Ionis reports third quarter 2021 financial results and recent business achievements

November 3, 2021

Olezarsen (IONIS-APOCIII-L Rx) Phase 3 CORE study in patients with sHTG initiated
Donidalorsen (IONIS-PKK-L Rx) Phase 2 data to be presented at ACAAI Annual Meeting; Phase 3 initiation on track for year-end
Tofersen Phase 3 VALOR study missed primary endpoint; signs of reduced disease progression observed across multiple secondary and exploratory endpoints
Webcast today, November 3, 2021, at 11:30 a.m. Eastern Time

CARLSBAD, Calif., Nov. 3, 2021 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today reported financial results for the three and nine months ended September 30, 2021 and recent business achievements.

"Among recent business highlights, we further expanded our broad late-stage pipeline to seven Phase 3 programs now that the olezarsen Phase 3 CORE study in patients with severe hypertriglyceridemia is underway. We were encouraged that while tofersen did not achieve the primary endpoint in the Phase 3 VALOR study, trends favoring tofersen were seen across multiple secondary and exploratory measures of disease progression in patients with SOD1-ALS. We also expanded our LICA platform capabilities by licensing technology from Bicycle Therapeutics," said Brett P. Monia, Ph.D., chief executive officer of Ionis. "We are looking forward to multiple near-term catalysts, beginning with the presentation of donidalorsen Phase 2 data in patients with hereditary angioedema at the ACAAI Annual Meeting this weekend. We anticipate initiating the donidalorsen Phase 3 study before year-end. We also expect multiple catalysts in 2022, including results from the eplontersen Phase 3 study in patients with TTR polyneuropathy mid-year 2022. Furthermore, at our virtual investor day on December 9th, we look forward to outlining commercial preparations for our lead programs ahead of our first potential launch with eplontersen in patients with TTR polyneuropathy in 2023. Based on our anticipated near- and mid-term catalysts, we remain on track to have 12 or more products on the market in 2026."

Third Quarter 2021 Financial Results

- Third quarter results reflect Ionis' focus on its strategic objectives
  - $133 million in total revenues
  - $185 million of operating expenses on a non-GAAP basis(1) and $219 million on a GAAP basis
  - Net loss of $48 million on a non-GAAP basis(1) and $82 million on a GAAP basis
- Well capitalized with cash and investments of $2 billion as of September 30, 2021

"Since our last quarterly update, we further advanced our strategic objectives through investments in our expanding Phase 3 pipeline and technology. We also advanced our commercial readiness initiatives in anticipation of multiple product launches potentially beginning as early as 2023," said Elizabeth L. Hougen, chief financial officer of Ionis. "We remain on track to achieve our 2021 financial guidance driven by increased R&D revenue in the fourth quarter as several of our partner programs advance. We also project increased expenses in the fourth quarter as we continue to invest for growth. Importantly, with $2 billion in cash, we remain well-capitalized with the resources we need to achieve our strategic objectives."

(1)All non-GAAP amounts referred to in this press release exclude non-cash compensation expense related to equity awards and expenses related to the Akcea Merger and restructured commercial operations and the related tax effects. Please refer to the section below titled "Financial Impacts of Akcea Merger and Restructured Commercial Operations" for a summary of the costs specific to these transactions. Additionally, please refer to the detailed reconciliation of non-GAAP and GAAP measures, which is provided later in this press release.

Third Quarter 2021 Marketed Products Highlights

- SPINRAZA®: the global market leader for the treatment of spinal muscular atrophy (SMA) patients of all ages
  - $444 million in worldwide sales in the third quarter
  - More than 11,000 patients worldwide on therapy at the end of the third quarter across commercial, expanded access and clinical trial settings
  - Biogen plans to initiate the Phase 3b ASCEND study evaluating the potential benefit of an investigational higher dose of nusinersen in children, teens and adults with later-onset SMA previously treated with Evrysdi® (risdiplam)
- TEGSEDI® and WAYLIVRA®: important medicines approved for the treatment of patients with severe rare diseases
  - TEGSEDI achieved innovative drug pricing in Brazil reflecting the significant unmet medical need and prevalence of TTR polyneuropathy in Brazil
  - WAYLIVRA was approved in Brazil as the first and only treatment for patients with familial chylomicronemia syndrome

Third Quarter 2021 and Recent Events

- Advancing Ionis' leading cardiovascular and metabolic disease pipeline
  - Initiated the Phase 3 CORE study of olezarsen (IONIS-APOCIII-L_{Rx}) in patients with severe hypertriglyceridemia (sHTG)
  - Reached 50 percent enrollment in the Phase 3 Lp(a) HORIZON outcome study of pelacarsen for patients with established cardiovascular disease and elevated Lp(a), resulting in a $25 million payment from Novartis
  - Achieved full enrollment in the Bayer Phase 2b RE-THINc ESRD study of fesomersen (IONIS-FXI-L_{Rx}), with data expected in the first half of 2022
  - Achieved proof-of-mechanism, a strong indication of proof-of-concept and good safety and tolerability in a Phase 2 study and a preliminary assessment from an open-label extension study of cimdelirsen (IONIS-GHR-L_{Rx}) in acromegaly patients uncontrolled on standard of care therapy, supporting continued development. Data from the ongoing open-label extension study and monotherapy study are expected in 2022. The results from the Phase 2 study of cimdelirsen are posted to Ionis' website and may be accessed here
- Addressing substantial unmet medical need with Ionis' broad neurological disease pipeline
  - The Biogen Phase 3 VALOR study of tofersen in patients with SOD1-ALS did not meet the primary endpoint of change from baseline to week 28 in the ALS Functional Rating Scale-Revised (ALSFRS-R); however, signs of reduced disease progression across multiple secondary and exploratory endpoints were observed
  - Achieved full enrollment in the Phase 3 NEURO-TTRansform study of eplontersen in patients with TTR polyneuropathy, with data expected in mid-2022
  - Reported data from the Biogen Phase 1/2 study of IONIS-$MAPT_{Rx}$ in patients with Alzheimer's disease, demonstrating durable, time and dose-dependent reductions in CSF tau protein; IONIS-$MAPT_{Rx}$ was generally well tolerated
- Investing in expanding the reach of Ionis' technology
  - Entered a license agreement with Bicycle Therapeutics for exclusive rights to Bicycle's peptide technology targeting transferrin receptor 1 to expand the capabilities of Ionis' LICA technology
  - Entered a license agreement with Flamingo Therapeutics for the development and commercialization of programs from Ionis' oncology pipeline

2021 Pipeline Milestones(2)

Anticipated Key 2021 Data Readouts

Program	Phase	Anticipated Indication	H1	H2
Donidalorsen	2	Hereditary angioedema (top-line data)	√	
IONIS-AGT-L_{Rx}	2	Hypertension	√	
Tominersen	3	Huntington's disease	√	
IONIS-ENAC-2.5$_{Rx}$	2	Cystic fibrosis	√	
IONIS-$MAPT_{Rx}$	1/2	Alzheimer's disease		√
Tofersen	3 (VALOR)	SOD1-ALS		√
Cimdelirsen	2 + OLE	Acromegaly		√
Donidalorsen	2	Hereditary angioedema (full data)		•
ION449 (PCSK9)	1 (MAD)	Dyslipidemia		•
Vupanorsen	2b	sHTG/CVD risk reduction		•

Anticipated Key 2021 Study Initiations

Program	Phase	Anticipated Indication	H1	H2
SPINRAZA	4 (RESPOND)	SMA, suboptimal gene therapy response	√	
Tofersen	3 (ATLAS)	Presymptomatic SOD1-ALS	√	
ION363	3	FUS-ALS	√	
IONIS-AGT-L_{Rx}	2 & 2b	Heart failure & resistant hypertension	√	
ION373	2/3	Alexander disease	√	

ION224	2b	NASH	√	
Olezarsen	3 (CORE)	Severe hypertriglyceridemia (sHTG)		√
Donidalorsen	3	Hereditary angioedema		•
SPINRAZA	3b (ASCEND)	SMA, previous risdiplam treatment		•
ION582	2	Angelman syndrome		•

√ = achieved • = planned

(2) Timing of partnered program catalysts based on partners' most recent publicly available disclosures

Third Quarter 2021 Financial Results

Revenue

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

	Three months ended September 30,		Nine months ended September 30,	
	2021	2020	2021	2020
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$67	$74	$199	$212
TEGSEDI and WAYLIVRA revenue, net	15	19	47	51
Licensing and royalty revenue	3	2	9	6
Total commercial revenue	85	95	255	269
R&D revenue:				
Amortization from upfront payments	17	19	57	68
Milestone payments	28	44	48	73
License fees	-	-	-	15
Other services	3	2	10	14
Total R&D revenue	48	65	115	170
Total revenue	$133	$160	$370	$439

In the third quarter of 2021, the Company continued to advance its late-stage pipeline, including reaching 50 percent enrollment in the Phase 3 Lp(a) HORIZON study of pelacarsen for which it earned a $25 million milestone payment from Novartis. As its partnered programs advance, the Company expects R&D revenue to increase in the fourth quarter of 2021 compared with the third quarter of 2021.

In the second quarter of 2021, the Company successfully completed the transition of its TEGSEDI operations in North America to Sobi. As a result, the Company's commercial revenue from product sales shifted to distribution fees based on net sales generated by Sobi. In the third quarter of 2021, the Company earned a $4 million milestone payment from PTC Therapeutics when WAYLIVRA was approved in Brazil.

Financial Impacts of Akcea Merger and Restructured Commercial Operations

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. For the three and nine months ended September 30, 2021, the Company incurred $3 million and $24 million of costs in conjunction with the Akcea merger and restructuring of the Company's commercial operations, respectively. The Company excluded these costs from its non-GAAP amounts for those periods. Please refer to the detailed reconciliation of non-GAAP and GAAP measures that is provided later in this press release.

Operating Expenses

Ionis' operating expenses for the three and nine months ended September 30, 2021 increased compared with the same periods last year driven by an increase in R&D expenses, partially offset by a decrease in SG&A expenses. Higher R&D expenses were primarily driven by the Company's investments in advancing its late-stage wholly owned pipeline, including advancing the Phase 3 program for eplontersen and start-up costs associated with the Phase 3 study for a second indication for olezarsen. Additionally, the Company recognized $35 million in R&D expense in the third quarter of 2021 for licensing Bicycle's technology. Lower SG&A expenses primarily reflect operating efficiencies achieved from integrating Akcea and restructuring the Company's commercial operations. The Company projects its operating expenses to increase in the fourth quarter as it continues to invest for growth.

Net Loss Attributable to Ionis Common Stockholders

Net loss attributable to Ionis' common stockholders for the three and nine months ended September 30, 2021 increased compared with the same periods in the prior year for the reasons discussed above.

Balance Sheet

As of September 30, 2021, Ionis had cash, cash equivalents and short-term investments of $2.0 billion, compared with $1.9 billion as of December 31, 2020. The Company intends to utilize $62 million of its cash to pay the remaining principal balance of its 1 percent convertible notes at maturity in November 2021.

The Company revised its 2020 amounts to reflect the simplified convertible instruments guidance the Company adopted retrospectively on January 1, 2021.

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 neurological and cardiometabolic franchises. Our scientific innovation began and continues with the knowledge that sick people depend on us, which fuels our vision of becoming one of the most successful biotechnology companies.

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) and WAYLIVRA (volanesorsen) and Ionis' technologies and 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, 2020, and the most recent Form 10-Q quarterly filing, which are on file with the SEC. 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 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 September 30,		Nine months ended September 30,	
	2021	2020	2021	2020
		(as revised*)		(as revised*)
		(unaudited)		
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$67	$74	$199	$212
TEGSEDI and WAYLIVRA revenue, net	15	19	47	51
Licensing and royalty revenue	3	2	9	6
Total commercial revenue	85	95	255	269
Research and development revenue under collaborative agreements	48	65	115	170
Total revenue	133	160	370	439
Expenses:				
Cost of sales	3	3	9	9

Research, development and patent	185	125	464	364
Selling, general and administrative	31	69	148	215
Total operating expenses	219	197	621	588
Loss from operations	(86)	(37)	(251)	(149)
Other income (expense):				
Loss on early retirement of debt	-	-	(9)	-
Other income, net	2	5	6	29
Loss before income tax benefit (expense)	(84)	(32)	(254)	(120)
Income tax benefit (expense)	2	(5)	1	(4)
Net loss	($82)	($37)	($253)	($124)
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	$-	$13	$-	$34
Net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders	($82)	($24)	($253)	($90)
Basic and diluted net loss per share	($0.58)	($0.18)	($1.80)	($0.64)
Shares used in computing basic and diluted net loss per share	141	140	141	139

*The Company revised its 2020 amounts to reflect the simplified convertible instruments guidance the Company adopted retrospectively on January 1, 2021.

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

	Three months ended September 30,		Nine months ended September 30,	
	2021	2020	2021	2020
		(as revised*) (unaudited)		(as revised*)
As reported research, development and patent expenses according to GAAP	$185	$125	$464	$364
Excluding compensation expense related to equity awards	(23)	(25)	(72)	(77)
Excluding Akcea merger and restructured commercial operation costs**	(2)	-	(8)	-
Non-GAAP research, development and patent expenses	$160	$100	$384	$287
As reported selling, general and administrative expenses according to GAAP	$31	$69	$148	$215
Excluding compensation expense related to equity awards	(7)	(20)	(26)	(57)
Excluding Akcea merger and restructured commercial operation costs**	(1)	-	(16)	-
Non-GAAP selling, general and administrative expenses	$23	$49	$106	$158
As reported operating expenses according to GAAP	$219	$197	$621	$588
Excluding compensation expense related to equity awards	(31)	(46)	(98)	(135)
Excluding Akcea merger and restructured commercial operation costs**	(3)	-	(24)	-
Non-GAAP operating expenses	$185	$151	$499	$453
As reported loss from operations according to GAAP	($86)	($37)	($251)	($149)
Excluding compensation expense related to equity awards	(31)	(46)	(98)	(135)
Excluding Akcea merger and restructured commercial operation costs**	(3)	-	(24)	-
Non-GAAP income (loss) from operations	($52)	$9	$(129)	($14)
As reported net loss attributable to Ionis Pharmaceuticals, Inc. common stockholders according to GAAP	($82)	($24)	($253)	($90)

Excluding compensation expense related to equity awards attributable to Ionis Pharmaceuticals, Inc. common stockholders	(31)	(42)	(98)	(126)
Excluding Akcea merger and restructured commercial operation costs**	(3)	-	(24)	-
Income tax effect related to compensation expense related to equity awards attributable to Ionis Pharmaceuticals, Inc. common stockholders	-	6	-	18
Non-GAAP net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders according to GAAP	($48)	$12	($131)	$18

* The Company revised its 2020 amounts to reflect the simplified convertible instruments guidance the Company adopted retrospectively on January 1, 2021.

** 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.

Reconciliation of GAAP to Non-GAAP Basis

As illustrated in the Selected Financial Information in this press release, non-GAAP operating expenses, non-GAAP income (loss) from operations, and non-GAAP net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders 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 include: 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.
Condensed Consolidated Balance Sheets
(In Millions)

	September 30, 2021	December 31, 2020
		(as revised*)
	(unaudited)	
Assets:		
Cash, cash equivalents and short-term investments	$1,987	$1,892
Contracts receivable	9	76
Other current assets	160	162
Property, plant and equipment, net	180	181
Other assets	79	79
Total assets	$2,415	$2,390
Liabilities and stockholders' equity:		
Other current liabilities	$120	$183
Current portion of 1% convertible senior notes, net	62	309
Current portion of deferred contract revenue	98	108
0% convertible senior notes, net	618	-
0.125% convertible senior notes, net	542	540
Long-term obligations, less current portion	81	83
Long-term deferred contract revenue	363	424
Total stockholders' equity	531	743
Total liabilities and stockholders' equity	$2,415	$2,390

*The Company revised its 2020 amounts to reflect the simplified convertible instruments guidance the Company adopted retrospectively on January 1, 2021.

View original content to download multimedia:https://www.prnewswire.com/news-releases/ionis-reports-third-quarter-2021-financial-results-and-recent-business-achievements-301414847.html

SOURCE Ionis Pharmaceuticals, Inc.

Ionis Pharmaceuticals Investor Contact: 760-603-2331 OR Ionis Pharmaceuticals Media Contact: 760-603-2681