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

SCHEDULE 14A INFORMATION

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 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:

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☐ 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:

Ionis Pharmaceuticals, Inc.

Annual General Meeting of Shareholders

To be Held on May 24, 2017

Supplemental Information Regarding Proposal 3

To our Stockholders:

We write to you to underscore the importance of your independent analysis of the proposals presented for your consideration at our Annual Meeting of Stockholders scheduled to be held on Wednesday, May 24, 2017 (the "Annual Meeting"). The proposals are described in detail in our proxy statement, which has been made available to you and filed with the U.S. Securities and Exchange Commission (the "SEC"). We encourage you to read our proxy statement as well as the additional soliciting material we have filed with the SEC.

Our Board of Directors recommends that you vote your shares "FOR" the election of each of the director nominees for re-election at the Annual Meeting, and "FOR" each of the other proposals presented for a shareholder vote at the Annual Meeting.

We would like to draw your attention specifically to Proposal 3, which is an advisory vote on our executive compensation. Institutional Shareholder Services and Glass Lewis & Co. have particularly focused on an increase in executive pay for the year while our stock price had a negative one-year return. While we recognize that our stockholders make their voting decisions independently, and often apply their own internal guidelines, we also understand that the advisory firms' reports are utilized as research tools by many of our stockholders. For the reasons set forth below, we disagree with the proxy advisory firms' recommendations.

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

The increase in compensation for Ionis' named executive officers from 2015 to 2016, was largely driven by the increase in the Company Performance Factor for the performance MBO.

As previously noted in the proxy statement, the Compensation Committee set the Company Performance Factor for the 2016 MBO at 150%. Even though Ionis' stock price declined for the year, the Compensation Committee felt the 150% Company Performance Factor was appropriate due to our strong achievements for the year across drug discovery, development and corporate development. Since our CEO and COO are ultimately responsible for the Company's performance, their Individual Performance Factors were the same as the Company Performance Factor.

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. For reference, at the end of these supplemental materials as Schedule 1 we have included the full chart of these goals and measures and related evaluation for 2016 we previously published in the proxy statement.

There were a number of goals where Ionis greatly exceeded expectations for the year. However, the Compensation Committee and management also recognized that Ionis' one-year TSR was negative for the year. As such, the Compensation Committee had to evaluate where Ionis had greatly exceeded expectations in its strategic performance and financial performance for the year against its stock price performance.

Strategic performance: Ionis greatly exceeded a number of the strategic goals set for the year. Notably:

- Ionis had a goal and measure related to SPINRAZA of filing and acceptance of the NDA and MAA for SPINRAZA with Biogen paying us the license fee to exercise its option to take a license to SPINRAZA. Ionis not only achieved the stated goal, Ionis and Biogen *achieved FDA approval* of SPINRAZA for the treatment of SMA in pediatric and adult patients. Achieving this approval so quickly (approximately 3 months from filing) for the broad patient population was an extraordinary achievement and greatly exceeded expectations for the year, especially since NDA approvals for an orphan drug can typically take between 9-12 months from acceptance of the filing to approval, if at all. SPINRAZA's approval and the commercial revenue associated with SPINRAZA is a reflection of the evolution of our business and our progress towards sustained profitability.
- Ionis and Akcea formed a strategic collaboration with Novartis to develop and commercialize AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx, valued at over $1 billion plus potential product royalties, including $225 million in near term payments.

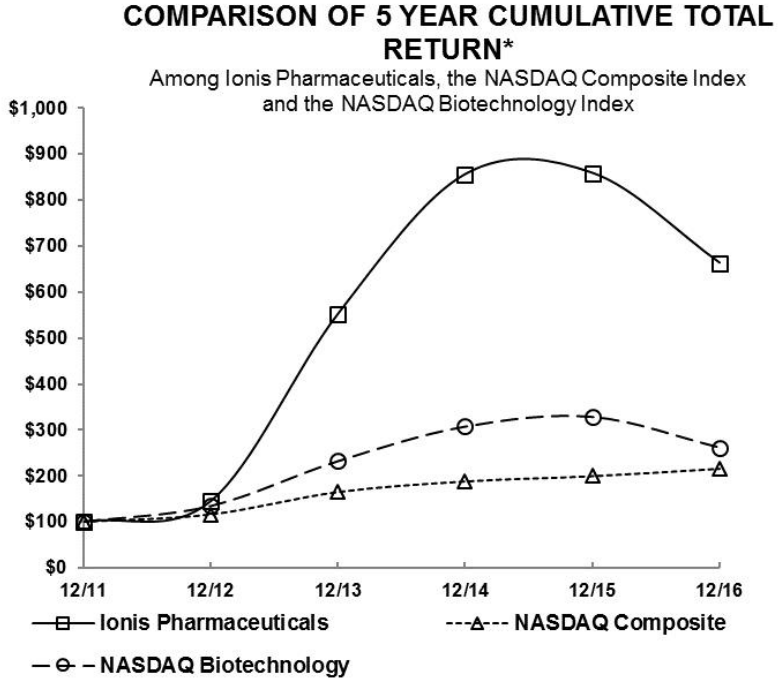
The Compensation Committee recognized the strategic value of these achievements. The near-term impact of SPINRAZA's FDA approval and the Novartis transaction are already delivering value as reflected in Ionis' strong financial performance in the first quarter of 2017. Notably Ionis achieved:

- a profitable first quarter with operating income of $14 million.
- More than $110 million in revenue for the quarter.

Financial performance: Ionis exceeded its financial performance goal of meeting its budget and financial projections for the year. In fact, Ionis significantly improved upon its financial guidance for the year. Notably:

- Ionis finished the year with pro forma operating income of $25.8 million, where when setting goals for the year, it had projected a pro forma operating loss in the low $60 million range, representing an improvement of more than 140%.
- Ionis generated $347 million of revenue, compared to its guidance of $240 million, representing an improvement of 45%.
- Ionis ended the year with $665 million in cash, exceeding year end cash guidance by $65 million.
- In 2017 Ionis expects to be breakeven or profitable at the operating line on a pro forma basis, driven in part by the revenue from SPINRAZA.

Stock performance: Ionis has a positive three, and extremely positive five-year stockholder return, as reflected in the chart below. Although our stock was down for 2016, our stock outperformed *both* the median of the Nasdaq Biotechnology Index and the median of the Executive Peer Group we use to evaluate compensation. Outperforming the median of the Nasdaq Biotechnology Index was a performance objective and measure the Board set for management at the beginning of 2016. As such, Ionis met the *pre-defined*, *objective*, *stock price performance measure* set for the year.



*$100 invested on December 31, 2010 in stock or index, including reinvestment of dividends. Fiscal year ending December 31.

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN

Among Ionis Pharmaceuticals, Inc., the NASDAQ Composite Index,

and the NASDAQ Biotechnology Index

	Dec-11	Dec-12	Dec-13	Dec-14	Dec-15	Dec-16
Ionis Pharmaceuticals, Inc.	$ 100.00	$ 144.80	$ 552.57	$ 856.31	$ 858.95	$ 663.38
NASDAQ Composite Index	$ 100.00	$ 116.41	$ 165.47	$ 188.69	$ 200.32	$ 216.54
NASDAQ Biotechnology Index	$ 100.00	$ 134.68	$ 232.37	$ 307.67	$ 328.76	$ 262.08

Conclusion. As such, although CEO pay was above the 50th percentile of the executive peer group, the compensation committee believed CEO pay was appropriate given the excellent performance for the year, Ionis met the pre-defined stock price measure for the year and has had strong long- term stock performance.

For the reasons set forth above, and in further detail in our proxy statement, we request that our stockholders vote “FOR” Proposal 3.

Sincerely,

Patrick R. O’Neil

Corporate Secretary

Special Note Regarding Forward-Looking Statements

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

Schedule 1

Evaluation of 2016 Key Corporate Goals

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

Evaluation of 2016 Corporate Objectives		
	Objective & Pre-Approved Measures	**Evaluation**
1	Prepare for Filing/Approval:	Ionis *exceeded* this objective:
	· File NDA and MAA for SPINRAZA (filing accepted), achieve Biogen Licensing Fee	· Biogen filed the NDA and MAA for SPINRAZA; and paid Ionis the $75 million license fee. Ionis and Biogen achieved FDA approval of SPINRAZA in 3 months under Priority Review for the treatment of SMA in pediatric and adult patients
	· Pass regulatory inspections post filing (GMP and GCP)	· The regulatory inspections supported approval for SPINRAZA
	· NDA/MAA sections complete and reviewed for volanesorsen, except Phase 3 data	· Ionis and Akcea completed the NDA/MAA sections for volanesorsen, except Phase 3 data
	· Complete all pre-clinical and clinical study reports for IONIS-TTR_{Rx} except for the ongoing Neuro-TTR study	· Ionis completed the Pre-Clinical and Clinical study reports for IONIS-TTR_{Rx} other than the ongoing Neuro-TTR study
	· Complete summary shells and CMC sections for the IONIS-TTR_{Rx} NDA to the extent possible	· Ionis substantially completed the summary shells and CMC sections for the IONIS-TTR_{Rx} NDA
	· Complete position pieces on key issues	· Ionis substantially completed the position pieces for key issues
	· Manage process with GSK to enable a smooth transfer for NDA filing for IONIS-TTR_{Rx} should GSK exercise its option	· Ionis implemented a process to transfer NDA filing for IONIS-TTR_{Rx} should GSK exercise its option
	· Ensure smooth transitioning of API site and process changes to GSK/CMO to enable a successful launch for IONIS-TTR_{Rx}	· Ionis worked with GSK to transition API manufacturing for IONIS-TTR_{Rx} to enable a successful launch for IONIS-TTR_{Rx}

2	Advance Pipeline: · Screening closed in volanesorsen FPL Phase 3 study · Positive data for IONIS-DMPK-2.5_{Rx} and Biogen agreement to advance program · Positive data for IONIS-FXI_{Rx} and Bayer agreement to advance program (milestone payment) · Solidify most rapid route leading to regulatory success and commercialization for IONIS-APO(a)-L_{Rx} (finalized plan). · Initiate first Phase 2/3 Clinical Trials on ≥3 drugs · Positive Phase 2 Clinical data on ≥5 drugs · Initiate Phase 1 Clinical Trials on ≥4 drugs · ≥4 new drugs into the pipeline	Ionis *met* this objective: · Due to improved study designs, closing for screening in the volanesorsen FPL Phase 3 Study is planned for 2017 · Ionis completed this study, observed encouraging biomarker trends and learned more about the disease. However, Ionis did not achieve the desired potency in muscle · Ionis reported positive data from the Phase 2 study of IONIS-FXI_{Rx} in patients with end-stage renal disease on hemodialysis. Bayer, plans to advance IONIS-FXI_{Rx} and expanded the collaboration by licensing the follow-on LICA drug, IONIS-FXI-L_{Rx} · Ionis and Akcea formed a strategic collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx}, which allows Ionis and Akcea to move more rapidly to Phase 3 cardiovascular outcomes studies with both therapies than their original development plans · Ionis initiated Phase 2 clinical trials for three drugs · Ionis reported positive Phase 2 data for six studies · Ionis initiated Phase 1 clinical trials on two drugs · Ionis added five new drugs to its development pipeline

3	Make Biogen Idec relationship successful: · Positive data for IONIS-DMPK-2.5_{Rx} and Biogen agreement to advance program · Initiate Phase 1 clinical trial for IONIS-$BIIB4_{Rx}$ · Identify ≥1 development candidate and two new target sanctions · Achieve ≥$100 million in revenue across all Biogen collaborations	Ionis *met* this objective: · Ionis completed this study, observed encouraging biomarker trends and learned more about the disease. However, Ionis did not achieve the desired potency in muscle · Ionis advanced the program but the Phase 1 clinical trial for IONIS-$BIIB4_{Rx}$ did not initiate until the first half of 2017 · Ionis achieved two target sanctions, and made significant progress towards identifying a development candidate · Ionis exceeded this measure by generating nearly $210 million in revenue across all Biogen collaborations
4	Make AstraZeneca relationship successful: · Successful outcome of STAT3-PDL1 Phase 1/2 study · Achieve development candidate approval for IONIS-AZ4-2.5-L_{Rx} · Successfully complete IONIS-KRAS-2.5_{Rx} nonclinical study and achieve $15 million milestone · Advance two new programs to target sanction	Ionis *met* this objective: · Although the study progressed in 2016, we do not expect the study to complete until 2017 · Ionis achieved development candidate approval for IONIS-AZ4-2.5-L_{Rx} and received a $25 million milestone · Ionis complete the IONIS-KRAS-2.5_{Rx} nonclinical study and received a $15 million milestone · Ionis advanced two new programs to target sanction
5	Demonstrate the value of technology advancements in the clinic: · Advance ≥3 LICA drugs through Phase 1 with ED50 ≤20 mg/wk · ≥4 new Gen 2.5 drugs into development · uORF and TSE approaches fully enabled for drug discovery activities	Ionis *partially met* this objective: · Ionis advanced three LICA drugs into Phase 1 and achieved an ED50 ≤20 mg/wk · Ionis advanced two new Gen 2.5 drugs into development · Ionis fully enabled drug discovery for uORF and TSE

6	Meet budget and financial projections for the year	Ionis *exceeded* this objective: · Ionis significantly improved upon its financial guidance for the year · Ionis met its budget
7	Stock price performance by a percentage greater than or equal to median of the companies listed in the NASDAQ Biotechnology Index; or if SPINRAZA filing successful 110%	Ionis *met* this objective: · Ionis' stock price outperformed the median stock price change for companies listed in the NASDAQ Biotechnology Index
8	Successful Akcea IPO (at prespecified valuation target) assuming reasonable market conditions	Ionis *partially met* this objective: · We made substantial progress preparing for Akcea's IPO
9	Partner IONIS-APO(a)-L_{Rx} or alternative successful Akcea transaction	Ionis *exceeded* this objective: · Ionis and Akcea formed a strategic collaboration with Novartis to develop and commercialize AKCEA-APO(a)-L_{Rx} and AKCEA-APOCIII-L_{Rx} for the treatment of lipid disorder
10	Complete one additional partnership either by expanding or adding a new partner	Ionis *exceeded* this objective: · The Novartis transaction noted in item 9 above also included AKCEA-APOCIII-L_{Rx}
11	Pre-commercial activity for volanesorsen on track for early 2018 launch: · Initial US and EU Commercial infrastructure in place	Ionis *met* this objective: · Akcea made significant progress regarding its pre-commercial activity for volanesorsen for planned early 2018 launch

Unplanned Accomplishments for 2016	
12	The FDA approved SPINRAZA in record time
13	Biogen reported positive data from an end of study analysis of the ENDEAR Phase 3 study in patients with infantile-onset (consistent with type 1) SMA at the British Pediatric Neurology Association. annual conference. Ionis previously reported data from an interim analysis of ENDEAR, which along with several other studies, formed the basis for the marketing application for SPINRAZA in the U.S.
14	Ionis and Biogen reported positive data from an interim analysis of the Phase 3 CHERISH study in patients with later-onset (consistent with Type 2) SMA
15	Ionis and Akcea reported that the Phase 3 COMPASS study for volanesorsen met its primary endpoint
16	Ionis sold the global rights to develop and commercialize KYNAMRO to Kastle Therapeutics and earned a $15 million upfront payment
17	Ionis and MD Anderson Cancer Center formed a strategic alliance to advance novel cancer therapies
18	Ionis completed a satellite company transaction with Dynacure to discover, develop and commercialize drugs to treat neuromuscular diseases
19	Ionis received funding from Cystic Fibrosis Foundation for Ionis' program targeting ENAC for treating cystic fibrosis
20	Ionis settled its dispute with OncoGenex on favorable terms