



Q3 and YTD 2019 Financial Results and Highlights

November 6, 2019



On Today's Earnings Call



Stanley Crooke, M.D., Ph.D.
*Chief Executive Officer
and Chairman*



Beth Hougen
Chief Financial Officer



Brett Monia, Ph.D.
Chief Operating 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, including the business of Akcea Therapeutics, Inc., Ionis' majority owned affiliate. 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, 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, 2018 and the 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



Stanley Crooke, M.D., Ph.D.
Chief Executive Officer and Chairman

Investing Broadly and Aggressively in our Business

While Returning Value in the Short- and Long-Term

Substantially increasing 2019 guidance

- Increased guidance driven by strong YTD 2019 financial performance
- On track to deliver fourth year of operating income and third year of net income*

Returning near-term value to shareholders with share repurchase program

Positive momentum building with Akcea

- TEGSEDI and WAYLIVRA launches demonstrating progress
- Strengthened organization is positioned for continuing success

Achieving substantial pipeline and technology success

- Phase 3 programs with AKCEA-APO(a)-L_{Rx} and AKCEA-TTR-L_{Rx} beginning soon
- Pfizer, Bayer and GSK advancing our medicines for broad patient populations
- Biogen initiated Phase 1/2 study of ION859 (LRRK2) in patients with Parkinson's disease

YTD 2019 Financial Performance



Beth Hougen
Chief Financial Officer

Strong YTD 2019 Financial Performance

Investing Broadly in the Business While Returning Value to Shareholders

**On Track
for Third Year of
Net Income***

**~\$630 million in
revenue**

>50% increase
over YTD 2018

\$217 million
of operating income*

\$189 million
of net income*



\$212 million

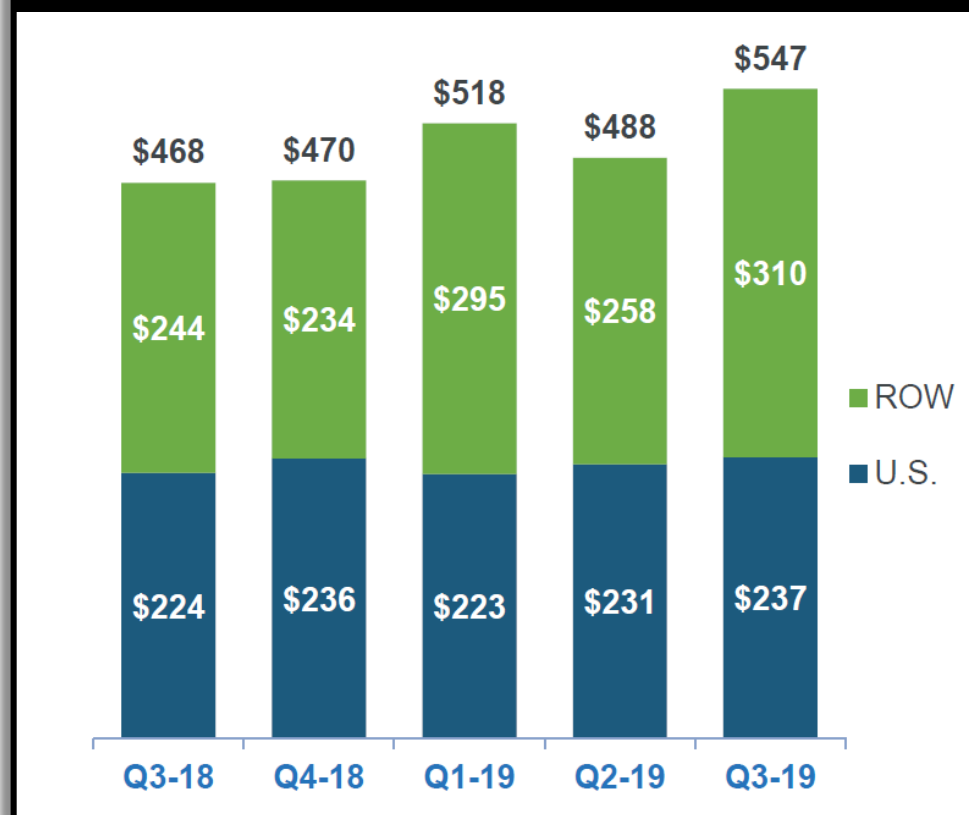
>25% increase
over YTD 2018

\$2.2 billion of cash

Enabling investment in
marketed products, pipeline &
technology while returning
value to shareholders

Continued Blockbuster Performance with over \$1.5 Billion in Global Sales YTD 2019

\$212M in Royalties to Ionis



- **~9,300 patients** now on SPINRAZA therapy worldwide*
 - ~11% increase in patients on therapy worldwide
 - ~8% increase in adult patients in the U.S.**
 - Strong performance outside the U.S. in established markets and key markets in Latin America and Asia Pacific
 - Patients initiated treatment in China
- **Approved in over 50 countries**
- **Formal reimbursement in 40 countries**

TEGSEDI and WAYLIVRA: Two Transformational Medicines Approved for Serious Diseases*

\$29 million in TEGSEDI and WAYLIVRA product sales YTD



- **Launched** in **Sweden, Austria**, and across the **UK**; achieved pricing in **Germany**
- Preparing to **launch** in additional **EU countries**
- **Approved** in **Brazil**; PTC starting **launch activities** in **Latin America** immediately



- **Launched** in **Germany**; preparing to launch in additional **EU countries**
- PTC preparing to **expand** into **Latin America**
- New data and EU experience **supported U.S. & Canadian** regulator discussions



*Commercialized by Akcea Therapeutics

R&D Revenue Remains a Significant and Sustainable Source of Revenue

1

License Fees

2

Amortization of upfront fees

3

Milestone Payments

4

Services provided to partners

Substantially Improved 2019 Financial Guidance Driven by Strong YTD Financial Results

**Total
revenue**

~\$1
billion

Previous: >\$725 million

**Operating
income**

>\$375
million*

Previous: >\$100 million

**Net
income**

>\$300
million*

*Previous:
achieve net income*

**Cash
balance**

~\$2.2
billion

Previous: ~\$2 billion

**Returning Near-Term Shareholder Value:
Board Authorized up to \$125M Share Repurchase**

*Non-GAAP – please see reconciliation to GAAP in Q319 press release; R&D expense and SG&A expense guidance unchanged



Key Pipeline Accomplishments

Brett Monia, Ph.D.
Chief Operating Officer



SPINRAZA is the established foundation-of-care for the treatment of SMA patients of all ages

NURTURE study of presymptomatic infants

- On treatment ~45 months
- Patients continuing to develop similar to healthy counterparts

SHINE OLE study in later-onset SMA

- On treatment up to nearly 6 years
- Patients achieving stabilization or improvement in measures of motor function

Biogen initiating Phase 2/3 DEVOTE study

- Evaluating a higher dose of SPINRAZA w/ fewer loading doses
- Potential to achieve even greater efficacy
- Will enroll SMA patients of all ages including adults

Advancing follow-on medicine for SMA

- Focused on less-frequent dosing (bi-annual or annual)
- Potential to advance into development in 2020



Logan, living with SMA

Key Recent Pipeline Achievements

AKCEA-ANGPTL3-L_{Rx}

- Pfizer licensed for \$250M upfront & milestones up to \$1.3B + tiered double-digit royalties
- Millions of people with cardiovascular and metabolic diseases worldwide

IONIS-FXI-L_{Rx}

- \$10M milestone from Bayer to advance IONIS-FXI-L_{Rx}
- Millions of people with thromboembolic disorders worldwide

HBV_{Rx}/HBV-L_{Rx}

- \$25M from GSK to license HBV program
- More than 200 million people with chronic hepatitis B virus infection worldwide

AKCEA-APO(a)-L_{Rx}

- Novartis' Phase 3 CV outcomes study starting, patient enrollment planned in early 2020
- More than 8 million people with Lp(a)-driven cardiovascular disease worldwide

AKCEA-TTR-L_{Rx}

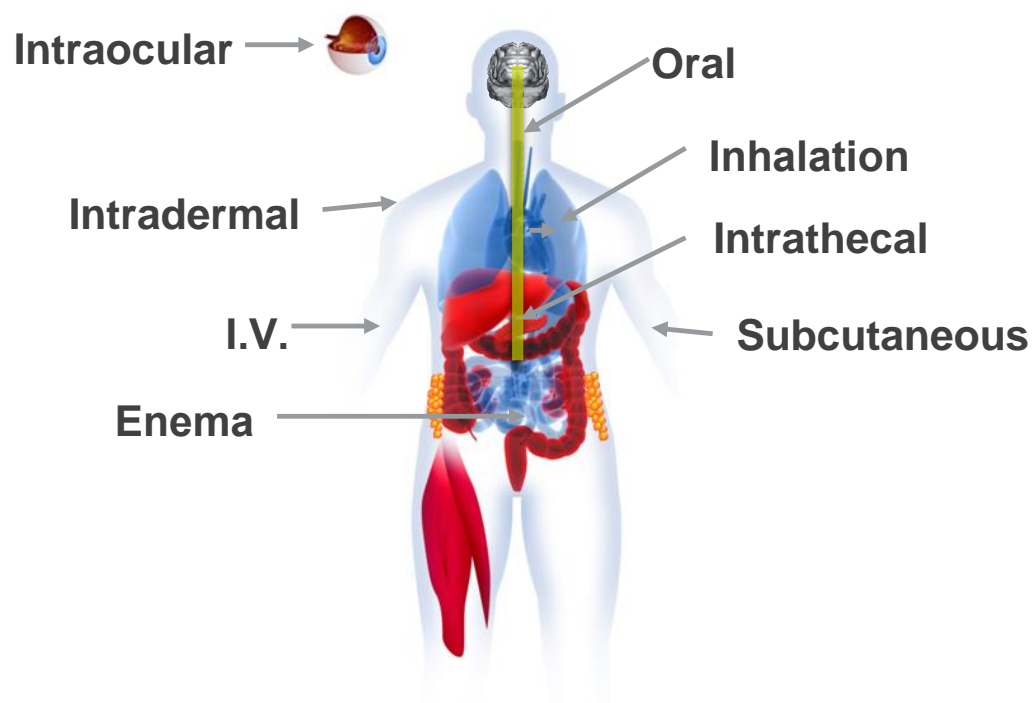
- Phase 3 program in polyneuropathy and cardiomyopathy starting soon
- More than 300K people with ATTR worldwide (>200K with TTR cardiomyopathy)

ION859 (LRRK2_{Rx})

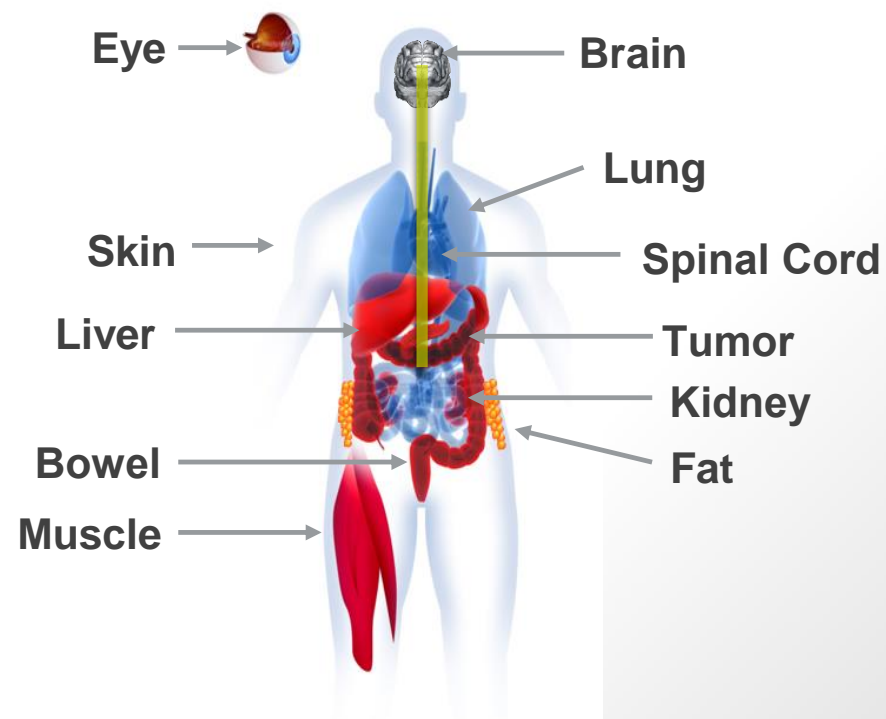
- \$8M from Biogen for initiation of Phase 1/2 study of patients with Parkinson's disease
- Approximately 3 million people with Parkinson's disease worldwide

Methods of Administration and Technology Advances Create Breadth in Our Pipeline Today

ADMINISTERED THROUGH MULTIPLE ROUTES OF DELIVERY



BROAD CLINICAL ACTIVITY IN MULTIPLE TISSUES



**MULTIPLE ROUTES OF DELIVERY,
MULTIPLE TARGET TISSUES**

Delivering Value Today and in the Future

Numerous Upcoming Value Inflection Points

3

Marketed Medicines

✓ SPINRAZA ✓ TEGSEDI ✓ WAYLIVRA

4

Phase 3 Study Starts Planned

✓ IONIS-HTT_{Rx}, ✓ Tofersen

AKCEA-APO(a)-L_{Rx}, AKCEA-TTR-L_{Rx}

6+

Phase 2 Study Readouts Planned

✓ Tofersen ✓ HTT_{Rx} ✓ DGAT2_{Rx} ✓ FXI_{Rx}/FXI-L_{Rx} ✓ HBV_{Rx}/HBV-L_{Rx}

AKCEA-APOCIII-L_{Rx}, AKCEA-ANGPTL3-L_{Rx}
and more



2019 and Beyond

Stanley Crooke, M.D., Ph.D.
Chief Executive Officer and Chairman

Ionis: Creating Patient and Shareholder Value Driven by a Pipeline of Potentially Transformative Medicines

Pioneer of
RNA technology

Novel business model

Culture of **YES**

30 years advancing
technology

Ever-**better**
performance

Greater commercial
opportunities

3 medicines
approved globally

40+ medicines in
development

4 Phase 3
programs underway
by YE **2019**

Q&A



Stanley Crooke, M.D., Ph.D.
Chief Executive Officer and Chairman

A black and white photograph of a family of four is the background for the lower half of the image. A man is in the foreground, smiling broadly with his eyes closed, being embraced from behind by a young girl. Another girl is visible behind her, also smiling. To the right, a woman is smiling and making a peace sign with her hand. The overall mood is joyful and affectionate.

IONIS: A FORCE FOR LIFE