Q1:22 Financial Results and Business Update

May 4, 2022

Nasdaq: IONS

On Today's Earnings Call

Brett Monia, Ph.D.
Chief Executive Officer

Beth Hougen
Chief Financial Officer

Eugene Schneider, M.D.
Executive Vice President,
Chief Clinical Development Officer

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Executive Vice President, Research

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Executive Vice President,
Chief Product Strategy and Operations Officer

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, which is on file with the SEC. 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

IONIS

First Quarter Progress

Near-Term Commercial Opportunities

- Advancing eplontersen, olezarsen and donidalorsen
- Expecting eplontersen Ph 3 NEURO-TTRansform data mid-year; NDA planned for 2H:22
- Increased CARDIO-TTRansform study size & duration with aim to generate even more robust data to compete in growing and dynamic market

Rich Mid- & Late-Stage Pipeline

- Reported positive Ph 2b ION449 (PCSK9) data
- Achieved AGT-L_{Rx} Ph 2b study full enrollment, data expected 2H:22
- Expecting Ph 2b fesomersen, bepirovirsen, & cimdelirsen data 2H:22

Financial Strength

- Well capitalized and on track to achieve our 2022 financial guidance

Positioned for Substantial Future Growth

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Q1 2022 Financial Performance

Beth Hougen
Chief Financial Officer

IONIS

Q1 2022 Financial Results

On Track to Achieve 2022 Financial Guidance

$142 million in revenue

Includes new eplontersen joint development revenue

$39 million net loss*

$173 million in operating expenses*

Investments in advancing our medicines, go-to-market activities and our technology

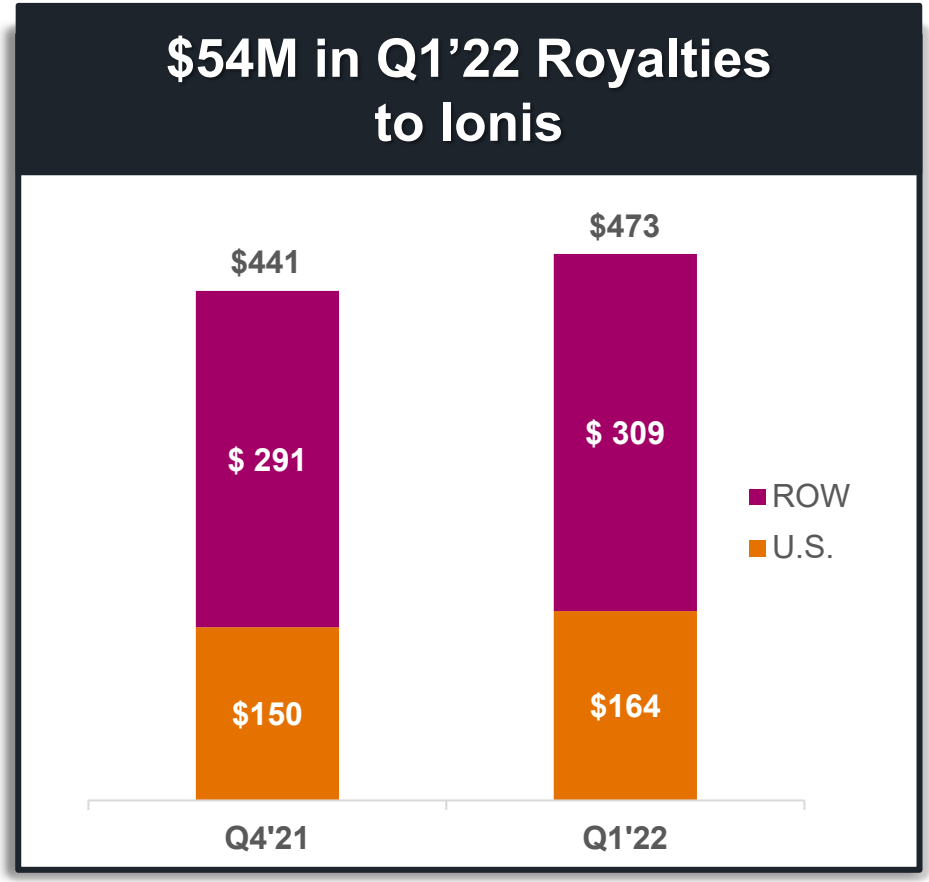
$2.1 billion of cash

Well capitalized with resources to fund planned investments

*Non-GAAP – please see reconciliation to GAAP in Q1'22 press release

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Global Leader for the Treatment of SMA: $473M in Q1 2022 Sales



- **>7% increase SPINRAZA sales quarter-over-quarter**
  - **U.S**: 9% Q-o-Q increase; new patient starts reached a two-year high
  - **ROW**: 6% Q-o-Q increase; strong initial uptake in China in SPINRAZA's first full quarter on the market
- **Biogen continues to expand the body of evidence supporting SPINRAZA's proven profile in SMA patients of all ages:**
  - New data presented from the **NURTURE**[1] presymptomatic study and updates from the advancing **ASCEND**[2] and **RESPOND**[3] studies in patients previously treated with competitive products
  - **DEVOTE**[4] study of higher-dose SPINRAZA in SMA patients of all ages continued to advance

Source: Biogen Q1 2022 Financial Results and Business Update; 1. NURTURE: https://clinicaltrials.gov/ct2/show/NCT02386553 2. ASCEND: clinicaltrials.gov/NCT05067790; 3. RESPOND: clinicaltrials.gov/NCT04488133; 4. DEVOTE: clinicaltrials.gov/NCT04089566

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Q1 2022 Financial Results

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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:

- **Advancing our near-term commercial opportunities**
- **Building our Ionis owned pipeline**
- **Expanding and diversifying our technology**

*Non-GAAP – please see reconciliation to GAAP in Q1'22 press release

Pipeline Performance

Eugene Schneider, M.D.
Executive Vice President, Chief Clinical Development Officer

CARDIO-TTRansform

Phase 3 Study in Patients with ATTR Cardiomyopathy

DESIGN

A global, randomized, double-blind, placebo-controlled study in up to ~1,000 patients with hereditary or wild-type TTR amyloid cardiomyopathy

MRI sub-study to understand eplontersen impact on cardiac structure and function

PRIMARY ENDPOINT

Cardiovascular death & frequency of cardiovascular clinical events at Week 140 (~32 months)

PROTOCOL AMENDMENT (April 2022)

Increased enrollment to ~1,000 patients from 750 and duration to 140 weeks from 120 weeks

On track for data in 1H:2025[1]

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

Key 2022 Pipeline Events[1]

REGULATORY FILINGS			H1	H2
Eplontersen (TTR)	ATTRv polyneuropathy	NDA filing		●
DATA READOUTS			**H1**	**H2**
Tominersen (HTT)	Phase 3 post hoc	Huntington's disease	✓	
Donidalorsen (PKK)	Phase 2	Hereditary angioedema (HAE)	✓	
ION449 (PCSK9)	Phase 2b	Cardiovascular disease (CVD)	✓	
IONIS-C9$_{Rx}$ (BIIB078)	Phase 1/2	C9-ALS	✓	
Tofersen	Phase 3 OLE	SOD1-ALS	●	
Eplontersen (TTR)	Phase 3	ATTRv polyneuropathy	●	
IONIS-AGT-L$_{Rx}$	Phase 2b	Treatment-resistant hypertension (TRH)		●
Fesomersen (FXI)	Phase 2b	Thrombosis		●
Bepirovirsen (HBV)	Phase 2b	Hepatitis B virus (HBV) infection		●
Donidalorsen (PKK)	Phase 2 OLE	HAE		●
Cimdelirsen (GHR)	Phase 2	Acromegaly (monotherapy)		●
STUDY INITIATIONS			**H1**	**H2**
Sapablursen (TMPRSS6)	Phase 2	Polycythemia vera	✓	
IONIS-MAPT$_{Rx}$ (BIIB080)	Phase 2	Alzheimer's disease		●
ION904 (AGT)	Phase 2	Uncontrolled hypertension (HTN)		●
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)			●

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

● Wholly owned ● Partnered ✓ Achieved ● Expected

Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

IONIS

Well Positioned for Accelerated Growth

Building the Ionis **Commercial Pipeline**

Expanding and **Diversifying** our Technology

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

Q&A

Brett Monia, Ph.D.
Chief Executive Officer

IONIS®

A Force for Life