

Ionis reports first quarter financial results and recent business achievements

May 4, 2022

On track to achieve 2022 financial guidance

Webcast today, May 4, 2022, at 11:30 a.m. Eastern Time

CARLSBAD, Calif., May 4, 2022 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today reported financial results for the first quarter of 2022 and recent business achievements.

"We are off to a strong start this year highlighted by progress in our rich late- and mid-stage pipeline. We remain on track for data from the NEURO-TTRansform study of eplontersen in patients with hereditary ATTR polyneuropathy by mid-year. Assuming positive data, we plan to file for regulatory approval by the end of this year. We recently increased the size and duration of our CARDIO-TTRansform study of eplontersen in patients with ATTR cardiomyopathy. Our aim is to generate even more robust data and ensure a highly positive study outcome to successfully compete in this growing and dynamic market," said Brett P. Monia, Ph.D., chief executive officer of Ionis. "We also reported positive data from two potential best-in-class medicines. In the Phase 2b ETESIAN study, ION449, our investigational medicine targeting PCSK9, demonstrated robust LDL-C and PCSK9 reductions in statin-treated patients with hypercholesterolemia. ION449 was generally well tolerated in this study. Additional positive data from the Phase 2 study of donidalorsen demonstrated significant improvements in quality of life in people with hereditary angioedema. Looking ahead, we expect to provide additional key mid-stage data readouts and updates on our technology advancements. These upcoming catalysts, together with our recent achievements, position us well to continue to drive substantial growth and value for all stakeholders."

First Quarter 2022 Summary Financial Results

On track to achieve 2022 financial guidance, based on the following first quarter results:

- \$142 million in total revenues
- \$173 million of operating expenses on a non-GAAP basis⁽¹⁾ and \$199 million on a GAAP basis
- \$39 million net loss on a non-GAAP basis⁽¹⁾ and \$65 million on a GAAP basis
- \$2.1 billion of cash and short-term investments

"A key element of Ionis' financial strength is our ability to generate substantial revenue from multiple diverse sources on a sustained basis. Our first quarter financial results in which revenues grew more than 25 percent year over year were an excellent example of this. We generated revenues from our marketed products, including SPINRAZA, and from numerous partnered medicines as they advanced. Our first quarter financial results also reflect our investments in our rich late-stage pipeline and in activities to prepare for our launches of eplontersen, olezarsen and donidalorsen," said Elizabeth L. Hougen, chief financial officer of Ionis. "We are on track to meet our 2022 financial guidance. With \$2.1 billion of cash, we are well capitalized with the resources we need to continue investing in our large agenda to drive substantial future growth."

Recent Marketed Products Highlights

SPINRAZA®: the global market leader for the treatment of spinal muscular atrophy (SMA) patients of all ages

- \$473 million in worldwide SPINRAZA sales in the first quarter
- Biogen provided updates from the ASCEND, RESPOND and NURTURE studies of SPINRAZA at the Muscular Dystrophy Association (MDA) Clinical and Scientific conference and the American Academy of Neurology (AAN) annual meeting

TEGSEDI® and WAYLIVRA®: important medicines approved for the treatment of patients with polyneuropathy caused by hereditary TTR amyloidosis and familial chylomicronemia syndrome, respectively

- Continued to progress into new and existing markets in Europe and Latin America in the first quarter through Swedish Orphan Biovitrum AB (Sobi) and PTC Therapeutics, respectively

First Quarter 2022 and Recent Events

Advancing Ionis' near-term commercial opportunities toward the market

- Increased study size and duration in the Phase 3 CARDIO-TTRansform study of eplontersen in patients with ATTR cardiomyopathy with the aim to generate even more robust data and ensure a highly positive study outcome to successfully compete in this growing and dynamic market. Data from this study are expected in the first half of 2025
- The U.S. FDA granted orphan drug designation to eplontersen for the treatment of patients with ATTR
- Published positive data from the Phase 2 study of olezarsen in patients with hypertriglyceridemia and either at high risk for or with established cardiovascular disease in the *European Heart Journal*
- Initiated a study of olezarsen in patients with hypertriglyceridemia to support the broad Phase 3 program
- Published positive data from the Phase 2 study of donidalorsen in patients with hereditary angioedema (HAE) in the *New England Journal of Medicine*
- Presented additional positive data from the Phase 2 study of donidalorsen in patients with HAE at the American Academy of Allergy, Asthma and Immunology (AAAAI) annual meeting

Advancing Ionis' leading cardiovascular disease franchise

- AstraZeneca presented positive data from the Phase 2b ETESIAN study of ION449 (AZD8233) targeting PCSK9 in statin treated patients with dyslipidemia at the American College of Cardiology (ACC) annual scientific session
- Achieved full enrollment in the Phase 2b study of IONIS-AGT-L_{Rx} in patients with treatment-resistant hypertension, with data expected in the second half of 2022

Advancing Ionis' leading neurological disease franchise

- Roche plans to initiate a new Phase 2 study of tominersen in patients with Huntington's disease based on findings from a post-hoc analysis of the GENERATION-HD1 study
- Biogen initiated a Phase 1/2 study of ION260 (BIIB132) targeting ataxin-3 (ATXN3) in patients with spinocerebellar ataxia type 3 (SCA3), resulting in an \$8 million milestone payment from Biogen
- Biogen advanced the Phase 1/2 study of ION859 (BIIB094) targeting LRRK2 in patients with Parkinson's disease, resulting in a \$10 million milestone payment from Biogen
- Announced the discontinuation of IONIS-C9_{Rx} (BIIB078) due to lack of patient benefit demonstrated in the Phase 1/2 study in patients with C9orf72-ALS

2022 Pipeline Milestones⁽²⁾

Anticipated 2022 Regulatory Updates

Program	Anticipated Indication	Regulatory Action	H1	H2
Eplontersen	ATTRv polyneuropathy	NDA filing		•

Anticipated Key 2022 Data Readouts

Program	Data Readout	Anticipated Indication	H1	H2
Tominersen	Phase 3 post hoc	Huntington's disease	✓	
ION449 (PCSK9)	Phase 2b (ETESIAN)	Cardiovascular disease	✓	
Donidalorsen	Phase 2	HAE	✓	
IONIS-C9 _{Rx} (BIIB078)	Phase 1/2	C9-ALS	✓	
Tofersen	Phase 3 OLE	SOD1-ALS	•	
Eplontersen	Phase 3	ATTRv polyneuropathy		•
IONIS-AGT-L _{Rx}	Phase 2b	Treatment-resistant hypertension		•
Fesomersen (FXI)	Phase 2b	Thrombosis		•
Bepirovirsen (HBV)	Phase 2b	Hepatitis B virus infection		•
Donidalorsen	Phase 2 OLE	HAE		•
Cimdelirsen (GHR)	Phase 2 (monotherapy)	Acromegaly		•

Anticipated Key 2022 Study Initiations

Program	Phase	Anticipated Indication	H1	H2
Sapablursen	2	Polycythemia vera	✓	
IONIS-MAPT _{Rx} (BIIB080)	2	Alzheimer's disease		•
ION904 (AGT)	2	Uncontrolled hypertension		•
ION717 (PRNP)	1/2	Prion disease		•

Anticipated Key 2022 Technology Advancements

Program	Anticipated Advancement	H1	H2
SMA	Advance follow-on program	✓	
Muscle LICA	Advance into preclinical development (IND-supporting)		•
MsPA Backbone	Advance into preclinical development (IND-supporting)		•

✓ = achieved • = planned

(1) All non-GAAP amounts referred to in this press release exclude non-cash compensation expense related to equity awards. In 2021 all non-GAAP amounts also excluded expenses related to the Akcea Merger and restructured commercial operations and the related tax effects. Please refer to the detailed reconciliation of non-GAAP and GAAP measures, which is provided later in this press release.

(2) Partnered program milestones are based on partners' most recent publicly available disclosures.

First Quarter 2022 Financial Results

Revenue

Ionis' revenue was comprised of the following (amounts in millions):

	Three months ended	
	March 31,	
	2022	2021
Revenue:		
Commercial revenue:		
SPINRAZA royalties	\$54	\$60
TEGSEDI and WAYLIVRA revenue, net	6	20
Licensing and royalty revenue	12	5
Total commercial revenue	72	85
Research and development revenue:		
Amortization from upfront payments	17	20
Milestone payments	27	5
License fees	2	-
Other services	4	2
Collaborative agreement revenue	50	27
Eplontersen joint development revenue	20	-
Total research and development revenue	70	27
Total revenue	\$142	\$112

The Company's revenue in the first quarter of 2022 increased more than 25 percent compared to the same period last year. The increase was driven by significant partner payments across multiple partnered programs, including \$20 million from AstraZeneca for its share of the global Phase 3 program costs for eplontersen. Since Ionis is conducting the ongoing Phase 3 program for eplontersen, Ionis recognizes revenue for the reimbursements it receives from AstraZeneca for development expenses in the same period Ionis recognizes the related development expenses. Refer to the detailed table of costs and reimbursements for the eplontersen collaboration provided later in this release. The Company also earned \$40 million from Biogen for advancing several neurology disease programs.

The Company successfully completed the transition of its TEGSEDI and WAYLIVRA operations in the EU and North America to Sobi in the first and second quarters of 2021, respectively. The decrease in TEGSEDI and WAYLIVRA revenue in the first quarter of 2022 compared to the same period last year was due to the shift from product sales to distribution fees based on net sales generated by Sobi. As part of the transition, Ionis restructured its commercial operations in 2021 resulting in substantial cost savings.

Operating Expenses

Ionis is advancing a large late-stage pipeline and as a result, its non-GAAP operating expenses increased in the first quarter of 2022 compared to the same period in 2021. Higher R&D expenses were driven by the expanded number of Phase 3 studies the Company is conducting, which doubled over the course of 2021 from three to six studies. Lower SG&A expenses were largely due to the substantial savings Ionis achieved from integrating Akcea and restructuring its commercial operations. These savings were offset in part by the investments Ionis made in advancing its go-to-market activities for its near-term commercial opportunities.

Net Loss

Ionis' net loss in the first quarter of 2022 decreased compared to the same period in 2021 primarily related to the changes in revenue and operating expenses, as discussed above.

Balance Sheet

As of March 31, 2022 and December 31, 2021, Ionis had cash, cash equivalents and short-term investments of \$2.1 billion. Ionis' debt obligations and working capital did not change significantly from December 31, 2021 to March 31, 2022.

Webcast

Ionis will conduct a webcast today at 11:30 a.m. Eastern time to discuss this announcement and related activities. Interested parties may access the webcast [here](#). A webcast replay will be available for a limited time at the same address.

About Ionis Pharmaceuticals, Inc.

For more than 30 years, Ionis has been the leader in RNA-targeted therapy, pioneering new markets and changing the standards of care with its novel antisense technology. Ionis currently has three marketed medicines and a premier late-stage pipeline highlighted by industry leading cardiovascular and neurological franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming a leading, fully integrated biotechnology company.

To learn more about Ionis visit www.ionispharma.com or follow us on Twitter @ionispharma.

Ionis' Forward-looking Statement

This press release includes forward-looking statements regarding Ionis' business, financial guidance and the therapeutic and commercial potential of SPINRAZA (nusinersen), TEGSEDI (inotersen), WAYLIVRA (volanesorsen), eplontersen, olezarsen, donidalorsen, ION363, pelacarsen, tofersen, Ionis' technologies and Ionis' other products in development. Any statement describing Ionis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, including those related to the impact COVID-19 could have on our business, and including 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. 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, 2021, which is on file with the SEC. Copies of this and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Ionis," "Company," "we," "our" and "us" all refer to Ionis Pharmaceuticals and its subsidiaries.

Ionis Pharmaceuticals® is a registered trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics® is a registered trademark of Akcea Therapeutics, Inc. TEGSEDI® is a registered trademark of Akcea Therapeutics, Inc. WAYLIVRA® is a registered trademark of Akcea Therapeutics, Inc. SPINRAZA® is a registered trademark of Biogen.

IONIS PHARMACEUTICALS, INC.
SELECTED FINANCIAL INFORMATION
Condensed Consolidated Statements of Operations
(In Millions, Except Per Share Data)

	Three months ended March 31,	
	2022	2021
	(unaudited)	
Revenue:		
Commercial revenue:		
SPINRAZA royalties	\$54	\$60
TEGSEDI and WAYLIVRA revenue, net	6	20
Licensing and royalty revenue	12	5
Total commercial revenue	72	85
Research and development revenue:		
Collaborative agreement revenue	50	27
Eplontersen joint development revenue	20	-
Total research and development revenue	70	27
Total revenue	142	112
Expenses:		
Cost of sales	4	3
Research, development and patent	161	140
Selling, general and administrative	34	61
Total operating expenses	199	204
Loss from operations	(57)	(92)
Other income (expense):		
Other income (expense), net	(7)	2
Loss before income tax expense	(64)	(90)
Income tax expense	(1)	-
Net loss	(\$65)	(\$90)
Basic and diluted net loss per share	(\$0.46)	(\$0.64)
Shares used in computing basic and diluted net loss per share	142	141

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

	Three months ended March 31,	
	2022	2021
	(unaudited)	
As reported research, development and patent expenses according to GAAP	\$161	\$140
Excluding compensation expense related to equity awards	(19)	(26)
Excluding Akcea merger and restructured commercial operation costs*	-	(3)
Non-GAAP research, development and patent expenses	\$142	\$111
As reported selling, general and administrative expenses according to GAAP	\$34	\$61
Excluding compensation expense related to equity awards	(7)	(12)

Excluding Akcea merger and restructured commercial operation costs*	-	(4)
Non-GAAP selling, general and administrative expenses	<u>\$27</u>	<u>\$45</u>
As reported operating expenses according to GAAP	\$199	\$204
Excluding compensation expense related to equity awards	(26)	(38)
Excluding Akcea merger and restructured commercial operation costs*	-	(7)
Non-GAAP operating expenses	<u>\$173</u>	<u>\$159</u>
As reported loss from operations according to GAAP	(\$57)	(\$92)
Excluding compensation expense related to equity awards	(26)	(38)
Excluding Akcea merger and restructured commercial operation costs*	-	(7)
Non-GAAP loss from operations	<u>(\$31)</u>	<u>(\$47)</u>
As reported net loss according to GAAP	(\$65)	(\$90)
Excluding compensation expense related to equity awards	(26)	(38)
Excluding Akcea merger and restructured commercial operation costs*	-	(7)
Income tax effect related to compensation expense related to equity awards	-	-
Non-GAAP net loss according to GAAP	<u>(\$39)</u>	<u>(\$45)</u>

*In October 2020, Ionis completed a merger transaction with Akcea such that following the completion of the merger Akcea became a wholly owned subsidiary of Ionis. Additionally, in December 2020 and April 2021, Ionis restructured its European operations and its North American TEGSEDI operations, respectively, as a result of entering into distribution agreements with Sobi. The Company excluded these costs from its non-GAAP amounts for the applicable periods.

Reconciliation of GAAP to Non-GAAP Basis

As illustrated in the Selected Financial Information in this press release, non-GAAP operating expenses, non-GAAP loss from operations, and non-GAAP net loss were adjusted from GAAP to exclude compensation expense related to equity awards and costs related to the Akcea merger and restructured commercial operations and the related tax effects. Compensation expense related to equity awards are non-cash. Costs related to the Akcea merger and restructured commercial operations included: severance costs, retention costs and other costs related to commercial operations. Ionis has 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. Ionis reports 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 Ionis' non-GAAP results is consistent with how Ionis' management internally evaluates the performance of its operations.

IONIS PHARMACEUTICALS, INC.

Summary of the Financial Impacts of the Eplontersen Collaboration with AstraZeneca For the Three Months Ended, March 31, 2022

Collaboration Activities	Financial Statement Line	Impact of Cost-Sharing Provisions on Ionis' Statement of Operations
Phase 3 Development: Ionis leads and conducts	Eplontersen Joint Development Revenue (R&D Revenue)	\$20M 55% of Ionis' Phase 3 development expenses, including internal+external costs & CMC costs
	Development Expenses (R&D Expenses)	\$36M 100% of Ionis' Phase 3 development expenses

Ionis' financial results for the first quarter of 2022 reflected the cost-sharing provisions related to its eplontersen collaboration with AstraZeneca to develop and commercialize eplontersen for the treatment of ATTR. Under the terms of the collaboration agreement, AstraZeneca is paying 55 percent of the costs associated with the ongoing global Phase 3 development program. Because Ionis is leading and conducting the Phase 3 development program, Ionis is recognizing the 55 percent of cost-share funding AstraZeneca is responsible for as R&D revenue in the same period Ionis incurs the related development expenses. Ionis will receive \$20 million from AstraZeneca related to development expenses Ionis incurred in the first quarter of 2022.

As AstraZeneca is responsible for the majority of the medical affairs and commercial costs in the U.S. and all costs associated with bringing eplontersen to market outside the U.S., Ionis is recognizing cost-share funding it receives from AstraZeneca related to these activities as a reduction of its medical affairs (R&D expenses) and commercialization expenses (SG&A expenses). In the first quarter of 2022, Ionis recognized \$0.4 million and \$0.2 million of medical affairs expenses and commercialization expenses for eplontersen, respectively, net of cost-share funding from AstraZeneca. Ionis expects its medical affairs and commercialization expenses to increase as this collaboration progresses.

(In Millions)

	March 31, 2022	December 31, 2021
	(unaudited)	
Assets:		
Cash, cash equivalents and short-term investments	\$2,052	\$2,115
Contracts receivable	26	62
Other current assets	175	168
Property, plant and equipment, net	178	178
Other assets	88	89
Total assets	<u>\$2,519</u>	<u>\$2,612</u>
Liabilities and stockholders' equity:		
Other current liabilities	\$137	\$143
Current portion of deferred contract revenue	91	98
0% convertible senior notes, net	620	619
0.125% convertible senior notes, net	543	542
Long-term obligations, less current portion	85	86
Long-term deferred contract revenue	333	352
Total stockholders' equity	<u>710</u>	<u>772</u>
Total liabilities and stockholders' equity	<u>\$2,519</u>	<u>\$2,612</u>

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