Ionis reports fourth quarter and full year 2021 financial results and recent business achievements

February 24, 2022

Exceeded 2021 financial guidance with revenues of more than $800 million
Webcast today, February 24, 2022, at 11:30 a.m. Eastern Time

CARLSBAD, Calif., Feb. 24, 2022 /PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today reported financial results for the fourth quarter and full year ended December 31, 2021, and recent business achievements.

"During 2021, we made significant progress towards achieving our vision of becoming a leading fully-integrated biotechnology company. We advanced our commercial strategy and go-to-market plans for our near-term commercial opportunities, eplontersen, olezarsen and donidalorsen. Our collaboration with AstraZeneca to jointly develop and commercialize eplontersen enables us to potentially maximize benefit for patients, bolster our commercial organization and accelerate preparations for our near-term product launches. Most recently, we initiated Phase 3 studies with olezarsen in patients with severely high triglycerides and donidalorsen in patients with hereditary angioedema. This expands our Phase 3 pipeline to six medicines addressing eight indications. We also advanced our technology, positioning us to build on our leadership in RNA-targeted therapeutics and add value for our future medicines," said Brett P. Monia, Ph.D., chief executive officer of Ionis. "We look forward to a steady cadence of catalysts throughout this year, highlighted by eplontersen Phase 3 data in patients with hATTR polyneuropathy planned for mid-year. We expect to file for regulatory approval for eplontersen before year end, assuming positive data. We also expect to make continued advancements to expand and diversify our technology. Based on our anticipated near- and mid-term catalysts, we believe we are well positioned to drive increasing value for patients and shareholders."

2021 Summary Financial Results

- Exceeded 2021 financial guidance
  - $810 million in total revenues
  - $695 million of operating expenses on a non-GAAP basis(1) and $840 million on a GAAP basis
  - Net income of $116 million on a non-GAAP basis(1) and a net loss of $29 million on a GAAP basis
- Well capitalized with cash and short-term investments of $2.1 billion at year-end, enabling accelerating investments in 2022 with the goal 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
  - $1.9 billion in worldwide SPINRAZA sales in 2021
  - More than 11,000 patients worldwide on therapy at the end of 2021 across commercial, expanded access and clinical trial settings
  - Biogen continued to expand upon SPINRAZA's competitive profile through the ongoing ASCEND, RESPOND and DEVOTE studies
- TEGSEDI® and WAYLIVRA®: important medicines approved for the treatment of patients with hereditary TTR amyloidosis with polyneuropathy and familial chylomicronemia syndrome, respectively
  - TEGSEDI and WAYLIVRA achieved innovative drug pricing in Brazil
  - WAYLIVRA is under review in Brazil for the treatment of familial partial lipodystrophy (FPL). If approved, WAYLIVRA will be the first approved treatment for patients with FPL in Brazil

Fourth Quarter 2021 and Recent Events

- Advancing Ionis' near-term commercial opportunities toward the market
  - Eplontersen: potential to change the standard-of-care for patients with TTR amyloidosis (ATTR)
    - Initiated a collaboration with AstraZeneca to jointly develop and commercialize eplontersen valued at up to $3.6 billion in an upfront and potential milestone payments, plus cost-sharing and royalties
    - The U.S. FDA granted orphan drug designation to eplontersen for the treatment of patients with ATTR
  - Olezarsen: potential first-in-class treatment for patients with elevated triglycerides
    - Initiated the Phase 3 CORE study of olezarsen in patients with severe hypertriglyceridemia (SHTG) with data expected in 2024
    - Reported positive data from the Phase 2 study of olezarsen in patients with moderate hypertriglyceridemia and at high risk for or with established cardiovascular disease in the *European Heart Journal*

    - Donidalorsen: potential best-in-class prophylactic treatment for patients with hereditary angioedema (HAE)
        - Initiated the Phase 3 OASIS-HAE study of donidalorsen in patients with HAE with data expected in 2024
        - Presented positive data from the Phase 2 study of donidalorsen in patients with HAE at the ACAAI annual scientific meeting
- Advancing Ionis' leading cardiovascular disease franchise
    - AstraZeneca presented new data from the Phase 1 multiple ascending dose study of ION449 (AZD8233) targeting PCSK9 in statin treated subjects with dyslipidemia at the AHA scientific sessions
- Addressing substantial unmet medical needs with Ionis' broad neurological disease franchise
    - Biogen licensed ION306 (BIIB115) for the treatment of SMA with the potential for extended dosing intervals, resulting in a $60 million payment from Biogen
    - Biogen reported that while the Phase 3 VALOR study of tofersen in patients with SOD1-ALS did not meet the primary endpoint, signs of reduced disease progression across multiple secondary and exploratory endpoints were observed. Biogen continues to engage with regulators to discuss a path forward for tofersen
    - Roche announced plans to initiate a new Phase 2 study of tominersen in patients with Huntington's disease based on new findings from a post-hoc analysis of the Phase 3 GENERATION-HD1 study
    - Initiated the Phase 1/2 HALOS study of ION582 (BIIB121) in patients with Angelman syndrome, resulting in a $10 million payment from Biogen
    - Advanced three neurological disease programs, resulting in $23 million in payments from Biogen
    - Dynacure advanced IONIS-DNM2-2.5$_{Rx}$, resulting in $7.5 million in payments from Dynacure
- Advancing additional programs in Ionis' clinical pipeline for diseases with unmet medical need
    - Initiated a Phase 2 study of sapablursen (formerly known as IONIS-TMPRSS6-L$_{Rx}$) in patients with polycythemia vera, the second indication for sapablursen
    - Reported topline results from the Phase 2 study of cimdelirsen (formerly known as IONIS-GHR-L$_{Rx}$) in patients with uncontrolled acromegaly, achieving proof of mechanism with a strong indication of proof of concept
    - Advanced two metabolic disease programs, resulting in $40 million in payments from AstraZeneca

2022 Pipeline Milestones[(2)]

Anticipated 2022 Regulatory Filings

Program	Anticipated Indication	H1	H2
Eplontersen	hATTR polyneuropathy		•

Anticipated Key 2022 Data Readouts

Program	Data Readout	Anticipated Indication	H1	H2
Tominersen	Phase 3 post hoc	Huntington's disease	✓	
Eplontersen	Phase 3	hATTR polyneuropathy	•	
ION449 (PCSK9)	Phase 2b	Cardiovascular disease	•	
Donidalorsen	Phase 2	HAE	•	
IONIS-C9$_{Rx}$ (BIIB078)	Phase 2	C9-ALS	•	
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	Phase 2	Acromegaly (monotherapy)		•

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

2021 Financial Results and 2022 Financial Guidance

"Over the last year, we achieved numerous pipeline and technology milestones, advanced multiple medicines towards the market and accelerated preparations for our near-term commercial launches. We also exceeded our 2021 financial guidance, driven by revenue from advancing multiple

partnered programs and by strengthening and streamlining our business," said Elizabeth L. Hougen, chief financial officer of Ionis. "We have a long history of financial responsibility that provides us with a strong financial foundation. With more than $2 billion of cash and a substantial and sustainable base of commercial and R&D revenues, we are well positioned to accelerate our investments in 2022 to drive substantial future growth."

2022 Financial Guidance

Ionis' full year 2022 financial guidance consists of the following components (on a non-GAAP basis)[(1)]:

	Guidance
Revenue	>$575 million
Operating Expenses [(1)]	$825 million to $850 million
Net Loss [(1)]	<$275 million
Cash and Short-Term Investments	~$1.7 billion

(1)All non-GAAP amounts referred to in this press release exclude non-cash compensation expense related to equity awards. In 2021 and 2020 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 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.

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

Revenue

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

	Three months ended December 31,		Year ended December 31,	
	2021	2020	2021	2020
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$69	$75	$268	$287
TEGSEDI and WAYLIVRA revenue, net	9	19	56	70
Licensing and royalty revenue	9	2	18	8
Total commercial revenue	87	96	342	365
R&D revenue:				
Amortization from upfront payments	21	12	78	80
Milestone payments	40	110	88	183
License fees	290	71	291	86
Other services	2	1	11	15
Total R&D revenue	353	194	468	364
Total revenue	$440	$290	$810	$729

The Company's revenue increased by more than 10 percent compared to 2020 driven in large part by significant partner payments across multiple partnered programs. In 2021, the Company earned $200 million from its new collaboration with AstraZeneca to jointly develop and commercialize eplontersen. The Company also earned more than $160 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 2021 compared to 2020 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 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 2021 compared to 2020. Higher R&D expenses were driven by the expanded number of Phase 3 studies the Company was conducting, which doubled over the course of 2021 from 3 to 6 studies. Additionally, the Company recognized $35 million in R&D expense in the third quarter of 2021 for licensing Bicycle Therapeutic's technology. Lower SG&A expenses primarily reflected operating efficiencies achieved from integrating Akcea and restructuring the Company's commercial operations.

Net Loss Attributable to Ionis Common Stockholders

Net loss attributable to Ionis' common stockholders in 2021 decreased compared to 2020 for the reasons discussed above. Also contributing to the decrease in Ionis' net loss in 2021 compared to 2020 was the non-cash adjustment of the valuation allowance Ionis recorded against its federal net deferred tax assets in 2020.

Balance Sheet

As of December 31, 2021, Ionis had cash, cash equivalents and short-term investments of $2.1 billion, compared with $1.9 billion as of December 31, 2020.

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

	Three months ended, December 31,		Year ended December 31,	
	2021	2020	2021	2020
		(as revised*) (unaudited)		(as revised*)
Revenue:				
Commercial revenue:				
SPINRAZA royalties	$69	$75	$268	$287
TEGSEDI and WAYLIVRA revenue, net	9	19	56	70
Licensing and royalty revenue	9	2	18	8
Total commercial revenue	87	96	342	365
Research and development revenue under collaborative agreements	353	194	468	364
Total revenue	440	290	810	729
Expenses:				
Cost of sales	2	3	11	12
Research, development and patent	179	171	643	535
Selling, general and administrative	38	139	186	354
Total operating expenses	219	313	840	901
Income (loss) from operations	221	(23)	(30)	(172)
Other income (expense):				
Loss on early retirement of debt	-	-	(9)	-
Other income, net	4	8	9	37
Income (loss) before income tax benefit (expense)	225	(15)	(30)	(135)
Income tax benefit (expense)	-	(341)	1	(345)
Net income (loss)	$225	($356)	($29)	($480)
Net loss attributable to noncontrolling interest in Akcea Therapeutics, Inc.	-	1	-	36
Net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders	$225	($355)	($29)	($444)

Basic net income (loss) per share	$1.59	($2.54)	($0.20)	($3.18)
Diluted net income (loss) per share	$1.41	($2.54)	($0.20)	($3.18)
Shares used in computing basic net income (loss) per share	141	140	141	140
Shares used in computing diluted net income (loss) per share	160	140	141	140

*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 December 31,		Year ended December 31,	
	2021	2020 (as revised*)	2021	2020 (as revised*)
	(unaudited)			
As reported research, development and patent expenses according to GAAP	$179	$171	$643	$535
Excluding compensation expense related to equity awards	(16)	(22)	(88)	(99)
Excluding Akcea merger and restructured commercial operation costs**	(1)	(26)	(9)	(26)
Non-GAAP research, development and patent expenses	$162	$123	$546	$410
As reported selling, general and administrative expenses according to GAAP	$38	$139	$186	$354
Excluding compensation expense related to equity awards	(7)	(15)	(33)	(72)
Excluding Akcea merger and restructured commercial operation costs**	1	(64)	(15)	(64)
Non-GAAP selling, general and administrative expenses	$32	$60	$138	$218
As reported operating expenses according to GAAP	$219	$313	$840	$901
Excluding compensation expense related to equity awards	(23)	(36)	(121)	(171)
Excluding Akcea merger and restructured commercial operation costs**	-	(90)	(24)	(90)
Non-GAAP operating expenses	$196	$187	$695	$640
As reported income (loss) from operations according to GAAP	$221	($23)	($30)	($172)
Excluding compensation expense related to equity awards	(23)	(36)	(121)	(171)
Excluding Akcea merger and restructured commercial operation costs**	-	(90)	(24)	(90)
Non-GAAP income from operations	$244	$103	$115	$89
As reported net income (loss) attributable to Ionis Pharmaceuticals, Inc. common stockholders according to GAAP	$225	($355)	($29)	($444)
Excluding compensation expense related to equity awards attributable to Ionis Pharmaceuticals, Inc. common stockholders	(23)	(36)	(121)	(162)
Excluding Akcea merger and restructured commercial operation costs**	-	(90)	(24)	(90)
Income tax effect related to compensation expense related to equity awards attributable to Ionis Pharmaceuticals, Inc. common stockholders	-	(16)	-	2
Income tax effect related to the Akcea merger and restructured commercial operation costs**	-	(340)	-	(340)
Non-GAAP net income attributable to Ionis Pharmaceuticals, Inc. common stockholders according to GAAP	$248	$127	$116	$146

*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. 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 incurred $24 million and $90 million of costs in conjunction with the Akcea merger and restructuring of the Company's commercial operations for 2021 and 2020, respectively. The Company excluded these costs from its non-GAAP amounts for those 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 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)

	December 31, 2021	December 31, 2020 (as revised*)
Assets:		
Cash, cash equivalents and short-term investments	$2,115	$1,892
Contracts receivable	62	76
Other current assets	168	162
Property, plant and equipment, net	178	181
Other assets	89	79
Total assets	$2,612	$2,390
Liabilities and stockholders' equity:		
Other current liabilities	$143	$183
Current portion of 1% convertible senior notes, net	-	309
Current portion of deferred contract revenue	98	108
0% convertible senior notes, net	619	-
0.125% convertible senior notes, net	542	540
Long-term obligations, less current portion	86	83
Long-term deferred contract revenue	352	424
Total stockholders' equity	772	743
Total liabilities and stockholders' equity	$2,612	$2,390

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

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