



FY 2021 Financial Results and Business Update

February 24, 2022

Nasdaq: IONS

On Today's Earnings Call



Brett Monia, Ph.D.
Chief Executive Officer



Beth Hougen
Chief Financial Officer



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



Eric Swayze, Ph.D.
Executive Vice President, Research



Onaiza Cadoret
*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, 2020 and our most recent Form 10-Q quarterly filing, which are 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.

Ionis Pharmaceuticals® is a registered trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics® is a registered trademark of Akcea Therapeutics, Inc. TEGSEDI® is a trademark of Akcea Therapeutics, Inc. WAYLIVRA® is a registered trademark of Akcea Therapeutics, Inc. SPINRAZA® is a registered trademark of Biogen.

Introduction



Brett Monia, Ph.D.
Chief Executive Officer

Executing on a Clear Vision to Become a Leading Fully Integrated Biotechnology Company

Rich Mid- & Late-Stage Pipeline

- Focused on our 3 near-term commercial opportunities
- Expanded and advanced our leading cardiovascular and neurological disease franchises

Technology Leadership


- Significantly advanced our technology to add value for our future medicines

Financial Strength

- Substantially exceeded our 2021 financial guidance

**Positioned
for
Substantial
Future
Growth**

FY 2021 Financial Performance & FY 2022 Financial Guidance



Beth Hougen
Chief Financial Officer

2021 Financial Results

Significantly Exceeded our 2021 Financial Guidance

\$810 million in revenue

Guidance: >\$600 million

\$116 million in net income*

Guidance: <\$110 million net loss*

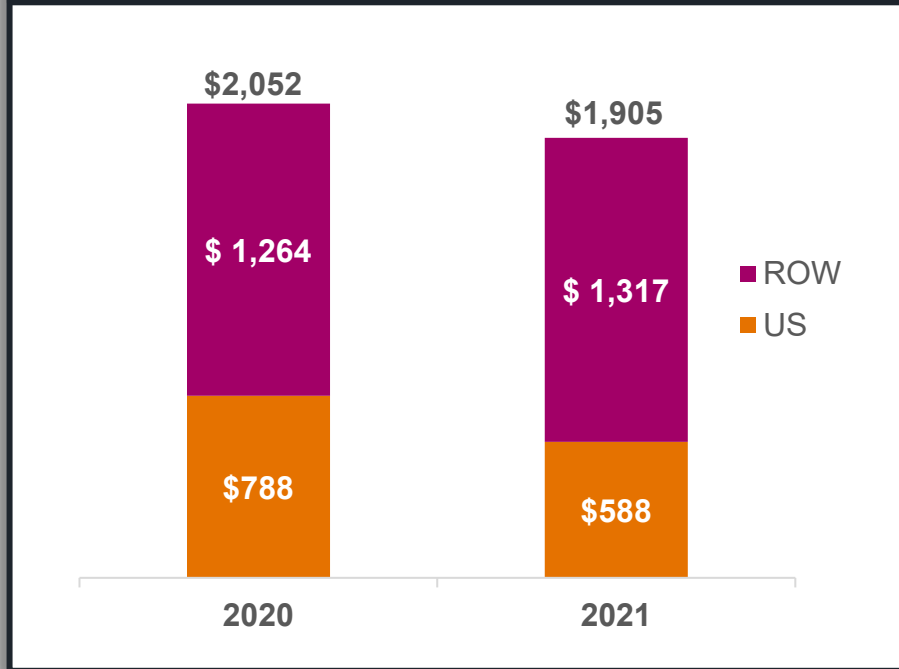
\$695 million in operating expenses*

Guidance: \$710-\$750 million*

\$2.1 billion of cash

Global Leader for the Treatment of SMA: \$1.9B in FY 2021 Sales

\$268M in FY:21 Royalties to Ionis



Source: Biogen Q4 2021 Financial Results and Business Update; 1. Includes patients from post-marketing, EAP and clinical settings; 2. As of December 31, 2021; 3. ASCEND: clinicaltrials.gov/NCT05067790; 4. DEVOTE: clinicaltrials.gov/NCT04089566; 5. RESPOND: clinicaltrials.gov/NCT04488133

- >11,000 patients on SPINRAZA worldwide^{1,2}
- Biogen continued to expand upon SPINRAZA's competitive profile through ongoing studies:
 - **ASCEND:** evaluating an investigational higher dose of SPINRAZA in later-onset SMA patients previously treated with risdiplam³
 - **DEVOTE:** evaluating an investigational higher dose of SPINRAZA in infants, children and adult SMA patients⁴
 - **RESPOND:** evaluating SPINRAZA in SMA patients with a suboptimal response to gene therapy⁵

2021 Financial Results

Significantly Exceeded our 2021 Financial Guidance

\$810 million in revenue

Numerous diverse sources

\$116 million in net income*

Continued financial strength

\$695 million in operating expenses*

Investments in advancing our medicines and our technology

\$2.1 billion of cash

Enabling accelerating investments in 2022

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

Overview of Eplontersen Collaboration Cost-Sharing Impact to Our Financial Statements

Collaboration Activities	Financial Statement Line	Financial Impact
Phase 3 development: Ionis leads & conducts 	R&D Revenue Development Expenses R&D expenses 	55% of Ionis' Phase 3 development expenses, including internal+external costs & CMC costs 100% of Ionis' Phase 3 development expenses
U.S. medical affairs: Ionis & AZ share responsibilities 	Medical Affairs Expenses R&D expenses 	100% of Ionis' medical affairs expenses, NET OF cost-sharing with AZ (Large majority covered by AZ)
U.S. commercialization: Ionis & AZ share responsibilities	Commercialization Expenses SG&A expenses	100% of Ionis' commercialization expenses, NET OF cost-sharing with AZ (Large majority covered by AZ)

Financial Strength to Drive Substantial Growth

Strong Financial Foundation

- Well capitalized with **>\$2 billion in cash¹**
- **Multiple sources of revenue** with diverse margin profiles

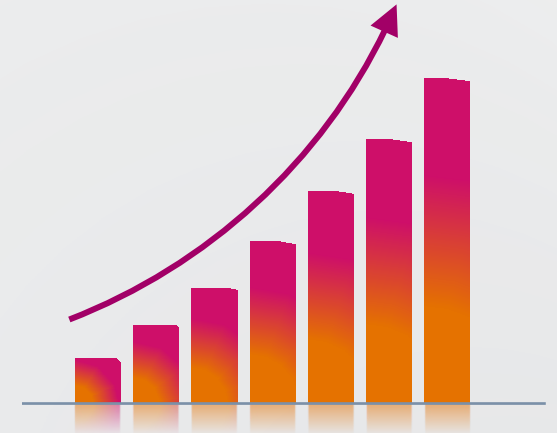


Accelerating Investments

- **Building** the Ionis commercial pipeline
- **Expanding** and diversifying our technology
- **Delivering** new medicines to the market



Substantial Growth



Pipeline Performance



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

Rich Phase 3 Pipeline

6 Medicines for 8 Indications



		Phase 3 Data ¹	Prevalence ²
Tofersen	SOD1-ALS	2021	~1.4K patients in G7 countries
Eplontersen	hATTR polyneuropathy	2022	>40K patients worldwide
Olezarsen	FCS	2023	~3-5K patients worldwide
Eplontersen	ATTR cardiomyopathy	2024	~300-500K 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
Pelacarsen	Lp(a) CVD	2025	>8M patients worldwide

● Cardiovascular ● Neurology ● Specialty Rare

Two Leading Therapeutic Franchises

Cardiovascular



Addressing major cardiovascular disease risk factors

4

Ongoing Phase 3 studies

Eplontersen • Olezarsen • Pelacarsen

8

Medicines in clinical development

- 3 in Phase 2
- 2 in Phase 1

Neurological



Addressing major neurological diseases

3

Ongoing Phase 3 studies

Eplontersen • ION363 (FUS-ALS) • Tofersen

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Medicines in clinical development

- 9 in Phase 2

Emerging Specialty-Rare Pipeline



Key 2022 Pipeline Events¹

REGULATORY FILINGS			H1	H2
Eplontersen	hATTR polyneuropathy			●
DATA READOUTS			H1	H2
Tominersen	Phase 3 post hoc	Huntington’s disease	✓	
Eplontersen	Phase 3	hATTR polyneuropathy		●
ION449 (PCSK9)	Phase 2b	Cardiovascular disease (CVD)	●	
Donidalorsen	Phase 2	Hereditary angioedema (HAE)	●	
IONIS-C9 _{Rx} (BIIB078)	Phase 2	C9-Amyotrophic lateral sclerosis (ALS)	●	
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	Phase 2 OLE	HAE		●
Cimdelirsen (GHR)	Phase 2	Acromegaly (monotherapy)		●
STUDY INITIATIONS			H1	H2
Sapablursen	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. Partnered program events based on partners' most recent publicly available disclosures

Conclusion



Brett Monia, Ph.D.
Chief Executive Officer

Well Positioned for Accelerated Growth

Building the Ionis
**Commercial
Pipeline**

Expanding and
Diversifying our
Technology

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

Delivering Life-changing Medicines



Celebrating Rare Disease Day 2022

Q&A



Brett Monia, Ph.D.
Chief Executive Officer



IONIS[®]

A Force for Life

