UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

SCHEDULE 14A

Proxy Statement Pursuant to Section 14(a) of the Securities Exchange Act of 1934 (Amendment No.)

Filed by the Registrant ☒
Filed by a Party other than the Registrant ☐
Check the appropriate box:
☐ Preliminary Proxy Statement
☐ **Confidential, for Use of the Commission Only (as permitted by Rule 14a-6(e)(2))**
☐ Definitive Proxy Statement
☒ Definitive Additional Materials
☐ Soliciting Material Pursuant to §240.14a-12

Ionis Pharmaceuticals, Inc.

(Name of Registrant as Specified In Its Charter)

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

Payment of Filing Fee (Check the appropriate box):
☒ No fee required.
☐ Fee computed on table below per Exchange Act Rules 14a-6(i)(1) and 0-11.
(1) Title of each class of securities to which transaction applies:

(2) Aggregate number of securities to which transaction applies:

(3) Per unit price or other underlying value of transaction computed pursuant to Exchange Act Rule 0-11 (set forth the amount on which the filing fee is calculated and state how it was determined):

(4) Proposed maximum aggregate value of transaction:

(5) Total fee paid:

☐ Fee paid previously with preliminary materials.
☐ Check box if any part of the fee is offset as provided by Exchange Act Rule 0-11(a)(2) and identify the filing for which the offsetting fee was paid previously. Identify the previous filing by registration statement number, or the Form or Schedule and the date of its filing.

(1) Amount Previously Paid:

(2) Form, Schedule or Registration Statement No.:

(3) Filing Party:

(4) Date Filed:

Persons who are to respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB control number

Ionis Pharmaceuticals, Inc.
2019 Annual Meeting of Stockholders
Supplemental Information Regarding Proposal 5

May 28, 2019

Dear Stockholders:

We are writing to ask for your support by voting in accordance with the recommendations of the Board of Directors (the "Board") of Ionis Pharmaceuticals, Inc. (the "Company" or "Ionis") on all of the Company's proxy proposals. In particular, we are asking for you to vote "FOR" Proposal 5: our advisory vote on executive compensation (our "Say-on-Pay Proposal").

Our compensation philosophy, program and 2018 decisions are described in detail in our 2019 proxy statement (the "Proxy Statement," available here), but to assist you in evaluating our Say-on-Pay Proposal, we would like to provide you with certain additional information and context.

To understand our executive compensation program, we believe it is important to understand our business and organizational strategy:

- *Business Strategy*: Ionis is a multi-product commercial company with a pipeline of first-in-class and/or best-in-class medicines discovered by Ionis that are designed to treat a broad range of diseases including neurological disease, cardiovascular disease, rare diseases, infectious diseases and cancer. Ionis has created an efficient, broadly applicable, drug discovery platform called antisense technology with the potential to treat diseases where no other therapeutic approaches have proven effective or ever existed. Ionis is committed to creating long-term value through innovation based on the efficiency of antisense technology. Ionis has been recognized as one of the top innovative companies in the biotechnology industry, based on number of granted patents, scientific strength, industry impact, technology strength and research intensity.

- *Organizational Strategy*: A key component of our business and organizational strategy is to maintain an optimal size to continue to foster innovation. We are able to maintain an optimal size by licensing our medicines at key value inflection points during development, thus avoiding the need to build the large, complex, inefficient organizations associated with fully integrated pharmaceutical companies. Ionis has an innovation-focused, science-driven culture that couples with the technology and business model to ensure long-term productivity and a commitment to patients and stockholders. With more than 1,800 issued patents (over three per employee) that provide substantial control of key elements of the technology for many years to come and a pipeline of more than 40 first-in-class and/or best-in-class medicines (one medicine in development per 11 employees), we, by design, demand more of every employee at Ionis, particularly the middle and senior level leaders, and we do not tolerate mediocrity.

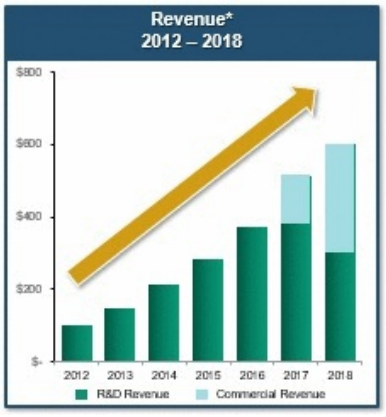
Ionis delivered significant performance in 2018, with a number of achievements demonstrating the productivity and strength of our business strategy:

- Our TSR outperformed the median of the Nasdaq Biotechnology Index over the previous one-, three- and five-year periods. Outperforming the median of the Nasdaq Biotechnology Index for 2018 was a performance objective and measure set for management at the beginning of 2018. As such, Ionis met the *pre-defined, objective, stock price performance measure* set for the year. Over the previous one-year period, our TSR also outperformed the Russell 3000 index and the peer group of 20 life science companies (the "Peer Group") that the Compensation Committee of our Board (the "Compensation Committee") uses for evaluating Ionis' compensation.
- We obtained approval to market TEGSEDI in the U.S., EU and Canada for the treatment of a devastating disease – polyneuropathy caused by hereditary TTR amyloidosis.

- As further described below, we earned an all-time high for revenue, substantially exceeding our 2018 financial guidance and achieving our third consecutive year of non-GAAP[1] operating income, despite receiving a Complete Response Letter for a medicine we hoped to commercialize in 2018.
- We achieved these financial successes while advancing a diverse pipeline of over 40 potentially transformative medicines, ten of which are advancing toward pivotal studies by the end of 2020, with four of those expected to enter pivotal studies by the end of 2019.
- While successfully advancing our pipeline and technology, we aggressively invested in commercializing TEGSEDI globally, achieving sales of over $2 million in the first partial quarter of being on the market.
- Ionis and Biogen received the prestigious International Prix Galien Award for the Best Biotechnology Product in 2018 for SPINRAZA.

Additional evidence of our productivity and the benefit of our business strategy is reflected by our strong financial position:

- We ended 2018 in a very strong financial position, with 2018 revenues of $600 million, an increase of more than 15% from 2017, and *Ionis' seventh consecutive year of revenue growth*.
- For the third year in a row, we were profitable, with non-GAAP operating income in 2018 of $70 million. This success is driven by the strength of our business strategy, which leverages numerous sources of revenue, with multiple opportunities for upside, while reducing risk.



* 2016 and 2017 revised for FASB Topic ASC 606 adjustment.

- We ended 2018 with a strong balance sheet with more than $2 billion in cash and short-term investments, making this the *sixth year out of seven that we have been cash accretive*. Our strong balance sheet provides us with the financial wherewithal to invest in expanding and advancing our pipeline, in commercializing our medicines through commercial affiliates, and advancing our technology.

[1] We use "non-GAAP" in place of "pro-forma" when discussing our financial results that exclude non-cash compensation expense related to equity awards because we believe that non-GAAP financial results better represent the economics of our business and how we manage our business.

Additionally, we believe it is important to reiterate how our executive compensation strategy is aligned with our business and organizational strategy as further context for our 2018 executive compensation decisions:

- *Simply put, we demand great performance and pay for that performance.* The Compensation Committee has structured the various components of our compensation system to reflect accountability for the successes and failures (both long-term and short-term) of Ionis, which means that a significant proportion of executive officers' compensation is "at risk" in the form of performance-based cash payments through our annual Performance Management By Objective Program ("Performance MBO Program") and long-term equity awards tied to stock price. We pay our senior management team for results and their use of judgment in executing the strategies established at the beginning of each year.

- *Our executive compensation program is designed to align with our strategic focus, organizational strategy and the creation of long-term stockholder value.* Drug discovery and development across a portfolio of many medicines is a long process that spans many years, where decisions we make today can have a positive or negative consequence five years, ten years, and even further into the future. As such, it is essential we set goals that incentivize our employees to execute our long-term strategy, because we believe our long-term strategy should continue to reward our stockholders into the future. For us to retain our technology leadership and effectively manage the technical complexity and broad scope of our pipeline, our most senior executives and the members of their teams must advance multiple drug development strategies and collaborative partnerships in parallel and consistently over many years, versus emphasizing one or two at the expense of others that deserve attention.

- *Our Performance MBO Program includes aggressive results-driven corporate objectives with objective measures, no guaranteed payouts, and maximum payout limits, and the Compensation Committee has negative discretion to reduce payouts after considering one-, three- and five-year total stockholder returns.* At the beginning of each year, the Compensation Committee approves annual performance objectives on which we believe our executive officers should focus during the year in order to achieve our business goals, including financial, operating and/or strategic plans, and we monitor and review progress against these objectives during and after each year. These objectives are aggressive results-driven corporate objectives and *include objective measures for each objective.*

  We typically include a number of objectives that are based on achieving positive data in the clinic. For example, in 2018 we had a corporate objective to make our relationship with Novartis successful with one of the objective measures being to achieve positive data from a Phase 2 dose-ranging study, and another corporate objective to advance our pipeline with one of the objective measures being to achieve positive proof-of-concept on five or more medicines. These types of objectives only reward our employees if the data are positive—we do this to encourage the prudent spending of stockholder money on development decisions. In other words, we want to structure our objectives to reward success based on good judgment, rather than the making of "bad bets."

  The Compensation Committee generally believes that a formulaic or purely quantitative approach to our Performance MBO Program is not the best way to align executive compensation with our business and organizational strategy and foster long-term success for Ionis and long-term value for stockholders. Other than stock price, budget 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.

Awards under our Performance MBO Program are not guaranteed (i.e., are 100% at risk) and include a multiplier, or performance factor, based on Ionis' performance (the "Company Performance Factor") and the employee's performance (the "Individual Performance Factor"). Therefore, if *either* Ionis or the employee performs poorly, the Performance MBO can be, and has been, zero. We establish rigorous corporate objectives and define excellent performance as a year in which we have met most of those objectives. The Compensation Committee considers our one-, three- and five-year total stockholder returns, and based on these returns has negative discretion to reduce the Corporate Performance Factor and Individual Performance Factor for each of our executive officers. As further described below, although Ionis met nine objectives, exceeded seven objectives, did not meet only one objective and had multiple significant unplanned accomplishments, the Company Performance Factor for 2018 was 115%, which reflects *a decrease of 20 percentage points from the 2017 Company Performance Factor of 135%.*

The Compensation Committee measures Ionis' performance based upon the achievement of the rigorous corporate objectives set at the beginning of the year. At that time, the Compensation Committee reviews the Company Performance Factor history from the prior ten years to form a comparison for our current year's successes and/or failures. The Compensation Committee also approves each executive officer's Individual Performance Factor based on the individual's performance. We have a maximum Company Performance Factor of 200% and a maximum Individual Performance Factor of 160%. Illustrating the rigor of our performance objectives and culture of high performance and accountability, our CEO's 2018 bonus was approximately 25% lower than in 2017.

- *The Compensation Committee annually considers the appropriate mix of equity awards and continues to believe that time-vested stock options and restricted stock unit ("RSU") awards are the appropriate mix for the following reasons*:

    - During the past several years, Ionis has discussed the use of time-vested stock options and RSU awards with our institutional stockholders, many of which acknowledged the prevalence of stock options in the biopharmaceutical industry and agreed that we had the right mix of equity vehicles for our industry and stage.

    - Stock options are inherently performance-based compensation. For the recipient of a stock option to recognize any economic value, the stock price must appreciate following the grant date and prior to vesting and exercise. Similarly, in the same way our stockholders' returns increase and decrease based on our stock's performance, the value to our employees of RSUs increases and decreases based on our stock's performance.

    - Time-vested stock options and RSUs facilitate a focus on the totality of Ionis' ongoing and future activities as potential contributors to stock price appreciation. Performance-based equity awards could promote excessive risk-taking that could adversely impact Ionis or its drug discovery and development efforts.

- *Our executive compensation program also reflects strong corporate governance attributes*. The Compensation Committee, with assistance from our independent compensation consultant, provides comprehensive oversight of our executive compensation program. The Compensation Committee regularly evaluates the economic, strategic and organizational challenges facing Ionis and periodically modifies our executive compensation program to address these and other factors that evolve over time. For example, in response to requests from some of our stockholders who asked that we provide more disclosure around the goal-setting process for our bonus program to demonstrate how the goals translate into measurable results, we recently have been providing more disclosure around our Performance MBO Program. We also maintain stock ownership and holding guidelines, have a strict policy prohibiting hedging and pledging, maintain a clawback policy, impose minimum vesting requirements for equity awards, do not provide tax gross-up payments other than for relocation, and do not guarantee bonuses or base salary increases or provide perquisites for any employees.

When designing our 2018 executive compensation program, the Compensation Committee remained steadfastly committed to aligning our executives' compensation with the interests of our stockholders and the performance of Ionis. We strongly believe that our 2018 executive compensation program fostered a culture of high performance and accountability and promoted long-term stockholder value creation.

As described in the Proxy Statement, the Compensation Committee set the Company Performance Factor for the 2018 Performance MBO Program at 115% due to our strong achievements for the year across drug discovery, development, corporate development and financial performance, particularly given:

- SPINRAZA significantly surpassed sales goals, generating 2018 global sales of over $1.7 billion, and is now the standard of care for all patients with spinal muscular atrophy, or SMA;

- Regulatory authorities in the U.S., EU and Canada approved marketing applications for TEGSEDI (inotersen) and Akcea launched the product in the U.S. and EU; and

- Ionis revenues for 2018 increased by more than 15% compared to 2017, the Company achieved non-GAAP operating income for the third consecutive year, and ended the year with more than $2 billion in cash and short-term investments on its balance sheet.

These positives were offset by a Complete Response Letter we and our affiliate, Akcea Therapeutics, Inc., received for WAYLIVRA. The Company's strong performance despite encountering this regulatory setback is a testament to the success of Ionis' business model, which relies on revenue from a variety of sources.

The Proxy Statement includes a table with a transparent, detailed and objective evaluation of each performance objective that the Board and management set at the beginning of the year, as well as a description of notable unplanned accomplishments that the Compensation Committee considered in evaluating the Company's 2018 performance. For reference, at the end of these supplemental materials as Schedule I we have included the full table previously published in the Proxy Statement. The Compensation Committee takes great care to ensure that compensation decisions are based on tangible performance in accordance with our pay-for-performance philosophy, as evidenced by the varied decisions related to pay that are reflected in our proxy.

As described above, although we define excellent performance as a year in which we have met most of the objectives, and for 2018, Ionis met nine objectives, exceeded seven objectives, did not meet only one objective and had multiple significant unplanned accomplishments, the 2018 Company Performance Factor of 115% reflects a decrease of 20 percentage points from the 2017 Company Performance Factor of 135%. This is in large part due to the Complete Response Letter received from the FDA for WAYLIVRA, but nevertheless reflects a strong year of performance against the preset strategic objectives. Further illustrating the rigor of our performance objectives and culture of high performance and accountability, our CEO's 2018 bonus was approximately 25% lower than in 2017. Notably, our CEO's target bonus percentage was below the median of our Peer Group and our other named executive officers' target bonuses were either at or below the median of our Peer Group.

Our Board remains committed to an executive compensation program that supports our strategic objectives and aligns with stockholders' interests.

The Compensation Committee takes into account stockholder feedback (including considering the results of our annual say-on-pay proposals) in evaluating and making executive compensation decisions, and is committed to maintaining an active dialogue with our stockholders on topics of particular concern to stockholders, including executive compensation matters. For the reasons set forth above and in our Proxy Statement, we urge you to vote "FOR" our Say-on-Pay Proposal (Proposal 5). Even if you have already voted, you can change your vote before the 2019 Annual Meeting of Stockholders, as described in more detail in our Proxy Statement (under the heading "*Can I change my vote after submitting my proxy*?").

We appreciate your time and consideration on these matters and ask for your support of the Board's recommendation.

Special Note Regarding Forward-Looking Statements

These materials include forward-looking statements regarding our business and the therapeutic and commercial potential of SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen) and our technologies and products in development, including the business of Akcea Therapeutics, Inc., our majority-owned affiliate. 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, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. 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, 2018, which is on file with the SEC. Copies of the 10-K and other documents are available from the Company.

In these materials, 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 these materials are the property of Ionis Pharmaceuticals, Inc. "Akcea," the Akcea logo, and other trademarks or service marks of Akcea Therapeutics, Inc. appearing in these materials are the property of Akcea Therapeutics, Inc. These materials contain 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 these materials may appear without the ® or TM symbols.

Schedule I

Evaluation of 2018 Corporate Objectives		
	Objective & Pre-Approved Objective Measures	**Evaluation**
1	SPINRAZA – Achieve successful commercialization: • 2018 sales ≥ $1.5 billion • Implement successful plan with Biogen for development of a new SMA medicine by achieving Development Candidate acceptance	Ionis *exceeded* this objective: • Ionis and Biogen significantly exceeded this goal, generating 2018 global sales of over $1.7 billion • Under Ionis' new collaboration with Biogen to discover new antisense medicines with enhanced properties to treat SMA, Ionis and Biogen successfully formulated a development plan
2	WAYLIVRA (volanesorsen) – Approval and successful launch for FCS: • 2018 sales ≥ a specified sales target following approval in US, EU and Canada • Organization in place and ready to launch in US, Canada, Germany, UK and France by approval dates • Plan for certain dosage strength agreed with regulators • Achieve defined pricing objectives in US, Canada and EU • Negotiate feasible REMS and RMP and have effective monitoring process in place at launch. • Complete enrollment in FPL study	Ionis *did not meet* this objective, with one exception: • Ionis and Akcea received a Complete Response Letter for WAYLIVRA in the 3rd quarter; Ionis and Akcea are engaged in ongoing discussions with FDA regarding a path forward • Ionis and Akcea continued to conduct the BROADEN study, a Phase 3 clinical trial, with data expected in 2019. The study completed enrollment in 2018.

Evaluation of 2018 Corporate Objectives		
	Objective & Pre-Approved Objective Measures	**Evaluation**
3	TEGSEDI (inotersen) – Approval and successful launch for hATTR polyneuropathy	Ionis *met* this objective:
	• 2018 sales ≥ a specified sales target	• Despite delayed PDUFA, Ionis and Akcea nevertheless generated $2 million in sales following approval in the 4th quarter
	• US and EU approval	• TEGSEDI was approved in the US, EU and Canada
	• Organization in place and ready to launch in US by approval dates	• Ionis and Akcea built the infrastructure necessary for launch in the US and Canada
	• Achieve defined pricing objectives in US, Canada and EU	• Ionis and Akcea achieved defined pricing objectives in US and EU
	• Negotiate feasible REMS and RMP and have effective monitoring process in place at launch.	• Ionis and Akcea negotiated a feasible REMS and RMP and implemented an effective monitoring process, including robust patient support resources and mobile phlebotomy
	• Supply chain in place at launch	• Ionis and Akcea implemented a supply chain with minimal delay
	• Expanded access program rapidly executed in accordance with plan	• Ionis and Akcea executed an expanded access program, affording certain patients the opportunity to obtain medicine prior to approval
	• Complete EU transaction and successfully work with partner to ensure rapid launch	• Ionis licensed to Akcea and is working with Akcea to successfully commercialize TEGSEDI in EU
	• Develop plan for regulatory approval/launch in key non-US/EU regions, including Brazil launch in 2019	• Ionis and Akcea developed a plan for launch in key non-US/EU regions and completed a transaction with PTC Therapeutics to commercialize TEGSEDI in Latin America. Regulatory filing accepted by ANVISA in Brazil and received priority review.
4	Establish and implement aggressive development plan for AKCEA-TTR-L_{Rx}:	Ionis *met* this objective:
	• Establish development plan for all forms of TTR amyloidosis with US and EU regulatory support	• Ionis and Akcea established a development plan for hATTR and wtATTR and had constructive meetings with FDA in early 2019 regarding agreement on design of pivotal study for 2019
	• Initiate Phase 1 study	• Ionis initiated a Phase 1/2 study for AKCEA-TTR-L_{Rx}
5	Make Novartis relationship successful:	Ionis *met* this objective:
	• AKCEA-APO(a)-L_{Rx} dose-ranging study complete with positive data	• Phase 2 dose-ranging study showed statistically significant dose-dependent reductions of Lp(a) compared to placebo at all dose levels and demonstrated favorable safety and tolerability profile
	• Positive end of Phase 2 meeting with FDA	• Ionis and Akcea had a positive end of Phase 2 meeting with FDA
	• Platelet monitoring frequency as per standard Phase 3 studies	• Phase 2 dose-ranging study demonstrated favorable safety and tolerability profile, supporting standard (non-ASO) platelet monitoring frequency
	• Trigger Novartis option exercise process.	• Completion of Phase 2 dose-ranging study with positive data and end of Phase 2 meeting with FDA triggered process for option decision
	• Complete enrollment for dose-ranging study for AKCEA-APOCIII-L_{Rx}	• Ionis and Akcea continued to conduct the dose-ranging study for AKCEA-APOCIII-L_{Rx}, with data expected in 2020.

Evaluation of 2018 Corporate Objectives		
	Objective & Pre-Approved Objective Measures	**Evaluation**
6	Complete Biogen strategic transaction: • Terms consistent with 2018 budget • Successful collaboration launch and add four new targets to collaboration	Ionis *exceeded* this objective: • Ionis and Biogen entered into a new strategic collaboration to develop novel medicines for a broad range of neurological diseases and received a $1 billion upfront payment, comprised of $625 million stock purchase at 25% premium and $375 million cash, with the potential to receive up to $270 million for each medicine that achieves marketing approval and royalties up to the 20% range. • Ionis and Biogen added *eleven* new targets to this collaboration
7	Make Biogen relationship successful: • Achieve enrollment target for IONIS-MAPT$_{Rx}$ in Phase 1/2 study • Initiate Phase 1/2a study for IONIS-C9$_{Rx}$ • Initiate second ALS target screen • Achieve ≥ 2 new target sanctions • Identify ≥ 1 development candidates • Achieve revenue target across all Biogen collaborations (excluding SPINRAZA)	Ionis *met* this objective: • Ionis initiated a dose escalation study for IONIS-MAPT$_{Rx}$ in patients with mild Alzheimer's disease, with data expected in 2020. Although the study did not achieve the desired enrollment in 2018, it remains on track to report data in 2020. • Ionis initiated a Phase 1/2 study in ALS patients with a mutation in the C9ORF72 gene, advancing a novel approach to a disease for which there is no cure • Ionis initiated a second ALS target screen • Ionis achieved two new target sanctions. • Ionis made significant progress in identifying a development candidate • Ionis exceeded the revenue target across all Biogen collaborations

Evaluation of 2018 Corporate Objectives		
	Objective & Pre-Approved Objective Measures	**Evaluation**
8	Make AstraZeneca oncology relationship successful: • Positive results from danvatirsen (formerly IONIS-STAT3-2.5$_{Rx}$) Phase 1b study with advancement to next stage of development with milestones • Positive completion of Phase 1 study for an oncology candidate with advancement to next stage of development • Development candidate approval for IONIS-AZ7-2.5$_{Rx}$	Ionis *met* this objective: • Phase 1b/2 study evaluating danvatirsen in combination with AstraZeneca's durvalumab, in recurrent metastatic head and neck cancer was successfully completed, earning a $17.5 million milestone payment • Candidate did not advance • Ionis achieved development candidate approval for IONIS-AZ7-2.5$_{Rx}$
9	Make AstraZeneca CVMD relationship successful: • Achieve one development candidate milestone approval • Achieve two target sanctions, one involving a novel LICA strategy	Ionis *exceeded* this objective: • Ionis achieved *two* development candidate approvals • Ionis achieved two new target sanctions, one of which involved a novel LICA strategy
10	Achieve revenue target across AstraZeneca oncology and CVMD collaborations:	Ionis *exceeded* this objective: • Ionis exceeded the revenue target across all AstraZeneca collaborations
11	Regulatory: • Obtain agreement from FDA and major European regulators on platelet monitoring for frequency similar to standard (non-ASO) clinical studies for LICA programs	Ionis *met* this objective: • Regulators acknowledged the favorable safety and tolerability profile of the Phase 2 dose-ranging study for AKCEA-APO(a)-L$_{Rx}$ and were supportive of standard (non-ASO) platelet monitoring frequency for LICA programs
12	Advance pipeline: • Initiate 1 Phase 3 trial • Initiate first Phase 2 trials on ≥ 4 medicines • Positive clinical proof-of-concept on ≥ 5 medicines • Initiate Phase 1 trials on ≥ 5 medicines • Add ≥ 5 new medicines into the pipeline • Add ≥ 5 target sanctions • Ribo to initiate Phase 2 in China for IONIS-GCGR$_{Rx}$	Ionis *exceeded* this objective: • Ionis made substantial progress toward initiating Phase 3 trial for RG6042 (formerly IONIS-HTT$_{Rx}$) in patients living with symptoms of Huntington's disease, with first patient enrolled in January 2019 • Ionis initiated Phase 2 clinical trials for four medicines • Ionis completed studies that demonstrated positive clinical proof-of-concept for *six* medicines • Ionis initiated Phase 1 clinical trials on *six* medicines • Ionis added *six* new medicines to its development pipeline • Ionis achieved target sanction on *eight* medicines • Preparations underway for Phase 2 study of IONIS-GCGR$_{Rx}$ in China and study expected to commence in the second quarter of 2019

Evaluation of 2018 Corporate Objectives		
	Objective & Pre-Approved Objective Measures	**Evaluation**
13	Achieve key technology advancements: • Plan and validate blood collection device to facilitate platelet monitoring for 2019 commercial use • Confirm that modulation of protein interactions result in improved *in vivo* properties • Initiate Phase 1 study with no identified safety issues for first Generation 2.5 medicine for respiratory diseases • Complete toxicology study on a specific development candidate incorporating a novel delivery approach to support dosing in first human subject in 2018 • Advance first Generation 2.5 LICA medicine into clinical testing	Ionis *met* this objective: • Collaboration underway for device to enable clinical use in 2019 • Ionis achieved this objective • Ionis initiated a Phase 1 study with no identified safety issues on the first Generation 2.5 medicine for respiratory diseases • Ionis completed a toxicology study on a specific development candidate incorporating a novel delivery approach and first human subject dosed in 2018 • Ionis advanced the first Generation 2.5 medicine into clinical testing
14	Meet budget/projections	Ionis *exceeded* this objective: • Ionis significantly exceeded its financial guidance for 2018 and ended 2018 in a very strong financial position • Ionis improved upon its budget
15	Establish a near-, mid- and long-term tax strategy and implementation plan	Ionis *met* this objective: • Ionis established a near-, mid- and long-term tax strategy and implementation plan
16	Increase stock price performance by a percentage greater than or equal to median of the companies listed in the Nasdaq Biotechnology Index	Ionis *exceeded* this objective: • Ionis' stock price outperformed the median stock price change for companies listed in the Nasdaq Biotechnology Index
17	Achieve successful management transitioning	Ionis *met* this objective: • New senior leaders contributed meaningfully to Ionis' and Akcea's success in 2018 • Ionis successfully established a Translational Medicine group

	Unplanned Accomplishments for 2018
18	Ionis licensed the worldwide rights to commercialize TEGSEDI and AKCEA-TTR-L$_{Rx}$ exclusively to Akcea
19	Ionis licensed the worldwide rights to develop and commercialize IONIS-FB-L$_{Rx}$ for the treatment of complement-mediated diseases exclusively to Roche and received a $75 million upfront payment
20	Biogen exercised its option to obtain a worldwide, exclusive royalty-bearing license to develop and commercialize IONIS-SOD1$_{Rx}$ (BIIB067) and paid Ionis a $35 million upfront payment
21	Ionis strengthened its clinical development team by completing significant hires
22	IONIS-HTT$_{Rx}$ (RG6042) demonstrated positive correlation between mHTT reduction and clinical outcomes in Phase 1/2 study
23	Akcea licensed the rights to commercialize TEGSEDI and WAYLIVRA in Latin America exclusively to PTC Therapeutics
24	Phase 1 study of IONIS-SOD1$_{Rx}$ (BIIB067) demonstrated robust clinical benefit in aggressive form of ALS
25	Ionis licensed the worldwide rights to develop and commercialize IONIS-RHO-2.5$_{Rx}$ for the treatment of autosomal dominant retinitis pigmentosa exclusively to ProQR Therapeutics
26	Ionis successfully developed a plan for a new corporate communications brand