



Q3 2020 Financial Results and Business Update

November 4, 2020

On Today's Earnings Call



Brett Monia, Ph.D.
Chief Executive Officer



Beth Hougén
Chief Financial Officer



Onaiza Cadoret-Manier
Chief Corp. Development & Commercial Officer



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



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



Kyle Jenne
Chief Commercial Officer, Akcea

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, including the business of Akcea Therapeutics, Inc., Ionis' wholly owned subsidiary. 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, 2019 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 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

Positioned to Achieve our Next Stage of Growth



Moving forward as a **stronger** organization positioned for **accelerated growth**



Building **commercial capabilities** to maximize the value of the **Ionis-owned pipeline**



Advancing our **late- and mid- stage programs**, positioning us for the **next wave of commercial products**



Using our substantial **financial strength** to achieve our goal of **sustained growth**

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Investor Day Coming up on December 7

Q3 2020 Financial Performance



Beth Hougen
Chief Financial Officer

Substantial Financial Strength

Continuing to invest in strategic priorities

**Financial position further strengthened through
Akcea acquisition**

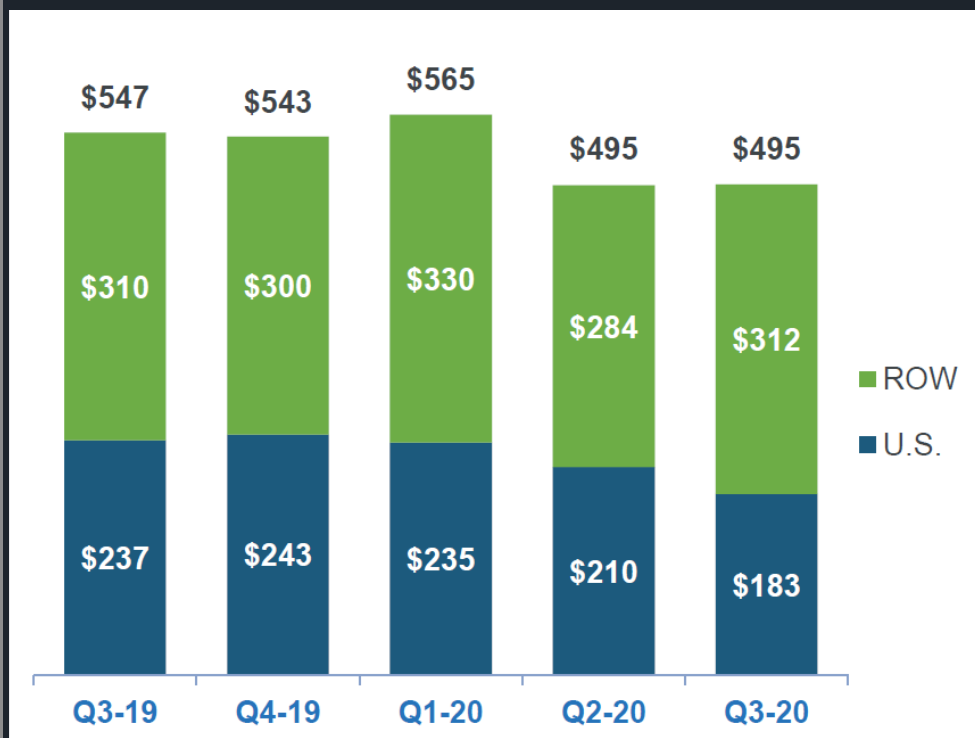
**Strong financial results, including revenue growth,
resulting in operating and net income***

On track for revenue and earnings growth next quarter

On track to achieve our 2020 financial guidance

Continued Blockbuster Performance with >\$1.5B in YTD 2020 Sales

\$74M in Royalties to Ionis¹



- >11,000 patients on SPINRAZA worldwide^{2,3}
 - 20% increase from prior year
- >60,000 SMA patients in markets with Biogen commercial presence⁴
- Approved in over 50 countries and formal reimbursement in over 40 countries
- Continued opportunities for growth

Source: Biogen Q3 2020 Financial Results and Business Update; 1. SPINRAZA royalty tier resets at the beginning of each year; 2. Includes patients from commercial, post-marketing, clinical and EAP settings; 3. As of September 30, 2020; 4. Biogen estimate, data on file

Continued Effort to Expand SPINRAZA Benefit in SMA Patients of all Ages



Logan, living with SMA

DEVOTE study of higher dose SPINRAZA¹

- Potential for even greater efficacy in SMA patients of all ages
- Open-label safety cohort fully enrolled, randomized pivotal cohort to follow

RESPOND study in infants and children²

- Strong rationale to evaluate SPINRAZA benefit in patients previously treated with gene therapy
- Expected to initiate early 2021

NURTURE study in presymptomatic infants³

- Unprecedented survival benefit in patients treated up to ~5 years

SHINE study in toddler to adult patients with SMA⁴

- Motor function stabilization/improvement in patients treated >6 years

TEGSEDI and WAYLIVRA

Continued quarterly growth

TEGSEDI

- Commercially available in 15 countries
- Secured reimbursement in multiple EU markets and Canada
- Expanding EU, Latin America commercial availability¹
- Won Prix Galien USA Award

WAYLIVRA

- Commercially available in 4 countries²
- Finalized pricing in multiple EU countries
- Expanding EU, Latin America commercial availability¹; planning U.S. NDA refiling next year



Q3 2020 Financial Performance

On track to achieve 2020 financial guidance

\$160 million in revenue

Driven by growth in commercial and R&D revenue

\$5 million of net income*

Continued financial strength



\$74 million

Continued blockbuster performance

\$2.3 billion of cash

Estimated \$1.8 billion of pro forma cash following Akcea acquisition

Maintaining our 2020 Financial Guidance

Revenue

>\$700 million

Operating Expenses

~\$650-\$690 million*

Meaningfully profitable*

Ionis' Evolution: Akcea Integration and Commercial Strategy



Onaiza Cadoret-Manier
Chief Corporate Development & Commercial Officer

Akcea Acquisition Strengthens the Business and Accelerates Our Commercial Preparations

- Transitioning into one stronger, more efficient organization
- Accelerates building Ionis' commercial capabilities



Pipeline Performance



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

Key Pipeline Catalysts and Highlights

Neurological

- ✓ ALS (ION541) Phase 1/2 study in nearly all forms of ALS initiated in 2H 2020¹
- ✓ Multiple system atrophy (ION454) Phase 1/2 study initiated in 2H 2020¹
- ✓ Medicines for Lafora and Alexander diseases granted Orphan Drug Designation in the U.S. Ionis-owned
- FUS-ALS (ION363) registrational study initiation expected in 1H 2021 Ionis-owned
- Tofersen Phase 3 data in SOD1-ALS patients expected in 2H 2021¹
- Tofersen pre-symptomatic SOD1-ALS study initiation expected in 2021¹
- C9_{Rx} Phase 1/2 data in C9-ALS patients expected in 2021¹
- Tominersen Phase 1/2 OLE and NHS data expected in 2021²; Phase 3 data & filing expected in 2022²
- TTR-L_{Rx} Phase 3 data in TTR polyneuropathy patients expected in 2023 Ionis-owned

Key Pipeline Catalysts and Highlights

Pulmonary and Allergy

- ✓ PKK-L_{Rx} proof-of-concept results in HAE patients reported in 2H 2020 Ionis-owned
- ✓ PKK-L_{Rx} investigator study in hospitalized COVID-19 patients in Brazil initiated in 2H 2020 Ionis-owned
- ✓ ENAC-2.5_{Rx} pulmonary delivery proof-of-concept data in healthy volunteers reported in 2H 2020 Ionis-owned
 - ENAC-2.5_{Rx} Phase 2 study initiation in COPD patients expected in 2H 2020 Ionis-owned
 - ENAC-2.5_{Rx} Phase 1/2 data in cystic fibrosis patients expected in 1H 2021 Ionis-owned
 - PKK-L_{Rx} Phase 2 data in HAE patients expected in 1H 2021 Ionis-owned

Cardio-renal

- ✓ Vupanorsen Phase 2b study in dyslipidemia patients initiated in 2H 2020, data expected in 2H 2021¹
- PCSK9 (ION449) oral and subQ program update at AHA 2020²
- AGT-L_{Rx} Phase 2 data in hypertension patients expected in 2H 2020 Ionis-owned
- APOCIII-L_{Rx} Phase 3 study initiation in FCS patients expected by YE 2020 Ionis-owned
- TTR-L_{Rx} Phase 3 data in TTR cardiomyopathy patients expected in 2024 Ionis-owned
- Pelacarsen Phase 3 data in Lp(a)-driven CVD patients expected in 2024³

Potential for >10 Marketing Applications through 2025

Should result in a large number of new marketed products, driving significant revenue growth

			ION363 <i>FUS-ALS</i>	IONIS-FXI-L _{Rx} <i>ESRD</i>
			AKCEA-APOCIII-L _{Rx} <i>Severe hypertriglyceridemia</i>	ION541 <i>Sporadic ALS</i>
			ION373 <i>Alexander disease</i>	IONIS-TMPRSS6-L _{Rx} <i>β-thalassemia</i>
			IONIS-GHR-L _{Rx} <i>Acromegaly</i>	IONIS-HBV _{Rx} <i>Hepatitis B virus infection</i>
		AKCEA-APOCIII-L _{Rx} <i>FCS</i>	IONIS-C9 _{Rx} <i>C9-ALS</i>	Vupanorsen <i>Cardiovascular disease</i>
		Tominersen <i>Huntington's disease</i>	IONIS-PKK-L _{Rx} <i>Hereditary angioedema</i>	ION716 <i>Prion diseases</i>
Tofersen <i>SOD1-ALS</i>	AKCEA-TTR-L _{Rx} <i>hATTR polyneuropathy</i>		AKCEA-TTR-L _{Rx} <i>ATTR cardiomyopathy</i>	Pelacarsen <i>Cardiovascular disease</i>

2021

2025 and beyond

Conclusion: 2020 and Beyond



Brett Monia, Ph.D.
Chief Executive Officer

Today, Ionis is Stronger than Ever

3

Marketed products*



6

Phase 3 studies by YE'20

Tominersen
Huntington's disease

Tofersen
SOD1 ALS

AKCEA-TTR-L_{Rx}
ATTR cardiomyopathy

Pelacarsen
Lp(a)-driven CVD

AKCEA-TTR-L_{Rx}
hATTR polyneuropathy

AKCEA-APOCIII-L_{Rx}[†]
FCS

- Financially strong, on track to achieve **2020 financial guidance**
- Stronger, more efficient business following **Akcea acquisition**
- Potential for **>10 marketing applications** through 2025
- Achieving success across the **Phase 3, mid-stage and early pipeline**
- Dedicated employees committed to improving the lives of **patients in need**



*In 1Q 2021, Biogen plans to initiate the Phase 4 RESPOND study of SPINRAZA in patients with suboptimal response to gene therapy clinicaltrials.org/NCT04488133. Biogen is also conducting the DEVOTE study of a higher dose of SPINRAZA clinicaltrials.gov/NCT04089566. † P3 study start by YE 2020

Congratulations to Ionis and Akcea



**2020 Prix Galien USA Award for Best Biotechnology
Product for TEGSEDI**

Q&A



Brett Monia, Ph.D.
Chief Executive Officer



IONIS™

IONIS: A FORCE FOR LIFE