



Q2 2021 Financial Results and Business Update

August 4, 2021



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

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

2021: Executing on our Key Strategic Objectives

Goals

Commercialize products of our own

Expand our drug discovery capabilities

12 or more marketed products in 2026

1H 2021 Progress

- Completed integration of Akcea
 - Completed transition of Tegsedi and Waylivra to Sobi
 - Building capabilities to support multiple Ionis launches
-
- Licensed transferrin receptor targeting technology from Bicycle
 - Advanced Genuity collaboration to identify novel targets
 - Broadened internal technology initiatives
-
- Tofersen VALOR study placebo-controlled portion completed
 - Eplontersen NEURO-TTRansform study fully enrolled
 - Pelacarsen Lp(a) HORIZON study 50% enrolled
 - ION363 Phase 3 study for FUS-ALS initiated
 - IONIS-PKK-L_{Rx} positive Phase 2 study reported

Q2 2021 Financial Performance



Beth Hougen
Chief Financial Officer

H1 2021 Financial Results

\$237 million in revenue

Driven by commercial revenues

\$81 million net loss*

Reflects strategy to drive growth



\$132 million

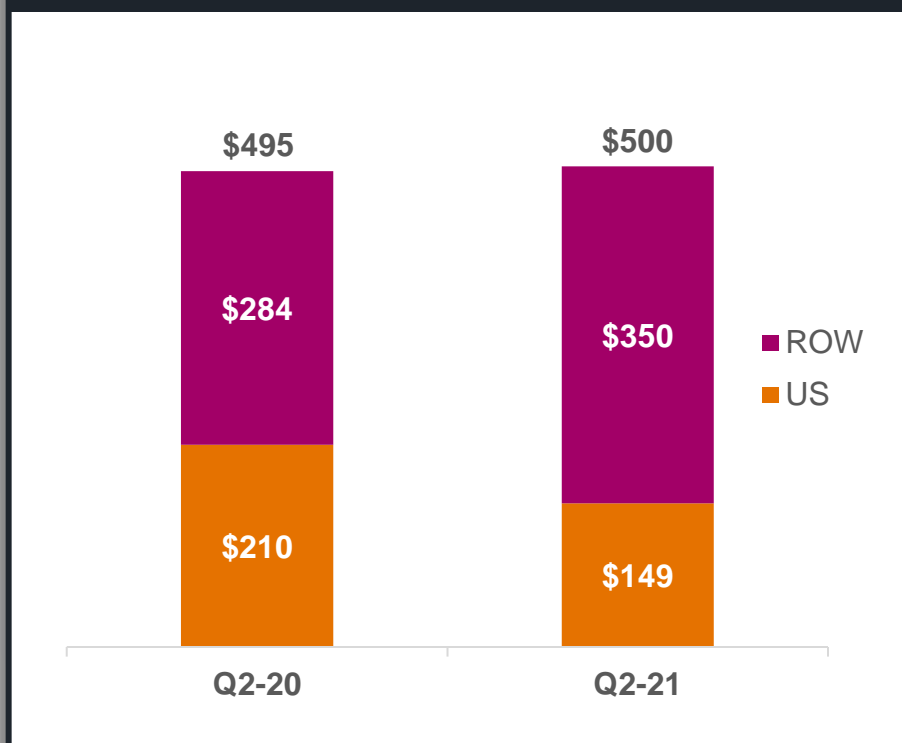
In royalties to Ionis

\$2.1 billion of cash

Financial strength to achieve strategic priorities

Continued Blockbuster Performance with >\$1B in H1 2021 Sales

\$132M in H1:21 Royalties to Ionis



- >11,000 patients on SPINRAZA worldwide^{1,2}
- >60,000 SMA patients in markets where Biogen has a commercial presence³
- Continuing to evaluate SPINRAZA's potential to drive improved outcomes in SMA patients of all ages
- **DEVOTE study:** New data support potential for improved long-term outcomes with SPINRAZA higher-dose SPINRAZA being evaluated in the DEVOTE study⁴
- **RESPOND study:** Phase 4 study evaluating SPINRAZA in SMA patients with suboptimal response to gene therapy⁵

Source: Biogen Q2 2021 Financial Results and Business Update; 1. Includes patients from post-marketing, EAP and clinical settings; 2. As of June 30, 2021; 3. Biogen estimate, data on file; 4. DEVOTE study: clinicaltrials.org/NCT04089566 5. RESPOND study: clinicaltrials.org/NCT04488133

TEGSEDI and WAYLIVRA

Generated \$31 million in revenue in H1 2021

**Completed transition to Sobi for distribution of
TEGSEDI and WAYLIVRA**

**Shifted TEGSEDI and WAYLIVRA revenues from product
sales to distribution fees***

H1 2021 Financial Results

\$237 million in revenue

Driven by commercial revenues

\$81 million net loss*

Reflects strategy to drive growth



\$132 million

In royalties to Ionis

\$2.1 billion of cash

Financial strength to achieve strategic priorities

Revised 2021 Financial Guidance

Reflects Bicycle Therapeutics Transaction

Revenue

>\$600 million

Unchanged

Revised Operating Expenses

\$710-\$750 million*

Prior: \$675-\$725 million

Revised Net Loss

<\$110 million*

Prior: <\$75 million

Reaffirming 2021 Revenue Guidance

Pipeline Performance



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

Pioneering New Markets & Changing Standards of Care

Advancing Phase 3 Pipeline



		Phase 3 Data ¹	Prevalence ²
Tofersen	SOD1-ALS Biogen	2021	~ 1.4K patients in G7 countries
Eplontersen	hATTR polyneuropathy Wholly owned	2022	> 50K patients worldwide
IONIS-APOCIII-L_{Rx}	FCS Wholly owned	2023	~ 3-5K patients worldwide
Pelacarsen	Lp(a) CVDRR Novartis	2024	> 8M patients worldwide
Eplontersen	ATTR cardiomyopathy Wholly owned	2024	> 200K patients worldwide
ION363	FUS-ALS Wholly owned	2024	~ 350 patients in G7 countries
IONIS-APOCIII-L_{Rx}	sHTG Wholly owned	2024	> 3M patients U.S.

Key 2021 Pipeline Events¹

DATA READOUTS			H1	H2
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		•
Vupanorsen	Phase 2b	sHTG/CVD risk reduction		•
PKK-L _{Rx}	Phase 2	Hereditary Angioedema (full data)		•
GHR-L _{Rx}	Phase 2 + OLE	Acromegaly		•
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 2b	Resistant hypertension	✓	
AGT-L _{Rx}	Phase 2	Heart failure with reduced ejection fraction	✓	
ION373	Phase 2/3	Alexander disease	✓	
ION224	Phase 2b	NASH	✓	
APOCIII-L _{Rx}	Phase 3	Second TG indication (sHTG)		•
ION582	Phase 1/2	Angelman syndrome		•

• Wholly owned • Partnered

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

Conclusion



Brett Monia, Ph.D.
Chief Executive Officer

Well Positioned for Accelerated Growth

Advancing
pipeline
&
technology

Pioneering new
markets
&
Changing
standards of care

**Financial
strength**
to invest in areas
with the greatest
**value-driving
potential**

Q&A



Brett Monia, Ph.D.
Chief Executive Officer



IONIS™

IONIS: A FORCE FOR LIFE