reporting trial results. Additionally, Independent Review Boards (“IRBs”) monitor the ethical conduct of our trials and have the authority to approve, modify or stop trials. Independent ethics committees, IRBs and health authorities review and approve essential clinical trial documents, such as protocols and informed consent forms before they are used.

Access to Medicines

At Ionis, we believe the goal of making life-changing medicines available to patients in need is achieved through rigorous science, innovation and well-designed clinical studies, followed by regulatory approval. We also recognize that to fulfill this goal, 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 the people we serve. We also have an Expanded Access Policy that aims to provide access to investigational products based on select criteria and to support those patients with a serious or immediately life-threatening condition who have exhausted all available medical options and are unable to enroll in any ongoing clinical study.



Human Resources Management

Our pursuit of excellence begins with our talent recruitment process. 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 that will add to our culture and organizational capacity. We also offer internships, post-doctorate fellowships and clinical fellowships to extend the reach of our talent pipeline.

In addition to our supportive and inclusive culture, we offer employees a combination of robust and meaningful benefits, compensation and well-being programs. Our compensation is awarded based on individual and Company performance. We recognize achievements with salary increases, equity awards, promotions and bonus opportunities. We offer highly competitive benefits to all regular employees who work at least 20 hours per week and a range of industry-leading wellness and stress management initiatives and programs.

Beginning with our employees' first day, we aim to provide them with tools and trainings necessary to succeed at every stage of their careers. Our robust training and development program illustrated in the graphic below, referred to as "The Learning Continuum," supports the development of our employees as they progress through their careers.



Diversity, Equity and Inclusion

Diversity, equity and inclusion ("**DEI**") is embedded within our culture at Ionis. We have a corporate objective to enhance and improve DEI initiatives across our organization supported by our employee-led DEI Advisory Council to our CEO. Our senior management regularly monitors performance against our objectives and our Board of Directors oversees our DEI programs through semi-annual reporting and discussion. We offer a three-part diversity training series, which focuses on unconscious bias, inclusion and belonging, and allyship and advocacy. We also provide mandatory anti-discrimination and anti-harassment training for all employees.



To promote DEI within our organization, we have employee-led, executive-sponsored Employee Resource Groups (“ERGs”). Our ERGs are designed to build cultural awareness, promote an inclusive and supportive culture and support our business goals. Many of our ERG employee leaders also serve on the CEO’s DEI Advisory Council. Our ERGs include:

- LGBTQIA+: supports our LGBTQIA+ community;
- empowHer: empowers women at Ionis;
- DEI Advocates: champions DEI initiatives and programs across the organization;
- Mental Health & Wellness: promotes employee mental health and wellness;
- The Parent Network: connects our employees who are parenting young children;
- Ionis NEXT: engages with middle- and high-school students to nurture the NEXT generation of minority science leaders;
- New Employee Opportunity Network: creates community for new employees as they integrate into the Company; and
- Veterans: supports our veteran and military family community.

Our ERGs are designed to build cultural awareness, promote an inclusive and supportive culture and support our business goals.

Employee Health and Safety

We strive to protect the health and safety of all employees, contractors and visitors. We are also committed to providing an injury-free workplace. We have implemented a safety management system that uses monitoring, auditing and target setting to continuously improve our occupational health and workplace safety. Regular safety training is provided to all laboratory and manufacturing employees, and health and safety compliance is audited routinely.

Employee Pay Equity

We are committed to paying our employees fairly, regardless of their gender, race or other personal characteristics. To achieve our objective, we benchmark and evaluate pay based on market data and consider factors such as an employee’s role, experience, performance as well as internal equity. We also regularly review our compensation practices, both in terms of our overall workforce and in terms of individual employees. In 2021, we engaged an independent third-party expert to perform a pay equity analysis that reviewed pay equity by gender, race and age. The results of this analysis did not reveal any pay gaps based on gender, race or age. In 2022, we performed an internal analysis, leveraging our biostatistics team. The analysis showed similar results to the analysis performed in 2021. In addition, we implemented a comprehensive plan to comply with the new California pay transparency law that went into effect on January 1, 2023.

Commitment to Our Communities

Every year we provide support—from financial assistance to employee volunteerism and beyond—to various organizations that have a positive impact in our communities. We seek sustainable partnerships and initiatives that encourage scientific innovation and help address unmet patient needs, including disease awareness, education and support. In 2022, we donated approximately \$2.9 million to charitable groups. We also coordinated volunteering days and provided in-kind support to a range of organizations, including:

- ALS Association, Greater San Diego Chapter: dedicated to finding a cure for ALS and to improving the lives of those living with and affected by ALS;
- ADAPT Functional Movement Center: providing a complete integrative recovery experience for individuals with chronic neurological conditions; and
- Life Science Cares: leveraging the influence of the life science industry to address issues of poverty and inequality in Boston, San Diego, Philadelphia, and the San Francisco Bay Area and through virtual options.

In addition, we have implemented the Adapt X Ionis Hope Scholarship grant program in collaboration with Adapt Functional Movement Center. This program provides fully sponsored care services, rehabilitation programs and education to individuals impacted by ALS. Scholarship grants under this program support ALS patients’ participation in group classes, massage therapy, meditation and functional movement therapy offered by Adapt Functional Movement Center located in Carlsbad, California.



Environmental Sustainability

We are committed to conducting our operations in an environmentally responsible manner to protect our employees, the environment and the communities in which we operate. We have established an environmental management system (“*EMS*”) that establishes policies and procedures, outlines processes for identifying risk and implementing preventative measures, assigns roles and responsibilities and sets performance standards to improve our environmental performance.

Our Carlsbad, California, headquarters was designed and built to meet energy-efficient Leadership in Energy and Environmental Design (“*LEED*”) standards, a green building rating system. Our conference center was also built to the U.S. Green Building Council’s Green Building Codes and Standards in alignment with LEED standards. In addition, we are in the process of constructing a new research and development facility and we recently began work on a new state-of-the-art manufacturing facility, both of which will include sustainability and environmental protection features. We have several solar photovoltaic systems in place for our current buildings and electric vehicle charging stations at our Carlsbad headquarters that are available to all employees and visitors.

Governance and Integrity

We are guided by our Code of Ethics and Business Conduct (“*Code*”) that applies to all employees, including executive officers and all members of our Board of Directors. We are committed to upholding a comprehensive and rigorous ethics program, including anti-bribery and anti-corruption commitments as detailed in our Code and our anti-bribery and anti-corruption policy. We maintain the Ionis Helpline, a confidential 24/7 helpline, hosted through a third-party provider, which is available by phone or web and provided in local languages. We proactively communicate the availability of the Ionis Helpline on our external website, on our internal intranet site and on posters in our buildings.

We encourage you to view our 2022 *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.



ELECTION OF DIRECTORS

Information about our Board

The Board is divided into three classes. Presently, the Board has nine members with two classes consisting of four Directors each and one class consisting of one Director. 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. Our Nominating, Governance and Review Committee of the Board reviews the Company's classified Board structure every year to evaluate whether it continues to be the appropriate structure for the Company. Following such evaluation, we believe maintaining this structure is critical at this time given the Company's recent CEO transition and to enable us to execute on our new commercial strategy, which we believe will generate long-term sustainable value for stockholders.

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 2023 Elections

The Board has nominated four individuals for election at the Annual Meeting. Each of the nominees currently serves as one of our Directors. Spencer R. Berthelsen, Joan E. Herman, B. Lynne Parshall, and Joseph H. Wender have each served as a Director for the periods set forth in the table below.

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

Dr. Berthelsen, Ms. Herman, Ms. Parshall, and Mr. Wender have each been previously re-elected by our stockholders. If re-elected, Dr. Berthelsen, Ms. Herman, Ms. Parshall, and Mr. Wender will serve until the 2026 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 13, 2023, 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 Dr. Berthelsen, Ms. Herman, Ms. Parshall, and Mr. Wender to be elected as Directors at the Annual Meeting. We provide below a short biography for each nominee. Dr. Berthelsen, Ms. Herman, Ms. Parshall, and Mr. Wender have agreed to serve if elected, and we have no reason to believe that they cannot serve. However, if they cannot serve, we may vote your proxy for another nominee proposed by the Board, or the Board may reduce the number of authorized Directors.



Board Skills Matrix

The following tables illustrate (i) the core skills the Nominating, Governance and Review Committee considers to be the most relevant to the Board's oversight role with respect to our business, and (ii) each of our Director's skills in such areas indicated by check mark. The lack of a check mark for a particular item for a Director does not mean the Director lacks that skill; rather, a check mark indicates a specific area of focus or expertise for which the Board relies on such Director. Additional information about each Director's background, business experience and other matters, including a description of how each individual's experience qualifies the Director to serve on the Board, is provided below beginning on the following page of this Proxy Statement.

Industry Experience	Relevant to an industry understanding and oversight of and contribution to our business and strategy
Executive/Leadership Experience	Allows our Directors to successfully advise on and oversee the Company's performance and represent stockholders' interests
Corporate Governance and Public Company Board Experience	Ensures Directors have the background and knowledge to perform oversight and governance roles
Accounting, Financial or Investment Experience	Enables our Directors to analyze our financial statements, oversee our capital structure and consider financial transactions
Scientific, Research or Development Experience	Facilitates the continual improvement of our science and technology and supports our vision of becoming the leader in genetic medicine
Commercial, Marketing, Reimbursement or Sales Experience	Ensures we have appropriate Board expertise to advance our commercial strategy

Director Skills and Qualifications	Spencer R. Berthelsen	Allene M. Diaz	Michael Hayden	Joan E. Herman	Joseph Klein III	Joseph Loscalzo	Brett Monia	B. Lynne Parshall	Joseph H. Wender
Industry Experience	✓	✓	✓	✓	✓	✓	✓	✓	✓
Executive/Leadership Experience	✓	✓	✓	✓	✓	✓	✓	✓	✓
Corporate Governance and Public Company Board Experience	✓	✓	✓	✓	✓	✓	✓	✓	✓
Accounting, Financial or Investment Experience		✓	✓	✓	✓			✓	✓
Scientific, Research or Development Experience	✓	✓	✓			✓	✓	✓	
Commercial, Marketing, Reimbursement or Sales Experience		✓		✓				✓	



Biographies of the Nominees for Election for a Three-Year Term Expiring at the 2026 Annual Meeting

Spencer R. Berthelsen, M.D., age 70², 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 69, 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 Elevance (formerly Anthem, which was 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). Ms. Herman also serves on the board of managers of Fifth Avenue Private Equity 17. 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. Ms. Herman also brings valuable cybersecurity experience to the Board through her cybersecurity certification from the National Association of Corporate Directors (“NACD”).

B. Lynne Parshall, age 68, has served as a Director of Ionis since September 2000. Ms. Parshall is CEO of Lyme Pinnacle Consulting, which provides strategic advisory services to biotechnology companies. Ms. Parshall was a Senior Strategic Advisor to Ionis from January 2018 to December 2022. 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 Foghorn Therapeutics Inc, a public biopharmaceutical company, since August 2022, Cytokinetics, Inc., a public biopharmaceutical company, since February 2013, and Akcea Therapeutics, Inc., from January 2015 until the completion of the Company’s merger with Akcea Therapeutics, Inc. (the “*Akcea Merger*”). Ms. Parshall also serves on the Board of Directors of several private biotechnology companies.

The Board believes Ms. Parshall is uniquely suited to serve on the Board primarily because, as the former Chief Operating Officer and former executive of the Company for over 26 years, she has valuable Company-specific experience and expertise. In addition, Ms. Parshall has over 35 years of experience structuring and negotiating strategic licensing and financing transactions in the life sciences field. She has also sat on the Boards of Directors of numerous biotechnology companies. Ms. Parshall recently received a directorship certification from the NACD for completion of a director education program designed as a framework for continuous learning. Ms. Parshall is also in the process of obtaining a cybersecurity certification from the NACD.

Joseph H. Wender, age 78, 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. He also has a deep understanding of our Company due to his tenure on the Board and provides invaluable advice as we grow and diversify our business.

² The ages of all our Directors are as of March 1, 2023.



Biography of the Director Whose Term Expires at the 2024 Annual Meeting

Brett P. Monia, Ph.D., age 61, 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 33 years to discovering and developing antisense-based drugs. Dr. Monia is the inventor on over 100 issued patents and has directly supervised programs resulting in the clinical development of more than 40 antisense-based drugs across a broad range of therapeutic areas.

Biographies of the Directors Whose Terms Expire at the 2025 Annual Meeting

Allene M. Diaz, age 58, 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 board of directors of Mersana Therapeutics since March 2021. Ms. Diaz served on the board of directors of Allena Pharmaceuticals from April 2019 to September 2022, BCLS Acquisition Corporation from October 2020 to October 2022, and 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 71, has served as a Director of Ionis since September 2018. Dr. Hayden has been Chief Executive Officer and Director 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 Xenon Pharmaceuticals until June 2022, and currently serves on the boards of, 89Bio, AbCellera Biologics and Oxford Biomedica.

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 “Skip” Klein, III, age 61, 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 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 71, has served as a Director of Ionis since February 2014 and as Chairman of the Board since June 2021. Dr. Loscalzo is the Hersey Distinguished Professor of the Theory and Practice of Medicine, the Samuel A. Levine Professor of Medicine at Harvard Medical School and Physician-in-Chief Emeritus 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.

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 32 years of research in the areas of vascular biology, thrombosis, and atherosclerosis, and practical knowledge as a practicing physician. Dr. Loscalzo’s expertise and role as a leading cardiologist is particularly valuable as we advance and grow our cardiovascular franchise.



Independence of the Board 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, although the Company does business with Goldman Sachs & Co. and Brigham and Women's Hospital, neither Mr. Wender nor Dr. Loscalzo, respectively, receives any personal compensation directly from revenue received from Ionis.

Information Regarding the Board and its Committees

Leadership Structure

Mr. Wender has served as our Independent Lead Director since December 2020 and Dr. Loscalzo has served as Chairman of our Board since June 2021. 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. In addition, following the Board's dissolution of the Agenda Committee of the Board in March 2021, Mr. Wender, Dr. Loscalzo and Dr. Monia have worked together to set the agenda for each Board meeting. We will continue to rely on our Chairman of the Board, Independent Lead Director and CEO to set the agendas for future Board meetings and believe this is the appropriate structure to ensure the Board focuses on the most important matters facing our business at each meeting.

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 18 through 23 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 Audit Committee is also responsible for reviewing and discussing the Company's cybersecurity risks.

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 has six committees: an Audit Committee, a Compensation Committee, a Nominating, Governance and Review Committee, a Science/Medical Committee, a Finance Committee, and a 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 2022. Each Director serving as of December 31, 2022 attended 75% or more of the aggregate number of meetings of the Board and the committees on which such Director served during 2022. 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 until September 2022.

Name	Audit	Compensation	Compliance	Finance	Nominating, Governance and Review	Science/ Medical**	Attended 2022 Annual Meeting
Dr. Spencer R. Berthelsen	--	X*	--	--	X	X	X
Ms. Allene M. Diaz	--	--	X	--	--	--	X
Dr. Michael Hayden	--	--	--	--	--	X*	--
Ms. Joan E. Herman	X	--	X	--	--	--	X
Mr. Joseph Klein, III	X*	--	--	--	--	--	X
Dr. Joseph Loscalzo	--	--	--	--	X	X	--
Dr. Brett P. Monia	--	--	--	--	--	--	X
Mr. Frederick T. Muto***	X	X	--	X	X	--	--
Ms. B. Lynne Parshall	--	--	X*	X	--	--	--
Mr. Joseph H. Wender	--	X	--	X*	X*	--	X
Total meetings in fiscal year 2022	9	10	5	4	3	3	

* Committee Chairperson

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

*** Mr. Muto resigned from the Board in July 2022.



The table below identifies our current Board and committee members as of September 2022.

Name	Audit	Compensation	Compliance	Finance	Nominating, Governance and Review	Science/ Medical**
Dr. Spencer R. Berthelsen	--	X*	--	--	X	X
Ms. Allene M. Diaz	X	--	X	--	--	--
Dr. Michael Hayden	--	--	--	--	--	X*
Ms. Joan E. Herman	X	X	X	--	--	--
Mr. Joseph Klein, III	X*	--	--	X	--	--
Dr. Joseph Loscalzo	--	--	--	--	X	X
Dr. Brett P. Monia	--	--	--	--	--	--
Ms. B. Lynne Parshall	--	--	X*	X	--	--
Mr. Joseph H. Wender	--	X	--	X*	X*	--

* Committee Chairperson

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

Audit Committee

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

The Audit Committee:

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

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

- receiving and considering our independent auditors' comments as to the audit of the financial statements and internal controls, adequacy of staff and management performance and procedures in connection with internal controls;
- reviewing and, if appropriate, approving related party transactions;
- establishing and enforcing procedures for the receipt, retention, and treatment of complaints regarding accounting or auditing improprieties;
- pre-approving all audit and non-audit services provided by our independent auditors that are not prohibited by law;
- 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 is responsible for reviewing and discussing the Company’s cybersecurity risks. The Audit Committee periodically meets with the Company’s informatics management and with the Company’s independent auditors regarding their annual audit procedures, which include information technology. Ms. Herman has obtained a cybersecurity certification from the NACD and Ms. Parshall is in the process of obtaining such cybersecurity certification. In addition, we utilize an information security awareness training program that is available to all employees. We are not aware of any breaches of our information security systems in the last three years.

The Audit Committee typically meets twice each quarter: once face-to-face in connection with quarterly Board of Directors meetings, and once by teleconference to review quarterly financial results and Form 10-Q or annual financial results and Form 10-K. In 2022, the Audit Committee met nine times. The Board has adopted a written Audit Committee charter, which you can find on our corporate website at www.ionispharma.com.³ Each member meets the membership criteria set forth in the Audit Committee charter and as stated above.

Compensation Committee

The primary function of the Compensation Committee of the Board is to review, modify (as needed) and approve our overall compensation strategy and policies for our executive officers and recommend that the Board approve the compensation and other terms of employment for 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 48 through 75 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 ten times in 2022. The Compensation Committee acted by unanimous written consent (“*UWC*”) 17 times, which number has increased in recent years 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

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

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



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, 2022, our Compensation Committee was composed of Dr. Berthelsen, Mr. Wender, Mr. Muto (until July 2022) and Ms. Herman (beginning in September 2022). 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 three times during 2022. You can find our Nominating, Governance and Review Committee charter on our corporate website at www.ionispharma.com.⁵

Director Nominations - Minimum Qualifications

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;
- 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.

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.



In considering Director nominations, the Nominating, Governance and Review Committee considers the total mix of competencies represented on the Board as a whole, as well as the competencies each member, or nominee, brings to the Board. In general, our Board members' experience falls into three large categories: (1) investment banking, financial accounting, and corporate governance experience; (2) medical and scientific expertise; and (3) experience with the commercialization of pharmaceutical products. 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 commercial strategy, we will benefit from Board members with backgrounds in the commercialization of pharmaceutical products. In different ways, these 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 advance our commercial strategy.

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 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

Board Diversity Matrix (as of February 8, 2023)				
Total Number of Directors	9			
	Female	Male	Non-Binary	Did Not Disclose Gender
Part I: Gender Identity	3	6	0	0
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+	1	--	--	--
Did not disclose demographic background	--	--	--	--

Director Nominations – Tenure

Our drug technology is a “platform technology,” which means the more knowledge and experience an individual has with our technology platform, the better equipped that individual is to create value at Ionis. This is no different for our non-employee Directors. While we believe it’s important to add new non-employee Directors that will bring fresh ideas and perspectives, given the uniqueness and complexity of our technology, it is also critical to retain the knowledge and experience of an appropriate number of outstanding long service non-employee Directors who can contribute to our future business decisions while understanding our history.



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.



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 2022.

Finance Committee

The primary function of the Finance Committee of the Board is to advise the Board and management on certain corporate finance matters for the Company and its subsidiaries, including capital structures, financings, investments, and share repurchase activities. The Finance Committee met four times in 2022.

Compliance Committee

The Compliance Committee met five times in 2022. 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

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



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, 2022), 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 2023 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 48 through 75. 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 2024 Annual Meeting of Stockholders.



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:

✓ General compensation principles	We design our compensation structure to drive the creation of long-term stockholder value and mitigate unnecessary or imprudent business risk taking. Specifically, we: <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.
✓ Align executive compensation with Company performance and design performance based awards to drive creation of long-term stockholder value	We tie a significant portion of our executive officers’ compensation to Company performance and design performance-based awards to drive the creation of long-term stockholder value. For example, we: <ul style="list-style-type: none"> • Allocated 65% of our Chief Executive Officer’s 2022 compensation in the form of performance-based compensation, which we consider to consist of cash bonuses, stock options and PRSUs; • Revised our PRSU structure for grants made in 2023 and going forward such that: <ul style="list-style-type: none"> ○ awards will have a single vesting period at the end of three years; and ○ the relative TSR percentile rank for maximum payout of the awards increased from the 75th percentile to the 90th percentile. • 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, which occurred in 2021.
✓ Stock ownership and holding guidelines	We maintain stock ownership and holding guidelines that require our executive officers and non-employee Directors to meet certain ownership thresholds. We increased such ownership requirements for non-employee Directors in 2023.
✓ Clawback policy	We use an executive “clawback” policy that applies to all Section 16 officers.
✓ Disallow hedging and pledging	We do not allow pledging, shorting, or hedging against our stock by Directors or employees.
✓ No option re-pricing or cash buyouts	We do not reprice or “cash-out” stock options without stockholder approval.
✓ Engage an independent compensation consultant	The Compensation Committee has retained a compensation consultant whose relationship with the Company was confirmed to be independent for 2022. The compensation consultant, among other things, assists us in selecting an appropriate peer group and annually reviewing our compensation levels, policies, practices, and procedures for our employees and non-employee Directors compared to our peer group.
✓ Use a “double trigger” for change of control for our executive officers	We use a “double trigger” for cash payments and equity acceleration for change of control for our executive officers.
✓ Hold a “say on pay” vote annually	Provides an effective way for us to obtain information on stockholder sentiment about our executive compensation program each year.



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

ADVISORY VOTE ON THE FREQUENCY OF THE VOTE ON EXECUTIVE COMPENSATION

The Dodd-Frank Act and Section 14A of the Exchange Act enable our stockholders to indicate their preference at least once every six years regarding how frequently we should solicit a non-binding advisory vote on the compensation of our named executive officers as disclosed in our proxy statement. Accordingly, consistent with the preference expressed by our stockholders at the 2017 Annual Meeting of Stockholders, as required by these rules, we are presenting this proposal, commonly known as a “say-on-frequency vote,” which gives you as a stockholder the opportunity to inform us regarding how often you wish us to include a “say-on-pay” proposal, similar to Proposal 2, in our Proxy Statement. Please note that as a stockholder you have the choice to vote for one of the following choices, as indicated on the proxy card: to hold the advisory vote on executive compensation every year, every two years, every three years, or to abstain from voting.

Board Recommendation

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

Required Vote of Stockholders

We will consider the frequency with the highest number of votes from the holders of shares present or represented by proxy at the Annual Meeting and entitled to vote as the frequency preferred by the stockholders. If you indicate on your proxy to “Abstain” from voting, it will not have an effect on this Proposal 3. Brokers do not have discretion to vote uninstructed shares with respect to this Proposal 3. Accordingly, if brokers do not receive voting instructions from beneficial owners of the shares, they cannot vote the shares. Therefore, broker non-votes will not affect the outcome of the voting on this Proposal 3.

While this say-on-frequency vote is advisory in nature and therefore will not bind us to adopt any particular frequency, our Board of Directors intends to carefully consider the stockholder vote resulting from the proposal in determining how frequently we will hold “say-on-pay” votes.

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



APPROVAL OF AN AMENDMENT OF OUR 2011 EQUITY INCENTIVE PLAN

In March 2011, the Compensation Committee of the Board, and the Board, adopted the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan (the “**2011 Plan**”) and the stockholders approved the Plan on June 16, 2011. The stockholders have approved amendments to the 2011 Plan to increase the aggregate number of shares of common stock authorized for issuance under the 2011 Plan as follows: on June 30, 2015, an increase of 5,500,000 to an aggregate of 11,000,000 shares; on May 24, 2017, an increase of 5,000,000 to an aggregate of 16,000,000 shares; on June 6, 2019, an increase of 7,000,000 to an aggregate of 23,000,000 shares; and in March 2021, an increase of 6,700,000 shares to an aggregate of 29,700,000 shares.

In this Proposal 4, we are requesting stockholders to approve an amendment of the 2011 Plan to increase the aggregate number of shares of common stock authorized for issuance under the 2011 Plan by 5,500,000 shares to an aggregate of 35,200,000 shares.

Our management, Board and Compensation Committee believe that stock options, restricted stock units (“**RSUs**”) and performance-based restricted stock units (“**PRSUs**”) are a key aspect of our ability to attract and retain qualified personnel in the face of intense competition for experienced scientists and other personnel among many pharmaceutical and health care companies. On March 14, 2023, the Board, upon the recommendation of the Compensation Committee, approved an amendment to the 2011 Plan to increase the aggregate number of shares of common stock authorized for issuance under the 2011 Plan by 5,500,000 to an aggregate of 35,200,000 shares, to ensure that for a period of at least one year, based on our current business plans, we can continue to grant stock options, RSUs and PRSUs to employees at appropriate levels as determined by the Compensation Committee. If the stockholders do not approve this Proposal 4, and as a consequence, we cannot continue to grant options, RSUs and PRSUs at competitive levels, we believe that it will negatively affect our ability to recruit and retain highly qualified personnel and our ability to manage future growth. Without these additional shares, management expects that the current shares available for grant under the 2011 Plan will not be sufficient to maintain our stock award practices for new employees or for promotions or merit awards for current employees.

Each year the Compensation Committee approves a budget that sets the number of stock options, RSUs and PRSUs we can grant our employees for annual merit awards. We do not grant options, RSUs or PRSUs that exceed this budget without the Compensation Committee’s approval. Over the past three years, the average merit award stock budget set by the Compensation Committee has been approximately 2.2% of our outstanding common stock on an issued and outstanding basis. This stock compensation budget, and therefore our equity compensation burn rate, is well below the ISS-adjusted 4.4% average of our peers.

The 2011 Plan was adopted to ultimately replace the Ionis Pharmaceuticals, Inc. 1989 Stock Option Plan (the “**89 Plan**”). There were only approximately 65,000 shares available as of March 31, 2023 for grant under the 89 Plan; however our practice is not to issue grants under this plan.

The 2011 Plan is our primary means of offering stock options, RSUs and PRSUs to our employees. There were only approximately 3.2 million shares available as of March 31, 2023 for grant under the 2011 Plan. The 2011 Plan also allows us to utilize a broad array of equity incentives and performance cash incentives to secure and retain the services of our employees and to provide long-term incentives that align the interests of our employees with the interests of our stockholders.

We also have the Ionis Pharmaceuticals, Inc. 2020 Equity Incentive Plan (the “**2020 Plan**”) that we assumed in connection with the Akcea Merger. Equity awards granted under the 2020 Plan are reserved solely for legacy employees of Akcea who were employed as of October 12, 2020, which was the completion date of the merger. As of March 31, 2023 we had only 40 employees eligible to receive stock awards under the 2020 Plan. There were approximately 1.0 million shares available as of March 31, 2023 for grant under the 2020 Plan.

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



Employee Equity Incentive Plans
(as of March 31, 2023)

	2011 Plan	2020 Plan	89 Plan
Total number of shares of common stock subject to outstanding stock options	14,006,213	412,681	11,824
Weighted-average exercise price of outstanding stock options	\$48.72	\$41.27	\$36.33
Weighted-average remaining term in years of outstanding stock options	4.59	7.85	0.14
Total number of shares of common stock subject to outstanding full value awards	3,112,666	185,366	--
Total number of shares of common stock available for grant under the plan	3,215,980	978,223	64,997
Total number of shares of common stock available for grant to non-employee Directors under the Non-Employee Director Plan ⁽¹⁾			606,333
Total number of shares of common stock available for grant under other equity incentive plans			--
Total number of shares of common stock outstanding			143,022,539
Per-share closing price of common stock as reported on Nasdaq Capital Market			\$35.74

(1) This amount reflects the number of shares of common stock available as of March 31, 2023 for grant under our 2002 Amended and Restated Non-Employee Directors' Stock Option Plan, which we use *solely* to offer equity awards to our non-employee Directors. With respect to the Non-Employee Directors' Stock Option Plan, the total number of shares of common stock subject to outstanding stock options is 927,000, the weighted-average exercise price of outstanding stock options is \$47.74, the weighted-average remaining term in years of outstanding stock options is 4.98, the total number of shares of common stock subject to outstanding full value awards is 58,658, and the total number of shares of common stock available for grant under the Non-Employee Directors' Stock Option Plan 606,333. We have no equity incentive plans other than the 2020 Plan, 2011 Plan, 89 Plan and the Non-Employee Directors' Stock Option Plan.

Required Vote and Board of Directors Recommendation

Approval of this Proposal 4 requires the affirmative vote of a majority of the holders of shares present or represented by proxy at the Annual Meeting and entitled to vote on the matter. If you indicate on your proxy to "Abstain" from voting, it will have the same effect as an "Against" vote for this Proposal 4. Broker non-votes will have no effect on the outcome of the vote.

Our Board believes that approval of Proposal 4 is in our best interests and the best interests of our stockholders for the reasons stated above.

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

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

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

The 2011 Plan:

- is administered by our Compensation Committee, which is composed entirely of independent Directors;
- has a term ending on June 15, 2031;
- contains a "fungible share counting" structure, whereby the number of shares of our common stock available for issuance under the 2011 Plan is reduced by (i) one share for each share issued pursuant to a stock option or stock appreciation right with an exercise price that is at least 100% of the fair market value of our common stock on the date of grant (an "*Appreciation Award*") granted under the 2011 Plan, and (ii) 1.7 shares for each share issued pursuant to a stock award that is not an *Appreciation Award* (a "*Full Value Award*"). As part of such fungible share counting structure, the number of shares of our common stock available for issuance under the 2011 Plan is increased by (i) one share for each share that becomes available again for issuance under the terms of the 2011 Plan subject to an *Appreciation Award*, and (ii) 1.7 shares for each share that is granted after June 2, 2021 under the 2011 Plan that becomes available again for issuance under the terms of the 2011 Plan subject to a *Full Value Award*;



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

Purpose

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

- retain the highest quality employees while motivating all employees to achieve key drivers of stock value;
- issue fewer shares, thereby reducing dilution;
- better align employee and stockholder interests; and
- encourage long-term holding by executive employees because stock settlement for RSUs does not necessarily require a same-day-sale.

In 2022, we granted our employees a combination of stock options and RSUs under our 2011 Plan, where we allocated 50% of the grant date dollar value to stock options and allocated 50% of the value to RSUs; and assumed that each share subject to an RSU was worth two shares subject to a stock option.



Background

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

Shares Available for Awards

If this Proposal 4 is approved, there will be a total of 35,200,000 shares of our common stock authorized for issuance under the 2011 Plan. If this Proposal 4 is not approved, there will only be approximately 3.2 million shares available for issuance under the 2011 Plan as of March 31, 2023, which, given our future hiring projections, we expect will not be sufficient to maintain our stock award practices for new employees or for promotions or merit awards for current employees.

The following table summarizes the equity awards granted over the last three years, and through March 31, 2023, to our employees under our equity plans. We grant most of our equity awards for each year in January of such year as part of the annual merit compensation process. We have not attempted to forecast our future grant activity due to the number of assumptions that would be necessary to do so and the potential unpredictability of such underlying assumptions and estimates.

Equity Award Grant History Under Employee Equity Plans ⁽¹⁾				
	2020	2021	2022	2023 (through March 31st)
Shares subject to equity awards granted	3,892,931	4,888,667	5,245,896	4,240,416
Shares subject to equity awards canceled	(712,131)	(2,103,394)	(2,464,566)	(1,356,954)
Net shares subject to equity awards ⁽²⁾	3,180,800	2,785,273	2,781,330	2,883,462

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

(2) Shares subject to equity awards that are canceled, forfeited, or withheld for taxes (except shares withheld for taxes for options and SARs) become available for re-issuance under the applicable equity plan. Therefore, net shares for any year is the total shares subject to awards granted in that year less the shares subject to awards canceled, forfeited, or withheld for taxes in such year.

Limited Recycling of Shares Related to Options and SARs

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

Eligibility

All of our employees in the United States and our Directors and consultants are eligible to participate in the 2011 Plan. Our practice, however, is not to grant awards to consultants or non-employee Directors under the 2011 Plan. As of March 31, 2023, we had a total of 758 employees who were eligible to participate in the 2011 Plan.



Administration

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

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

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

Under the 2011 Plan, the Board cannot reprice any outstanding options or SARs by reducing the exercise price of the stock award or cancel any outstanding options or SARs in exchange for cash or other stock awards without obtaining the approval of our stockholders within 12 months prior to the repricing or cancellation and re-grant event.

Minimum Vesting; Restrictions on Accelerated Vesting

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

Dividends and Dividend Equivalents

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

No Evergreen

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

Stock Options

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

Exercise Price; Payment

The exercise price of stock options may not be less than 100% of the fair market value of the common stock subject to the stock option on the date of grant. As of March 31, 2023, the closing price of our common stock as reported on the Nasdaq Global Select Market was \$35.74 per share.



Vesting

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

Term

In general, the term of stock options granted under the 2011 Plan was previously seven years, which we increased to ten years beginning with grants made in January 2022. The 2011 Plan does not allow stock options to have a term that exceeds ten years. Unless the terms of an option holder’s stock option agreement or other agreement with the Company provides for earlier or later termination:

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

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

Consideration

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

Transferability

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

Restricted Stock Unit Awards

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

Restricted Stock Awards

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



Stock Appreciation Rights

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

Performance Awards

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

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

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

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

Changes to Capital Structure

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

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



Corporate Transactions

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

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

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

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

Change in Control

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

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

Plan Amendments

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

Plan Termination

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



Federal Income Tax Information

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

Nonstatutory Stock Options

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

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

Restricted Stock Unit Awards

Generally, the recipient of a restricted stock unit award structured to comply with the requirements of Section 409A of the Code or an exemption to Section 409A of the Code will recognize ordinary income at the time the stock is delivered equal to the excess, if any, of the fair market value of the shares of our common stock received over any amount paid by the recipient in exchange for the shares of our common stock. To comply with the requirements of Section 409A of the Code, the shares of our common stock subject to a restricted stock unit award may generally only be delivered upon one of the following events: a fixed calendar date (or dates), separation from service, death, disability or a change in control. If delivery occurs on another date, unless the restricted stock unit award otherwise complies with or qualifies for an exemption to the requirements of Section 409A of the Code, in addition to the tax treatment described above, the recipient will owe an additional 20% federal tax and interest on any taxes owed.

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

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

Restricted Stock Awards

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

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



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

Stock Appreciation Rights

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

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

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

Section 162(m) Limitations

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

New Plan Benefits

Awards granted under the 2011 Plan to our executive officers and other employees are discretionary and are not subject to set benefits or amounts under the terms of the 2011 Plan, and our Board and our Compensation Committee have not granted any awards under the 2011 Plan subject to stockholder approval of this Proposal 2. Accordingly, the future benefits or amounts that will be received by or allocated to our executive officers and other employees under the 2011 Plan are not determinable.

Plan Benefits

The following table sets forth, for each of the individuals indicated, the total number of shares subject to awards that have been granted under the 2011 Plan as of March 31, 2023.

PLAN BENEFITS 2011 PLAN				
Name and Position	Total Number of Shares	Options	RSUs	PRSUs⁽¹⁾
Brett Monia Chief Executive Officer	1,205,292	757,513	272,339	175,440
Elizabeth L. Hougen Executive Vice President and Chief Financial Officer	436,383	330,048	89,948	16,387
Joseph T. Baroldi Executive Vice President, Chief Business Officer	170,609	106,365	58,099	6,145
Onaiza Cadoret-Manier Executive Vice President, Chief Global Product Strategy and Operations Officer	263,878	164,577	82,914	16,387
Richard S. Geary Executive Vice President, Chief Development Officer	414,548	320,327	79,410	14,811
All Executive Officers as a Group	4,122,751	2,904,447	923,275	295,029
All Non-Employee Directors as a Group	--	--	--	--
All Non-Executive Officer Employees as a Group	14,544,700	11,254,376	3,290,324	--

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

Please see page 47 for information regarding outstanding options and shares reserved for future issuance under our equity compensation plans as of March 31, 2023.



RATIFY INCREASING THE VESTING OF FUTURE INITIAL STOCK OPTION AND RESTRICTED STOCK UNIT AWARDS TO NEW NON-EMPLOYEE DIRECTORS FROM ONE YEAR TO THREE YEARS

In this Proposal 5, we are requesting our stockholders ratify increasing the vesting of future initial stock option and restricted stock unit awards of our new non-employee Directors upon joining the Board such that all initial awards granted under the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan will vest equally over three years on each annual anniversary of the date of grant. These initial awards currently vest on the one-year anniversary of the date of grant or the next regularly scheduled annual meeting of stockholders, whichever occurs earlier.

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 increasing the vesting of future initial stock option and restricted stock unit awards to new non-employee Directors from one year to three years. If you indicate on your proxy to "Abstain" from voting, it will have the same effect as an "Against" vote for this Proposal 5. Broker non-votes will have no effect on the outcome of the vote.

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

DESCRIPTION OF THE 2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN

Below is a high-level summary of the terms of the 2002 Non-Employee Directors' Stock Option Plan, as amended on March 14, 2023 (the "*Amended Directors' Plan*"). This summary is qualified in its entirety by reference to the complete text of the Amended Director's Plan. We encourage our stockholders to read the actual text of the Amended Directors Plan in its entirety, a copy of which we filed with this Proxy Statement as Appendix B. References in this Proposal 5 to our Board of Directors include the Compensation Committee of the Board, where applicable.

Purpose

The purpose of the Amended Directors' Plan is to:

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

Administration

Our Board administers the Amended Directors' Plan. Our Board is empowered to delegate administration of the Plan to a committee of the Board. The Board has the power to construe and interpret the Amended Directors' Plan and stock awards granted under it, and to establish, amend and revoke rules and regulations for its administration.

Stock Subject to the Amended Directors' Plan

An aggregate of 2.8 million shares of common stock are authorized by the Board for issuance under the Amended Directors' Plan. As of March 31, 2023, 606,333 shares were available for future grants under the Directors' Plan.

Eligibility, Option Grants, RSU Awards

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

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



Under the Amended Directors' Plan, awards are set at fixed amounts as follows:

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

Terms of Options

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

Vesting Schedule and Option Exercise. Options granted under the Amended Directors' Plan vest as follows:

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

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

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

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

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

- an optionholder's spouse, children (by birth or adoption), stepchildren, grandchildren, or parents;
- a trust or other entity established solely for the optionholder's benefit or the benefit of the optionholder's spouse, children (by birth or adoption), stepchildren, grandchildren, or parents for estate planning purposes; or
- an organization that is exempt from taxation under Section 501(c)(3) of the Code or to which tax-deductible charitable contributions may be made under Section 170 of the Code.

Furthermore, an optionholder may, by delivering written notice to us, in a form satisfactory to us, designate a third party who, in the event of the optionholder's death, will thereafter be entitled to exercise the option.



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

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

Terms of Restricted Stock Unit Awards

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

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

Vesting. The Amended Directors' Plan provides that each RSU award vests as follows:

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

Payment. An RSU award may be settled by the delivery of shares of common stock, their cash equivalent, any combination thereof or in any other form of consideration, as determined by the Board and contained in the RSU award agreement. RSU awards settle on July 15th of the year in which they vest.

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

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

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

Adjustment Provisions

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

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



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

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

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

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

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

Duration, Amendment and Termination

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

Unless sooner terminated by our Board, the Amended Directors' Plan will terminate on June 1, 2030.

Federal Income Tax Information

Nonstatutory Stock Options

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

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



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

Restricted Stock Unit Awards

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

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

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



PROPOSAL 6

RATIFICATION OF SELECTION OF INDEPENDENT AUDITORS

The Audit Committee has selected Ernst & Young LLP as our independent registered public accounting firm for our 2023 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. If you indicate on your proxy to "Abstain" from voting, it will have the same effect as an "Against" vote for this Proposal 6. Broker non-votes will have no effect on the outcome of the vote.

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, 2022 and 2021, Ernst & Young LLP billed us approximately \$1.9 million and \$1.7 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 \$180,000 and approximately \$400,000 in 2022 and 2021, respectively, related to corporate transactions.

Audit Related Fees

For the fiscal years ended December 31, 2022 and 2021, there were no audit related fees billed by Ernst & Young LLP.

Tax Fees

For the fiscal years ended December 31, 2022 and 2021, Ernst & Young LLP billed us approximately \$120,000 and \$365,000 for each year, respectively, primarily related to professional services on tax projects, of which approximately \$46,000 in 2021 was related to the Akcea Merger.

All Other Fees

During the fiscal years ended December 31, 2022 and 2021, all other fees billed by Ernst & Young LLP were approximately \$11,000 and \$4,000 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, 2022, 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 6.



SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

This table outlines the ownership of our common stock as of March 31, 2023 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	21,307,519	14.90%
The Vanguard Group ⁽⁴⁾ 100 Vanguard Boulevard Malvern, PA 19355	13,546,694	9.47%
T. Rowe Price Investment Management, Inc. ⁽⁵⁾ 101 E. Pratt Street Baltimore, MD 21201	11,678,259	8.16%
BB Biotech AG ⁽⁶⁾ Schwertstrasse 6 CH-8200, Schaffhausen Switzerland	9,635,000	6.74%
BlackRock, Inc. ⁽⁷⁾ 55 East 52 nd Street New York, NY 10055	9,182,911	6.42%
Spencer R. Berthelsen ⁽⁸⁾	256,217	*
Allene M. Diaz ⁽⁹⁾	26,000	*
Michael Hayden ⁽¹⁰⁾	93,109	*
Joan Herman ⁽¹¹⁾	86,665	*
Joseph Klein, III ⁽¹²⁾	118,891	*
Joseph Loscalzo ⁽¹³⁾	172,472	*
B. Lynne Parshall ⁽¹⁴⁾	358,691	*
Joseph H. Wender ⁽¹⁵⁾	220,969	*
Joseph Baroldi ⁽¹⁶⁾	35,379	*
Frank Bennett ⁽¹⁷⁾	294,153	*
Brian Birchler ⁽¹⁸⁾	178,634	*
Onaiza Cadoret-Manier ⁽¹⁹⁾	106,566	*
Richard Geary ⁽²⁰⁾	295,596	*
Elizabeth L. Hougen ⁽²¹⁾	322,199	*
Brett Monia ⁽²²⁾	629,296	*
Patrick R. O'Neil ⁽²³⁾	248,670	*
Eugene Schneider ⁽²⁴⁾	166,306	*
Eric Swayze ⁽²⁵⁾	182,444	*
All Directors and executive officers as a group (eighteen persons) ⁽²⁶⁾	3,792,257	2.65%



*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 143,022,539 shares of common stock outstanding on March 31, 2023, adjusted as required by rules promulgated by the SEC.
- (3) FMR LLC has sole voting power to direct the vote of 21,305,988 shares and sole power to dispose or direct the disposition of 21,307,519 shares. The Fidelity Growth Company Commingled Pool holds the interest of 9,164,615 shares of our common stock, which amounts to 6.41% of our total outstanding as of March 31, 2023.

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.
- (4) The Vanguard Group has shared voting power to direct the vote of 63,584 shares, sole power to dispose or direct the disposition of 13,349,072 shares, and shared dispositive power for 197,622 shares.
- (5) T. Rowe Price Investment Management, Inc. has sole voting power to direct the vote of 4,452,321 shares and sole power to dispose or direct the disposition of 11,678,259 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 8,795,247 shares and sole power to dispose or direct the disposition of 9,182,911 shares.
- (8) Includes 70 shares owned by Dr. Berthelsen's daughter for which he disclaims beneficial ownership. Includes 127,250 shares of common stock issuable upon exercise of options held by Dr. Berthelsen that are exercisable on or before April 30, 2023.
- (9) Includes 18,000 shares of common stock issuable upon exercise of options held by Ms. Diaz that are exercisable on or before April 30, 2023.
- (10) Includes 68,000 shares of common stock issuable upon exercise of options held by Dr. Hayden that are exercisable on or before April 30, 2023.
- (11) Includes 60,000 shares of common stock issuable upon exercise of options held by Ms. Herman that are exercisable on or before April 30, 2023.
- (12) Includes 6,100 shares held in trusts for the benefit of Mr. Klein's three children, 20,000 shares of common stock issuable upon exercise of options held by Mr. Klein that are exercisable on or before April 30, 2023, 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, 2023.
- (13) Includes 138,500 shares of common stock issuable upon exercise of options held by Dr. Loscalzo that are exercisable on or before April 30, 2023.
- (14) Includes 273,213 shares of common stock issuable upon exercise of options held by Ms. Parshall that are exercisable on or before April 30, 2023.



- (15) Includes 104,969 shares of common stock held by Mr. Wender in a trust, and 116,000 shares of common stock issuable upon exercise of options held by Mr. Wender that are exercisable on or before April 30, 2023.
- (16) Includes 851 shares of common stock held by Mr. Baroldi's wife, 27,093 shares of common stock issuable upon exercise of options held by Mr. Baroldi that are exercisable on or before April 30, 2023, and 3,822 shares of common stock issuable upon exercise of options held by Mr. Baroldi's wife that are exercisable on or before April 30, 2023.
- (17) Includes 224,119 shares of common stock issuable upon exercise of options held by Dr. Bennett that are exercisable on or before April 30, 2023.
- (18) Includes 143,309 shares of common stock issuable upon exercise of options held by Mr. Birchler that are exercisable on or before April 30, 2023.
- (19) Includes 85,339 shares of common stock issuable upon exercise of options held by Ms. Cadoret-Manier that are exercisable on or before April 30, 2023.
- (20) Includes 222,636 shares of common stock issuable upon exercise of options held by Dr. Geary that are exercisable on or before April 30, 2023.
- (21) Includes 246,540 shares of common stock issuable upon exercise of options held by Ms. Hougen that are exercisable on or before April 30, 2023.
- (22) Includes 483,991 shares of common stock issuable upon exercise of options held by Dr. Monia that are exercisable on or before April 30, 2023.
- (23) Includes 206,788 shares of common stock issuable upon exercise of options held by Mr. O'Neil that are exercisable on or before April 30, 2023.
- (24) Includes 130,254 shares of common stock issuable upon exercise of options held by Dr. Schneider that are exercisable on or before April 30, 2023.
- (25) Includes 149,928 shares of common stock issuable upon exercise of options held by Dr. Swayze that are exercisable on or before April 30, 2023.
- (26) Includes an aggregate of 2,820,782 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, 2023.

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, 2022:

Plan Category	Number of Shares to be Issued Upon Exercise of Outstanding Options, Warrants and Rights	Weighted Average Exercise Price of Outstanding Options, Warrants and Rights	Number of Shares Remaining Available for Future Issuance
Equity compensation plans approved by stockholders ⁽¹⁾	17,880,481	\$ 50.57	8,158,690 ⁽²⁾
Equity compensation plans not approved by stockholders	--	--	--
Total	17,880,481	\$ 50.57	8,158,690 ⁽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 492,176 remained available for purchase under the ESPP as of December 31, 2022.



Compensation Discussion and Analysis

2022 NEOs, 2022 “Say on Pay” Vote and Summary of Recent Compensation and Governance Changes

Named Executive Officers. At December 31, 2022, our Chief Executive Officer, Chief Financial Officer, and our three other most highly compensated executive officers, called our “named executive officers” or “NEOs,” were as follows:

Name	Title
Brett P. Monia	Chief Executive Officer
Elizabeth L. Hougen	Executive Vice President, Finance and Chief Financial Officer
Joseph T. Baroldi	Executive Vice President, Chief Business Officer
Onaiza Cadoret-Manier	Executive Vice President, Chief Global Product Strategy and Operations Officer
Richard S. Geary	Executive Vice President, Chief Development Officer

“Say on Pay” Vote. In June 2022, 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 85% of stockholder votes cast in favor of our “say on pay” resolution. In evaluating our general compensation practices during 2022 and in early 2023, we were mindful of the strong support our stockholders expressed for our compensation philosophies and practices. We remain committed to considering stockholder feedback on an ongoing basis and ensuring that our compensation practices align with market trends.

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. We believe these changes 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 beginning 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;
- revised the structure of our performance-based equity awards such that they have a single vesting period at the end of three years and require a higher relative TSR percentile rank for maximum payout of the awards (increased from the 75th percentile to the 90th percentile);
- increased the ownership requirements in our stock ownership and holding guidelines applicable to our executive officers and non-employee Directors for 2022, and further increased such holding guidelines for our non-employee Directors in 2023;
- 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 at the 2020 Annual Meeting of Stockholders 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 in 2021 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.

In addition, at the 2023 Annual Meeting of Stockholders, we are asking our stockholders to ratify increasing the vesting term of future initial equity awards granted to our non-employee Directors upon joining the Board such that all initial awards will vest equally over three years instead of vesting at one year.



Business Overview and 2022 Achievements

Overview. We were founded over 30 years ago to deliver new innovative medicines for diseases with great medical need. Today, we are building on our advancements in RNA-targeted therapeutics to move us closer to achieving our vision to be the leader in genetic medicine. We believe our medicines have the potential to pioneer new markets, change standards of care and transform the lives of people with devastating diseases.

Our Vision. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming the leader in genetic medicine, utilizing a multi-platform approach to discover, develop and deliver life-transforming therapies. To achieve our vision, we are focused on the following strategic priorities: delivering an abundance of new medicines to the market, establishing an integrated commercial organization and expanding the reach of our technology platform.

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.

We currently have three marketed medicines: SPINRAZA, TEGSEDI and WAYLIVRA. We also have two medicines currently under regulatory review, that if approved, will add to our commercial portfolio. These medicines are eplontersen to treat patients with polyneuropathy caused by hereditary transthyretin amyloidosis (“**ATTRv-PN**”), and tofersen to treat patients with superoxide dismutase 1 amyotrophic lateral sclerosis (“**SOD1-ALS**”). The FDA accepted the new drug application (“**NDA**”) for eplontersen in March 2023 and accepted the NDA for tofersen in July 2022. Additionally, the European Medicines Agency (“**EMA**”) accepted the Marketing Authorization Application (“**MAA**”) for tofersen in December 2022. The FDA has given the application for eplontersen a Prescription Drug User Fee Act (“**PDUFA**”) action date of December 22, 2023 and the application for tofersen a PDUFA action date of April 25, 2023. In addition to our commercial medicines and medicines under regulatory review, we have a rich innovative late- and mid-stage pipeline primarily focused on our leading cardiovascular and neurology franchises. We currently have seven medicines in Phase 3 development. In addition to our advancing pipeline, in 2022 we expanded and diversified our technology when we advanced new medicines into preclinical development that improve muscle targeting and utilize mesyl phosphoramidate (“**MsPA**”) backbone chemistry. We also entered into a collaboration with Metagenomi to add next generation gene editing capabilities to our technologies.

Our Commercial Vision. Our commercial vision is centered on maximizing the value of our innovative medicines. Today, 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. As we approach our first launches, we have accelerated our commercial build out over the past year. After our planned launch with AstraZeneca of eplontersen for ATTRv-PN, we are well positioned for our first independent launches with olezarsen and donidalorsen, assuming positive data and approved regulatory submissions.

Our Financial Strength. Our financial strength has been an enduring quality of Ionis for many years. Our multiple sources of revenue and strong balance sheet enable us to continue investing in our strategic priorities to achieve commercial readiness for multiple late-stage programs and advance our innovative pipeline. 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 were founded over 30 years ago to deliver new innovative medicines for diseases with great medical need. Today, we are building on our advancements in RNA-targeted therapeutics to move us closer to achieving our vision to be the leader in genetic medicine.



2022 Achievements that Advanced Our Strategic Priorities⁽¹⁾

	Advanced Ionis Near-term Commercial Opportunities Towards the Market	<ul style="list-style-type: none"> ✓ Delivered positive Phase 3 eplontersen NEURO-TTRansform data in ATTRv-PN ✓ Submitted eplontersen NDA for ATTRv-PN ✓ Strengthened Phase 3 eplontersen CARDIO-TTRansform study in ATTR-CM ✓ Completed enrollment in olezarsen Phase 3 BALANCE study in FCS, on track for data H2:2023 ✓ Delivered positive longer-term donidalorsen Phase 2 OLE data in HAE
	Advanced our Rich Late-stage Pipeline	<ul style="list-style-type: none"> ✓ NDA and MAA for tofersen under review ✓ Delivered 9 positive late- and mid-stage data readouts ✓ Delivered positive bepirovirsen & IONIS-FB-L_{Rx} data, on track for Phase 3 starts in H1:23 ✓ Completed enrollment in pelacarsen Phase 3 Lp(a) HORIZON study, on track for data in 2025
	Built our Commercial Organization	<ul style="list-style-type: none"> ✓ Developed core capabilities to enable eplontersen, olezarsen and donidalorsen launches
	Expanded and Diversified Our Technology	<ul style="list-style-type: none"> ✓ Added gene editing capabilities through Metagenomi collaboration ✓ Advanced new programs using advanced medicinal chemistry approaches (e.g., muscle LICA & MsPA backbone) into preclinical development ✓ Initiated clinical development of SPINRAZA follow-on program in SMA
	Strengthened Our Financial Foundation	<ul style="list-style-type: none"> ✓ Began negotiations on royalty financing transaction that was executed in January 2023, generating up to \$1.1B to support investment in long term growth ✓ Executed sale leaseback transaction, valued at up to \$400M

(1) Timing expectations are based on current assumptions and are subject to change.

Our accomplishments last year led us to meet our 2022 financial guidance, achieve revenues of \$587 million and end the year with \$2 billion in cash.



(2) Non-GAAP. See footnote below for additional information regarding non-GAAP financial results⁸.

⁸ We use “non-GAAP” in place of “pro-forma” when discussing our financial results that exclude non-cash compensation expense related to equity awards, 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 Appendix C.

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.

✓ General compensation principles	We design our compensation structure to drive the creation of long-term stockholder value and mitigate unnecessary or imprudent business risk taking. Specifically, we: <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.
✓ Align executive compensation with Company performance and design performance based awards to drive creation of long-term stockholder value	We tie a significant portion of our executive officers’ compensation to Company performance and design performance-based awards to drive the creation of long-term stockholder value. For example, we: <ul style="list-style-type: none"> • Allocated 65% of our Chief Executive Officer’s 2022 compensation in the form of performance-based compensation, which we consider to consist of cash bonuses, stock options and PRSUs; • Revised our PRSU structure for grants made in 2023 and going forward such that: <ul style="list-style-type: none"> ○ awards will have a single vesting period at the end of three years; and ○ the relative TSR percentile rank for maximum payout of the awards increased from the 75th percentile to the 90th percentile. • 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, which occurred in 2021.
✓ Stock ownership and holding guidelines	We maintain stock ownership and holding guidelines that require our executive officers and non-employee Directors to meet certain ownership thresholds. We increased such ownership requirements for our non-employee Directors in 2023.
✓ Clawback policy	We use an executive “clawback” policy that applies to all Section 16 officers.
✓ Disallow hedging and pledging	We do not allow pledging, shorting, or hedging against our stock by Directors or employees.
✓ No option re-pricing or cash buyouts	We do not reprice or “cash-out” stock options without stockholder approval.
✓ Engage an independent compensation consultant	The Compensation Committee has retained a compensation consultant whose relationship with the Company was confirmed to be independent for 2022. The compensation consultant, among other things, assists us in selecting an appropriate peer group and annually reviewing our compensation levels, policies, practices, and procedures for our employees and non-employee Directors compared to our peer group.
✓ Use a “double trigger” for change of control for our executive officers	We use a “double trigger” for cash payments and equity acceleration for change of control for our executive officers.
✓ Hold a “say on pay” vote annually	Provides an effective way for us to obtain information on stockholder sentiment about our executive compensation program each year.



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 recommends that the Board approve the total compensation for our Chief Executive Officer and approves the total compensation for our other 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 recommending that the Board approve the total compensation for our Chief Executive Officer and reviewing and approving the total compensation for our other executive officers;
- reviewing and recommending that the Board approve the 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 2022, Aon primarily provided the Compensation Committee advice in the following areas:

- assessing Board of Directors compensation;
- providing guidance with respect to the implementation of a program to defer vesting of RSU grants to the Board of Directors;
- selecting the 2022 Peer Group used to assess officer and non-employee director compensation;
- reviewing the mix of stock options and RSUs for all employees;
- assessing executive officer compensation, including base salary, bonus and equity grants;
- assessing changes to the Severance Benefits Plan that applies to all employees at the Vice President level and above;
- performing the valuation calculations for our CEO's PRSU awards that vested and paid out in 2022; and
- performing the valuation calculations for equity awards granted in 2020, 2021 and 2022 to calculate compensation actually paid pursuant to Item 402(v) of Regulation S-K.



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 2022, we paid Aon approximately \$173,000 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 2022 that were not related to Aon's Compensation Committee consulting services. Our Human Resources department obtained general benchmarking survey data and performance analytics data from an affiliate of Aon, for which we paid approximately \$40,000 in the aggregate in 2022. Additionally, our Finance department engaged an affiliate of Aon for insurance brokerage services, for which we paid approximately \$780,000 in 2022. 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 in consultation with the Audit Committee of the Board.

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 and create long-term stockholder value:



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. For 2022 performance, the Compensation Committee awarded a Company Performance Factor of 125% in recognition of the Company’s achievement of most of its goals for the year across all aspects of our business.

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 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 stockholders with the payout that the executive officers receive at the end of the performance period.

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.

For PRSU grants made before 2023, one third of such 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. In addition, PRSU grants made before 2023 include an alternative three-year payout mechanism (the “*Alternative Calculation*”) that requires an alternative payout calculation at the end of the final three-year measurement period assuming the only measurement period for all shares under the award was the three-year period. If the Alternative Calculation is greater than payouts under the sum of years one, two and three, then such PRSU award will pay out to achieve the number of shares payable under the Alternative Calculation. For PRSU grants made before 2023, 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.

We evaluated our PRSU structure in 2022 to ensure that it is consistent with market practices and will best incentivize our CEO and executive officers to deliver stockholder value. As a result of this evaluation, beginning with PRSU grants made in 2023, such grants will have a single vesting period at the end of three years. In addition, we increased the relative TSR percentile rank required for maximum payout of the awards from the 75th percentile to the 90th percentile and added additional payout thresholds. The payout thresholds for grants made in 2023 and going forward are as follows:

We evaluated our PRSU structure in 2022 to ensure that it is consistent with market practices and will best incentivize our CEO and executive officers to deliver stockholder value.

Relative TSR Percentile Rank	TSR Performance Multiplier
<25th percentile	0%
25th percentile (Threshold)	50%
50th percentile (Target)	100%
60th percentile	125%
75th percentile	150%
90th percentile (Maximum)	200%

Importantly, **all** of the PRSU grants made since inception of our PRSU program include the following **limitations**:

- 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 the maximum amount depending on the Company’s relative TSR; and
- If the Company’s TSR is negative over the performance period, the payout will not exceed 100% of the target number even if the percentile rank exceeds the 50th percentile.

No number of PRSUs is guaranteed to vest.
If the Company’s TSR is negative over the performance period, the payout will not exceed 100% of the target number.

The PRSUs granted to all of our executive officers in 2022, including our NEOs, paid out to our NEOs in January 2023 as follows:

Performance Period	Ionis' TSR	Relative TSR Percentile Ranking	Percent of Target Number	Total Shares Earned
1 of 3	21.63%	81 st	150%	Dr. Monia: 25,372 Ms. Hougen: 4,140 Ms. Cadoret-Manier: 4,140 Dr. Geary: 3,822

The PRSUs granted to our CEO in 2020 and 2021 paid out in January 2023 as follows:

Grant	Performance Period	Ionis' TSR	Relative TSR Percentile Ranking	Percent of Target Number	Total Shares Earned
2020	3 of 3	-36.01%	54 th	100%	6,511 ⁽¹⁾⁽²⁾
2021	2 of 3	-36.33%	69 th	100%	17,210 ⁽²⁾

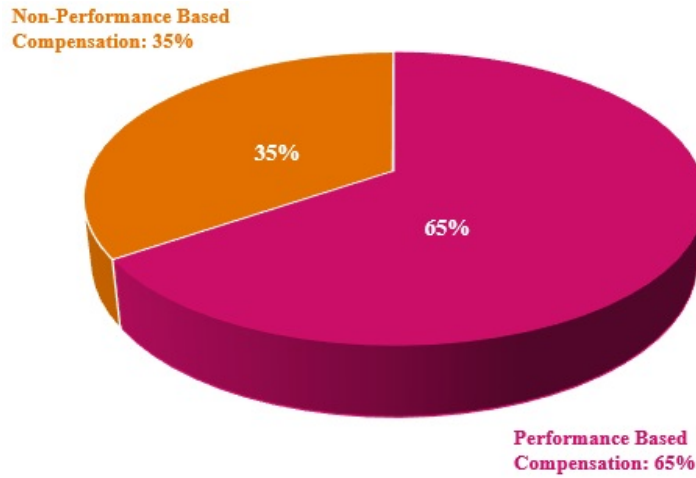
- (1) This PRSU award paid out less than 100% of target for the first and second performance periods, and after conducting the Alternative Calculation, resulted in an additional payout of 1,146 shares under the first performance period and 1,586 shares under the second performance period, yielding in the aggregate a payout for the third performance period of 6,511 shares.
- (2) Despite greater than 50th percentile performance, payout was capped at 100% due to negative TSR.

2022 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) 2022 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.

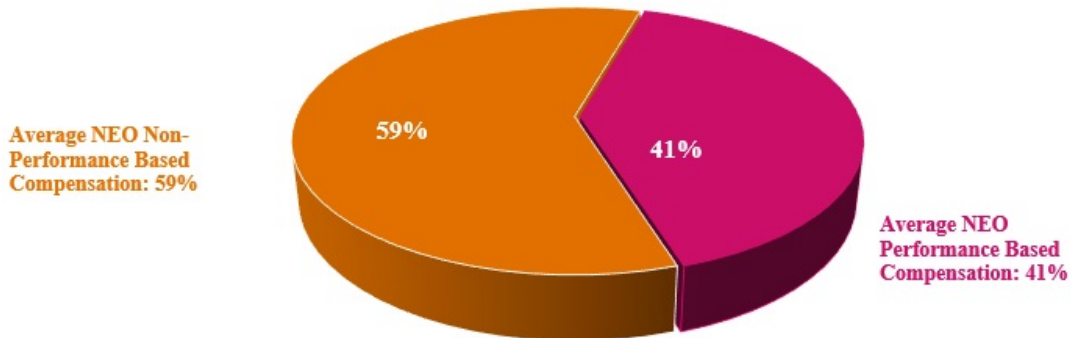
2022 CEO Compensation: Performance Based vs. Non-Performance Based

The performance based compensation reflected below includes the CEO's cash bonus for 2022 performance (\$837,688), fair value of stock options granted in 2022 (\$1,761,806) and fair value of PRSU awards granted in 2022 (\$2,145,668). The non-performance based compensation reflected below includes the CEO's 2022 base salary (\$824,800) and fair value of RSU awards granted in 2022 (\$1,678,645).



2022 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 2022 performance (\$331,003) and average fair value of stock options granted in 2022 (\$787,120). The non-performance based compensation reflected below includes the NEOs' (excluding the CEO) average 2022 base salary (\$534,651) and fair value of RSU awards granted in 2022 (\$1,100,109). Beginning in 2022, the NEOs (excluding the CEO) receive 20% of their total equity awards in the form of PRSUs.



Internal Pay Equity

An executive officer's salary plus bonus represents the officer's total cash compensation. Our philosophy has been to have the CEO's total cash compensation be between 20-30 times the lowest levels of compensation received by an employee. Historically, the total cash compensation of our CEO over a rolling three-year period has been, on average, approximately 30 times that of the average cash compensation for our lowest level employees, and two to three times greater than the average of that of our other executive officers. Our CEO's total cash compensation over the last three years was on average approximately 19 times greater than the average cash compensation for our lowest level employees, and 1.57 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 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.

At the beginning of each year, we set aggressive corporate objectives, including objective measures, that our Board approves. We strive to structure our corporate objectives such that they are results driven rather than task driven to encourage the prudent spending of stockholder money. In other words, we want to structure our objectives to reward success based on judgment, rather than the making of "bad bets." 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, rich 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:

- 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 current executive officers have on average approximately 21 years and individually as much as over 33 years of tenure at Ionis.

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 towards achieving these objectives.

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

- 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 “Career Achievement Award” 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. We recently added 15-year and 25-year milestone anniversaries for which Commitment to Ionis Awards will be awarded and 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 2022, Dr. Geary was awarded such “catch-up” award to recognize his 25 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 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 does 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 and Board’s assessment of our CEO’s and executive officers’ individual performance;

- competitive compensation practices;
- general economic conditions, industry conditions and the Compensation Committee’s and Board’s collective business judgment;
- increased efficiencies and process improvements;
- effective collaboration and teamwork;
- individual expertise, skills and knowledge;
- the need to retain and motivate;
- the impact an individual’s judgment has on our success or failure; and
- the advice of the Compensation Committee’s independent compensation consultant.

We do not have specific weightings assigned to these factors, as the importance of each factor can vary among the executive officers and from year to year.

Peer Group

The Compensation Committee considers relevant market pay practices when setting executive compensation to ensure our ability to recruit and retain high performing talent. As such, on an annual basis, the Compensation Committee compares the compensation opportunity for our executive officers to similarly situated executives at the 25th, 50th and 75th percentiles of the Peer Group as a “market check” to ensure, in its judgment, that the executive officers’ compensation remains appropriate. The Compensation Committee also reviews our compensation policies, practices, and procedures compared to the Peer Group to benchmark compensation for both our executive officers and non-employee Directors. While the Compensation Committee uses these data to inform and shape decision-making, it does not strictly adhere to quantitative benchmarks. The 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’ 2022 compensation (the “*Peer Group*”). The Compensation Committee reviews the compensation of our named executive officers and non-employee Directors against the Peer Group’s executive compensation to ensure that our compensation is competitive and to inform and shape its decision-making when setting compensation.

The 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 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 and non-employee Directors is not available and cost of living is different) or companies in industries whose compensation programs are not comparable to our programs, such as non-life science companies.

In June 2022, the Compensation Committee reviewed the Peer Group using the criteria listed above and publicly available data as of May 2022. The Compensation Committee noted Ionis’ 30-day average market capitalization was approximately \$5.3 billion and trailing 12-month revenue was approximately \$810 million. As part of this process, the Compensation Committee looked at companies in Ionis’ industry with an emphasis on companies with 30-day average market capitalizations of between \$1.5 billion and \$15 billion and trailing 12-month 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 Ironwood Therapeutics to the Peer Group because it fell within the target market capitalization and revenue ranges and is in Ionis’ sector. The Compensation Committee also added Sage Therapeutics to the Peer Group because it fell within the target market capitalization range and is in Ionis’ sector. The Compensation Committee removed BeiGene and Bluebird Bio because they both fell outside the target market capitalization and revenue ranges.

The following table lists the companies in the 2022 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 Peer Group in June 2022.

Company (ticker)	Annual Revenues (in millions) ⁽¹⁾	Market Capitalization (in millions) ⁽²⁾	Stage of Lead Drug
Acadia Pharmaceuticals (ACAD)	\$484.1	\$4,072.8	Market
Agius Pharmaceuticals (AGIO)	\$0.0	\$1,603.1	NDA
Alkermes (ALKS)	\$1,173.8	\$4,472.2	Market
Alnylam Pharmaceuticals (ALNY)	\$844.3	\$19,632.9	Market
BioMarin Pharmaceuticals (BMRN)	\$1,846.3	\$14,897.9	Market
Exact Sciences Corp (EXAS)	\$1,767.1	\$11,923.1	--
Exelixis (EXEL)	\$1,435.0	\$7,086.5	Market
Horizon Therapeutics (HZNP)	\$3,226.4	\$25,026.5	Market
Incyte Corporation (INCY)	\$2,986.3	\$17,543.1	Market
Ironwood Pharmaceuticals (IRWD)	\$413.8	\$1,991.8	Market
Jazz Pharmaceuticals (JAZZ)	\$3,094.2	\$9,908.4	Market
Nektar Therapeutics (NKTR)	\$101.9	\$1,059.1	Market
Neurocrine Biosciences (NBIX)	\$1,133.5	\$9,104.3	Market
PTC Therapeutics (PTCT)	\$538.6	\$2,852.2	Market
Sage Therapeutics (SAGE)	\$6.3	\$2,068.0	Market
Sarepta Therapeutics (SRPT)	\$701.9	\$7,129.9	Market
Ultragenyx Pharmaceutical (RARE)	\$351.4	\$5,201.9	Market
United Therapeutics (UTHR)	\$1,685.5	\$8,252.0	Market
Ionis Pharmaceuticals, Inc. (IONS)	\$810.5	\$5,310.0	Market
Ionis' Percentile Rank	46%	42%	N/A

(1) Trailing 12-month revenue.

(2) 30-day average market cap.

Our Productivity and Strength

In 2022, we had a number of achievements that demonstrated our productivity and strength:

- Earned \$587 million in revenue, met our 2022 financial guidance and ended the year with \$2 billion in cash.
- Announced positive topline results from a 35-week interim analysis of the Phase 3 NEURO-TTRansform study of eplontersen in patients with ATTRv-PN and submitted an NDA with the FDA for eplontersen for the treatment of ATTRv-PN.
- Delivered nine positive data readouts from our mid- and late-stage pipeline, positioning us to add new products to our commercial portfolio and expand our late-stage pipeline.
- Expanded and diversified our technology when we advanced new medicines with enhanced muscle targeting capabilities and utilizing new MsPA backbone chemistry into preclinical development and completed the Metagenomi transaction.

Earned \$587 million in revenue, met our 2022 financial guidance and ended the year with \$2 billion in cash.

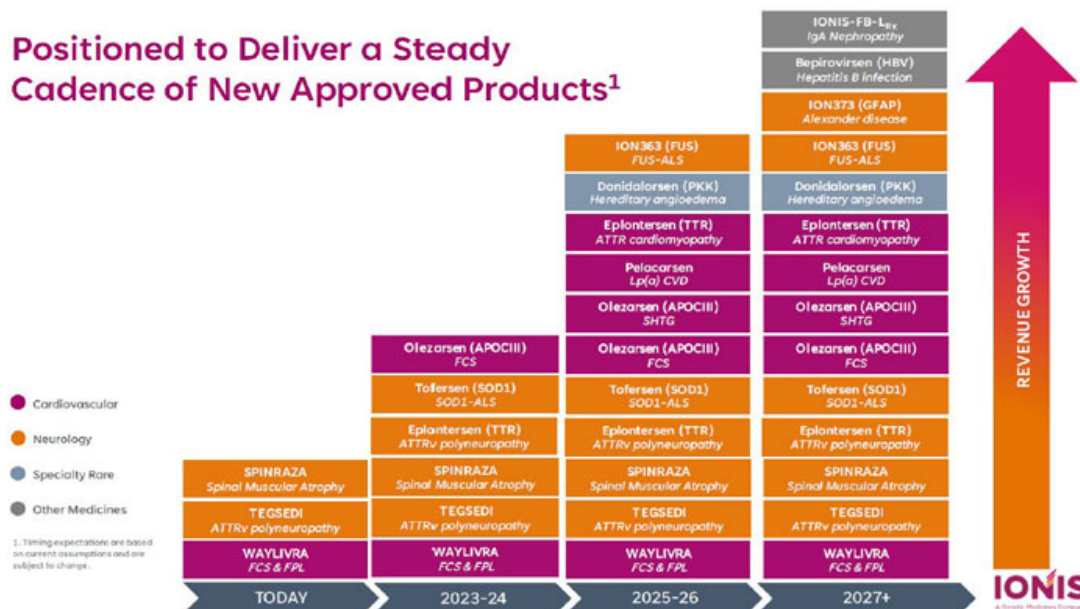
Achieved these financial successes while announcing positive topline results in the study of eplontersen in patients with ATTRv-PN, submitting an NDA for eplontersen for the treatment of ATTRv-PN, delivering nine positive data readouts from our mid- and late-stage pipeline, expanding and diversifying our technology and advancing our commercial strategy and go-to-market plans for eplontersen, olezarsen and donidalorsen.

- Advanced our commercial strategy and go-to-market plans for our near-term commercial opportunities, eplontersen, olezarsen and donidalorsen.
- As a consequence of our strong performance, our stock performed at approximately the 81st percentile of the Nasdaq Biotechnology Index (“*NBI*”) in 2022.

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

Advancing Our Pipeline

We now have seven Phase 3 medicines for nine indications advancing toward the market. 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 stockholders.



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:

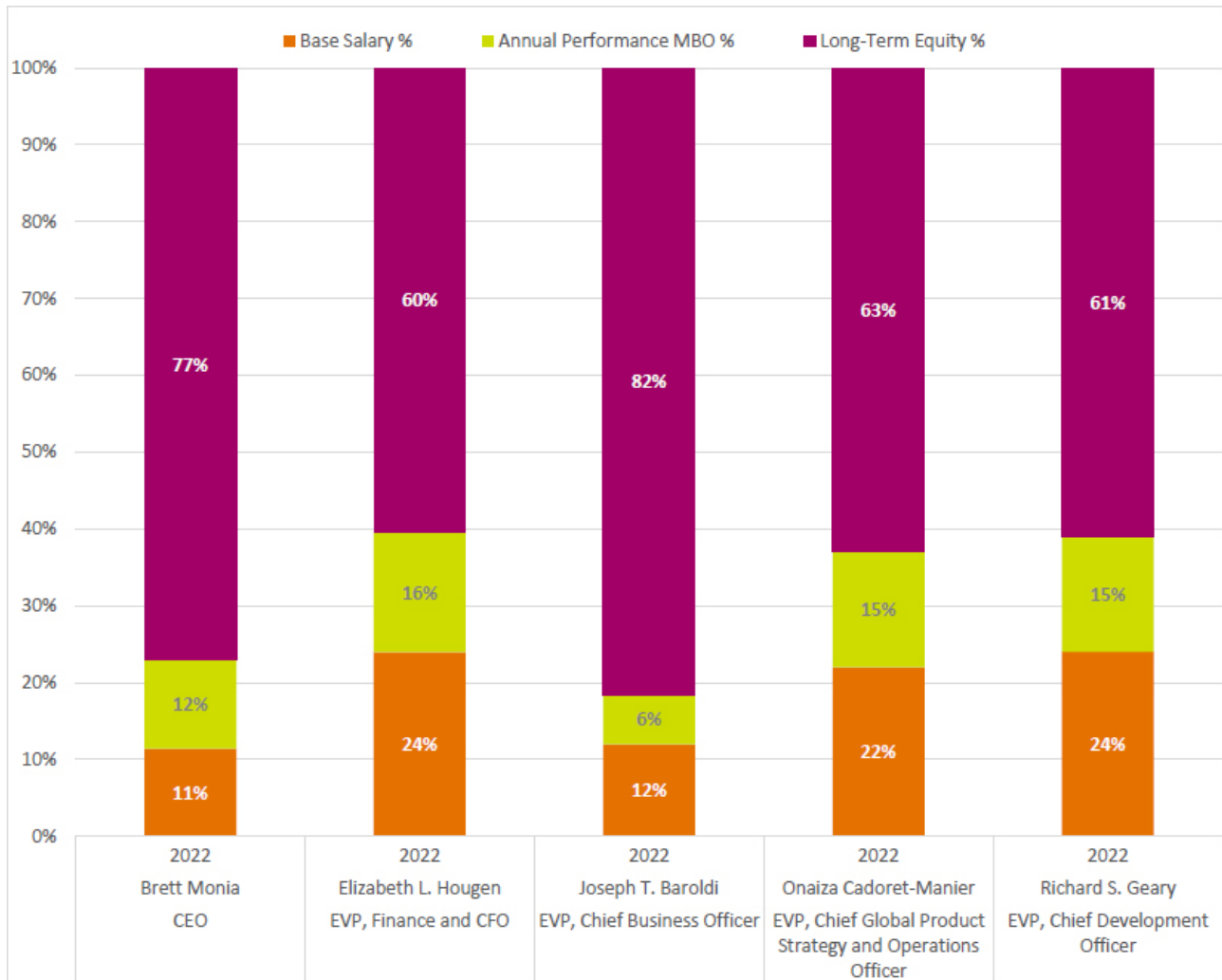
- A significant portion of cash compensation is at risk. The Compensation Committee structures cash compensation such that a significant proportion of our CEO’s and other executive officers’ cash compensation is at risk;
- More of total compensation is long-term equity. The Compensation Committee structures 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 2022:



Name	Year	Base Salary	Annual Performance MBO	Long-Term Equity	% of Total Direct Compensation		
					Base Salary %	Annual Performance MBO %	Long-Term Equity %
Brett P. Monia CEO	2022	\$824,800	\$837,688	\$5,586,119	11%	12%	77%
Elizabeth L. Hougen EVP, Finance and CFO	2022	\$584,480	\$379,912	\$1,472,746	24%	16%	60%
Joseph T. Baroldi EVP, Chief Business Officer	2022	\$476,500	\$257,310	\$3,244,069 ⁽¹⁾	12%	6% ⁽²⁾	82%
Onaiza Cadoret-Manier EVP, Chief Global Product Strategy and Operations Officer	2022	\$530,929	\$345,104	\$1,472,746	22%	15%	63%
Richard S. Geary EVP, Chief Development Officer	2022	\$546,694	\$341,684	\$1,359,351	24%	15%	61%

(1) Includes new hire equity awards granted to Mr. Baroldi when he joined the Company.

(2) Mr. Baroldi's Annual Performance MBO bonus was prorated for time served during 2022, as he joined Ionis on January 31, 2022.

2022 Compensation Decisions and Results

Base Salary

We determine base compensation levels for all our employees primarily by market forces. Accordingly, the Compensation Committee and Board believe that it is important when making 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 and Board review 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 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 1,700 life sciences companies. The Compensation Committee and Board use these data to inform and shape their decision-making but do not strictly adhere to quantitative benchmarks. In addition, we assess whether the scope of job responsibilities and internal equity warrant a given base salary.

We determine base compensation levels for all our employees primarily by market forces. Accordingly, the Compensation Committee and Board believe that it is important when making compensation decisions to be informed as to the current practices of comparable publicly held companies with which we compete for top talent.

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 and general economic conditions such as inflation. 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 2022 was 3.5%, 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, or for the CEO, recommend Board approval of, such executive officer's 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 recommends Board approval of the CEO's merit increase and approves the merit increases for the remaining executive officers. The Board then meets in executive session and approves our CEO's merit increase. 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 (+) Market Adjustment (if applicable) = New Base Salary

2022 Base Salary Calculations

The table below reflects the 2022 base salary calculations effective December 26, 2021 for our named executive officers. The Compensation Committee, or in the case of our CEO, the Board, 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 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 and the Board decided not to give Dr. Monia a market adjustment in 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 and given each individual's strong performance for the year, 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
Joseph T. Baroldi ⁽¹⁾	N/A	N/A	N/A	\$476,500
Onaiza Cadoret-Manier	\$482,000	3.9%	\$29,000	\$530,929
Richard S. Geary	\$527,697	3.6%	--	\$546,694

(1) Mr. Baroldi joined Ionis in January 2022; therefore, no salary or merit increase data for 2021 is available.

2023 Base Salary Calculations

The table below reflects the 2023 base salary calculations effective December 25, 2022 for our named executive officers. The Compensation Committee, or in the case of our CEO, the Board, approved merit increases to the salaries of the named executive officers of 4.4% 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 2022, the Compensation Committee noted that the salaries of our named executive officers were within the competitive range of the Peer Group, with the exceptions of Dr. Monia and Mr. Baroldi, whose salaries were below the competitive range. To address Dr. Monia's and Mr. Baroldi's lower salary positions to the market and given each individual's strong performance for the year, the Compensation Committee, or in the case of Dr. Monia, the Board, approved a market adjustment for Mr. Baroldi and Dr. Monia as reflected in the table below.

Name	2022 Base Salary	Merit Increase for 2023	Market Adjustment	2023 Base Salary
Brett P. Monia	\$824,800	4.2%	\$97,326	\$960,855
Elizabeth L. Hougen	\$584,480	4.75%	--	\$612,243
Joseph T. Baroldi	\$476,500	4.0%	\$20,000	\$514,374
Onaiza Cadoret-Manier	\$530,929	4.75%	--	\$556,148
Richard S. Geary	\$546,694	4.2%	--	\$569,655

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 2022 for Executive Vice Presidents was 40% and for the 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 2022 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%
Joseph T. Baroldi	0%	128%
Onaiza Cadoret-Manier	0%	128%
Richard S. Geary	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 2022 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, based on the individual's performance, the Compensation Committee recommends Board approval of the CEO's Individual Performance Factor and approves the Individual Performance Factor for our other executive officers.

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 2022 Key Corporate Objectives. On December 15, 2022, the Compensation Committee completed its evaluation of the Company's performance against the 2022 Key Corporate Objectives. 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 2022, as well as a description of notable unplanned accomplishments that the Compensation Committee considered in evaluating the Company's performance. The Compensation Committee set the Company Performance Factor for the 2022 Performance MBO at 125%. This was in recognition of a year full of many accomplishments across all aspects of our business, including the following:

- Earned \$587 million in revenue, met our 2022 financial guidance and ended the year with \$2 billion in cash.
- Announced positive topline results from a 35-week interim analysis of the Phase 3 NEURO-TTRansform study of eplontersen in patients with ATTRv-PN and submitted an NDA with the FDA for eplontersen for the treatment of ATTRv-PN.
- Delivered nine positive data readouts from our mid- and late-stage pipeline, positioning us to add new products to our commercial portfolio and expand our late-stage pipeline.
- Expanded and diversified our technology when we advanced new medicines with enhanced muscle targeting capabilities and utilizing new MsPA backbone chemistry into preclinical development and completed the Metagenomi transaction.

- Advanced our commercial strategy and go-to-market plans for our near-term commercial opportunities, eplontersen, olezarsen and donidalorsen.
- As a consequence of our strong performance, our stock performed at approximately the 81st percentile of the NBI in 2022.

Evaluation of 2022 Key Corporate Objectives		
	Objective & Pre-Approved Objective Measures	Evaluation
1	<p>Meet financial goals:</p> <ul style="list-style-type: none"> • Meet financial guidance • Meet budget 	<p>Ionis <i>partially met</i> this objective:</p> <ul style="list-style-type: none"> • We met our financial guidance • We exceeded our cash budget; however, we ended the year below our revenue budget and above our operating expense budget, driven in part by the upfront payment we made in connection with the Metagenomi transaction
2	<p>Achieve key eplontersen milestones:</p> <ul style="list-style-type: none"> • Positive Phase 3 data in polyneuropathy with competitive profile • File NDA • Establish strong co-commercialization alliance with AstraZeneca and implement an effective joint commercialization plan for eplontersen • Establish plan to transition commercial manufacturing to AstraZeneca • Achieve full enrollment for the eplontersen Phase 3 study in patients with transthyretin-mediated amyloid cardiomyopathy 	<p>Ionis <i>exceeded</i> this objective:</p> <ul style="list-style-type: none"> • Obtained positive Phase 3 data in polyneuropathy with competitive profile • We filed the NDA for eplontersen • Established a strong co-commercialization alliance with AstraZeneca and effective joint commercialization plan • Established plan to transition commercial manufacturing to AstraZeneca ahead of schedule • Achieved our original enrollment target, first resizing target, and are on track to hit new enrollment target in 2023
3	<p>Achieve key olezarsen milestones:</p> <ul style="list-style-type: none"> • Complete enrollment for the Phase 3 study of olezarsen for familial chylomicronemia syndrome (“<i>FCS</i>”) on time and prepare for 2023 NDA filing • Keep enrollment for the Phase 3 study of olezarsen for severe hypertriglyceridemia (“<i>sHTG</i>”) on track with specified enrollment target • Initiate second supportive Phase 3 study for sHTG • Complete switch of Waylivra FCS patients in the U.S. and Canada to olezarsen • Establish and implement olezarsen brand plan 	<p>Ionis <i>substantially met</i> this objective:</p> <ul style="list-style-type: none"> • Completed enrollment for the Phase 3 study of olezarsen for FCS on time and made progress towards preparation for an NDA filing in 2023 • Kept enrollment on track and hit our specified enrollment target in January 2023 • Initiated a second supportive Phase 3 study for sHTG • Completed switch of Waylivra FCS patients in the U.S. and Canada to olezarsen • Established and implemented a brand plan for olezarsen

4	<p>Achieve key donidalorsen milestones:</p> <ul style="list-style-type: none"> ● Keep Phase 3 enrollment on track with specified enrollment target ● Initiate open label extension (“<i>OLE</i>”) and SWITCH studies ● Establish and implement donidalorsen brand plan 	<p>Ionis <i>substantially met</i> this objective:</p> <ul style="list-style-type: none"> ● Kept Phase 3 enrollment on track but did not hit our specified enrollment target ● Initiated the OLE and SWITCH studies ● Established and implemented a brand plan for donidalorsen
5	<p>Increase stock price performance by a specified target percentage greater than or equal to median of the companies listed in the NBI</p>	<p>Ionis <i>exceeded</i> this objective:</p> <ul style="list-style-type: none"> ● Ionis’ stock price significantly outperformed the median stock price change for companies listed on the NBI, with Ionis stock at 24.12% of the NBI and the NBI median at -34.97% at December 31, 2022
6	<p>Advance key initiatives related to independently commercializing medicines from our wholly owned pipeline:</p> <ul style="list-style-type: none"> ● Define commercial and medical affairs operating models ● Establish and implement framework, process and decision-making for portfolio planning ● Establish and implement right-sized and effective compliance and governance processes ● Establish and implement process for asset progression and partnering decisions ● Optimize process and integration of commercial and product team input into research and development management committees ● Design and establish enterprise organization structure ● Approval of longer-term neurology commercial strategy by Executive Leadership Team (“<i>ELT</i>”) ● Define and initiate IT systems and enterprise data roadmap 	<p>Ionis <i>exceeded</i> this objective:</p> <ul style="list-style-type: none"> ● Completed the operating models for commercial and medical affairs ahead of schedule ● Established and implemented the framework, process and decision-making for portfolio planning ● Established and implemented right-sized and effective compliance and governance processes ● Advanced process for asset progression and partnering decisions ● Optimized process and integration of commercial and product team input into research and development management committees ● Designed and established enterprise organization structure ● ELT approved longer-term neurology commercial strategy ● Defined and initiated IT systems and enterprise data roadmap
7	<p>Achieve technology advancements in specified areas:</p> <ul style="list-style-type: none"> ● Advance SPINRAZA follow-on into the clinic ● Advance MsPA into development ● Identify medicinal chemistry solution for a specified delivery 	<p>Ionis <i>met</i> this objective:</p> <ul style="list-style-type: none"> ● Biogen licensed follow-on and initiated clinical dosing ● Advanced MsPA into development ● Identified MsPA backbone chemistry as solution for specified delivery

	<ul style="list-style-type: none"> Identify optimal LICA scaffold for delivery to specific tissue with path forward Establish resource plan to support new non-antisense technology platform 	<ul style="list-style-type: none"> Identified optimal scaffold for specific tissue with clear path forward for 2023 Established resource plan to support new non-antisense technology platform, which is included in 2023 budget
8	<p>Achieve additional Phase 3 pipeline goals:</p> <ul style="list-style-type: none"> Full enrollment for pelacarsen Keep FUS-ALS enrollment on track Positive decision to initiate Phase 3 development for at least one drug Implement positive path forward for tominersen or tofersen 	<p>Ionis <u>exceeded</u> this objective:</p> <ul style="list-style-type: none"> Achieved full enrollment for pelacarsen in August 2022 Exceeded our patient enrollment goal for the FUS-ALS study Positive decision to initiate Phase 3 development for two drugs Identified positive path forward for both tominersen and tofersen: <ul style="list-style-type: none"> Roche approved Phase 2 study start for tominersen Received positive OLE data and NDA acceptance with priority review by FDA for tofersen. EMA submission was also accepted for review
9	<p>Achieve key mid- and early-stage pipeline goals</p> <ul style="list-style-type: none"> Positive mid-stage pipeline readouts on at least four drugs Initiate at least three new Phase 2 studies Initiate at least three first-in-human trials including for two specified programs Advance at least three new drugs into development 	<p>Ionis <u>substantially met</u> this objective:</p> <ul style="list-style-type: none"> Achieved positive mid-stage pipeline readouts on five drugs Initiated three new Phase 2 studies Initiated three first-in-human trials including for one specified program Advanced three new drugs into development
10	<p>Complete key business development transactions</p> <ul style="list-style-type: none"> Secure ex-US commercial partner for at least one wholly-owned asset Complete bundled out-license transaction for selected assets Completed strategic partnership in one new non-antisense platform technology 	<p>Ionis <u>did not meet</u> this objective:</p> <ul style="list-style-type: none"> Did not achieve Did not achieve Achieved with Metagenomi transaction
11	<p>Implement long-range growth and space plan</p> <ul style="list-style-type: none"> Advance design and construction of new office/lab building in line with long-term growth plans Design and begin renovating conference center Secure site for new manufacturing facility Advance plan to support external CMO API manufacturing while building internal capability to manufacture new chemistries to support 2023 development candidates 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> Advanced design and construction plans for new office/lab building Renovation in progress and will be completed in 2023 Secured new site in October 2022 Advanced plan to support external CMO API manufacturing while building internal capability to manufacture new chemistries to support 2023 development candidates
12	<p>Increase involvement in our corporate responsibility initiatives internally and increase awareness of these initiatives externally</p> <ul style="list-style-type: none"> Establish corporate responsibility team and charter Continue diversity, equity and inclusion (“<i>DEI</i>”) efforts across the Company and with the Board Include appropriate description of Ionis’ corporate responsibility efforts in corporate presentations, on our website and in relevant public filings 	<p>Ionis <u>met</u> this objective:</p> <ul style="list-style-type: none"> Established corporate responsibility team and charter Continued our DEI efforts across the Company and with the Board Incorporated our corporate responsibility efforts into corporate presentations, on our website and in relevant public filings

13	Support inline products Tegsedi and Waylivra <ul style="list-style-type: none"> Achieve MAA submissions for Waylivra and Tegsedi in accordance with Sobi and PTC commercial filings and launch plans Effectively manage Sobi and PTC partnerships Achieve compliance with global commercial product authorizations and license on time 	Ionis <i>met</i> this objective: <ul style="list-style-type: none"> Completed submissions in accordance with Sobi and PTC commercial filings and launch plans Continued to effectively manage Sobi and PTC partnerships Timely achieved compliance with global commercial product authorizations and license
Unplanned Accomplishments for 2022		
14	Completed sale-leaseback transaction	
15	Completed transaction to build new manufacturing facility	
16	Established new 10-year strategic financial plan and updated periodic review process	

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 for our CEO, recommends Board approval of, and for all other executive officers, approves MBO awards accordingly. The following table illustrates the Performance MBO awards approved for 2022 performance:

Name	2022 Base Salary	Target Performance MBO %	Company Performance Factor	Individual Performance Factor	Resulting Performance MBO	Results Considered When Setting Individual Performance Factor ⁽¹⁾
Brett P. Monia	\$824,800	65%	125%	125% ⁽²⁾	\$837,688	1-16
Elizabeth L. Hougen	\$584,480	40%	125%	130%	\$379,912	1, 5, 6, 11, 12, 14-16
Joseph T. Baroldi	\$476,500	40%	125%	120%	\$257,310	1, 10 & 13
Onaiza Cadoret-Manier	\$530,929	40%	125%	130%	\$345,104	1-4 & 6
Richard S. Geary	\$546,694	40%	125%	125%	\$341,684	1-4, 6-9 & 11

- (1) The numbers correspond to the enumerated key objectives in the table entitled "Evaluation of Key 2022 Corporate Objectives" on pages 66 through 70. The Compensation Committee reviews the individual's contribution towards the key corporate objectives and other accomplishments set forth above when determining or recommending the Individual Performance Factors.
- (2) 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%.

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 allocated 50% of option equivalents to stock options and 50% to RSUs. For our executive officers' 2022 awards, we allocated 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 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 automatically 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 that are beyond the control of management. Measuring our performance in this way also 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 deliver stockholder value.

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 that are beyond the control of management. Measuring our performance in this way also provides rewards that are more directly aligned with performance through different economic cycles.

For PRSU grants made before 2023, one third of such PRSUs may vest at the end of three separate performance periods spread over the three years following the date of grant. As discussed above, we evaluated our PRSU structure in 2022 to ensure that it is consistent with market practices and will best incentivize long term stock price performance. As a result of such evaluation, beginning with PRSU grants made in 2023, such grants will have a single vesting period at the end of three years. In addition, we increased the relative TSR percentile rank for maximum payout of the awards from the 75th percentile to the 90th percentile and added additional payout thresholds. The payout thresholds for grants made in 2023 and going forward are as follows:

Relative TSR Percentile Rank	TSR Performance Multiplier
<25 th percentile	0%
25 th percentile (Threshold)	50%
50 th percentile (Target)	100%
60 th percentile	125%
75 th percentile	150%
90 th percentile (Maximum)	200%

Importantly, **all** of the PRSU grants made since inception of our PRSU program include the following **limitations**:

- 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 the maximum amount depending on the Company's relative TSR; and
- If the Company's TSR is negative over the performance period, the payout will not exceed 100% of the target number even if the percentile rank exceeds the 50th percentile.

No number of PRSUs is guaranteed to vest.

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

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). For 2022 performance, in January 2023, Dr. Monia received 118,673 time-vested stock options, 89,005 time-vested RSUs and 146,127 PRSUs (target payout of 73,064, multiplied by 200% 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 and a total of 200,193 stock options expired underwater for our executive officers in the first quarter of 2023.

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 2.2% of our outstanding common stock on an issued and outstanding basis. This stock compensation budget, and therefore our equity compensation burn rate, is well below the ISS-adjusted Peer Group average of 4.4% from 2019 through 2021. We believe this stock budget is an important tool to balance our compensation objectives with stockholder interests. For 2022 performance, the Compensation Committee set a merit stock award budget that resulted in approximately 1.5 million stock options, approximately 1.1 million RSUs and a target number of approximately 140,000 PRSUs awarded to our employees (as applicable), including the executive officers. Together these shares represent approximately 1.9% of our outstanding common stock on an issued and outstanding basis for that year. This budget, as well as each employee’s position level and performance in the previous year, ultimately determines the size of the individual annual stock grants.

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

Corporate Governance

Stock Ownership Guidelines and Holding Periods

Our executive officers and members of our Board of Directors must meet a stock 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 accumulate shares of our stock up to specified amounts. 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 2022 we increased the ownership guidelines for our executive officers and in 2023 we increased the ownership guidelines for our non-employee Board members such that the current ownership 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	5 times Base Annual Cash Retainer

As of March 31, 2023, all of our non-employee Directors except Ms. Diaz and all of our executive officers except Mr. Baroldi and Ms. Cadoret-Manier met these guidelines. Due to the recent increase in the stock ownership guidelines coupled with their recent appointments, Ms. Diaz, Mr. Baroldi and Ms. Cadoret-Manier do not yet hold enough shares sufficient to meet the guidelines; however, Ms. Diaz currently holds enough shares such that she is only missing the guidelines by approximately 5% as of March 31, 2023.

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 October 2022, the SEC adopted final rules implementing the incentive-based compensation recovery (clawback) provisions of the Dodd-Frank Act. The final rules direct the stock exchanges to establish listing standards requiring listed companies to develop and implement a policy providing for the recovery of erroneously awarded incentive-based compensation received by current or former executive officers and to satisfy related disclosure obligations. Nasdaq has proposed its listing standards, and once they are final, our Nominating, Governance and Review Committee will promptly adopt appropriate updates to this policy to comport with such listing standards.

Anti-Hedging Policy and Anti-Pledging Policy

We explicitly prohibit employees from “shorting” and hedging against our stock and from pledging 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, which plans may be established when the individual is not in possession of material non-public information. 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.

In early 2023, we modified our Rule 10b5-1 trading program to comply with the SEC’s final rules released in December 2022 that impose new conditions on the availability of the Rule 10b5-1 affirmative defense to insider trading and require enhanced disclosures regarding the adoption, modification and termination of Rule 10b5-1 plans and other trading arrangements.

Perquisites

We are committed to using stockholder money responsibly, to building stockholder value and ensuring our processes are 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.

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 86, we adopted a Change in Control and Severance Benefit Plan to provide certain economic benefits to our employees at or above the level of Vice President 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), 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 to such covered employees.

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 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, 2022, 2021, and 2020, compensation awarded to or paid to, or earned by, our named executive officers.

Summary Compensation Table

Name and Principal Position	Year	Salary (\$)	Bonus ⁽¹⁾ (\$)	Stock Awards ⁽²⁾		Option Awards ⁽⁴⁾ (\$)	All Other Compensation (\$)	Total (\$)
				RSUs ⁽³⁾ (\$)	PRSUs (\$)			
Brett P. Monia, President, Chief Executive Officer	2022	\$824,800	\$837,688	\$1,678,645	\$2,145,668	\$1,761,806	\$50,470 ⁽⁵⁾	\$7,299,077
	2021	\$800,000	\$469,300	\$4,081,860	\$3,984,360 ⁽⁶⁾	\$3,919,810	\$50,343	\$13,305,673
	2020	\$700,000	\$601,738	\$4,094,657 ⁽⁷⁾	\$1,055,547 ⁽⁷⁾	\$4,470,351	\$40,747	\$10,963,040
Elizabeth L. Hougen, Executive Vice President, Finance and Chief Financial Officer	2022	\$584,480	\$379,912	\$547,772	\$350,061	\$574,914	\$50,949 ⁽⁸⁾	\$2,488,088
	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
Joseph T. Baroldi, Executive Vice President, Chief Business Officer	2022	\$476,500	\$257,310	\$1,776,050 ⁽⁹⁾	--	\$1,468,020 ⁽⁹⁾	\$38,693 ⁽¹⁰⁾	\$4,016,572
	2021	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾
	2020	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾	N/A ⁽¹¹⁾
Onaiza Cadoret-Manier, Executive Vice President, Chief Global Product Strategy and Operations Officer	2022	\$530,929	\$345,104	\$547,772	\$350,061	\$574,914	\$54,787 ⁽¹²⁾	\$2,403,567
	2021	\$482,000 ⁽¹⁰⁾	\$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
Richard S. Geary, Executive Vice President, Chief Development Officer	2022	\$546,694	\$341,684	\$505,595	\$323,127	\$530,630	\$57,881 ⁽¹³⁾	\$2,305,611
	2021	\$527,697	\$240,630	\$1,391,914	--	\$1,336,671	\$34,807	\$3,531,719
	2020	\$509,630	\$281,167	\$1,502,162	--	\$1,639,968	\$78,379	\$4,011,036

- (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 2023 we paid bonuses for 2022 performance.
- (2) We present stock awards in the years they were awarded, not in the year earned. For example, in January 2023 we granted stock awards for 2022 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 5, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2022 regarding assumptions underlying valuation of equity awards.
- (4) 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 5, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2022 regarding assumptions underlying valuation of equity awards.
- (5) Includes AD&D (\$126), basic life (\$6,057), medical (\$25,808), dental (\$2,225), vision (\$12), long term disability (\$840), and 401(k) matching contributions (\$15,250), which are available to all employees. Also includes individual disability insurance (\$152), which is only available to employees whose annual base salary exceeds \$406,000.
- (6) 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. 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. *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 5, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2022 regarding assumptions underlying valuation of equity awards.
- (7) Includes equity awards granted to Dr. Monia in connection with his promotion to CEO in 2020.
- (8) Includes AD&D (\$126), basic life (\$6,057), medical (\$25,808), dental (\$2,270), vision (\$503), long term disability (\$840), and 401(k) matching contributions (\$15,250), which are available to all employees. Also includes individual disability insurance (\$95), which is only available to employees whose annual base salary exceeds \$406,000.

- (9) Mr. Baroldi received the following new hire equity awards when he joined the Company in January 2022: 86,700 stock options and 43,350 restricted stock units. As an executive officer, Mr. Baroldi will receive 20% of his annual equity awards in the form of performance based restricted stock units beginning in 2023.
- (10) Includes AD&D (\$116), basic life (\$1,636), medical (\$23,657), dental (\$2,651), vision (\$12), long term disability (\$770), and 401(k) matching contributions (\$8,205), which are available to all employees. Also includes individual disability insurance (\$1,646), which is only available to employees whose annual base salary exceeds \$406,000.
- (11) Mr. Baroldi joined Ionis in January 2022.
- (12) Includes AD&D (\$126), basic life (\$4,125), medical (\$25,808), dental (\$5,319), vision (\$322), long term disability (\$840), and 401(k) matching contributions (\$15,250), which are available to all employees. Also includes individual disability insurance (\$2,997), which is only available to employees whose annual base salary exceeds \$406,000.
- (13) Includes AD&D (\$120), basic life (\$10,698), medical (\$18,063), dental (\$761), vision (\$688), long term disability (\$840), and 401(k) matching contributions (\$14,134), which are available to all employees. Also includes individual disability insurance (\$77), which is only available to employees whose annual base salary exceeds \$406,000, and a Commitment to Ionis Award (\$12,500).

Grants of Plan-Based Awards

The following table shows for the fiscal year ended December 31, 2022, certain information regarding grants of plan-based awards to our named executive officers:

Grants of Plan-Based Awards in Fiscal 2022

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	1/3/22	--	--	--	--	101,489	\$32.60	\$1,761,806
	1/15/22	--	--	--	50,745	--	--	\$1,678,645
	1/15/22	25,373	50,745	76,117	--	--	--	\$2,145,668
Elizabeth L. Hougen	1/3/22	--	--	--	--	33,118	\$32.60	\$574,914
	1/15/22	--	--	--	16,559	--	--	\$547,772
	1/15/22	4,140	8,279	12,419	--	--	--	\$350,061
Joseph T. Baroldi	1/31/22	--	--	--	--	86,700	\$31.80	\$1,468,020
	4/15/22	--	--	--	43,350	--	--	\$1,776,050
Onaiza Cadoret-Manier	1/3/22	--	--	--	--	33,118	\$32.60	\$574,914
	1/15/22	--	--	--	16,559	--	--	\$547,772
	1/15/22	4,140	8,279	12,419	--	--	--	\$350,061
Richard S. Geary	1/3/22	--	--	--	--	30,567	\$32.60	\$530,630
	1/15/22	--	--	--	15,284	--	--	\$505,595
	1/15/22	3,715	7,462	11,463	--	--	--	\$323,127

- (1) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with ASC 718 for RSU, PRSU 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 5, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2022 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 3, 2022 for their 2021 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, 2022 for their 2021 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, 2023.

In 2022, Dr. Monia received thirty-three percent of his total equity awards in the form of PRSUs. For these PRSU awards, one third of such 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 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.

Pay Versus Performance

Pay Versus Performance Table

As required by Section 953(a) of the Dodd-Frank Wall Street Reform and Consumer Protection Act, and Item 402(v) of Regulation S-K (“**Item 402(v)**”), we are providing the following information about the relationship between executive compensation actually paid and certain financial performance of the Company. The amounts set forth below under the headings “Compensation Actually Paid to PEO” and “Average Compensation Actually Paid to non-PEO NEOs” have been calculated in a manner consistent with Item 402(v). Use of the term “compensation actually paid” is required by the SEC’s rules and as a result of the calculation methodology required by the SEC, such amounts differ from compensation actually received by the individuals and the compensation decisions described in the CD&A section of this Proxy Statement. For further information concerning the Company’s pay-for-performance philosophy and how the Company aligns executive compensation with the Company’s performance, refer to the CD&A section of this Proxy Statement.

Year	Summary Compensation Table Total for PEO ⁽¹⁾	Compensation Actually Paid to PEO ⁽²⁾	Average Summary Compensation Table Total for Non-PEO NEOs ⁽³⁾	Average Compensation Actually Paid to Non-PEO NEOs ⁽⁴⁾	Value of Initial Fixed \$100 Investment Based On:		Net Income (Loss) ⁽⁷⁾	One-Year Relative Total Shareholder Return ⁽⁸⁾
					Total Shareholder Return ⁽⁵⁾	Peer Group Total Shareholder Return ⁽⁶⁾		
2022	\$7,299,077	\$5,033,980	\$2,803,964	\$2,735,368	\$62.52	\$113.65	(\$269,722,000)	81 st percentile
2021	\$13,305,673	(\$3,095,776)	\$3,834,223	\$713,811	\$50.37	\$126.45	(\$28,597,000)	41 st percentile
2020	\$10,963,040	\$3,439,140	\$5,450,933	\$1,822,613	\$93.59	\$126.42	(\$479,743,000)	35 th percentile

- (1) The dollar amounts reported are the amounts of total compensation reported for Dr. Monia (our Chief Executive Officer) for each corresponding year in the “Total” column of the Summary Compensation Table on page 76 of this Proxy Statement.
- (2) The dollar amounts represent the amount of compensation actually paid to Dr. Monia, as computed in accordance with Item 402(v). The dollar amounts do not reflect the actual amount of compensation earned by or paid to Dr. Monia during the applicable year. In accordance with the requirements of Item 402(v), the following adjustments were made to Dr. Monia’s total compensation for each year to determine the compensation actually paid:

Year	Reported Summary Compensation Table Total for PEO	Deduct: Reported Value of Equity Awards ^(a)	Add: Equity Award Adjustments ^(b)	Add: Reported Change in the Actuarial Present Value of Pension Benefits ^(c)	Add: Pension Benefit Adjustments ^(c)	Compensation Actually Paid to PEO
2022	\$7,299,077	(\$5,586,119)	\$3,321,022	\$ -	\$ -	\$5,033,980
2021	\$13,305,673	(\$11,986,030)	(\$4,415,419)	\$ -	\$ -	(\$3,095,776)
2020	\$10,963,040	(\$9,620,555)	\$2,096,655	\$ -	\$ -	\$3,439,140

- (a) The grant date fair value of equity awards represents the total of the amounts reported in the “Stock Awards” and “Option Awards” columns in the Summary Compensation Table for the applicable year.
- (b) The equity award adjustments for each applicable year include the addition (or subtraction, as applicable) of the following: (i) the year-end fair value of any equity awards granted in the applicable year that are outstanding and unvested as of the end of the year; (ii) the amount of change as of the end of the applicable year (from the end of the prior fiscal year) in fair value of any awards granted in prior years that are outstanding and unvested as of the end of the applicable year; (iii) for awards that are granted and vest in the same applicable year, the fair value as of the vesting date; (iv) for awards granted in prior years that vest in the applicable year, the amount equal to the change as of the vesting date (from the end of the prior fiscal year) in fair value; (v) for awards granted in prior years that are determined to fail to meet the applicable vesting conditions during the applicable year, a deduction for the amount equal to the fair value at the end of the prior fiscal year; and (vi) the dollar value of any dividends or other earnings paid on stock or option awards in the applicable year prior to the vesting date that are not otherwise reflected in the fair value of such award or included in any other component of total compensation for the applicable year. The amounts deducted or added in calculating the equity award adjustments are as follows:

Year	Year End Fair Value of Equity Awards	Year over Year Change in Fair Value of Outstanding and Unvested Equity Awards	Fair Value as of Vesting Date of Equity Awards Granted and Vested in the Year ⁽ⁱ⁾	Year over Year Change in Fair Value of Equity Awards Granted in Prior Years that Vested in the Year	Fair Value at the End of the Prior Year of Equity Awards that Failed to Meet Vesting Conditions in the Year	Value of Dividends or other Earnings Paid on Stock or Option Awards Not Otherwise Reflected in Fair Value or Total Compensation ⁽ⁱⁱ⁾	Total Equity Award Adjustments
2022	\$5,731,326	(\$2,549,358)	\$ -	\$326,316	(\$187,261)	\$ -	\$3,321,022
2021	\$4,655,272	(\$8,289,894)	\$ -	(\$716,002)	(\$64,795)	\$ -	(\$4,415,419)
2020	\$7,071,074	(\$4,319,642)	\$ -	(\$654,778)	\$ -	\$ -	\$2,096,655

- (i) We do not grant any equity awards that vest in the same year as grant.
- (ii) We do not pay dividends or other earnings on stock or option awards.
- (c) We do not provide pension benefits to any employees of the Company.
- (3) The dollar amounts reported represent the average of the amounts reported for the Company's NEOs as a group (excluding Dr. Monia) in the "Total" column of the Summary Compensation Table of the Proxy Statement for each applicable year. The names of each of the NEOs (excluding Dr. Monia) included for purposes of calculating the average amounts in each applicable year are as follows:
- (i) For 2022, Elizabeth L. Hougen (EVP & CFO), Joseph T. Baroldi (EVP, Chief Business Officer), Onaiza Cadoret-Manier (EVP, Chief Global Product Strategy and Operations Officer) and Richard S. Geary (EVP, Chief Development Officer);
- (ii) For 2021, Elizabeth L. Hougen (EVP & CFO), Patrick R. O'Neil (EVP, Chief Legal Officer and General Counsel), Onaiza Cadoret-Manier (EVP, Chief Global Product Strategy and Operations Officer) and Eric E. Swayze (EVP, Research; and
- (iii) For 2020, Elizabeth L. Hougen (EVP & CFO), Stanley Crooke (Executive Chairman of the Board), Richard S. Geary (EVP, Chief Development Officer) and Patrick R. O'Neil (EVP, Legal and General Counsel).
- (4) The dollar amounts reported represent the average amount of compensation actually paid to the NEOs as a group (excluding Dr. Monia), as computed in accordance with Item 402(v). The dollar amounts do not reflect the actual average amount of compensation earned by or paid to the NEOs as a group (excluding Dr. Monia) during the applicable year. In accordance with the requirements of Item 402(v), the following adjustments were made to average total compensation for the NEOs as a group (excluding Dr. Monia) for each year to determine the compensation actually paid, using the same methodology described above in Note 2:

Year	Average Reported Summary Compensation Table Total for Non-PEO NEOs	Deduct: Average Reported Value of Equity Awards	Add: Average Award Adjustments ^(a)	Add: Average Reported Change in the Actuarial Present Value of Pension Benefits ^(b)	Add: Average Pension Benefit Adjustments ^(b)	Average Compensation Actually Paid to Non-PEO NEOs
2022	\$2,803,964	(\$1,887,231)	\$1,818,634	\$ -	\$ -	\$2,735,368
2021	\$3,834,223	(\$3,039,250)	(\$81,162)	\$ -	\$ -	\$713,811
2020	\$5,450,933	(\$4,484,784)	\$856,465	\$ -	\$ -	\$1,822,613

- (a) The amounts deducted or added in calculating the total average equity award adjustments are as follows:

Year	Year End Fair Value of Equity Awards	Year over Year Change in Fair Value of Outstanding and Unvested Equity Awards	Fair Value as of Vesting Date of Equity Awards Granted and Vested in the Year ⁽ⁱ⁾	Year over Year Change in Fair Value of Equity Awards Granted in Prior Years that Vested in the Year	Fair Value at the End of the Prior Year of Equity Awards that Failed to Meet Vesting Conditions in the Year	Value of Dividends or other Earnings Paid on Stock or Option Awards Not Otherwise Reflected in Fair Value or Total Compensation ⁽ⁱⁱ⁾	Total Equity Award Adjustments
2022	\$1,962,339	(\$164,642)	\$ -	\$20,938	\$ -	\$ -	\$1,818,634
2021	\$1,171,440	(\$1,216,952)	\$ -	(\$35,650)	\$ -	\$ -	(\$81,162)
2020	\$3,366,846	(\$2,476,142)	\$ -	(\$34,239)	\$ -	\$ -	\$856,465

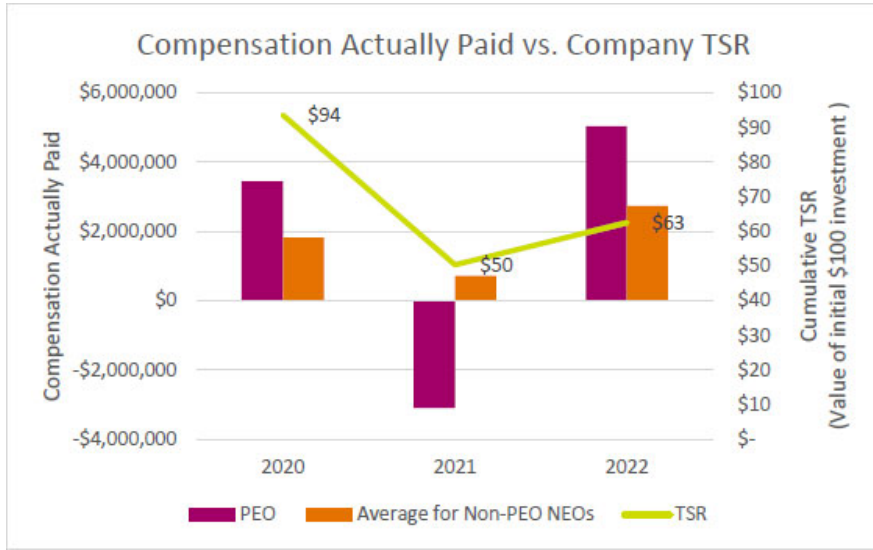
- (i) We do not grant any equity awards that vest in the same year as grant.
- (ii) We do not pay dividends or other earnings on stock or option awards.
- (b) We do not provide pension benefits to any employees of the Company.
- (5) Cumulative TSR is calculated by dividing the sum of the cumulative amount of dividends for the measurement period, assuming dividend reinvestment, and the difference between the Company's stock price at the end and the beginning of the measurement period by the Company's stock price at the beginning of the measurement period.
- (6) Represents the weighted peer group TSR, weighted according to the respective companies' stock market capitalization at the beginning of each period for which a return is indicated. The peer group used for this purpose is the Nasdaq Biotechnology Index.
- (7) The dollar amounts reported represent the amount of net income (loss) reflected in the Company's audited financial statements for the applicable year.
- (8) One-year relative TSR shown is the percentile rank of the Company's TSR as compared to the TSRs of all members of the Nasdaq Biotechnology Index, ranked in descending order, for the one-year period commencing on January 15th of the applicable year and ending January 15th of the following year, which time period is consistent with the one-year measurement period used in the PRSUs awarded in 2020-2022.

Analysis of the Information Presented in the Pay Versus Performance Table

While the Company utilizes several performance measures to align executive compensation with Company performance, all of those Company measures are not presented in the Pay Versus Performance Table (“*PVP Table*”). Moreover, the Company generally seeks to incentivize long-term performance, and therefore does not specifically align the Company’s performance measures with compensation that is actually paid (as computed in accordance with Item 402(v)) for a particular year. In accordance with Item 402(v), the Company is providing the descriptions and graphs below regarding the relationships between certain information presented in the PVP Table.

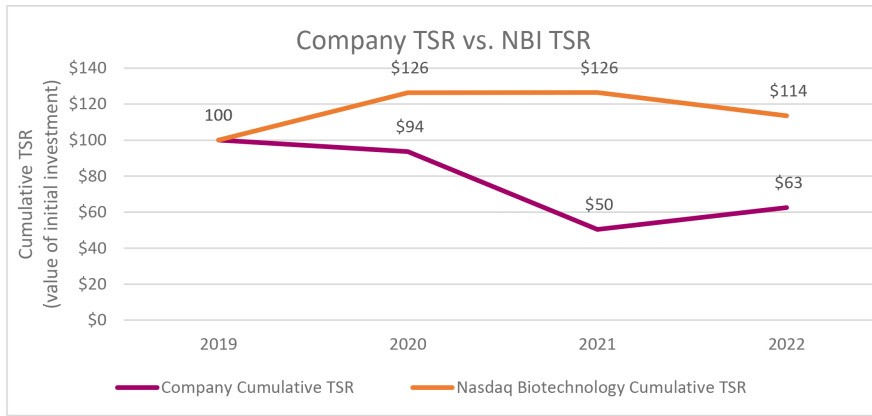
Compensation Actually Paid and Cumulative TSR

As demonstrated by the following graph, the amount of compensation actually paid to Dr. Monia and the average amount of compensation actually paid to the Company’s NEOs as a group (excluding Dr. Monia) is aligned with the Company’s cumulative TSR over the three years presented in the table.



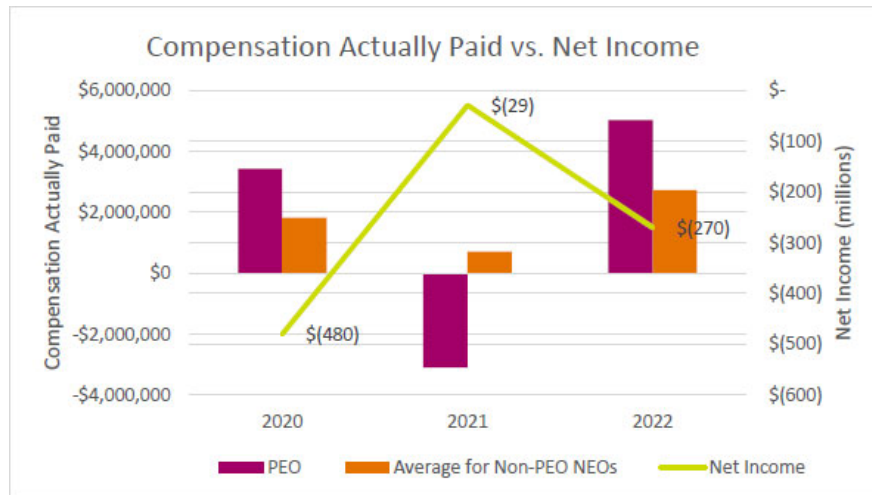
Cumulative TSR of the Company and Cumulative TSR of the NBI

The graph below shows the Company’s cumulative TSR over the three-year period against the cumulative TSR of the peer group presented for this purpose, the Nasdaq Biotechnology Index.



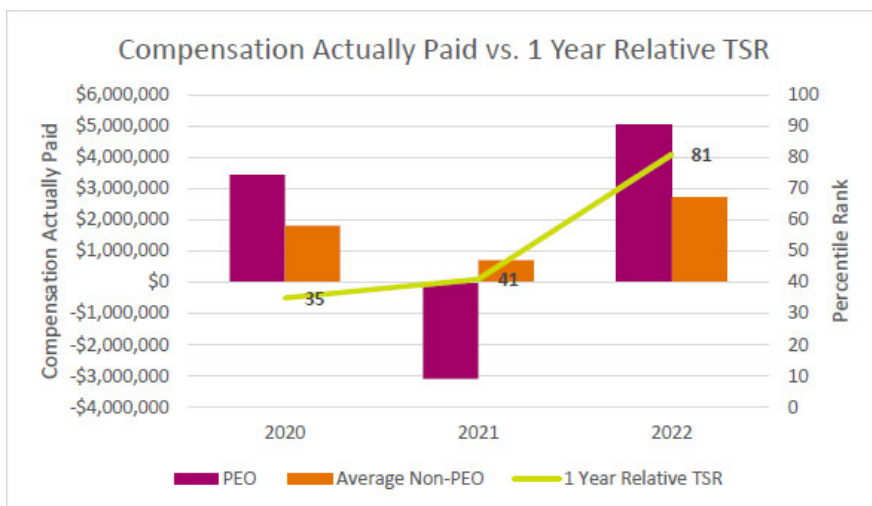
Compensation Actually Paid and Net Income

The graph below shows the amount of compensation actually paid to Dr. Monia and the average amount of compensation actually paid to the Company’s NEOs as a group (excluding Dr. Monia) and the Company’s net income over the three years presented in the table. As noted above, the Company does not use compensation actually paid to set executive compensation.



Compensation Actually Paid and Relative Total Shareholder Return

The graph below shows the amount of compensation actually paid to Dr. Monia and the average amount of compensation actually paid to the Company’s NEOs as a group (excluding Dr. Monia) and the Company’s one-year relative total shareholder return shown as a percentile rank of the Company’s TSR as compared to the TSRs of all members of the Nasdaq Biotechnology Index for each of the three years presented in the table.



Financial Performance Measures

As described in greater detail in the CD&A, we design our executive compensation program to drive the creation of long-term stockholder value and mitigate unnecessary or imprudent business risk taking. To that end, we structure our executive compensation program to align executive compensation with Company performance. The most important financial performance measures used by the Company in fiscal year 2022 to link executive compensation actually paid to the Company’s NEOs to the Company’s performance are listed in the table to the right.

Most Important Financial Performance Measures
Revenue
Relative TSR Versus the NBI
Whether We Met Our Non-GAAP Net Operating Loss Guidance

All information provided above under the “Item 402(v) Pay Versus Performance” heading will not be deemed to be incorporated by reference into any filing of the Company under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing, except to the extent the Company specifically incorporates such information by reference.

Outstanding Equity Awards at Fiscal Year-End – Executive Officers

The following table shows for the fiscal year ended December 31, 2022, 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, 2022.

Outstanding Equity Awards as of December 31, 2022

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	1/4/2016	38,240 ⁽⁶⁾	--	\$61.68	1/3/2023	--	--	--	--
	1/3/2017	48,000	--	\$47.34	1/2/2024	--	--	--	--
	1/2/2018	58,125	-	\$49.25	1/1/2025	--	--	--	--
	1/14/2018	30,000	-	\$53.22	1/13/2025	--	--	--	--
	1/2/2019	100,756	2,144	\$53.77	1/1/2026	--	--	--	--
	1/2/2020	78,481	29,151	\$60.89	1/1/2027	--	--	--	--
	1/2/2020	29,766	11,056	\$60.89	1/1/2027	--	--	--	--
	1/4/2021	71,813	78,059	\$56.78	1/3/2028	--	--	--	--
	1/3/2022	--	101,489	\$32.60	1/2/2032	--	--	--	--
	1/15/2020	--	--	--	--	11,432	\$431,787	--	--
	1/15/2021	--	--	--	--	23,918	\$903,383	--	--
	1/15/2022	--	--	--	--	9,071	\$342,612	--	--
	1/15/2019	--	--	--	--	49,957	\$1,886,876	--	--
	1/15/2020	--	--	--	--	50,745	\$1,916,639	--	--
1/15/2020	--	--	--	--	--	--	1,890	\$71,385	
1/15/2021	--	--	--	--	-	-	17,210	\$650,022	
1/15/2022	--	--	--	--	--	--	25,373	\$958,338	
Elizabeth L. Hougen	1/4/2016	38,240 ⁽⁶⁾	--	\$61.68	1/3/2023	--	--	--	--
	1/3/2017	45,225	--	\$47.34	1/2/2024	--	--	--	--
	1/2/2018	54,619	--	\$49.25	1/1/2025	--	--	--	--
	1/2/2019	48,762	1,038	\$53.77	1/1/2026	--	--	--	--
	1/2/2020	43,968	16,331	\$60.89	1/1/2027	--	--	--	--
	1/4/2021	29,249	31,792	\$56.78	1/3/2028	--	--	--	--
	1/3/2022	--	33,118	\$32.60	1/2/2032	--	--	--	--
	1/15/2022	--	--	--	--	5,532	\$208,944	--	--
	1/15/2019	--	--	--	--	13,400	\$506,118	--	--
	1/15/2020	--	--	--	--	20,346	\$768,468	--	--
	1/15/2021	--	--	--	--	16,559	\$625,433	--	--
1/15/2022	--	--	--	--	--	--	4,140	\$156,368	
Joseph T. Baroldi	1/31/2022	-	86,700	\$31.80	1/30/2032	--	--	--	--
	4/15/2022	-	--	--	--	43,350	\$1,637,330	--	--
Onaiza Cadoret-Manier	1/9/2020	37,187	13,813	\$63.27	1/8/2027	--	--	--	--
	1/4/2021	26,121	28,392	\$56.78	1/3/2028	--	--	--	--
	1/3/2022	--	33,118	\$32.60	1/2/2032	--	--	--	--
	4/15/2020	--	--	--	--	11,333	\$428,047	--	--
	1/15/2021	--	--	--	--	18,171	\$686,319	--	--
	1/15/2022	--	--	--	--	16,559	\$625,433	--	--
1/15/2022	--	--	--	--	--	--	4,140	\$156,368	
Richard S. Geary	1/4/2016	38,240 ⁽⁶⁾	--	\$61.68	1/3/2023	--	--	--	--
	1/3/2017	21,225	--	\$47.34	1/2/2024	--	--	--	--
	1/2/2018	58,125	--	\$49.25	1/1/2025	--	--	--	--
	1/2/2019	56,693	1,207	\$53.77	1/1/2026	--	--	--	--
	1/2/2020	39,711	14,750	\$60.89	1/1/2027	--	--	--	--
	1/4/2021	24,489	26,618	\$56.78	1/3/2028	--	--	--	--
	1/3/2022	-	30,567	\$32.60	1/2/2032	--	--	--	--
	1/15/2019	--	--	--	--	6,432	\$242,937	--	--
	1/15/2020	--	--	--	--	12,102	\$457,093	--	--
	1/15/2021	--	--	--	--	17,035	\$643,412	--	--
	1/15/2022	--	--	--	--	15,284	\$577,277	--	--
	1/15/2022	--	--	--	--	--	--	3,821	\$144,319

- (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 \$37.77, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 30, 2022, the last trading day of fiscal 2022.
- (4) Represents the threshold payout of shares under the PRSU awards granted to our NEOs.
- (5) Market value of PRSUs was determined by multiplying the threshold payout of shares by \$37.77, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 30, 2022, the last trading day of fiscal 2022.
- (6) These options expired on January 3, 2023.

Option Exercises and Stock Vested – Executive Officers

The following table shows for the fiscal year ended December 31, 2022, 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	--	\$ --	65,673	\$1,999,452
Elizabeth L. Hougen	--	\$ --	22,050	\$ 664,146
Joseph T. Baroldi	--	\$ --	--	\$ --
Onaiza Cadoret-Manier	--	\$ --	11,724	\$ 414,841
Richard S. Geary	--	\$ --	21,391	\$ 644,297

Post-Employment Compensation

Pension Benefits and Nonqualified Deferred Compensation

Our executive officers are eligible to participate in our 401(k) contributory defined contribution plan. In 2022, 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 2022, the maximum matching contribution was \$15,250. 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 Covered Employees under the Plan; however, payments, benefits or distributions to or for the benefit of the Covered Employee under the Plan may be reduced if doing so would result in a more favorable after-tax position for the Covered Employee.

Conditions

As a condition to receiving benefits under the Change of Control and Severance Benefit Plan described above, the Covered Employee 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 Covered Employee'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, 2022. 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, 2022. The estimates in this table are forward-looking statements. Please see the special note regarding forward-looking statements on page 97 of this Proxy Statement.

Name	Total – Change of Control Event	Total – Non-Change of Control Event
Brett P. Monia	\$3,239,439	\$2,117,301
Elizabeth L. Hougen	\$1,337,173	\$646,552
Joseph T. Baroldi	\$1,131,648	\$548,683
Onaiza Cadoret-Manier	\$1,211,697	\$585,339
Richard S. Geary	\$1,230,482	\$592,460

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, 2022, we paid our non-employee Directors a base cash retainer of \$60,000 with additional role-based compensation as noted below:

Role	2022 Cash Compensation
Board Member (Base)	\$60,000 ⁽¹⁾
Non-Executive Chairman of the Board	\$40,000
Independent Lead Director	\$40,000
Committee Chairs (Additional)	
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)	
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 2022, each non-employee Director also received automatic stock award grants under our Non-Employee Director Plan. On July 1, 2022, 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 \$38.06 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 governing compensation the Company pays to its non-employee Directors (the “**Director Compensation Policy**”). In addition to stating the cash compensation amounts set forth above and the equity grants each non-employee Director will receive upon joining the Board and annually thereafter pursuant to the amended and restated 2002 Non-Employee Directors’ Stock Option Plan, the Director Compensation Policy also includes an annual equity cap whereby (1) the Compensation Committee, with input from its independent consultant, may reduce the number of shares to be automatically issued to non-employee Directors 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 2022, 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 2022 did not exceed \$500,000; thus, for 2022, each non-employee Director received an annual award of 12,000 stock options and 5,333 RSUs.

The Compensation Committee reviews pay levels for non-employee Directors 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. In March 2022 the Compensation Committee reviewed Aon’s assessment in which Aon did not recommend any changes to our non-employee Director compensation program for 2022. Following review and discussion of such report the Compensation Committee did not recommend any changes to the Board regarding our non-employee Director compensation program for 2022. We will continue to assess our non-employee Director compensation program annually with the assistance of Aon.

In December 2022 the Company adopted a deferral program for annual RSUs granted to non-employee Directors beginning in January 2023 and going forward. Such deferral program allows non-employee Directors to defer receipt of shares that may vest under future RSU grants until (1) separation from service to Ionis, or (2) the earlier to occur of five years following the vesting date of the RSUs and separation from service to Ionis, subject in all cases to earlier delivery of deferred RSUs upon a change in control of the Company.

The following table shows for the fiscal year ended December 31, 2022 certain information with respect to the compensation of our non-employee Directors:

Director Compensation for Fiscal 2022

Name	Cash Compensation Earned or Paid (\$)	Stock Awards (\$) ⁽¹⁾	Option Awards (\$) ⁽¹⁾	All Other Compensation (\$) ⁽²⁾	Total (\$)
Spencer R. Berthelsen	\$100,000	\$202,974	\$274,724	\$--	\$577,698
Allene M. Diaz	\$73,000	\$202,974	\$274,724	\$19,044	\$569,743
Michael Hayden	\$80,000	\$202,974	\$274,724	\$18,141	\$575,839
Joan E. Herman	\$84,500	\$202,974	\$274,724	\$--	\$562,198
Joseph Klein, III	\$86,500	\$202,974	\$274,724	\$28,646	\$592,845
Joseph Loscalzo	\$120,000	\$202,974	\$274,724	\$--	\$597,698
Frederick T. Muto	\$55,251	\$202,974	\$274,724	\$10,000 ⁽³⁾	\$542,949
B. Lynne Parshall	\$90,000	\$202,974	\$274,724	\$244,641 ⁽⁴⁾	\$1,037,339
Joseph H. Wender	\$150,000	\$202,974	\$274,724	\$--	\$627,698

- (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 5, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2022 regarding assumptions underlying valuation of equity awards.
- (2) For Ms. Diaz, Dr. Hayden, Mr. Klein, and Ms. Parshall, includes medical, dental and vision benefits, which are available to all non-employee directors and all employees of the Company.
- (3) Mr. Muto resigned from the Board in July 2022. In December 2022, Mr. Muto received a \$10,000 Legacy Award, which he elected to donate to non-profit organizations.
- (4) On January 15, 2018, Ms. Parshall transitioned out of her role as Chief Operating Officer and retired from Ionis after 28 years of service. Thereafter, she became a Senior Strategic Advisor to the Company and entered into an Advisory Services Agreement. As a result of this transition, Ms. Parshall's "All Other Compensation" for 2022 includes \$225,000 in consulting fees earned under her Advisory Services Agreement. Ms. Parshall's Advisory Services Agreement terminated on December 31, 2022.

Outstanding Equity Awards at Fiscal Year-End – Directors

The following table shows for the fiscal year ended December 31, 2022, certain information regarding outstanding awards at fiscal year-end of all our non-employee Directors:

Outstanding Equity Awards as of December 31, 2022

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	--	\$28.47	6/30/2023	7,110	\$268,545
	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		
	16,000	4,000	\$42.88	7/1/2028		
	12,000	--	\$64.80	6/30/2029		
	12,000	--	\$60.20	6/30/2030		
	12,000	--	\$40.05	6/30/2031		
--	12,000	\$38.06	6/30/2032			
Allene M. Diaz	18,000	--	\$40.05	6/30/2031	5,333	\$201,427
	--	12,000	\$38.06	6/30/2032		
Michael Hayden	32,000	--	\$50.80	9/19/2028	7,110	\$268,545
	12,000	--	\$64.80	6/30/2029		
	12,000	4,000	\$60.20	6/30/2030		
	12,000	--	\$40.05	6/30/2031		
	--	12,000	\$38.06	6/30/2032		
Joan E. Herman	24,000	8,000	\$63.90	6/8/2029	10,665	\$402,817
	12,000	4,000	\$64.80	6/30/2029		
	12,000	--	\$60.20	6/30/2030		
	12,000	--	\$40.05	6/30/2031		
	--	12,000	\$38.06	6/30/2032		
Joseph Klein, III	16,000	-	\$57.16	6/30/2025	7,110	\$268,545
	12,000	-	\$24.42	6/30/2026		
	16,000	-	\$52.22	7/2/2027		
	16,000	4,000	\$42.88	7/1/2028		
	12,000	-	\$64.80	6/30/2029		
	12,000	-	\$60.20	6/30/2030		
	12,000	-	\$40.05	6/30/2031		
	--	12,000	\$38.06	6/30/2032		
Joseph Loscalzo	22,500	--	\$49.09	2/2/2024	7,110	\$268,545
	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		
	16,000	--	\$42.88	7/1/2028		
	12,000	4,000	\$64.80	6/30/2029		
	12,000	--	\$60.20	6/30/2030		
	12,000	--	\$40.05	6/30/2031		
	--	12,000	\$38.06	6/30/2032		
Frederick T. Muto ⁽⁵⁾	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		
	16,000	--	\$42.88	7/1/2028		
	12,000	--	\$64.80	6/20/2029		
	12,000	--	\$60.20	6/30/2030		
	12,000	--	\$40.05	6/30/2031		
B. Lynne Parshall ⁽⁶⁾	107,549	--	\$61.68	1/3/2023	7,110	\$268,545
	117,638	--	\$47.34	1/2/2024		
	103,575	--	\$49.25	1/1/2025		
	16,000	--	\$42.88	7/1/2028		
	12,000	4,000	\$64.80	6/30/2029		
	12,000	--	\$60.20	6/30/2030		
	12,000	--	\$40.05	6/30/2031		
	--	12,000	\$38.06	6/30/2032		
Joseph H. Wender	16,000	--	\$35.53	6/30/2024	7,110	\$268,545
	16,000	--	\$57.16	6/30/2025		
	16,000	--	\$24.42	6/30/2026		
	16,000	--	\$52.22	7/2/2027		
	16,000	--	\$42.88	7/1/2028		
	12,000	4,000	\$64.80	6/30/2029		
	12,000	--	\$60.20	6/30/2030		
	12,000	--	\$40.05	6/30/2031		
	--	12,000	\$38.06	6/30/2032		

(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 the 2002 Non-Employee Directors' Stock Option Plan. Initial options granted upon commencement of Board service prior to June 4, 2020 vest at the rate of 25% per year over four years and those granted on or after June 4, 2020 vest 100% on the first anniversary of the date of grant. Annual options that were granted prior to June 4, 2020 vest equally over four years on each anniversary of the date of grant or the next regularly scheduled annual meeting of stockholders, whichever occurs earlier. Annual options that were granted on or after June

4, 2020 vest 100% on either (1) the annual anniversary of the date of grant, or (2) the next regularly scheduled annual meeting of stockholders, whichever occurs earlier. The options Ms. Parshall received as an employee vest at the rate of 25% for the first year and then at the rate of 2.08% per month for 36 months thereafter.

- (2) Except for the awards Ms. Parshall received as an employee, the RSUs were granted out of our the 2002 Non-Employee Directors' Stock Option 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 equal to five 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 \$37.77, which was the closing market price of our common stock on the Nasdaq Global Select Market on December 31, 2022, the last trading day of fiscal year 2022.
- (5) Mr. Muto did not receive equity grants in 2022 as he retired from the Board in July 2022.
- (6) Includes awards received by Ms. Parshall during her tenure as an executive officer of the Company.

Option Exercises and Stock Vested - Directors

The following table shows for the fiscal year ended December 31, 2022, certain information regarding option exercises and stock awards vested during the last fiscal year with respect to our non-employee Directors:

Option Exercises and Stock Vested in Fiscal 2022

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	11,250	\$ 394,088	7,998	\$ 314,401
Allene M. Diaz	--	\$ --	8,000	\$ 314,480
Michael Hayden	--	\$ --	8,887	\$ 362,160
Joan E. Herman	--	\$ --	10,665	\$ 403,066
Joseph Klein, III	--	\$ --	7,998	\$ 314,401
Joseph Loscalzo	--	\$ --	7,998	\$ 314,401
Frederick T. Muto	11,250	\$ 428,175	7,998	\$ 314,401
B. Lynne Parshall ⁽¹⁾	--	\$ --	13,752	\$ 487,712
Joseph H. Wender	--	\$ --	7,998	\$ 314,401

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

Certain Relationships and Related Transactions

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

Mariana Baroldi is a Director in our Corporate Operations department and the wife of Joseph T. Baroldi, EVP and Chief Business Officer. In addition, Grant Swayze joined Ionis as a Research Associate in September 2022 and is the son of Eric E. Swayze, EVP, Research. We reviewed Ms. Baroldi's and Mr. G. Swayze's compensation and determined they are within the range that we target for other employees at the same levels at Ionis.

For the fiscal year 2022, Ms. Baroldi and Mr. G. Swayze received the following compensation:

Name and Principal Position	Year	Salary (\$)	Bonus ⁽¹⁾ (\$)	Stock Awards ⁽²⁾ (\$)	Option Awards ⁽²⁾⁽³⁾ (\$)	All Other Compensation ⁽⁴⁾ (\$)	Total (\$)
Mariana Baroldi, Director, Corporate Operations	2022	\$204,986	\$49,883	\$47,139	\$49,457	\$18,773	\$370,238
Grant Swayze, Research Associate	2022	\$16,962	\$0	\$23,180	\$25,229	\$3,580	\$68,951

- (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 2023 we paid bonuses for 2022 performance. As Mr. G. Swayze joined Ionis in late 2022, he was not eligible to receive a bonus in 2022.
- (2) Amounts represent the aggregate expense recognized for financial statement reporting purposes in accordance with ASC 718 for stock and option awards granted to Ms. Baroldi and Mr. G. Swayze. 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 5, *Stockholders' Equity*, of the consolidated financial statements in our Annual Report on Form 10-K for the year ended December 31, 2022 regarding assumptions underlying valuation of equity awards.
- (3) This amount represents the estimated fair value of a stock option grant we recognized as share-based compensation expense. The estimated fair value amount was determined using an option-pricing model and is not indicative of whether Ms. Baroldi or Mr. G. Swayze will realize the estimated fair value or any financial benefits from the award.
- (4) For Ms. Baroldi, includes AD&D, basic life, long term disability and 401(k) matching contributions, which are available to all employees. For Mr. G. Swayze, includes AD&D, basic life, medical, dental, vision, long term disability and 401(k) matching contributions, which are available to all employees.

B. Lynne Parshall, who was employed by Ionis for 28 years, became a Senior Strategic Advisor to the Company in January 2018. Under Ms. Parshall's Advisory Services Agreement, she provided strategic advisory services to the Company, including in strategic planning, business development, and with the Company's important relationship with Biogen. Pursuant to the Advisory Services Agreement, Ms. Parshall received consulting fees of \$225,000 for services provided in 2022. Ms. Parshall's Advisory Services Agreement terminated on December 31, 2022.

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 amount of approximately \$260,000 in 2022, which is substantially less than 5% of Goldman's gross revenues for its 2022 fiscal year.

One of our Directors, Joseph Loscalzo, is Physician-in-Chief Emeritus at Brigham and Women's Hospital, a not-for-profit corporation that is part of Mass General Brigham, which we engage from time to time for clinical research support services. We paid Brigham and Women's Hospital an aggregate amount of approximately \$2.6 million in 2022, which is substantially less than 5% of Mass General Brigham's gross revenues for its 2022 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 did not make a cash donation to the n-Lorem Foundation in 2022 but has made cash donations to n-Lorem in the past. Ms. Parshall, Dr. Hayden and Dr. Loscalzo, three of the Company's non-employee Directors, also serve as directors for the n-Lorem Foundation. Additionally, Dr. Bennett, our EVP and CSO, serves as a director and the chief technical officer for the n-Lorem Foundation, and until February 2022, Mr. O'Neil, our EVP, General Counsel and Corporate Secretary, served as the corporate secretary for the n-Lorem Foundation. None of our executive officers or Directors is compensated for 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 Legal 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 for 2022 using the following methodology:

- We included all employees of Ionis who were employed by us on December 31, 2022.
- We identified our median employee from this employee population based on the W-2 income for 2022. We did not annualize any of these amounts.

Using this approach, we determined our median employee for 2022 and calculated the annual total compensation of this employee for 2022 in accordance with the requirements of the Summary Compensation Table.

For 2022, the median of the annual total compensation of our employees (other than our CEO) was \$183,487 and the annual total compensation of our CEO, as reported in the Summary Compensation Table included in this Proxy Statement, was \$7,299,077. 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 40 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 57 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 2023 Annual Meeting of Stockholders.

The Compensation Committee

Spencer R. Berthelsen, *Chairman*

Joan E. Herman

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 2022, 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. In addition, the Audit Committee regularly holds separate, private, executive sessions with senior management, the independent auditors, and the 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, 2022 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, which is 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 that 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, 2022, 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, 2022 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 2023.

The Audit Committee
Joseph Klein, III, *Chair*
Allene M. Diaz
Joan E. Herman

* 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 Plan 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, 2022 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.com⁹) to view our 2022 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, 2023

⁹ 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, tofersen, pelacarsen, bepirovirsen 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 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, 2022, 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.

Appendix A

AMENDED AND RESTATED IONIS PHARMACEUTICALS, INC.
2011 EQUITY INCENTIVE PLAN

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

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

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

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

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

AMENDED: JUNE 2, 2021 (Amendment approved by Board on March 26, 2021
and by the Stockholders on June 2, 2021)

Amendment approved by Board on March 14, 2023

SUBJECT TO APPROVAL BY STOCKHOLDERS

1. GENERAL.

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

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

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

2. ADMINISTRATION.

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

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

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

(ii) To construe and interpret the Plan and Awards granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Stock Award Agreement or in the written terms of a Performance Cash Award, in a manner and to the extent it shall deem necessary or expedient to make the Plan or Award fully effective.

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

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

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

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

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

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

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

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

(c) Delegation to Committee.

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

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

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

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

(f) **Prohibition on Reduction of Exercise Prices, Cancellation and Re-Grant of Stock Awards.** Neither the Board nor any Committee (or subcommittee) shall have the authority to: (i) reduce the exercise price of any outstanding Options or Stock Appreciation Rights under the Plan, or (ii) cancel any outstanding Options or Stock Appreciation Rights that have an exercise price or strike price greater than the current Fair Market Value of the Common Stock in exchange for cash or other Stock Awards under the Plan, unless the stockholders of the Company have approved such an action within 12 months prior to such an event.

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

3. SHARES SUBJECT TO THE PLAN.

(a) **Share Reserve.** Subject to Section 9(a) relating to Capitalization Adjustments, the aggregate number of shares of Common Stock that may be issued pursuant to Stock Awards from and after the Effective Date shall not exceed 35,200,000 shares (the "**Share Reserve**"). For clarity, the Share Reserve in this Section 3(a) is a limitation on the number of shares of the Common Stock that may be issued pursuant to the Plan and does not limit the granting of Stock Awards except as provided in Section 7(a). Shares may be issued in connection with a merger or acquisition as permitted by, as applicable, NASDAQ Listing Rule 5635(c) or, if applicable, NYSE Listed Company Manual Section 303A.08, AMEX Company Guide Section 711 or other applicable rule, and such issuance shall not reduce the number of shares available for issuance under the Plan. Furthermore, if a Stock Award or any portion thereof (i) expires or otherwise terminates without all of the shares covered by such Stock Award having been issued or (ii) is settled in cash (*i.e.*, the Participant receives cash rather than stock), such expiration, termination or settlement shall not reduce (or otherwise offset) the number of shares of Common Stock that may be available for issuance under the Plan. Subject to Section 3(b), the number of shares of Common Stock available for issuance under the Plan will be reduced by: (A) one share for each share of Common Stock issued pursuant to an Option or SAR with respect to which the exercise or strike price is at least 100% of the Fair Market Value of the Common Stock subject to the Option or SAR on the date of grant; and (B) one and seven tenths (1.7) shares for each share of Common Stock issued pursuant to a Full Value Award.

(b) **Reversion of Shares to the Share Reserve.** If (A) any shares of Common Stock subject to a Stock Award are not issued because such Stock Award or any portion thereof expires or otherwise terminates without all of the shares covered by such Stock Award having been issued or is settled in cash (*i.e.*, the Participant receives cash rather than stock), (B) any shares of Common Stock issued pursuant to a Stock Award are forfeited back to the Company because of the failure to meet a contingency or condition required to vest such shares in the Participant, or (C) with respect to a Full Value Award, any shares of Common Stock are reacquired or withheld (or not issued) by the Company to satisfy a tax withholding obligation in connection with such Full Value Award, such shares will again become available for issuance under the Plan (collectively, the "**2011 Plan Returning Shares**"). For clarity, any shares underlying an Option or a Stock Appreciation Right that are reacquired by the Company pursuant to Section 8(f) or as consideration for the exercise of an Option or a Stock Appreciation Right shall not again become available for issuance under the Plan. For each 2011 Plan Returning Share subject to a Full Value Award granted prior to June 2, 2021, the number of shares of Common Stock available for issuance under the Plan will increase by one share, and for each 2011 Plan Returning Share subject to a Full Value Award granted on or after June 2, 2021, the number of shares of Common Stock available for issuance under the Plan will increase by one and seven tenths (1.7) shares.

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

4. ELIGIBILITY.

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

5. PROVISIONS RELATING TO OPTIONS AND STOCK APPRECIATION RIGHTS.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(a) **Restricted Stock Awards.** Each Restricted Stock Award Agreement shall be in such form and shall contain such terms and conditions as the Board shall deem appropriate. To the extent consistent with the Company's Bylaws, at the Board's election, shares of Common Stock may be (i) held in book entry form subject to the Company's instructions until any restrictions relating to the Restricted Stock Award lapse; or (ii) evidenced by a certificate, which certificate shall be held in such form and manner as determined by the Board. The terms and conditions of Restricted Stock Award Agreements may change from time to time, and the terms and conditions of separate Restricted Stock Award Agreements need not be identical; *provided, however*, that each Restricted Stock Award Agreement shall conform to (through incorporation of the provisions hereof by reference in the agreement or otherwise) the substance of each of the following provisions:

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

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

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

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

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

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

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

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

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

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

(c) **Performance Awards.**

(i) **Performance Stock Awards.** A Performance Stock Award is a Stock Award that may vest or may be exercised contingent upon the attainment during a Performance Period of certain Performance Goals. A Performance Stock Award may, but need not, require the completion of a specified period of Continuous Service. The length of any Performance Period, the Performance Goals to be achieved during the Performance Period, and the measure of whether and to what degree such Performance Goals have been attained shall be conclusively determined by the Committee, in its sole discretion. The Board may provide for or, subject to such terms and conditions as the Board may specify, may permit a Participant to elect for, the payment of any Performance Stock Award to be deferred to a specified date or event. In addition, to the extent permitted by applicable law and the applicable Award Agreement, the Board may determine that cash may be used in payment of Performance Stock Awards.

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

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

7. **COVENANTS OF THE COMPANY.**

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

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

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

8. **MISCELLANEOUS.**

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

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

(c) **Stockholder Rights.** No Participant shall be deemed to be the holder of, or to have any of the rights of a holder with respect to, any shares of Common Stock subject to such Stock Award unless and until (i) such Participant has satisfied all requirements for exercise of the Stock Award pursuant to its terms, if applicable, and (ii) the issuance of the Common Stock subject to such Stock Award has been entered into the books and records of the Company.

(d) No Employment or Other Service Rights. Nothing in the Plan, any Stock Award Agreement or any other instrument executed thereunder or in connection with any Award granted pursuant thereto shall confer upon any Participant any right to continue to serve the Company or an Affiliate in the capacity in effect at the time the Stock Award was granted or shall affect the right of the Company or an Affiliate to terminate (i) the employment of an Employee with or without notice and with or without cause, (ii) the service of a Consultant pursuant to the terms of such Consultant's agreement with the Company or an Affiliate, or (iii) the service of a Director pursuant to the Bylaws of the Company or an Affiliate, and any applicable provisions of the corporate law of the state in which the Company or the Affiliate is incorporated, as the case may be.

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

(f) Withholding Obligations. Unless prohibited by the terms of an Award Agreement, the Company may, in its sole discretion, satisfy any federal, state or local tax withholding obligation relating to an Award by any of the following means or by a combination of such means: (i) causing the Participant to tender a cash payment; (ii) withholding shares of Common Stock from the shares of Common Stock issued or otherwise issuable to the Participant in connection with the Award; *provided, however,* that no shares of Common Stock are withheld with a value exceeding the minimum amount of tax required to be withheld by law (or such lesser amount as may be necessary to avoid classification of the Stock Award as a liability for financial accounting purposes); (iii) withholding cash from an Award settled in cash; (iv) withholding payment from any amounts otherwise payable to the Participant; or (v) by such other method as may be set forth in the Award Agreement.

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

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

(i) Compliance with Section 409A. To the extent that the Board determines that any Award granted hereunder is subject to Section 409A of the Code, the Award Agreement evidencing such Award shall incorporate the terms and conditions necessary to avoid the consequences specified in Section 409A(a)(1) of the Code. To the extent applicable, the Plan and Award Agreements shall be interpreted in accordance with Section 409A of the Code. Notwithstanding anything to the contrary in this Plan (and unless the Award Agreement specifically provides otherwise), if the shares of Common Stock are publicly traded and a Participant holding an Award that constitutes "deferred compensation" under Section 409A of the Code is a "specified employee" for purposes of Section 409A of the Code, no distribution or payment of any amount shall be made upon a "separation from service" before a date that is six months following the date of such Participant's "separation from service" (as defined in Section 409A of the Code without regard to alternative definitions thereunder) or, if earlier, the date of the Participant's death.

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

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

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

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

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

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

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

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

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

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

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

10. TERMINATION OR SUSPENSION OF THE PLAN.

(a) **Plan Term.** The Board may suspend or terminate the Plan at any time. Unless terminated sooner by the Board, the Plan shall automatically terminate on June 15, 2031. No Awards may be granted under the Plan while the Plan is suspended or after it is terminated.

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

11. EFFECTIVE DATE OF PLAN.

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

12. CHOICE OF LAW.

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

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

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

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

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

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

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

(f) "*Change in Control*" means the consummation, in a single transaction or in a series of related transactions, of any one or more of the following events:

(i) any Exchange Act Person becomes the Owner, directly or indirectly, of securities of the Company representing more than 50% of the combined voting power of the Company's then outstanding securities other than by virtue of a merger, consolidation or similar transaction. Notwithstanding the foregoing, a Change in Control shall not be deemed to occur (A) on account of the acquisition of securities of the Company directly from the Company, (B) on account of the acquisition of securities of the Company by an investor, any affiliate thereof or any other Exchange Act Person that acquires the Company's securities in a transaction or series of related transactions the primary purpose of which is to obtain financing for the Company through the issuance of equity securities, or (C) solely because the level of Ownership held by any Exchange Act Person (the "**Subject Person**") exceeds the designated percentage threshold of the outstanding voting securities as a result of a repurchase or other acquisition of voting securities by the Company reducing the number of shares outstanding, provided that if a Change in Control would occur (but for the operation of this sentence) as a result of the acquisition of voting securities by the Company, and after such share acquisition, the Subject Person becomes the Owner of any additional voting securities that, assuming the repurchase or other acquisition had not occurred, increases the percentage of the then outstanding voting securities Owned by the Subject Person over the designated percentage threshold, then a Change in Control shall be deemed to occur;

(ii) there is consummated a merger, consolidation or similar transaction involving (directly or indirectly) the Company and, immediately after the consummation of such merger, consolidation or similar transaction, the stockholders of the Company immediately prior thereto do not Own, directly or indirectly, either (A) outstanding voting securities representing more than 50% of the combined outstanding voting power of the surviving Entity in such merger, consolidation or similar transaction or (B) more than 50% of the combined outstanding voting power of the parent of the surviving Entity in such merger, consolidation or similar transaction, in each case in substantially the same proportions as their Ownership of the outstanding voting securities of the Company immediately prior to such transaction;

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

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

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

Notwithstanding the foregoing or any other provision of this Plan, (A) the term Change in Control shall not include a sale of assets, merger or other transaction effected exclusively for the purpose of changing the domicile of the Company, and (B) the definition of Change in Control (or any analogous term) in an individual written agreement between the Company or any Affiliate and the Participant (validly executed by an authorized Executive Officer of the Company or such Affiliate) shall supersede the foregoing definition with respect to Awards subject to such agreement; *provided, however*, that if no definition of Change in Control or any analogous term is set forth in such an individual written agreement, the foregoing definition shall apply.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(t) “**Exchange Act Person**” means any natural person, Entity or “group” (within the meaning of Section 13(d) or 14(d) of the Exchange Act), except that “Exchange Act Person” shall not include (i) the Company or any Subsidiary of the Company, (ii) any employee benefit plan of the Company or any Subsidiary of the Company or any trustee or other fiduciary holding securities under an employee benefit plan of the Company or any Subsidiary of the Company, (iii) an underwriter temporarily holding securities pursuant to a registered public offering of such securities, (iv) an Entity Owned, directly or indirectly, by the stockholders of the Company in substantially the same proportions as their Ownership of stock of the Company; or (v) any natural person, Entity or “group” (within the meaning of Section 13(d) or 14(d) of the Exchange Act) that, as of the Effective Date, is the Owner, directly or indirectly, of securities of the Company representing more than 50% of the combined voting power of the Company’s then outstanding securities.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(ff) “**Performance Goals**” means, for a Performance Period, the one or more goals established by the Board for the Performance Period based upon the Performance Criteria. Performance Goals may be based on a Company-wide basis, with respect to one or more business units, divisions, Affiliates, or business segments, and in either absolute terms or relative to the performance of one or more comparable companies or the performance of one or more relevant indices. Unless specified otherwise by the Board (i) in the Award Agreement at the time the Award is granted or (ii) in such other document setting forth the Performance Goals at the time the Performance Goals are established, the Board shall appropriately make adjustments in the method of calculating the attainment of Performance Goals for a Performance Period as follows: (1) to exclude restructuring and/or other nonrecurring charges; (2) to exclude exchange rate effects, as applicable, for non-U.S. dollar denominated Performance Goals; (3) to exclude the effects of changes to generally accepted accounting principles; (4) to exclude the effects of any statutory adjustments to corporate tax rates; (5) to exclude the effects of items that are “unusual” in nature or occur “infrequently” as determined under generally accepted accounting principles; and (6) to exclude accounting expenses relating to share-based compensation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix B

IONIS PHARMACEUTICALS, INC.
AMENDED AND RESTATED
2002 NON-EMPLOYEE DIRECTORS' STOCK OPTION PLAN
ADOPTED BY THE BOARD OF DIRECTORS SEPTEMBER 11, 2001
APPROVED BY STOCKHOLDERS MAY 31, 2002
EFFECTIVE DATE: MAY 31, 2002

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

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

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

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

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

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

AMENDED AND RESTATED: JUNE 4, 2020 (Amendment and Restatement approved by Board on March 24, 2020 and by the Stockholders on June 4, 2020)

AMENDED: MARCH 14, 2023

1. PURPOSES.

- (a) **Amendment and Restatement.** This Plan was originally an amendment and restatement of the Ionis Pharmaceuticals, Inc. 1992 Non-Employee Directors' Stock Option Plan, and is an amendment of the Ionis Pharmaceuticals, Inc. 2002 Non-Employee Directors' Stock Option Plan, as amended and restated on June 4, 2020.
- (b) **Eligible Recipients.** The persons eligible to receive Stock Awards are the Non-Employee Directors of the Company.
- (c) **Available Stock Awards.** The purpose of the Plan is to provide a means by which Non-Employee Directors may be given an opportunity to benefit from increases in value of the Common Stock through the granting of Stock Awards.
- (d) **General Purpose.** The Company, by means of the Plan, seeks to retain the services of its Non-Employee Directors, to secure and retain the services of new Non-Employee Directors and to provide incentives for such persons to exert maximum efforts for the success of the Company and its Affiliates.

2. DEFINITIONS.

- (a) **"Affiliate"** means any parent corporation or subsidiary corporation of the Company, whether now or hereafter existing, as those terms are defined in Sections 424(e) and (f), respectively, of the Code.
- (b) **"Annual Grant"** means an Option and/or RSU Award granted annually to all Non-Employee Directors who meet the criteria specified in subsection 6(b) of the Plan.
- (c) **"Board"** means the Board of Directors of the Company.
- (d) **"Capitalization Adjustment"** has the meaning ascribed to that term in Section 12(a).

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

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

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

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

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

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

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

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

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

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

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

(i) **“Consultant”** means any person, including an advisor, (i) engaged by the Company or an Affiliate to render consulting or advisory services and who is compensated for such services or (ii) serving as a member of the Board of Directors of an Affiliate and who is compensated for such services. However, the term “Consultant” shall not include Directors who are not compensated by the Company for their services as Directors, and the payment of a director’s fee by the Company for services as a Director shall not cause a Director to be considered a “Consultant” for purposes of the Plan.

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

- (k) **“Corporate Transaction”** means the occurrence, in a single transaction or in a series of related transactions, of any one or more of the following events:
- Subsidiaries;
- (i) a sale or other disposition of all or substantially all, as determined by the Board in its discretion, of the consolidated assets of the Company and its Subsidiaries;
 - (ii) a sale or other disposition of at least 90% of the outstanding securities of the Company;
 - (iii) a merger, consolidation or similar transaction following which the Company is not the surviving corporation; or
 - (iv) a merger, consolidation or similar transaction following which the Company is the surviving corporation but the shares of Common Stock outstanding immediately preceding the merger, consolidation or similar transaction are converted or exchanged by virtue of the merger, consolidation or similar transaction into other property, whether in the form of securities, cash or otherwise.
- (l) **“Director”** means a member of the Board of Directors of the Company.
- (m) **“Disability”** means the permanent and total disability of a person within the meaning of Section 22(e)(3) of the Code.
- (n) **“Employee”** means any person employed by the Company or an Affiliate. Service as a Director or payment of a director’s fee by the Company or an Affiliate shall not be sufficient to constitute “employment” by the Company or an Affiliate.
- (o) **“Entity”** means a corporation, partnership or other entity.
- (p) **“Exchange Act”** means the Securities Exchange Act of 1934, as amended.
- (q) **“Exchange Act Person”** means any natural person, Entity or “group” (within the meaning of Section 13(d) or 14(d) of the Exchange Act), except that “Exchange Act Person” shall not include (A) the Company or any Subsidiary of the Company, (B) any employee benefit plan of the Company or any Subsidiary of the Company or any trustee or other fiduciary holding securities under an employee benefit plan of the Company or any Subsidiary of the Company, (C) an underwriter temporarily holding securities pursuant to an offering of such securities, or (D) an Entity Owned, directly or indirectly, by the stockholders of the Company in substantially the same proportions as their Ownership of stock of the Company.
- (r) **“Fair Market Value”** means, as of any date, the value of the Common Stock determined as follows:
- (i) If the Common Stock is listed on any established stock exchange or traded on the Nasdaq National Market or the Nasdaq SmallCap Market, the Fair Market Value of a share of Common Stock shall be the closing sales price for such stock (or the closing bid, if no sales were reported) as quoted on such exchange or market (or the exchange or market with the greatest volume of trading in the Common Stock) on the last market trading day prior to the day of determination, as reported in The Wall Street Journal or such other source as the Board deems reliable.
 - (ii) In the absence of such markets for the Common Stock, the Fair Market Value shall be determined in good faith by the Board.
- (s) **“Holder”** means a person to whom an Option or RSU Award is granted pursuant to the Plan or, if applicable, such other person who holds an outstanding Option or RSU Award.
- (t) **“Initial Grant”** means an Option and/or RSU granted to a Non-Employee Director who meets the criteria specified in subsection 6(a) of the Plan.
- (u) **“Non-Employee Director”** means a Director who is not an Employee.
- (v) **“Nonstatutory Stock Option”** means an Option not intended to qualify as an incentive stock option within the meaning of Section 422 of the Code and the regulations promulgated thereunder.

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

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

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

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

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

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

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

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

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

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

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

3. ADMINISTRATION.

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

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

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

(ii) To construe and interpret the Plan and Stock Awards granted under it, and to establish, amend and revoke rules and regulations for its administration. The Board, in the exercise of this power, may correct any defect, omission or inconsistency in the Plan or in any Option Agreement or RSU Agreement, in a manner and to the extent it shall deem necessary or expedient to make the Plan fully effective.

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

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

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

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

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

4. SHARES SUBJECT TO THE PLAN.

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

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

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

5. ELIGIBILITY.

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

6. NON-DISCRETIONARY GRANTS.

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

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

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

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

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

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

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

7. OPTION PROVISIONS.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8. RESTRICTED STOCK UNIT PROVISIONS.

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

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

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

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

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

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

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

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

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

9. COVENANTS OF THE COMPANY.

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

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

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

10. USE OF PROCEEDS FROM STOCK.

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

11. MISCELLANEOUS.

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

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

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

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

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

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

12. ADJUSTMENTS UPON CHANGES IN STOCK.

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

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

(c) **Corporate Transaction.** In the event of a Corporate Transaction, any surviving corporation or acquiring corporation may assume any or all Stock Awards outstanding under the Plan or may substitute similar stock awards for Stock Awards outstanding under the Plan (it being understood that similar stock awards include, but are not limited to, options to acquire, or restricted stock unit rights to receive, the same consideration paid to the stockholders or the Company, as the case may be, pursuant to the Corporate Transaction). In the event that any surviving corporation or acquiring corporation does not assume any or all such outstanding Stock Awards or substitute similar stock awards for such outstanding Stock Awards, then with respect to Stock Awards that have been neither assumed nor substituted and that are held by Holders whose Continuous Service has not terminated prior to the effective time of the Corporate Transaction, the vesting of such Stock Awards (and, if applicable, the time at which such Stock Awards may be exercised) shall (contingent upon the effectiveness of the Corporate Transaction) be accelerated in full to a date prior to the effective time of such Corporate Transaction as the Board shall determine (or, if the Board shall not determine such a date, to the date that is 5 days prior to the effective time of the Corporate Transaction), and the Stock Awards shall terminate if not exercised at or prior to such effective time. With respect to Stock Awards outstanding under the Plan that have been neither assumed nor substituted and that are held by Holders whose Continuous Service has terminated prior to the effective time of the Corporate Transaction, the vesting of such Stock Awards (and, if applicable, the time at which such Stock Award may be exercised) shall not be accelerated unless otherwise provided in a written agreement between the Company or any Affiliate and the holder of such Stock Award, and such Stock Awards shall terminate if not exercised prior to the effective time of the Corporate Transaction.

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

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

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

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

13. AMENDMENT OF THE PLAN AND STOCK AWARDS.

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

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

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

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

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

14. TERMINATION OR SUSPENSION OF THE PLAN.

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

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

15. EFFECTIVE DATE OF PLAN.

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

16. CHOICE OF LAW.

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

Appendix C

Reconciliation of GAAP to Non-GAAP Basis

As illustrated in the table below, non-GAAP operating expenses, non-GAAP income (loss) from operations, and non-GAAP net income (loss) were adjusted from GAAP to exclude compensation expense related to equity awards and the related tax effects. Compensation expense related to equity awards are non-cash. In 2022 our non-GAAP net loss excluded the gain on property related to the sale and leaseback transaction and the related tax effect. In 2021 all non-GAAP amounts also excluded expenses related to the Akcea Merger and restructured commercial operations. Expenses related to the Akcea Merger and restructured commercial operations included: severance costs, retention costs and other costs related to commercial operations. We have regularly reported non-GAAP measures for operating results as non-GAAP results. These measures are provided as supplementary information and are not a substitute for financial measures calculated in accordance with GAAP. We report these non-GAAP results to better enable financial statement users to assess and compare its historical performance and project its future operating results and cash flows. Further, the presentation of our non-GAAP results is consistent with how our management internally evaluates the performance of its operations.

IONIS PHARMACEUTICALS, INC.
Reconciliation of GAAP to Non-GAAP Basis:
Condensed Consolidated Operating Expenses, Income (Loss) From Operations, and Net Income (Loss)
(In Millions)

	Three months ended December 31,		Year ended December 31,	
	2022	2021	2022	2021
	(unaudited)			
As reported research, development and patent expenses according to GAAP	\$308	\$179	\$833	\$643
Excluding compensation expense related to equity awards	(19)	(16)	(74)	(88)
Excluding Akcea Merger and restructured commercial operation costs*	-	(1)	-	(9)
Non-GAAP research, development and patent expenses	\$289	\$162	\$759	\$546
As reported selling, general and administrative expenses according to GAAP	\$48	\$38	\$151	\$186
Excluding compensation expense related to equity awards	(7)	(7)	(26)	(33)
Excluding Akcea Merger and restructured commercial operation costs*	-	1	-	(15)
Non-GAAP selling, general and administrative expenses	\$41	\$32	\$125	\$138
As reported operating expenses according to GAAP	\$360	\$219	\$998	\$840
Excluding compensation expense related to equity awards	(25)	(23)	(100)	(121)
Excluding Akcea merger and restructured commercial operation costs*	-	-	-	(24)
Non-GAAP operating expenses	\$335	\$196	\$898	\$695
As reported income (loss) from operations according to GAAP	(\$208)	\$221	(\$411)	(\$30)
Excluding compensation expense related to equity awards	(25)	(23)	(100)	(121)
Excluding Akcea Merger and restructured commercial operation costs*	-	-	-	(24)
Non-GAAP income (loss) from operations	(\$183)	\$244	(\$311)	\$115
As reported net income (loss) according to GAAP	(\$52)	\$225	(\$270)	(\$29)
Excluding compensation expense related to equity awards	(25)	(23)	(100)	(121)
Excluding Akcea Merger and restructured commercial operation costs*	-	-	-	(24)
Excluding gain on sale of real estate assets**	150	-	150	-
Excluding income tax effect related to gain on sale of real estate assets	(9)	-	(9)	-
Non-GAAP net income (loss)	(\$168)	\$248	(\$311)	\$116

*In October 2020, we completed the Akcea Merger. Additionally, in December 2020 and April 2021, we restructured our European operations and our North American TEGSEDI operations, respectively, as a result of entering into distribution agreements with Sobi. We excluded the Akcea Merger and restructured commercial operation costs from our non-GAAP amounts for the applicable periods.

**In October 2022, we entered into a sale and leaseback transaction for several of our real estate assets. As a result, we recognized a \$150 million gain on sale of real estate assets in the fourth quarter of 2022. We excluded the gain on sale of real estate assets and the related tax effect from our non-GAAP amounts for the applicable periods.

IONIS PHARMACEUTICALS, INC.
 2655 GAZELLE COURT
 CARLSBAD, CALIFORNIA 92010
 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.virtualshareholdermeeting.com/IONS2023
 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 2026:</p>		For All	Withhold All	For All Except	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.		
		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	_____		
<p>1. Election of Directors</p> <p>Nominees</p> <p>01) Spencer R. Berthelsen 02) Joan E. Herman 03) B. Lynne Parshall 04) Joseph H. Wender</p>							
<p>The Board of Directors recommends you vote FOR the following proposal:</p>		For	Against	Abstain	For	Against	Abstain
<p>2. To approve, by non-binding vote, executive compensation.</p>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>5. To ratify increasing the vesting of future initial stock option and restricted stock unit awards to new non-employee Directors from one year to three years.</p>		
<p>The Board of Directors recommends you vote 1 YEAR on the following proposal:</p>		1 year	2 years	3 years	Abstain		
<p>3. To approve, by non-binding vote, the frequency of future advisory votes on executive compensation.</p>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<p>6. To ratify the Audit Committee's selection of Ernst & Young LLP as independent auditors for the 2023 fiscal year.</p>	
<p>The Board of Directors recommends you vote FOR proposals 4, 5 and 6.</p>		For	Against	Abstain	NOTE: Such other business as may properly come before the meeting or any adjournment thereof.		
<p>4. To approve an amendment of the Ionis Pharmaceuticals, Inc. 2011 Equity Incentive Plan to increase the aggregate number of shares of common stock authorized for issuance under such plan by 5,500,000 shares to an aggregate of 35,200,000 shares.</p>		<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
<p>Please sign exactly as your name(s) appear(s) hereon. When signing as attorney, executor, administrator, or other fiduciary, please give full title as such. Joint owners should each sign personally. All holders must sign. If a corporation or partnership, please sign in full corporate or partnership name by authorized officer.</p>							
<p>Signature [PLEASE SIGN WITHIN BOX]</p>		Date		<p>Signature (Joint Owners)</p>		Date	

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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 1, 2023 2:00 PM Pacific Time
This proxy is solicited by the Board of Directors of
Ionis Pharmaceuticals, Inc.

The undersigned hereby appoints Brett Monia and 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 1, 2023 at www.virtualshareholdermeeting.com/IONS2023 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, 1 YEAR for Proposal 3, FOR Proposal 4, FOR Proposal 5 and FOR Proposal 6 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