Q3 2021 Financial Results and Business Update

November 3, 2021

NASDAQ: IONS

On Today's Earnings Call

Brett Monia, Ph.D.
Chief Executive Officer

Beth Hougen
Chief Financial Officer

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Executive Vice President, Development

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Executive Vice President, Research

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Chief Corp. Development & Commercial Officer

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Forward Looking Language Statement

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA® (nusinersen), TEGSEDI® (inotersen), 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 our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these and other documents are available at www.ionispharma.com.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

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Introduction

Brett Monia, Ph.D.
Chief Executive Officer

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Executing on our Strategic Objectives

Pipeline

- Initiated olezarsen (APOCIII-L_{Rx}) Phase 3 CORE sHTG study
- Completed enrollment in eplontersen Phase 3 NEURO-TTRansform study
- On track to initiate donidalorsen (PKK-L_{Rx}) Phase 3 study

Commercial

- Advanced our strategy, plans and progress to successfully bring our most advanced wholly owned programs to market

Technology

- Licensed transferrin receptor targeting technology from Bicycle
- Advanced internal technology initiatives

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Q3 2021 Financial Performance

Beth Hougen
Chief Financial Officer

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YTD 2021 Financial Results

$370 million in revenue

Driven by commercial revenues

$131 million net loss*

Reflects strategy to invest for growth

SPINRAZA® (nusinersen) injection 12 mg/5 mL

$200 million

In royalties to Ionis

$2 billion of cash

Financial strength to achieve strategic priorities

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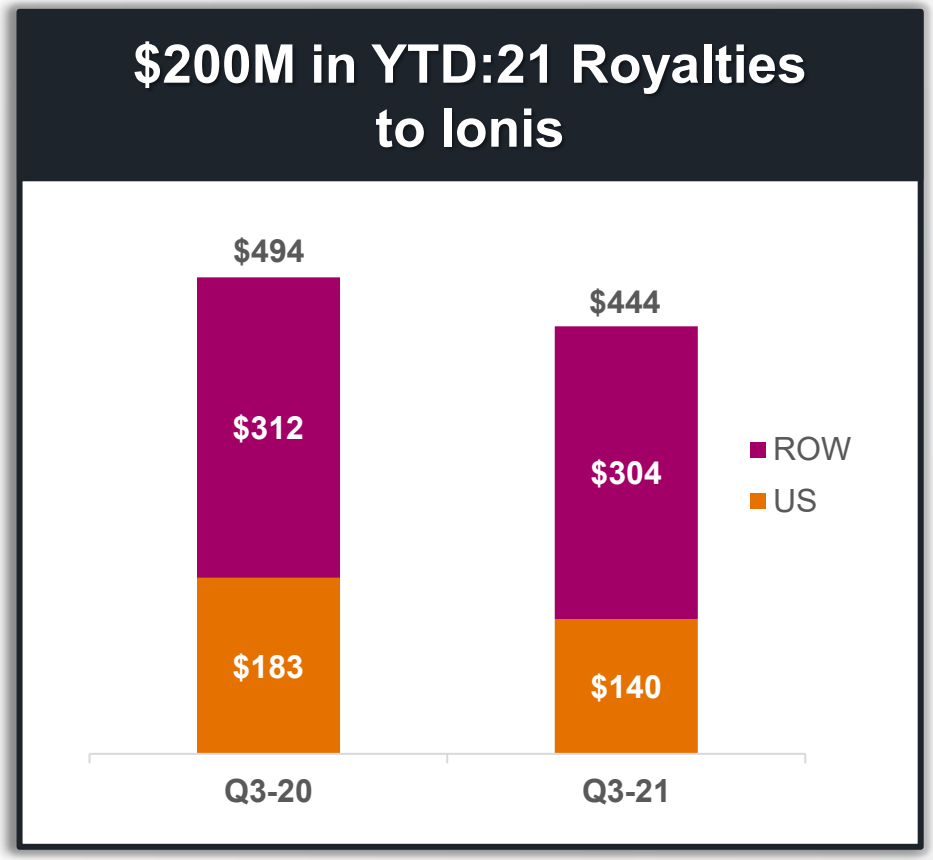
*Non-GAAP – please see Financial Impacts of Akcea Merger and Restructured Commercial Operations and reconciliation to GAAP in Q3'21 press release

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Global Leader for the Treatment of SMA: $1.5B in YTD 2021 Sales



Source: Biogen Q3 2021 Financial Results and Business Update; 1. Includes patients from post-marketing, EAP and clinical settings; 2. As of September 30, 2021; 3. ASCEND: clinicaltrials.gov/NCT05067790; 4. DEVOTE: clinicaltirals.gov/NCT04089566; 5. RESPOND: clinicaltrials.gov/NCT04488133

- **>11,000 patients on SPINRAZA worldwide[1,2]**
- **Potential to further inform SMA treatment and address the remaining unmet needs of SMA patients of all ages**
  - **ASCEND:** evaluating an investigational higher dose of nusinersen in later-onset SMA patients previously treated with risdiplam; aim to begin YE:21[3]
  - **DEVOTE:** evaluating an investigational higher dose of nusinersen in infants, children and adult SMA patients[4]
  - **RESPOND:** evaluating SPINRAZA in type 1 SMA patients with a suboptimal response to gene therapy[5]

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TEGSEDI and WAYLIVRA

Generated nearly $50 million in revenue YTD 2021[1]

TEGSEDI achieved innovative drug pricing in Brazil[2]

WAYLIVRA approved in Brazil as the first and only treatment for people with FCS[2,3]

1. Q3'21 combined TEGSEDI and WAYLIVRA commercial revenues primarily from distribution fees on net product sales from Sobi. Q2'21 was the first full quarter reflecting the shift from product sales to distribution fees following the transition of European and North American commercial operations to Sobi. 2. TEGSEDI and WAYLIVRA are commercialized by PTC Therapeutics in Latin America. 3. Ionis earned a $4M milestone payment from PTC Therapeutics for achieving WAYLIVRA approval in Brazil.

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2021 Financial Guidance

Revenue	Operating Expenses	Net Loss
>$600 million	$710-$750 million*	<$110 million*

Reaffirming 2021 Guidance

*Non-GAAP – please see Financial Impacts of Akcea Merger and Restructured Commercial Operations and reconciliation to GAAP in Q3'21 press release

Pipeline Performance

Richard Geary, Ph.D.
Executive Vice President, Development

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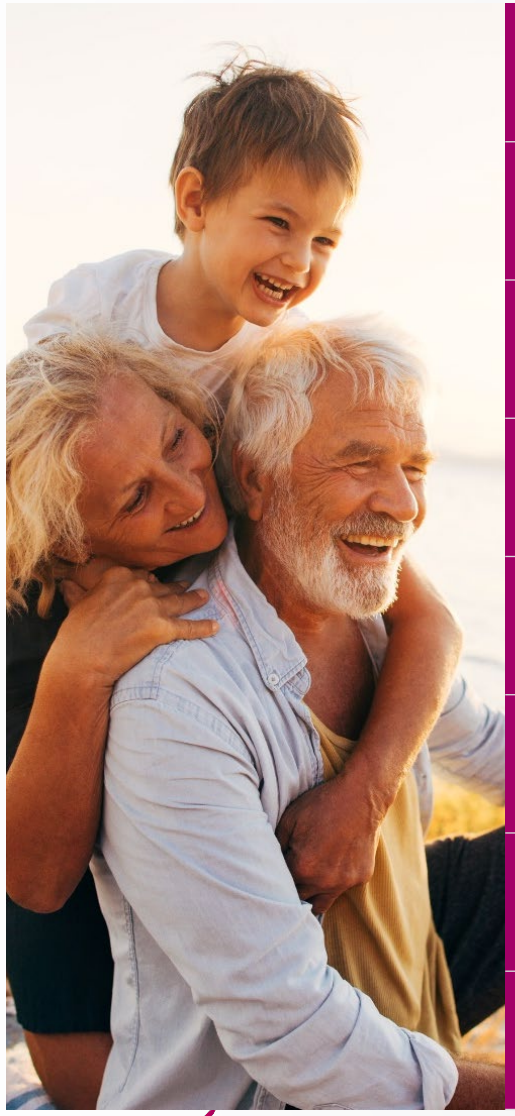
Pioneering New Markets & Changing Standards of Care

Advancing Phase 3 Pipeline



		Phase 3 Data[1]	Prevalence[2]
Tofersen[3]	**SOD1-ALS** Biogen	2021	**~ 1.4K patients** in G7 countries
Eplontersen	**hATTR polyneuropathy** Wholly owned	2022	**> 50K patients** worldwide
Olezarsen	**FCS** Wholly owned	2023	**~ 3-5K patients** worldwide
Eplontersen	**ATTR cardiomyopathy** Wholly owned	2024	**> 200K patients** worldwide
Olezarsen	**sHTG** Wholly owned	2024	**> 3M patients** U.S.
Donidalorsen[4]	**HAE** Wholly owned	2024	> **20K patients** in U.S. and EU
ION363	**FUS-ALS** Wholly owned	2024	**~ 350 patients** in G7 countries
Pelacarsen	**Lp(a) CVDRR** Novartis	2024	**> 8M patients** worldwide

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1. Data timing expectations are based on current estimates and are subject to change. Partnered program timelines are based on partners' most recent public disclosures. 2. Market data on file. 3. Biogen reported tofersen VALOR Phase 3 results at the ANA Annual Meeting on October 17, 2021. 4. Donidalorsen Phase 3 study expected initiation before YE 2021.
ALS, amyotrophic lateral sclerosis. FCS, familial chylomicronemia syndrome. hATTR, hereditary transthyretin amyloidosis. CVDRR, cardiovascular disease risk reduction.

Key 2021 Pipeline Events[1]

DATA READOUTS			H1	H2
Donidalorsen (PKK-L_{Rx})	Phase 2	Hereditary angioedema (top-line data)	✓	
AGT-L_{Rx}	Phase 2	Hypertension	✓	
Tominersen	Phase 3	Huntington's disease	✓	
ENAC-2.5$_{Rx}$	Phase 2	Cystic fibrosis	✓	
MAPT$_{Rx}$	Phase 1/2	Alzheimer's disease		✓
Tofersen	VALOR Phase 3	SOD1-ALS		✓
Cimdelirsen (GHR-L_{RX})	Phase 2 + OLE	Acromegaly		✓
Donidalorsen (PKK-L_{Rx})	Phase 2	Hereditary angioedema (full data)		•
ION449 (PCSK9)	Phase 1 (MAD)	Dyslipidemia		•
Vupanorsen	Phase 2b	sHTG/CVD risk reduction		•
KEY STUDY INITIATIONS			**H1**	**H2**
SPINRAZA	RESPOND Phase 4	SMA, Suboptimal gene therapy response	✓	
Tofersen	ATLAS Phase 3	Presymptomatic SOD1-ALS	✓	
ION363	Phase 3	FUS-ALS	✓	
AGT-L_{Rx}	Phase 2 & 2b	HF & resistant hypertension	✓	
ION373	Phase 2/3	Alexander disease	✓	
ION224	Phase 2b	NASH	✓	
Olezarsen (APOCIII-L_{Rx})	CORE Phase 3	Second TG indication (sHTG)		✓
Donidalorsen (PKK-L_{Rx})	Phase 3	Hereditary angioedema		•
SPINRAZA	ASCEND Phase 3b	SMA, previous risdiplam treatment		•
ION582	Phase 2	Angelman syndrome		•

1. Timing of partnered program catalysts based on partners' most recent publicly available disclosures

● Wholly owned ● Partnered ✓ Achieved • Expected

Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

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Coming up at Investor Day

Strategy, plans & progress for **commercial success**

Pipeline with substantial **value-creating potential**

Technology **advancements**

December 9 • Virtual Event

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Q&A

Brett Monia, Ph.D.
Chief Executive Officer

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IONIS: A FORCE FOR LIFE