

Ionis reports second quarter financial results and recent business achievements

August 9, 2022

Reported positive eplontersen ATTRv-PN data, on track to file NDA in H2:22

Tofersen NDA under priority review, PDUFA January 25, 2023

Completed enrollment in pelacarsen Lp(a) HORIZON and olezarsen BALANCE Phase 3 studies

On track to achieve 2022 financial guidance

Webcast today, August 9, 2022, at 11:30 a.m. Eastern Time

CARLSBAD, Calif., Aug. 9, 2022 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today reported financial results for the second quarter of 2022 and recent business achievements.

"Over the first half of this year, we moved significantly closer to delivering an abundance of new medicines to the market. We reported positive Phase 3 data from the NEURO-TTRansform study of eplontersen in patients with hereditary ATTR polyneuropathy and we are on track to file an NDA in the second half of this year. We were also pleased that the FDA accepted the NDA for tofersen and granted priority review, enabling tofersen to potentially be the first disease modifying treatment approved for a genetic form of ALS. These achievements mean eplontersen and tofersen could be our next marketed products as early as next year," said Brett P. Monia, Ph.D., chief executive officer of Ionis. "We also significantly advanced our late- and mid-stage pipeline. The pelacarsen Lp(a) HORIZON and olezarsen BALANCE Phase 3 studies recently completed enrollment. Additionally, we reported positive data from six mid-stage programs, positioning us to grow our rich Phase 3 pipeline to at least eight medicines across 10 indications. We are looking forward to continuing our positive momentum in the second half of this year by presenting Phase 3 eplontersen data at the International Symposium on Amyloidosis in September, filing our eplontersen NDA, and reporting data from several important programs. These upcoming catalysts, together with our recent achievements, position us well to drive increasing value for all stakeholders."

Second Quarter 2022 Summary Financial Results

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

- \$134 million in total revenues
- \$195 million of operating expenses on a non-GAAP basis⁽¹⁾ and \$220 million on a GAAP basis
- \$80 million net loss on a non-GAAP basis⁽¹⁾ and \$105 million on a GAAP basis
- \$2.0 billion of cash and short-term investments

"We had a strong first half with year-over-year revenue growth of more than 15 percent. We continued to generate revenue from multiple diverse sources, with just over half from our marketed products and the balance from our numerous advancing partnered medicines. Additionally, our financial results reflect our accelerating investments in our rich late-stage pipeline and in our commercial readiness activities for eplontersen, olezarsen and donidalsorsen," said Elizabeth L. Hougen, chief financial officer of Ionis. "With \$2 billion of cash and investments, we have the financial resources to achieve our goal of bringing transformational medicines to the market. These results for the first half of the year keep us on track to meet our 2022 financial guidance."

Recent Marketed Products Highlights

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

- \$431 million in worldwide SPINRAZA sales in the second quarter
- Biogen reported new results from the RESPOND study of SPINRAZA, stating the results indicate there are residual unmet clinical needs in infants and toddlers with SMA who were previously treated with gene therapy
- Biogen reported final data from Part A of the ongoing, three-part DEVOTE study demonstrating that a higher dosing regimen of SPINRAZA leads to higher levels of the drug in the cerebrospinal fluid and is generally well-tolerated

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

- Continued to expand into new markets in Europe and Latin America through Swedish Orphan Biovitrum AB (Sobi) and PTC Therapeutics, respectively

Second Quarter 2022 and Recent Events

Advancing Ionis' next two potential marketed products

- Reported eplontersen met the co-primary and key secondary endpoints in the interim analysis of the Phase 3 NEURO-TTRansform study in patients with ATTRv-PN; on track to file the New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) in the second half of this year
- Biogen reported longer-term data from the Phase 3 VALOR study and ongoing open-label extension study of tofersen showing clinical benefit in patients with SOD1-ALS at the European Network to Cure ALS (ENCALS) meeting

- Biogen reported that an NDA for tofersen was accepted and granted priority review by the FDA with a Prescription Drug User Fee Act (PDUFA) action date of January 25, 2023

Advancing Ionis' late-stage pipeline

- Novartis achieved full enrollment in the Phase 3 Lp(a) HORIZON cardiovascular outcomes study of pelacarsen in patients with established cardiovascular disease and elevated Lp(a) with data expected in 2025
- Achieved full enrollment in the Phase 3 BALANCE study of olezarsen in patients with FCS with data expected in 2023

Advancing Ionis' mid-stage pipeline

- GSK presented positive data from the Phase 2b B-Clear study of bepirovirsen in patients with chronic hepatitis B at the European Association for the Study of the Liver's (EASL) International Liver Congress™. Based on these results, GSK plans to advance bepirovirsen into a Phase 3 monotherapy study in the first half of 2023
- Roche reported positive data from the Phase 2 study of IONIS-FB-L_{Rx} in patients with immunoglobulin A nephropathy (IgAN). Based on these results, Roche licensed and plans to advance IONIS-FB-L_{Rx} into a Phase 3 study
- Bayer reported fesomersen met the primary endpoint in the Phase 2b RE-THINC ESRD study in patients with end-stage renal disease. Fesomersen also demonstrated substantial and statistically significant reductions in Factor XI activity levels
- 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
- Initiated a Phase 2 study of ION904, a follow-on medicine to IONIS-AGT-L_{Rx} in patients with treatment-resistant hypertension
- Granted orphan drug designation and rare pediatric disease designation by the FDA for ION582 for the treatment of patients with Angelman syndrome

2022 Pipeline Milestones⁽²⁾

Anticipated 2022 Regulatory Updates

Program	Regulatory Action	Anticipated Indication	H1	H2
Tofersen	NDA acceptance	SOD1-ALS		✓
Eplontersen (TTR)	NDA filing	ATTRv polyneuropathy		•

Anticipated Key 2022 Data Readouts

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

Anticipated Key 2022 Study Initiations

Program	Phase	Anticipated Indication	H1	H2
Sapablursen (TMPRSS6)	2	Polycythemia vera	✓	
ION904 (AGT)	2	Uncontrolled hypertension	✓	
IONIS-MAPT _{Rx} (BIIB080)	2	Alzheimer's disease		•
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 and the related tax effects. 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) Timing expectations based on current assumptions and subject to change.

Second Quarter 2022 Financial Results

Revenue

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

	Three months ended June 30,		Six months ended June 30,	
	2022	2021	2022	2021
Revenue:				
Commercial revenue:				
SPINRAZA royalties	\$60	\$72	\$113	\$132
TEGSEDI and WAYLIVRA revenue, net	10	12	17	31
Licensing and royalty revenue	8	2	20	7
Total commercial revenue	78	86	150	170
Research and development revenue:				
Amortization from upfront payments	18	20	36	40
Milestone payments	18	15	45	20
License fees	-	-	2	-
Other services	3	5	6	7
Collaborative agreement revenue	39	40	89	67
Eplontersen joint development revenue	17	-	37	-
Total Research and development revenue	56	40	126	67
Total revenue	\$134	\$126	\$276	\$237

The Company's revenue in the first half of 2022 increased more than 15 percent compared to the same period last year. The increase was driven by significant partner payments Ionis earned across multiple partnered programs, including \$37 million from AstraZeneca for its share of the global Phase 3 development costs for eplontersen. Refer to the detailed table of costs and reimbursements for the eplontersen collaboration provided later in this release. The Company also earned \$57 million from Biogen for advancing several neurology disease programs and \$22 million from Roche for advancing IONIS-FB-L_{RX}. Already in the third quarter of 2022, the Company has earned nearly \$45 million from Roche and Biogen.

The Company's commercial revenue in the first half of 2022 decreased 12 percent compared to the same period last year. SPINRAZA royalties decreased primarily due to competition outside of the U.S. In the U.S., SPINRAZA sales stabilized in the first half of 2022 compared to the same period last year, increasing two percent. TEGSEDI and WAYLIVRA revenue decreased due to the shift from product sales to distribution fees based on net sales generated by Sobi. 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. As part of the transition, Ionis restructured its commercial operations in 2021 resulting in substantial cost savings. These decreases were partially offset by increasing licensing and royalty revenue.

Operating Expenses

Ionis is advancing a large late-stage pipeline and as a result, its non-GAAP operating expenses increased in the first half 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 from three to six studies in 2021. Lower SG&A expenses were largely due to the substantial savings Ionis achieved from integrating Akcea and restructuring its commercial operations in 2021. Ionis is redeploying these savings to advance its pipeline and go-to-market activities for eplontersen, donalorsen and olezarsen.

Net Loss

Ionis' non-GAAP net loss in the first half of 2022 increased compared to the same period in 2021, primarily related to higher R&D expenses, partially offset by higher revenue and lower SG&A expenses, as discussed above.

Balance Sheet

As of June 30, 2022, Ionis had cash, cash equivalents and short-term investments of \$2.0 billion, compared with \$2.1 billion at December 31, 2021. Ionis' debt obligations and working capital did not change significantly from December 31, 2021 to June 30, 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, and most recent Form 10-Q, which are on file with the Securities and Exchange Commission. Copies of these 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, Six months ended			
	June 30,		June 30,	
	2022	2021	2022	2021
	(unaudited)			
Revenue:				
Commercial revenue:				
SPINRAZA royalties	\$60	\$72	\$113	\$132
TEGSEDI and WAYLIVRA revenue, net	10	12	17	31
Licensing and royalty revenue	8	2	20	7
Total commercial revenue	78	86	150	170
Research and development revenue:				
Collaborative agreement revenue	39	40	89	67
Eplontersen joint development revenue	17	-	37	-
Total research and development revenue	56	40	126	67
Total revenue	134	126	276	237
Expenses:				
Cost of sales	5	3	9	6
Research, development and patent	181	139	342	279
Selling, general and administrative	34	57	68	117
Total operating expenses	220	199	419	402
Loss from operations	(86)	(73)	(143)	(165)
Other expense	(17)	(8)	(24)	(5)
Loss before income tax expense	(103)	(81)	(167)	(170)
Income tax expense	(2)	-	(3)	(1)
Net loss	(\$105)	(\$81)	(\$170)	(\$171)
Basic and diluted net loss per share	(\$0.74)	(\$0.57)	(\$1.20)	(\$1.21)
Shares used in computing basic and diluted net loss per share	142	141	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		Six months ended	
	June 30,		June 30,	
	2022	2021	2022	2021

	(unaudited)			
As reported research, development and patent expenses according to GAAP	\$181	\$139	\$342	\$279
Excluding compensation expense related to equity awards	(19)	(23)	(38)	(49)
Excluding Akcea merger and restructured commercial operation costs*	-	(4)	-	(6)
Non-GAAP research, development and patent expenses	<u>\$162</u>	<u>\$112</u>	<u>\$304</u>	<u>\$224</u>
As reported selling, general and administrative expenses according to GAAP	\$34	\$57	\$68	\$117
Excluding compensation expense related to equity awards	(6)	(7)	(13)	(19)
Excluding Akcea merger and restructured commercial operation costs*	-	(11)	-	(16)
Non-GAAP selling, general and administrative expenses	<u>\$28</u>	<u>\$39</u>	<u>\$55</u>	<u>\$82</u>
As reported operating expenses according to GAAP	\$220	\$199	\$419	\$402
Excluding compensation expense related to equity awards	(25)	(30)	(51)	(68)
Excluding Akcea merger and restructured commercial operation costs*	-	(15)	-	(22)
Non-GAAP operating expenses	<u>\$195</u>	<u>\$154</u>	<u>\$368</u>	<u>\$312</u>
As reported loss from operations according to GAAP	(\$86)	(\$73)	(\$143)	(\$165)
Excluding compensation expense related to equity awards	(25)	(30)	(51)	(68)
Excluding Akcea merger and restructured commercial operation costs*	-	(15)	-	(22)
Non-GAAP loss from operations	<u>(\$61)</u>	<u>(\$28)</u>	<u>(\$92)</u>	<u>(\$75)</u>
As reported net loss according to GAAP	(\$105)	(\$81)	(\$170)	(\$171)
Excluding compensation expense related to equity awards	(25)	(30)	(51)	(68)
Excluding Akcea merger and restructured commercial operation costs*	-	(15)	-	(22)
Non-GAAP net loss	<u>(\$80)</u>	<u>(\$36)</u>	<u>(\$119)</u>	<u>(\$81)</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 the Akcea merger and restructured commercial operation 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 Six Months Ended, June 30, 2022 (Unaudited)

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)	\$37M 55% of Total Phase 3 development expenses, including internal+external costs & CMC costs, net of Ionis' share of AstraZeneca's Phase 3 development expenses
	Development Expenses (R&D Expenses)	\$71M 100% of Ionis' Phase 3 development expenses

Ionis' financial results for the first half of 2022 reflected the cost-sharing provisions related to its 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, net of Ionis' share of AstraZeneca's development expenses, as R&D revenue in the same period Ionis incurs the related development expenses. In the first half of 2022, Ionis earned \$37 million in joint development revenue under this collaboration.

Because 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 half of 2022, Ionis recognized \$0.8 million and \$0.7 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.

IONIS PHARMACEUTICALS, INC.
Condensed Consolidated Balance Sheets
(In Millions)

	June 30, 2022	December 31, 2021
	(unaudited)	
Assets:		
Cash, cash equivalents and short-term investments	\$2,022	\$2,115
Contracts receivable	7	62
Other current assets	163	168
Property, plant and equipment, net	177	178
Other assets	87	89
Total assets	<u>\$2,456</u>	<u>\$2,612</u>
Liabilities and stockholders' equity:		
Other current liabilities	\$175	\$143
Current portion of deferred contract revenue	93	98
0% convertible senior notes, net	621	619
0.125% convertible senior notes, net	543	542
Long-term obligations, less current portion	84	86
Long-term deferred contract revenue	315	352
Total stockholders' equity	<u>625</u>	<u>772</u>
Total liabilities and stockholders' equity	<u>\$2,456</u>	<u>\$2,612</u>

 View original content to download multimedia: <https://www.prnewswire.com/news-releases/ionis-reports-second-quarter-financial-results-and-recent-business-achievements-301601983.html>

SOURCE Ionis Pharmaceuticals, Inc.

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