Q3:22 Financial Results and Business Update

November 9, 2022

Nasdaq: IONS

On Today's Earnings Call

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Forward-Looking Statements

This presentation includes forward-looking statements regarding our 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 but not limited to those related to our commercial products and the medicines in our pipeline, and particularly 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 our most recent Form 10-Q quarterly filing, which are on file with the Securities and Exchange Commission. Copies of this 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.

Introduction

Brett Monia, Ph.D.
Chief Executive Officer

Substantial Progress This Year[1]

Next Potential Marketed Medicines	• Eplontersen: Positive Phase 3 NEURO-TTRansform results
	  ○ On track to file NDA by end of 2022
	• Tofersen: NDA under priority review
	  ○ PDUFA date April 25, 2023

Advancing & Expanding Pipeline & Technology	• 8 positive late- and mid-stage data readouts • 2 medicines expected to expand Phase 3 pipeline in H1:23 • 2 new technology advancements: muscle LICA, MsPA backbone
Next Potential Marketed Medicines	• On track to achieve our 2022 P&L guidance • Increased cash guidance to $2.0B from $1.7B • Two real estate transactions to support accelerating growth

Positioned for Substantial Growth

1. Timing expectations based on current assumptions and subject to change

Pipeline Performance

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

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Tofersen: Potential to Become First Ever Disease Modifying Therapy for a Genetic Cause of ALS

Tofersen to Treat SOD-1 ALS

12-Month VALOR[1] and OLE Integrated Data Included in NDA Showed Tofersen:

- Significantly slowed decline across multiple measures of ALS disease progression
- Led to robust and sustained reductions in neurofilament light chain
- Demonstrated a safety profile supportive of continued treatment

Data published in the *New England Journal of Medicine*

NDA under Priority Review

PDUFA Date: April 25, 2023

Next Potential Product to Enter the Market[2]

1. While statistical significance was not achieved on the primary endpoint of ALSFRS-R at week 28 in the Phase 3 VALOR study, signs of reduced disease progression across multiple secondary and exploratory endpoints were observed 2.Timing expectations based on current assumptions and subject to change

Positive Phase 3 Results Position Eplontersen for Approval In 2023[1]

ATTRv Polyneuropathy

Positive Phase 3 Data
On track to file NDA in U.S. by end of 2022

- Met co-primary and secondary endpoints
- Robust TTR reduction
- Showed clinically meaningful improvements in neuropathy impairment and quality of life

ATTR Cardiomyopathy

Enrollment underway
Data expected H1:2025

- Largest and longest study
- Increased enrollment to ~1,400
- Progressing well

ATTR Amyloidosis

Supportive Studies
Underway

- Profile-enhancing studies in patients with ATTRv-PN and ATTR-CM to bolster data package

1. Timing expectations based on current assumptions and subject to change

Broad Olezarsen Development Program Designed to Support Approval in the Large SHTG Market[1]

FCS

Balance
a familial chylomicronemia syndrome study

Data expected 2023

- FCS Phase 3 BALANCE study fully enrolled

Severe Hypertriglyceridemia

CORE
a hypertriglyceridemia study

CORE2
a hypertriglyceridemia study

Supportive Studies

Data expected 2024

- SHTG Phase 3 CORE study to address much larger indication is progressing well
- Confirmatory pivotal study
- ESSENSE study to build out safety database for large market
- Additional studies to further demonstrate value

1. Timing expectations based on current assumptions and subject to change

Donidalorsen Phase 3 Program Designed to Support Approval as a Potential Best-in-Class HAE Prophylactic Treatment[1]

Hereditary Angioedema Prophylaxis

Data expected 2024

- Phase 3 study on track
- Longer-term Phase 2 OLE data to be presented on November 13, 2022, at ACAAI

Data expected 2024

- SWITCH study for patients previously treated with other prophylactic therapies
- Phase 3 OLE study for patients who have completed OASIS

1. Timing expectations based on current assumptions and subject to change

Rich Phase 3 Pipeline

Expected to Expand to 8 Medicines for 10 Indications

		Phase 3 Data[1]	Prevalence[2]
Tofersen	**SOD1-ALS**	2021 2022 OLE	**~1.4K patients** in G7 countries
Eplontersen	**ATTRv polyneuropathy**	2022	**>40K patients** worldwide
Olezarsen	**FCS**	2023	**~3-5K patients** worldwide
Olezarsen	**SHTG**	2024	**>3M patients** in US
Donidalorsen	**HAE**	2024	>**20K patients** in US and EU
ION363	**FUS-ALS**	2024	**~350 patients** in G7 countries
Eplontersen	**ATTR cardiomyopathy**	2025	**~300-500K patients** worldwide
Pelacarsen	**Lp(a) CVD**	2025	**>8M patients** worldwide

Bepirovirsen for HBV and IONIS-FB-L$_{Rx}$ for IgAN expected to expand our Phase 3 pipeline in H1:23[1]

Cardiovascular Neurology Specialty Rare

1. Timing expectations are based on current assumptions and are subject to change. 2. Market data on file.

ALS, amyotrophic lateral sclerosis; ATTRv, hereditary transthyretin amyloidosis; FCS, familial chylomicronemia syndrome; SHTG, severe hypertriglyceridemia; HAE, hereditary angioedema; Lp(a), lipoprotein a; CVD, cardiovascular disease; HBV, hepatitis B virus; IgAN, Immunoglobulin A nephropathy

Key 2022 Pipeline Events[1]

REGULATORY FILINGS			H1	H2
Tofersen	NDA acceptance	SOD1-ALS		✓
Eplontersen (TTR)	NDA filing	ATTRv polyneuropathy		•
DATA READOUTS			**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 (CVD)	✓	
Bepirovirsen (HBV)	Phase 2b	Hepatitis B virus (HBV) infection	✓	
Donidalorsen (PKK)	Phase 2	Hereditary angioedema (HAE)	✓	
IONIS-C9$_{Rx}$ (BIIB078)	Phase 1/2	C9-Amyotrophic lateral sclerosis (ALS)	✓	
Fesomersen (FXI)	Phase 2b	Thrombosis		✓
IONIS-FB-L$_{RX}$	Phase 2	Immunoglobulin A nephropathy (IgAN)		✓
Donidalorsen (PKK)	Phase 2 OLE	HAE		•
IONIS-AGT-L$_{Rx}$	Phase 2b	Treatment-resistant hypertension (TRH)		•
Cimdelirsen (GHR)	Phase 2	Acromegaly (monotherapy)		•
STUDY INITIATIONS			**H1**	**H2**
Sapablursen (TMPRSS6)	Phase 2	Polycythemia vera	✓	
ION904 (AGT)	Phase 2	Uncontrolled hypertension (HTN)	✓	
IONIS-MAPT$_{Rx}$ (BIIB080)	Phase 2	Alzheimer's disease		•
ION717 (PRNP)	Phase 1/2	Prion disease		•
TECHNOLOGY ADVANCEMENTS			**H1**	**H2**
SMA	Advance follow-on program		✓	
Muscle LICA	Advance into preclinical development (IND-supporting)			✓
MsPA Backbone	Advance into preclinical development (IND-supporting)			✓

● Wholly owned ● Partnered
✓ Achieved • Expected

1. Timing expectations are based on current assumptions and are subject to change.

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Q3 2022 Financial Performance

Beth Hougen
Chief Financial Officer

Q3:2022 YTD Financial Results

On Track to Achieve 2022 P&L Guidance; Increased Cash Guidance to $2 Billion

$435 million in revenue
~20% increase Y-o-Y
Generated from numerous diverse sources

$562 million in operating expenses*
Investments in advancing our medicines, go-to-market activities and technology

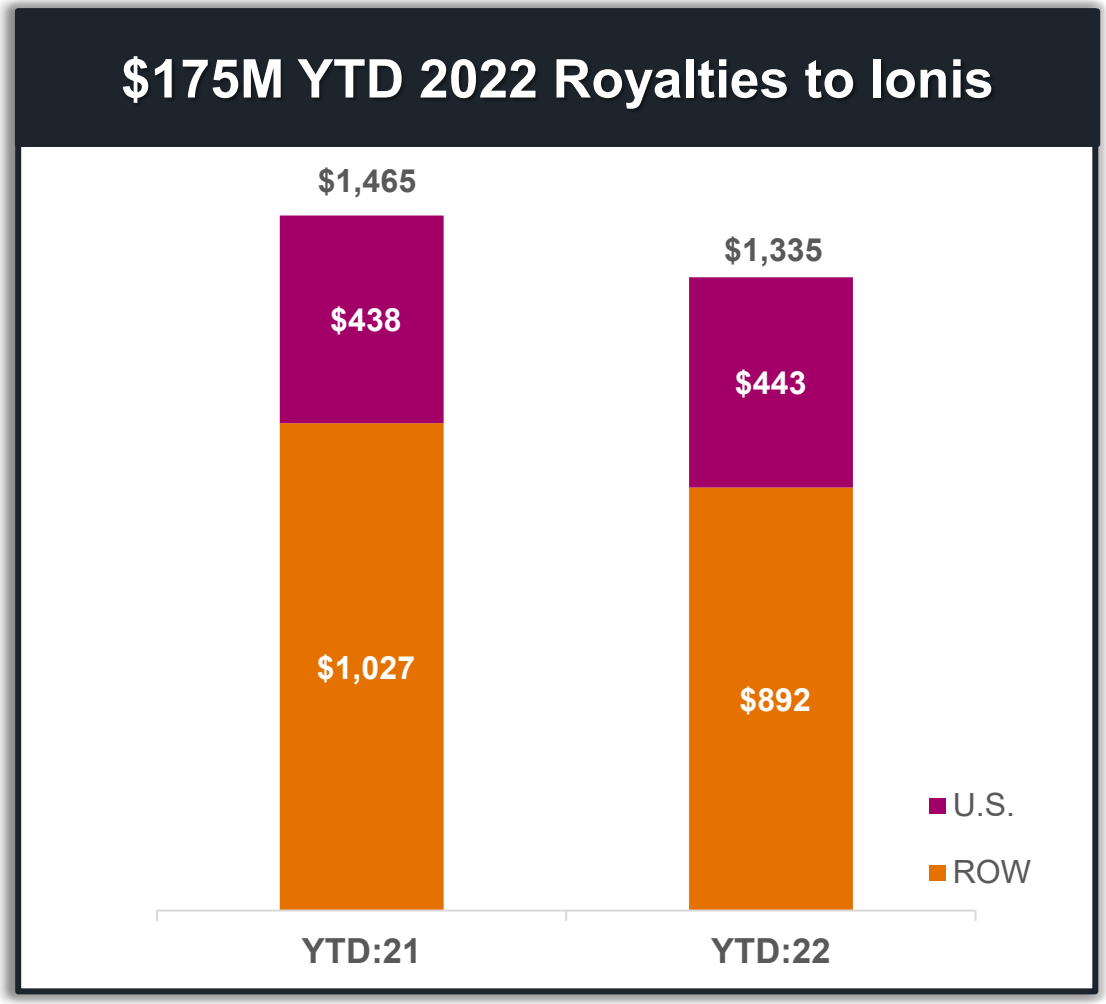
$142 million net loss*

$2 billion of cash
Substantial financial resources to bring transformational medicines to the market

*Non-GAAP – please see reconciliation to GAAP in Q3'22 press release

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Global Leader for the Treatment of SMA



- **$1.3B sales in 2022 YTD with $175M in royalties to Ionis**
  - **U.S.**: essentially flat Y-o-Y; stabilization
  - **ROW**: 13% Y-o-Y decrease; impacted by decreased pricing, foreign currency exchange and competition
- **$431M sales in Q3 QTD with $62M in royalties to Ionis**
  - **U.S. & ROW:** flat compared to Q2'22
- **Life cycle management program supporting SPINRAZA's potential for future growth**
  - Ongoing **ASCEND[1], RESPOND[2] and DEVOTE[3]** studies aim to address remaining unmet need and inform therapy decisions for the SMA community
  - Future of SMA franchise includes **SPINRAZA follow-on,** ION306

Source: Biogen Q3 2022 Financial Results and Business Update; 1. ASCEND: clinicaltrials.gov/NCT05067790; 2. RESPOND: clinicaltrials.gov/NCT04488133; 3. DEVOTE: clinicaltrials.gov/NCT04089566

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Q3:2022 YTD Financial Results

On Track to Achieve 2022 P&L Guidance; Increased Cash Guidance to $2 Billion

$435M **Revenue**

Commercial Revenue: $223M

- SPINRAZA comprised largest component

R&D Revenue: $212M

- Generated from several partners for advancing numerous programs

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$562M **Operating Expenses***

R&D Expenses*: $470M

- Increased Y-o-Y from advancing 6 Phase 3 studies

SG&A Expenses*: $83M

- Reflects Akcea integration & Sobi savings
- Increased spend on go-to-market activities

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2 **Real Estate Transactions**

New Manufacturing Facility

- Expands our capacity to bring our medicines to the market and expand into new chemistries

Sale-Leaseback Transaction

- Unlocked $240M, plus funding to expand R&D campus

*Non-GAAP – please see reconciliation to GAAP in Q3'22 press release

On Track to Achieve 2022 P&L Guidance

Increased Cash Guidance Reflects Sale-Leaseback Transaction

Revenue	Operating Expenses	Net Loss	Cash
>$575 million	$825-$850 million*	<$275 million*	~$2.0 billion
			Prior: $1.7 billion

Reflects investments in our strategic priorities:

- **Building the Ionis commercial pipeline**
- **Delivering an abundance of new transformational medicines to the market**
- **Expanding and diversifying technology**

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*Non-GAAP – please see reconciliation to GAAP in Q3'22 press release

Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

Well Positioned for Accelerated Growth

Building the Ionis **Commercial Pipeline**

Delivering an Abundance of New Medicines to the **Market**

Expanding and **Diversifying** our Technology

Q&A

Brett Monia, Ph.D.
Chief Executive Officer

IONIS®

A Force for Life