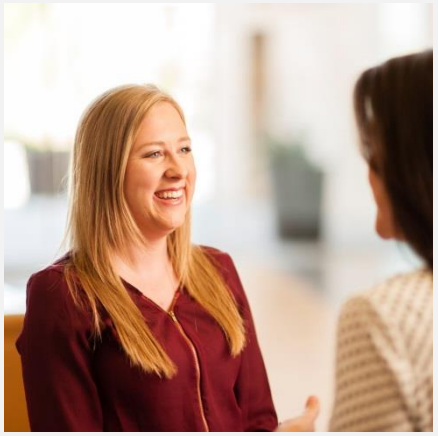


Q3 2018 Financial Results and Highlights

November 6, 2018

IONIS™ PHARMACEUTICALS

On Today's Earnings Call

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

Beth Hougen
Chief Financial Officer

Damien McDevitt, Ph.D.
Chief Business Officer

Brett Monia, Ph.D.
Chief Operating Officer

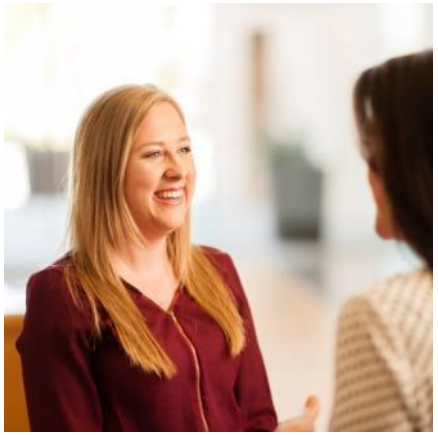
Forward Looking Language Statement

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of SPINRAZA, 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.

Q3 2018 Highlights

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

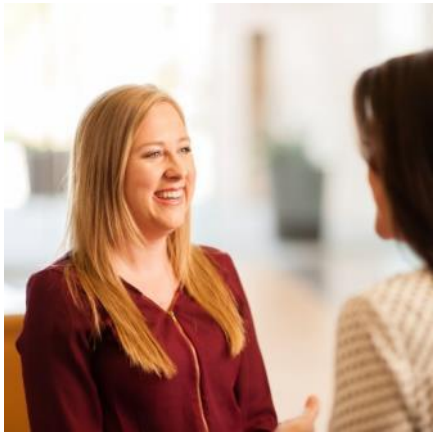


Key Recent Achievements

SPINRAZA	▪ Global SPINRAZA revenues of $1.3 billion in 2018 ▪ New NURTURE data further supports benefit of early diagnosis and treatment in presymptomatic infants ▪ U.S. adult SMA patients on treatment increased by 20% from Q2 2018 ▪ Patients on SPINRAZA treatment increased by ~20% to nearly 6,000 from Q2 2018
TEGSEDI	▪ TEGSEDI approved in the U.S., EU and Canada ▪ Commercial patients in Germany on TEGSEDI ▪ TEGSEDI prescriptions received in the U.S.
WAYLIVRA	▪ Preparing for EU launch assuming approval ▪ Early access program ongoing
Pipeline	▪ Reported positive Phase 2 data for AKCEA-APO(a)-L_{Rx} ▪ Roche expects to initiate a Phase 3 study for IONIS-HTT_{Rx} in HD patients this year ▪ Entered collaboration with Roche for development of IONIS-FB-L_{Rx} ▪ Reported positive Phase 1b/2 data for danvatirsen + durvalumab ▪ Achieved multiple pipeline milestones
Financial	▪ On track to achieve third consecutive year of pro forma operating income ▪ Revenue increased more than 15% compared to YTD 2017 ▪ SPINRAZA royalties increased by ~175% to $168M compared to YTD 2017 ▪ Substantial base of R&D revenue of $226M from numerous partnerships & programs

Financial Performance

Beth Hougen, Chief Financial Officer



Year-To-Date 2018 Financials at a Glance

On track to achieve third consecutive year of operating income in 2018

$408 million in revenue

Nearly three-fold increase in SPINRAZA revenues over 2017

$25 million in operating income*

Driven by a more than 15% increase in revenue over 2017

SPINRAZA® (nusinersen) injection 12 mg/5 mL

$168 million

in royalties

~$2 billion cash

Enabling investment in commercial products and pipeline

*Pro forma – please see reconciliation to GAAP in 3Q18 press release

Positioned for Continued Strength in Q4 2018

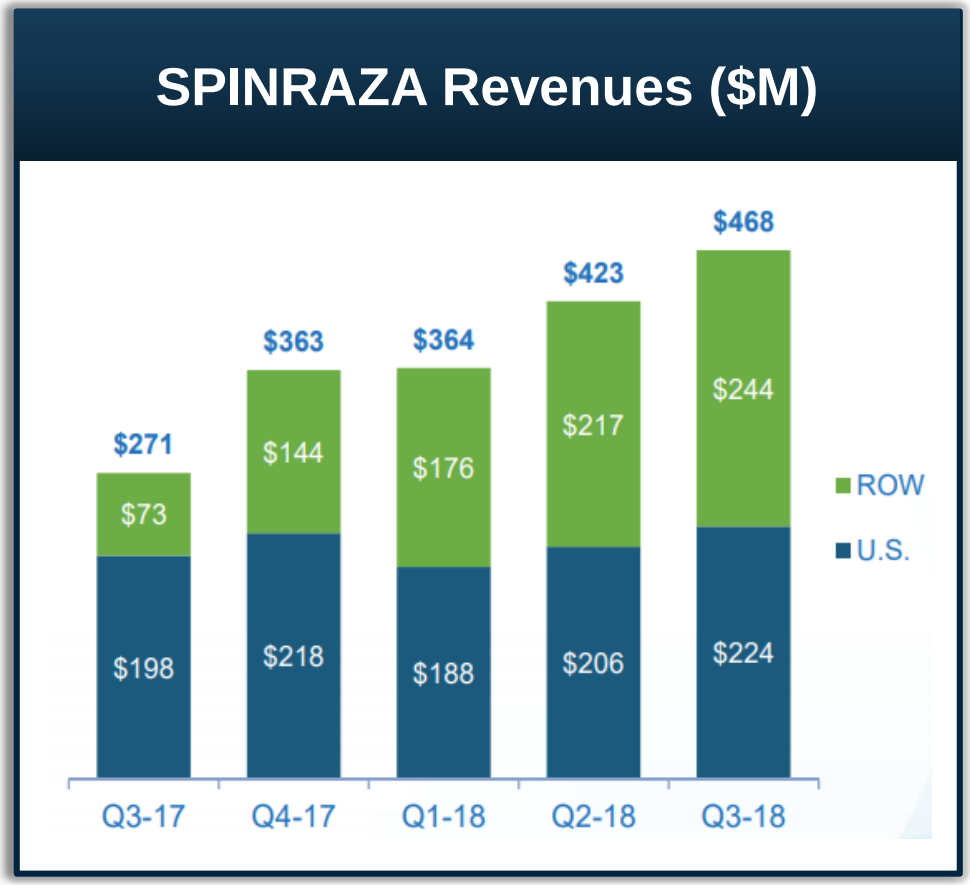
Growth in SPINRAZA sales at highest royalty rate

Addition of TEGSEDI product sales

Amortization of upfront payment from collaboration with Roche

Potential for milestone payments from partnered programs

2018 Global SPINRAZA Sales Exceed $1 Billion

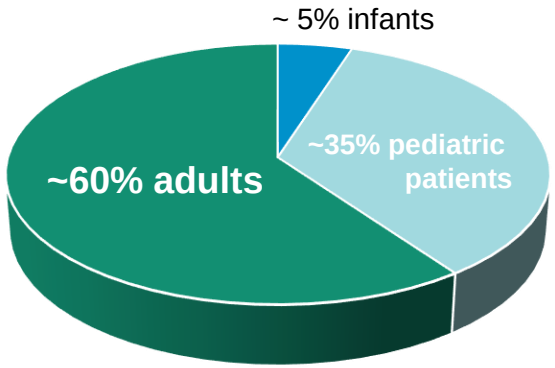


Note: Numbers may not foot due to rounding

Q3 2018 Highlights

- $70 million in Ionis commercial revenue from SPINRAZA royalties ($168 million year-to-date)
- ~6,000 patients on therapy
- Biogen significantly increased number of adult SMA patients on therapy, the largest patient segment
  - >50% of new U.S. patient starts were adults
  - >20% increase in adults on therapy in the U.S. versus Q2 2018
  - ~15% of adult (18+) SMA patients are on therapy in the U.S.

SMA Prevalence Assumptions



Source: Biogen Q3 2018 Financial Results and Business Update.

R&D Revenue to Continue to Contribute to Operating Profitability in 2018 and Beyond

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

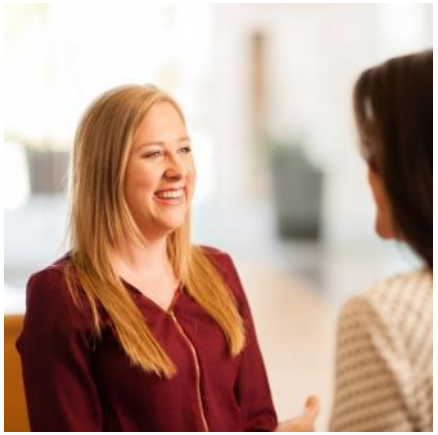
Significant and sustainable source of revenue

Three Key Drivers of R&D Revenue Growth

>Three-fold increase in R&D revenue since 2011

TEGSEDI™ and WAYLIVRA™ Update

Damien McDevitt, Ph.D., Chief Business Officer



Now Approved in the U.S., EU and Canada for Adults with Polyneuropathy in hATTR

Approved in the U.S. for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults

For full prescribing information, visit www.TEGSEDI.com

Approved in the EU for the treatment of stage 1 or stage 2 polyneuropathy in adults with hereditary transthyretin amyloidosis

For full prescribing information, visit www.TEGSEDI.eu

Approved in Canada for the treatment of stage 1 or stage 2 polyneuropathy in adults with hereditary transthyretin amyloidosis

For full prescribing information, visit www.TEGSEDI.ca

waylivra™ (volanesorsen sodium) Injection 300mg in 1.5mL

WAYLIVRA: Next Steps

Complete regulatory review in the EU; continue preparations to launch upon potential approval

Confirm regulatory path forward with FDA; engage Health Canada to confirm regulatory path forward

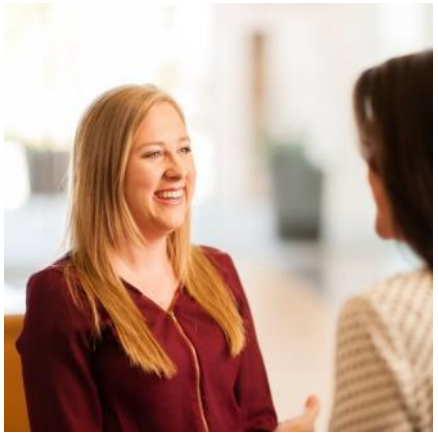
Continue conducting early access program

Complete BROADEN study in FPL in 2019; expand triglyceride franchise with AKCEA-APOCIII-L_{Rx}

AKCEA™ THERAPEUTICS

Key Pipeline Accomplishments

Brett Monia, Ph.D., Chief Operating Officer



Key Recent Pipeline Events

SPINRAZA	New NURTURE data further supports benefit of early diagnosis and treatment in presymptomatic infants
AKCEA-APO(a)-L_{Rx}	Reported positive Phase 2 data, demonstrating robust efficacy with favorable safety and tolerability driven by increased potency
Danvatirsen	Response rates with danvatirsen/durvalumab in Phase 1b/2 ~double compared to durvalumab alone in refractory head & neck cancer, based on previous studies
IONIS-HTT_{Rx}	Roche expects to initiate a Phase 3 study for IONIS-HTT_{Rx} in HD patients this year
IONIS-FB-L_{Rx}	Initiated collaboration with Roche to develop IONIS-FB-L_{Rx} for complement-mediated diseases, including GA
Across the Pipeline	Numerous study completions and initiations, with more detail to follow at investor day

Key Near-Term Milestones

Commercial and Regulatory Milestones

- ✓ **SPINRAZA:** Continued growth in sales and approval in additional markets
- ✓ **TEGSEDI:** Approval for hATTR in the EU
- ✓ **TEGSEDI:** Approval for hATTR in the U.S. and Canada
- ❑ **WAYLIVRA:** Approval for FCS in the EU; confirm path forward in U.S. and Canada
- ✓ **ZEMDRI:** Approval for complicated urinary tract infections (cUTI) in U.S.

Phase 2 Data Readouts

- ✓ **IONIS-HTT$_{Rx}$:** Phase 1/2 study for Huntington's disease
- ✓ **AKCEA-APO(a)-L$_{Rx}$:** Phase 2 study for high Lp(a)
- ✓ **Danvatirsen (IONIS-STAT3-2.5$_{Rx}$):** Phase 2 study for head & neck cancer
- ❑ **AKCEA-ANGPTL3-L$_{Rx}$:** Phase 2 study for rare hyperlipidemias & NASH
- ❑ **IONIS-DGAT2$_{Rx}$:** Phase 2 study for NASH
- ❑ **IONIS-SOD1$_{Rx}$:** Phase 1/2 study for ALS

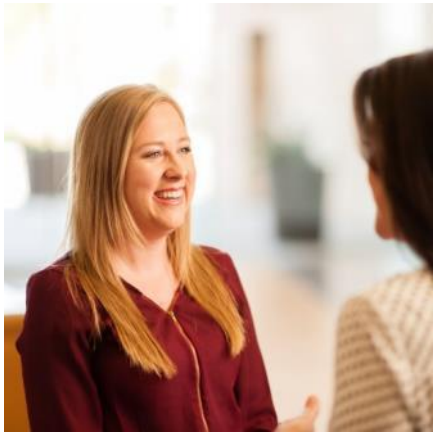
Pivotal Study Initiations

- ❑ **IONIS-HTT$_{Rx}$ (RG6042):** for Huntington's disease
- ❑ **AKCEA-APO(a)-L$_{Rx}$:** for high Lp(a) with CV risk
- ❑ **AKCEA-TTR-L$_{Rx}$:** for ATTR

Multiple POC clinical trial initiations and data readouts planned

2018 and Beyond

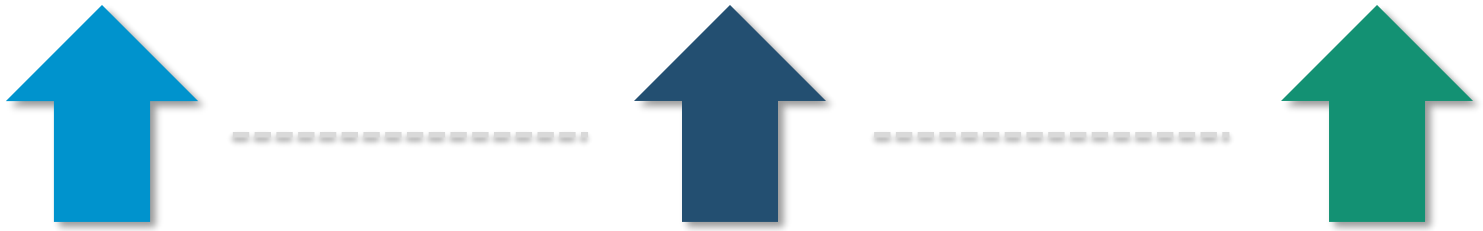
Stanley Crooke, M.D., Ph.D., Chief Executive Officer and Chairman



Ionis: Sustainably Profitable, Continuing to Deliver Transformational Medicines to Patients in Need

Positioned for Substantial Growth

DRIVEN BY

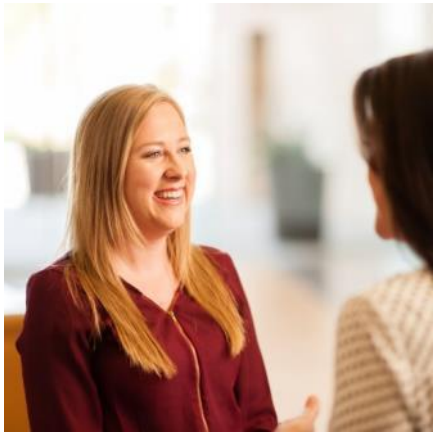


SHORT-TERM	MID-TERM	LONGER-TERM
Commercial revenue from SPINRAZA, TEGSEDI, WAYLIVRA on top of substantial base of R&D Revenue	3+ drugs potentially entering pivotal studies by YE19	Additional commercial drugs, growing Ionis-owned pipeline and broader application of antisense

Maximizing success, optimizing commercial value for each of our drugs

Q&A

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



Please Join us December 7 in NYC for Investor Day