Q2:22 Financial Results and Business Update

August 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 in H1 2022[1]

Next Potential Marketed Medicines

- Eplontersen: Positive Ph 3 NEURO-TTRansform results
  - On track to file NDA in H2:22
- Tofersen: NDA under priority review
  - PDUFA date January 25, 2023

Advancing & Expanding Late-Stage Pipeline

- 2 Ph 3 studies achieved full enrollment
- 8 positive late- and mid-stage data readouts
- 2 medicines advancing to Ph 3, expected to expand Ph 3 pipeline to at least 8 medicines for 10 indications

Financial Strength

- On track to achieve our 2022 financial guidance
- $2B in cash provides the resources to bring transformational medicines to the market

Positioned for Substantial Growth

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

Q2 2022 Financial Performance

Beth Hougen
Chief Financial Officer

H1 2022 Financial Results

On Track to Achieve 2022 Financial Guidance

$276 million in revenue
Generated from numerous diverse sources

$368 million in operating expenses*
Investments in advancing our medicines, go-to-market activities and technology

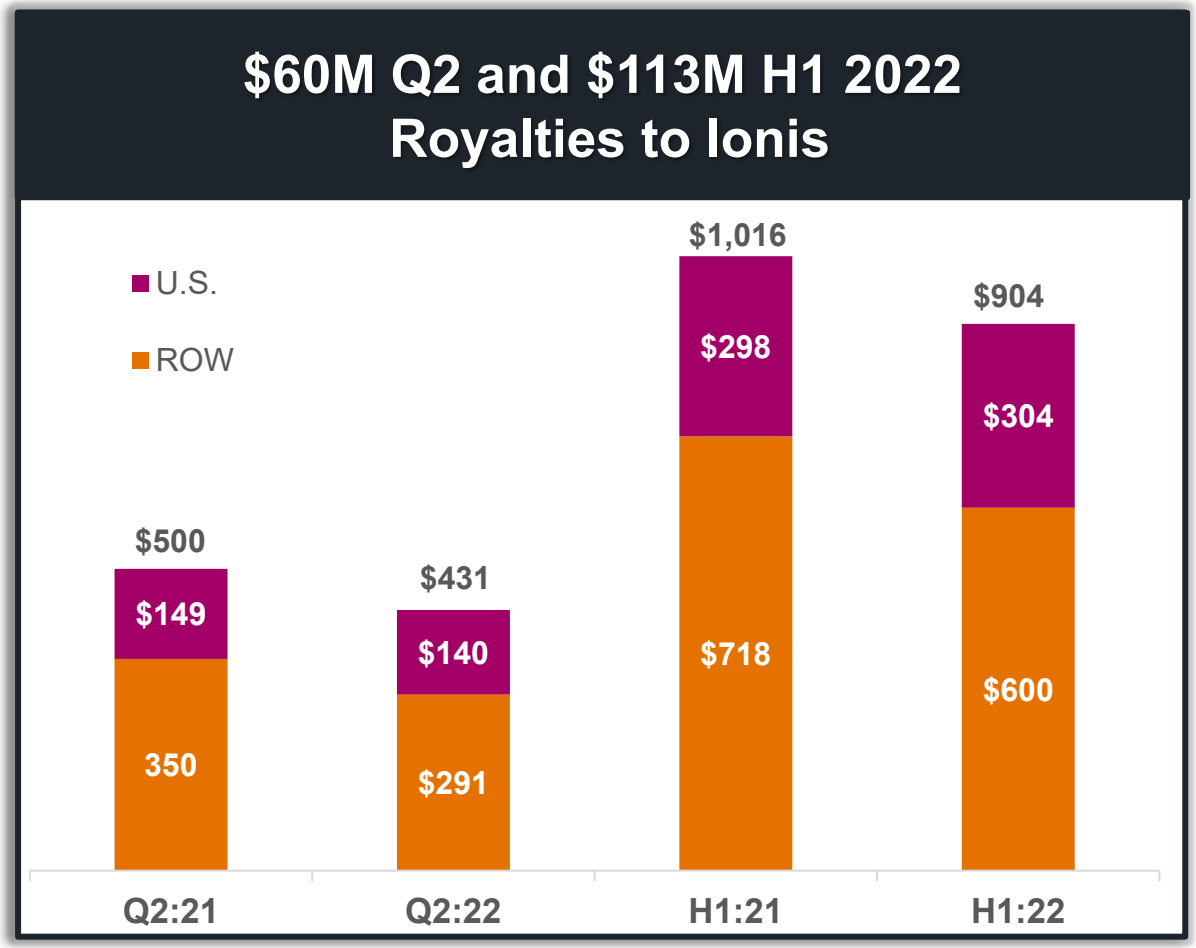
$119 million net loss*

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

*Non-GAAP – please see reconciliation to GAAP in Q2'22 press release

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Global Leader for the Treatment of SMA



- **$904M sales in H1 2022 with $113M in royalties to Ionis**
  - **U.S**: 2% Y-o-Y increase; stabilization; fewer discontinuations
  - **ROW**: 16% Y-o-Y decrease; impacted by competition
- **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
    - New supporting data presented from **RESPOND[2]** and **DEVOTE[3]**
  - Future of SMA franchise includes **SPINRAZA follow-on,** ION306

Source: Biogen Q2 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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H1 2022 Financial Results

On Track to Achieve 2022 Financial Guidance

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On Track to Achieve 2022 Financial Guidance

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

Reflects investments in our strategic priorities:

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

*Non-GAAP – please see reconciliation to GAAP in Q2'22 press release

Pipeline Performance

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

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

ATTRv Polyneuropathy

Positive Phase 3 Data

On track to file NDA in U.S. in H2:22

- Met co-primary and key secondary endpoints
- Demonstrated highly statistically significant and clinically meaningful improvements in neuropathy impairment and quality of life

ATTR Cardiomyopathy

Enrollment underway

Data expected H1:2025

- Largest and longest study in patients with ATTR cardiomyopathy
- Progressing well

ATTR Amyloidosis

Underway

- Additional profile-enhancing studies in patients with ATTRv-PN and ATTR-CM to bolster the eplontersen data evidence package

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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
- Our next potential Phase 3 data readout

Severe Hypertriglyceridemia

CORE
a hypertriglyceridemia study

Data expected 2024

- SHTG Phase 3 CORE study to address much larger indication is progressing well

CORE2
a hypertriglyceridemia study

Data expected 2024

- Confirmatory pivotal study on track to start later this year

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

Donidalorsen Phase 3 Program Designed to Support Approval as an HAE Prophylactic Treatment[1]

Hereditary Angioedema Prophylaxis

Data expected 2024

- Phase 3 study on track
- Longer-term Phase 2 OLE data planned for H2:22

Data expected 2024

- Open to HAE patients previously treated with other prophylactic therapies

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

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

Tofersen to Treat SOD-1 ALS

New 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
- Demonstrated a safety profile supportive of continued treatment

NDA under Priority Review

PDUFA Date: January 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

Industry Leading Cardiovascular Franchise

Addressing Major Cardiovascular Disease Risk Factors

		MID-STAGE (Phase 2-Phase 2b)	LATE-STAGE (Phase 3)
Olezarsen (APOCIII)	FCS		●
Eplontersen	ATTR cardiomyopathy		●
Olezarsen (APOCIII)	SHTG		●
Pelacarsen	Lp(a) CVD		●
ION449 (PCSK9)	CVD	●	
Fesomersen (FXI)	Clotting disorders	●	
IONIS-AGT-L_{Rx}	Treatment-resistant hypertension	●	
ION904		●	

7 Medicines in mid- and late-stage development

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[1]

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

Cardiovascular Neurology Specialty Rare

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)		✓
IONIS-AGT-L$_{Rx}$	Phase 2b	Treatment-resistant hypertension (TRH)		•
Donidalorsen (PKK)	Phase 2 OLE	HAE		•
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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Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

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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