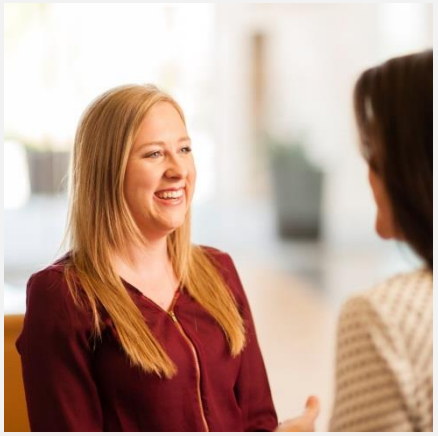


2018 Financial Results and Highlights

February 27, 2019

IONIS™ PHARMACEUTICALS

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

Damien McDevitt, Ph.D.
Chief Business Officer

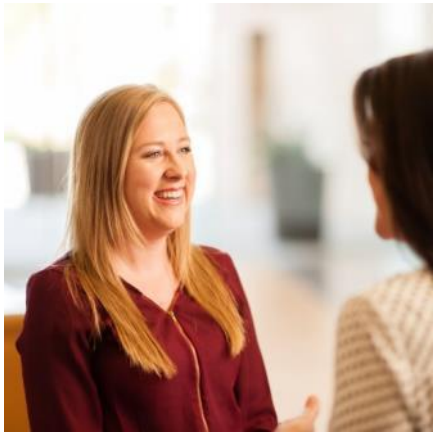
Forward Looking Language Statement

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA, 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 drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. 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, 2017 and the most recent Form 10-Q, 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.

Q4 2018 Highlights

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



Positioned for Continued Strength in 2019

Strongest financial position to date, positioned for growth in every element of the business

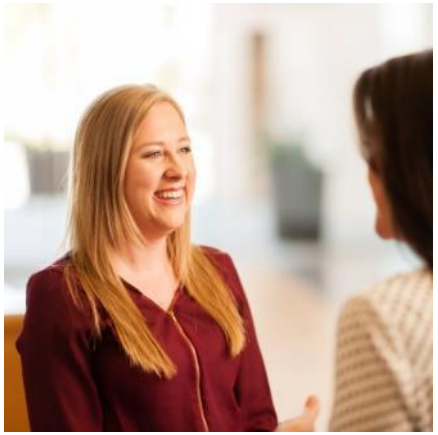
Growth in commercial revenue from SPINRAZA royalties and TEGSEDI product sales

Late-stage pipeline with 4+ medicines expected to be in pivotal studies by year-end

Ionis is in the Strongest Position in 30-year History

2018 Financial Performance

Beth Hougen, Chief Financial Officer



2018 Financials at a Glance

Exceeded 2018 operating income guidance*

$600 million in revenue

7th consecutive year of growth

$70 million in operating income*

3rd consecutive year of operating income*

SPINRAZA® (nusinersen) injection 12 mg/5 mL

$238 million

SPINRAZA royalty revenues more than doubled over 2017

>$2 billion cash

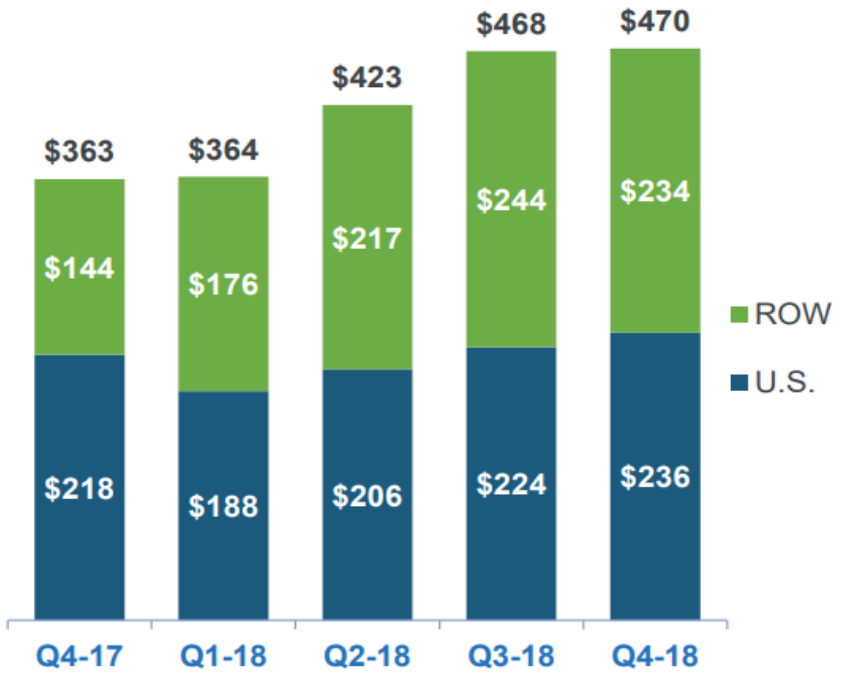
Enabling investment in commercial products and pipeline

*Non-GAAP – please see reconciliation to GAAP in 4Q18 press release

2018 Global SPINRAZA Sales Exceed $1.7 Billion

SPINRAZA Revenues ($M)

2018 Royalties to Ionis of **$238 MILLION**

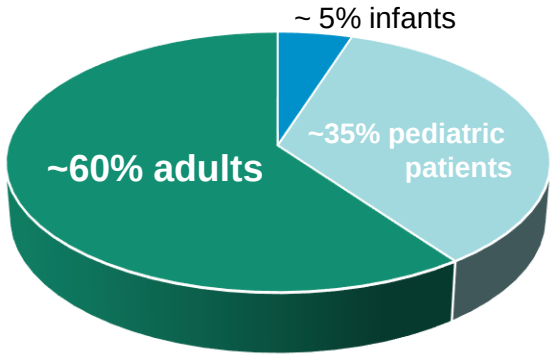


Note: Numbers may not foot due to rounding

2018 Highlights

- 2018 commercial revenue from SPINRAZA royalties more than doubled to $238 million compared to 2017
- > 6,600 patients now on therapy worldwide*
- Biogen continued to increase the number of adult SMA patients on therapy, the largest patient segment
  - > 15% of adult (18+) SMA patients are on therapy in the U.S
- SPINRAZA approved in over 40 countries^
  - Formal reimbursement in place in 30 countries^

SMA Prevalence Assumptions



Source: Biogen Q4 2018 Financial Results and Business Update
Results as of December 31, 2018 unless noted otherwise
**Includes patients in commercial setting, EAP and clinical trials*
^*As of January 25, 2019*

Global TEGSEDI Sales Exceed $2 Million in First Quarter of Launch

- $2.2 million in sales from the U.S. and EU in 4Q 2018
- Positive feedback from patients, physicians and payors
- Under priority review in Brazil through PTC Therapeutics

For safety information about serious side effects, including thrombocytopenia and glomerulonephritis, please see full prescribing information at www.TEGSEDI.com

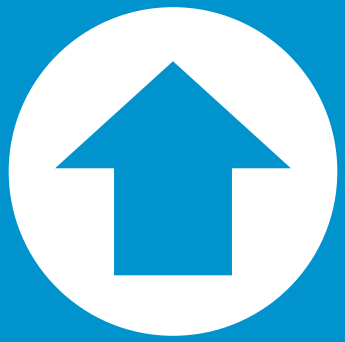
R&D Revenue Remains a Significant and Sustainable Source of Revenue

1. Amortization of upfront fees
+
2. Milestone payments
+
3. License fees
+
4. Services provided to partners

R&D Revenue Funds Large Portion of R&D Expenses*

*Non-GAAP – please see reconciliation to GAAP in 4Q18 press release

Positioned for Continued Growth in 2019 and Beyond

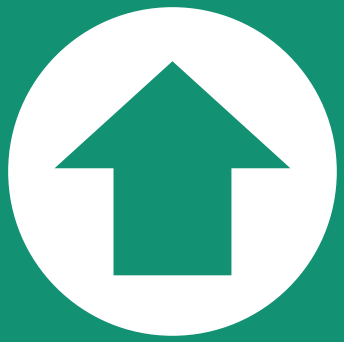


SPINRAZA

Growth in global sales in the mid- to high-teens*

TEGSEDI

Growing TEGSEDI product sales



R&D Revenue

Significant and sustainable source of revenue

Significant Momentum for 2019 and Beyond

*Biogen financial guidance as of January 29, 2019

2019 Financial Guidance: Positioned for Continued Strength

Total revenue

>$725 million

R&D expense ~ $360-390 million*

SG&A expense ~$260-290 million*

Operating income

>$100 million*

Cash balance

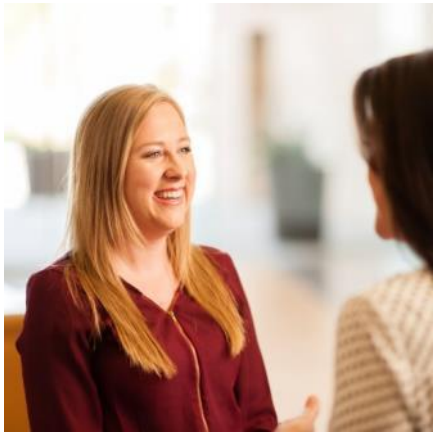
~$2 billion

Profitable at the Bottom Line*

*Non-GAAP – please see reconciliation to GAAP in 4Q18 press release

Key Pipeline Accomplishments

Brett Monia, Ph.D., Chief Operating Officer



Key Recent Achievements

Financial	▪ Exceeded 2018 non-GAAP operating income guidance ▪ Achieved 3rd consecutive year of operating income ▪ Revenue increased by 17% to $600M compared to 2017 ▪ Commercial revenue was > 40% of total revenue compared to < 25% in 2017 ▪ SPINRAZA royalties more than doubled to $238M compared to 2017 ▪ Substantial base of R&D revenue of $345M from numerous partnerships & programs ▪ Ended 2018 with cash and investments of > $2B
SPINRAZA	▪ 2018 global SPINRAZA revenues nearly doubled to $1.7B compared to 2017 ▪ Over 6,600 patients* from over 40 countries on SPINRAZA treatment ▪ U.S. adult SMA patients on treatment increased by 20% compared to Q3 2018
TEGSEDI	▪ Earned revenue of > $2M from TEGSEDI product sales ▪ PTC granted priority review for TEGSEDI in Brazil
Late-Stage Pipeline	▪ Earned $150M when Novartis licensed AKCEA-APO(a)-L_{Rx} ▪ Met with FDA, now finalizing plans for the AKCEA-TTR-L_{Rx} pivotal program ▪ Roche began enrolling patients in the Phase 3 study for IONIS-HTT_{Rx} in HD ▪ Earned $35M when Biogen licensed IONIS-$SOD1_{Rx,}$

*Includes patients from the commercial setting, EAP and clinical trials as of December 31, 2018

Potential Key Upcoming Milestones

Commercial and Regulatory Milestones

- **SPINRAZA:** Continued growth in sales and approval in additional markets
- **TEGSEDI:** Successful global launch
- **TEGSEDI:** Marketing authorization and reimbursement in Brazil
- **WAYLIVRA:** Continue discussions with regulators in the EU

Pivotal Study Initiations

- ✓ **IONIS-HTT$_{Rx}$ (RG6042):** for Huntington's disease
- **AKCEA-APO(a)-L$_{Rx}$ (TQJ23):** for high Lp(a) levels with established risk of CVD
- **AKCEA-TTR-L$_{Rx}$:** for ATTR
- **IONIS-SOD1$_{Rx}$:** for SOD1-related ALS*

Phase 2 Data Readouts

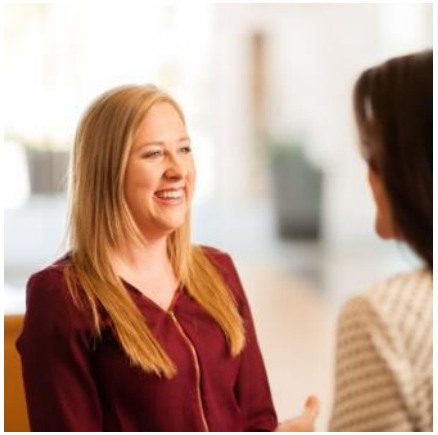
- **AKCEA-TTR-L$_{Rx}$:** for hATTR-PN (healthy subjects & patients)
- **IONIS-SOD1$_{Rx}$:** for SOD1-related ALS (Phase 1/2 data)
- **Danvatirsen:** for head & neck cancer (additional data)
- **IONIS-FXI$_{Rx}$:** for ESRD
- **IONIS-HBV$_{Rx}$**: for HBV
- **IONIS-DGAT2$_{Rx}$:** for fatty liver in T2D patients

Potential for Multiple Near-term Regulatory and Clinical Catalysts

*Biogen plans to add additional cohort to ongoing Phase 1/2 study with potential to support filing for marketing authorization

2019 and Beyond

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



Positioned for Continued Innovation and Value Creation for Patients and Shareholders

Pioneer of **RNA** technology

Novel business model

Culture of **YES**

30 years advancing technology

Ever-better performance

Greater commercial opportunities

2+ commercial medicines

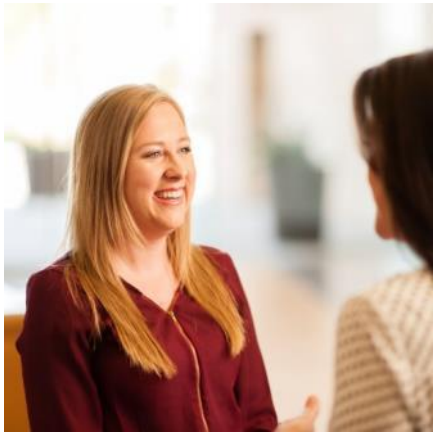
40+ in development

10+ pivotal studies potentially in **2 years**

4+ pivotal studies planned in **2019**

Q&A

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



Please Join us for our upcoming Investor Webcast series coming this Spring and Summer