



Q1 2021 Financial Results and Business Update

May 5, 2021

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



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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, 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.

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Introduction



Brett Monia, Ph.D.
Chief Executive Officer

2021: Investing for Growth

Commercial

- Investing in high-priority wholly owned programs
- Integrating core capabilities from Akcea commercial organization

Pipeline

- Reported positive PKK-L_{Rx} data supporting Phase 3 advancement
- Expect tofersen Phase 3 data this fall
- Launched FUS-ALS and Alexander disease pivotal studies

Infrastructure

- Increasing R&D and manufacturing capacity to support wholly owned pipeline, commercialization and technology advancements

Q1 2021 Financial Performance



Beth Hougen
Chief Financial Officer

Investing in Our Strategic Priorities to Drive Revenue and Earnings Growth

Advancing our high-priority wholly owned pipeline

Building capabilities to commercialize our wholly owned medicines

Broadening the reach of our technology

Continued Blockbuster Performance with \$521M in Q1 2021 Sales

\$60M in Q1'21 Royalties to Ionis



- >11,000 patients on SPINRAZA worldwide^{1,2}
- >60,000 SMA patients in markets where Biogen has a commercial presence³
- Ongoing commitment to improving outcomes for SMA patients of all ages
- **DEVOTE study:** safety, tolerability of higher-dose SPINRAZA consistent with currently approved dose in open-label safety cohort enabled dosing in pivotal, blinded cohort to begin⁴
- **RESPOND study:** dosing in SMA patients with suboptimal response to gene therapy underway⁵

Source: Biogen Q1 2021 Financial Results and Business Update; 1. Includes patients from post-marketing, EAP and clinical settings; 2. As of March 31, 2021; 3. Biogen estimate, data on file; 4. DEVOTE study: clinicaltrials.org/NCT04089566 5. RESPOND study: clinicaltrials.org/NCT04488133

TEGSEDI and WAYLIVRA

Generated \$20 million in combined revenue in Q1 2021

**Transition to distribution model complete in Europe,
underway in North America**

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

Q1 2021 Financial Results

\$112 million in revenue

Driven by commercial revenues

\$45 million net loss*

Reflects strategy to drive growth



\$60 million

In royalties to Ionis

\$1.8 billion of cash

Financial strength to achieve strategic priorities

On Track to Achieve 2021 Financial Guidance

Revenue

>\$600 million

Operating Expenses

\$675-\$725 million*

Net Loss

<\$75 million*

Well Capitalized to Support Next Phase of Growth

Issued \$630M
of convertible
notes at 0%
interest:

Fund large capital improvement project to expand our manufacturing and R&D capacity

Refinance \$310 million of 1% convertible notes

Significantly reduces interest expense while keeping potential future dilution nearly flat

Pipeline Performance



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

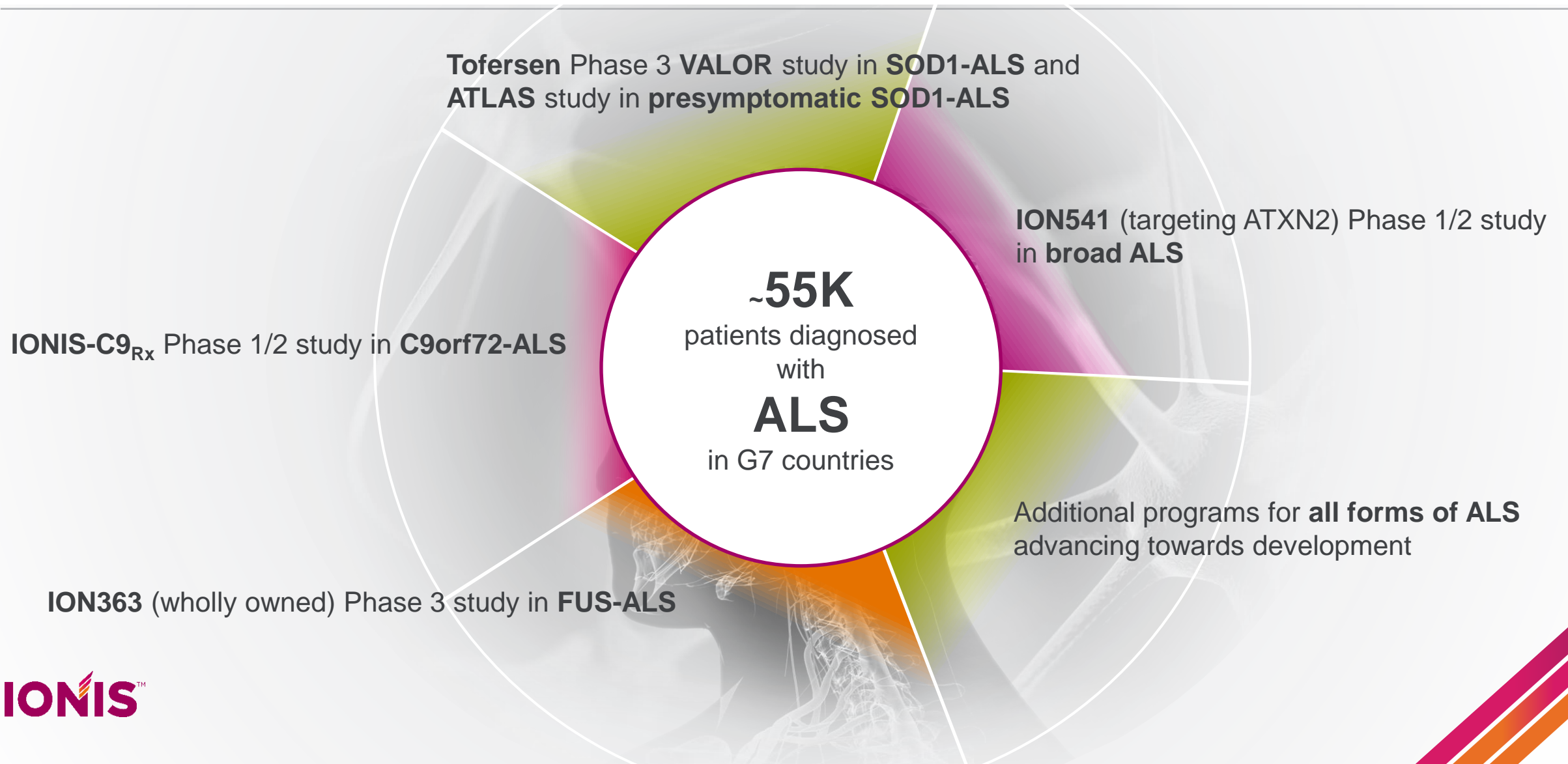
Key 2021 Pipeline Events

DATA READOUTS ¹			H1	H2
PKK-L _{Rx}	Phase 2	Hereditary Angioedema (top-line data)	✓	
AGT-L _{Rx}	Phase 2	Hypertension	✓	
Tominersen ²	Phase 3	Huntington's disease	✓	
ENAC-2.5 _{Rx}	Phase 2	Cystic Fibrosis	•	
GHR-L _{Rx}	Phase 2 + OLE	Acromegaly		•
MAPT _{Rx}	Phase 1/2	Alzheimer's Disease		•
PKK-L _{Rx}	Phase 2	Hereditary Angioedema (full data)		•
Vupanorsen	Phase 2b	Dyslipidemia		•
Tofersen	VALOR Phase 3	SOD1-ALS		•
KEY STUDY INITIATIONS ¹			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	Alexander disease	✓	
ION224	Phase 2b	NASH	•	
APOCIII-L _{Rx}	Phase 3	Second TG indication (sHTG)		•

1. Timing of partnered program catalysts based on partners' most recent publicly available disclosures
2. Dosing stopped in Phase 3 GENERATION HD1 Study, paused in GEN-EXTEND OLE study. GEN-PEAK and Roche HD Natural History study continuing

We Are Committed to Treating All Forms of ALS

Tofersen Phase 3 data readout expected fall 2021



Conclusion



Brett Monia, Ph.D.
Chief Executive Officer

Accelerating our Next Stage of Growth

Advancing
pipeline
&
technology

Pioneering new
markets
&
Changing
standards of care

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

**Positioned for 12+ products on the
market in 2026**

Q&A



Brett Monia, Ph.D.
Chief Executive Officer



IONIS™

IONIS: A FORCE FOR LIFE