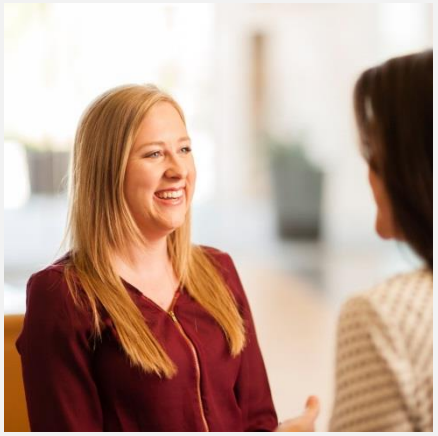


# Q2 2018 Financial Results and Highlights

**August 7, 2018**

IONIS™ PHARMACEUTICALS

# On Today's Earnings Call

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

**Beth Hougen**
*Chief Financial Officer*

**Sarah Boyce**
*President of Akcea Therapeutics*

**Brett Monia, Ph.D.**
*Chief Operating Officer*

**Damien McDevitt, Ph.D.**
*Chief Business Officer*

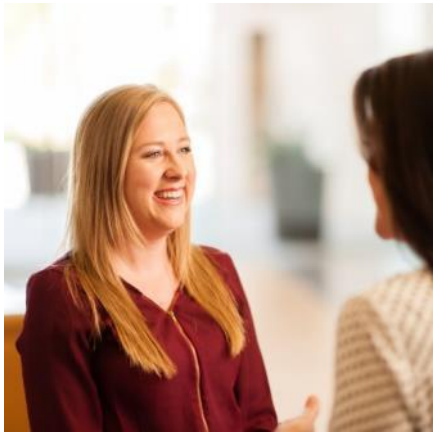
# Forward Looking Language Statement

This presentation includes forward-looking statements regarding 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 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.

# Q2 2018 Highlights

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

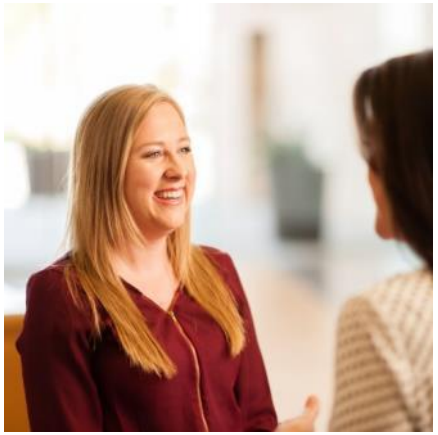


# Ionis: Positioned for Continued Growth

- **Multi-product, sustainably profitable** company positioned for growth
- Short-term growth driven by **SPINRAZA, TEGSEDI and WAYLIVRA** revenue
- Mid-term growth driven by **next wave of commercial opportunities**
- Longer-term growth driven by **capturing increased commercial value for our drugs**

# Financial Performance

**Beth Hougen, Chief Financial Officer**



# H1 2018 Financials at a Glance

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

## $262 million in revenue

>250% increase in SPINRAZA revenues

## $9 million in operating income*

Driven by 15% increase in revenue over H1 2017

SPINRAZA® (nusinersen) injection 12 mg/5 mL

## $98 million

in royalties

## $2 billion cash

Enabling investment in commercial products and pipeline

*Pro forma – please see reconciliation to GAAP in 2Q18 press release

# Positioned for Increased Operating Income in H2 2018

**Growth in SPINRAZA sales and higher royalty rates**

**Addition of TEGSEDI and WAYLIVRA product sales**

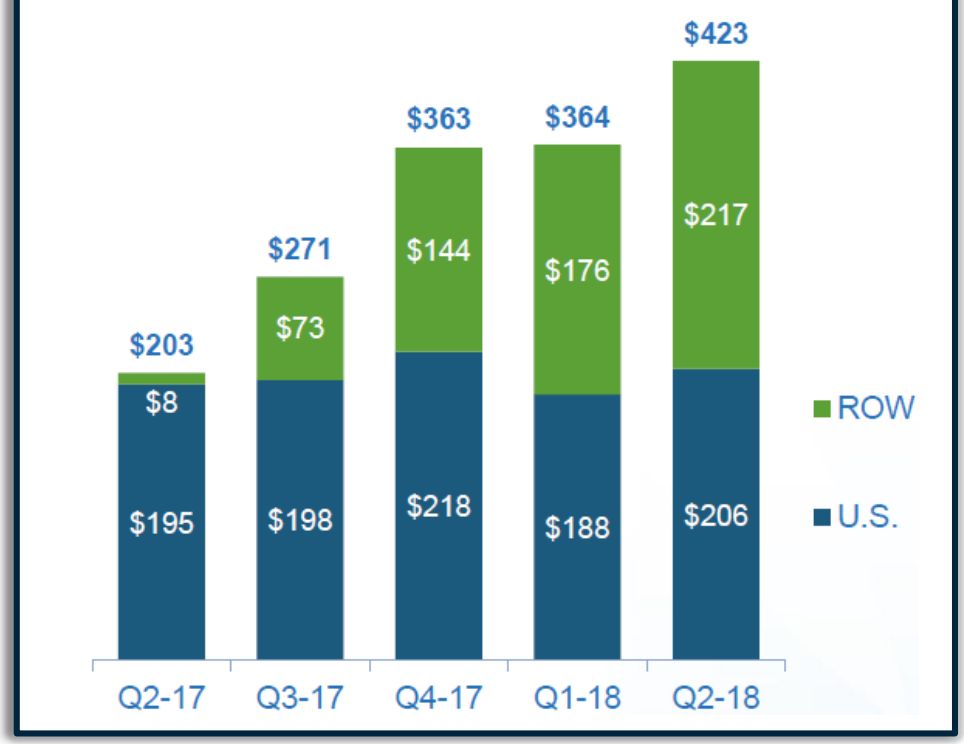
**Amortization of upfront payment from new Biogen strategic collaboration**

**Potential for numerous milestone payments from partnered programs**

# Global SPINRAZA Performance

## Biogen's Strong Global Launch Continues

### SPINRAZA Revenues ($M)

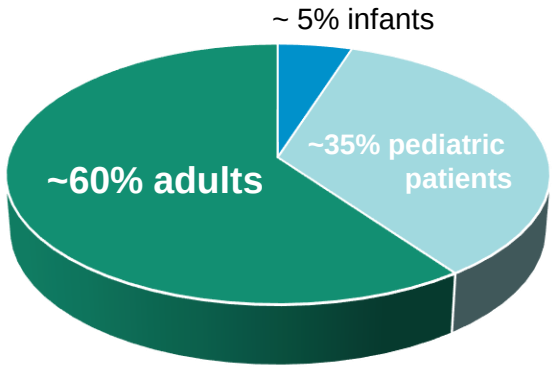



Note: Numbers may not foot due to rounding

### Q2 2018 Highlights

- $57 million in Ionis commercial revenue from SPINRAZA royalties ($98 million year-to-date)
- ~ 5,100 patients on therapy
- Biogen significantly increased number of adult SMA patients on therapy, the largest patient segment
  - > 20% increase in adults on therapy in the U.S. versus Q1 2018
  - ~ 10% of adult (18+) SMA patients are on therapy in the U.S

### SMA Prevalence Assumptions




*Source: Biogen Q2 2018 Financial Results and Business Update.*

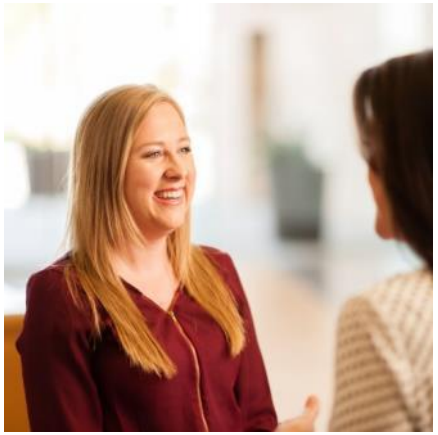
# R&D Revenue to Continue to Contribute to Operating Profitability in 2018 and Beyond

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

Commercial revenue building off a growing base of R&D revenue

# Commercial Preparations for TEGSEDI™ and WAYLIVRA™

**Sarah Boyce, President of Akcea Therapeutics**



# TEGSEDI: The World's First RNA-targeted Therapeutic Approved for Patients with hATTR Amyloidosis


**Now approved in the EU for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hATTR**

Visit TEGSEDI.eu for more information.

# Akcea on Track to Launch Two Drugs in 2018

**TEGSEDI approved in EU & Positive WAYLIVA AdComm**

**Commercial teams & patient support program with safety monitoring in place**

**Access to TEGSEDI & WAYLIVRA in Latin America accelerated w/ PTC Therapeutics**

**Regulatory reviews progressing in each jurisdiction**

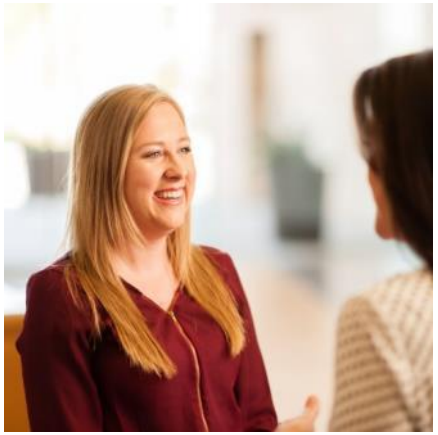
Tegsedi™ (inotersen) injection 284 mg/1.5 mL

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

Visit TEGSEDI.eu for more information.

# Key Pipeline Accomplishments

**Brett Monia, Chief Operating Officer**



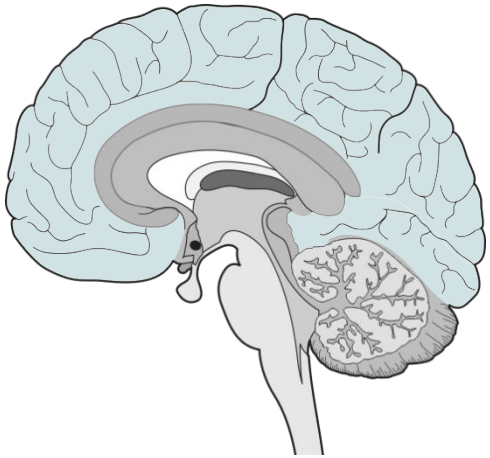
# Key Recent Events

| | |
|---|---|
| **SPINRAZA** | ▪ Global SPINRAZA revenues of $423 million in 2Q 2018<br>▪ 20% increase in U.S. adult SMA patients on treatment from 1Q 2018 (largest U.S. segment); achieved 10% penetration in 2Q 2018<br>▪ >5,000 patients on SPINRAZA treatment; 28% increase from 1Q 2018 |
| **TEGSEDI** | ▪ TEGSEDI approved in the EU; first launch planned in Germany post summer<br>▪ U.S. approval and launch on track in 2018<br>▪ Final results from Phase 3 NEURO-TTR study of TEGSEDI published in *NEJM*<br>▪ Access accelerated in Latin America with PTC Therapeutics license agreement<br>▪ Akcea's commercial organization staffed; robust patient support program in place |
| **WAYLIVRA** | ▪ U.S. and EU approval and launch on track in 2018<br>▪ Access accelerated in Latin America with PTC Therapeutics license agreement<br>▪ Akcea's commercial organization staffed; robust patient support program in place |
| **Pipeline** | ▪ IONIS-HTT$_{Rx}$ granted PRIME designation in the EU<br>▪ IONIS-MAPT$_{Rx}$ granted Orphan Drug Designation in the EU for people with FTD<br>▪ Positive Phase 1 data reported from four LICA programs |
| **Financial** | ▪ On track to achieve third consecutive year of pro forma operating income<br>▪ 15% increase in revenue from 1H 2017<br>▪ $98M in commercial sales from SPINRAZA royalties; >250% increase from 1H 2017<br>▪ $7.5 million received from Achaogen for FDA approval of ZEMDRI™ (plazomicin)<br>▪ $1.2B in payments from partners, including $1B from expanded Biogen collaboration |

# Potential Near-Term Phase 3 Opportunities

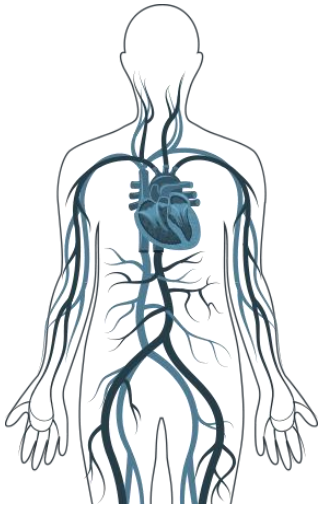
## Huntington's Disease

**IONIS-HTT$_{Rx}$ (RG6042)**



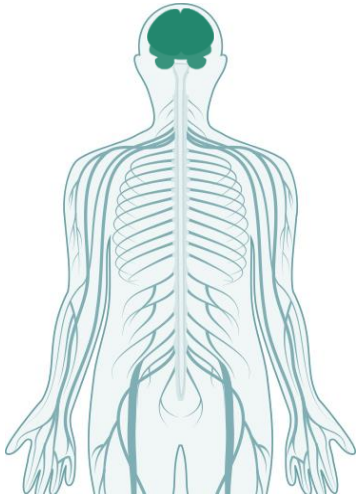
## High Lp(a) and Cardiovascular Disease

**AKCEA-APO(a)-L$_{Rx}$**



## ATTR Amyloidosis

**AKCEA-TTR-L$_{Rx}$**



# Advances in Ionis Technology are Translating into Tangible Value in the Pipeline Today

## 13 LICA Drugs in Pipeline

| Drugs | Indication | Current Phase | Target Reduction |
|---|---|---|---|
| AKCEA-APO(a)-$L_{Rx}$ | CVD | Ph. 2 | ✓ |
| AKCEA-ANGPTL3-$L_{Rx}$ | Mixed Dyslipidemias | Ph. 2 | ✓ |
| AKCEA-APOCIII-$L_{Rx}$ | CVD | Ph. 2 | ✓ |
| IONIS-FB-$L_{Rx}$ | Complement-Mediated Diseases | Ph. 1 | ✓ |
| IONIS-AGT-$L_{Rx}$ | Treatment-Resistant Hypertension | Ph. 1 | ✓ |
| IONIS-GHR-$L_{Rx}$ | Acromegaly | Ph. 1 | ✓ |
| IONIS-TMPRSS6-$L_{Rx}$ | β-Thalassemia | Ph. 1 | ✓ |
| IONIS-PKK-$L_{Rx}$ | HAE | Ph. 1 | ✓ |
| IONIS-HBV-$L_{Rx}$ | HBV | Ph. 2 | 2019 |
| IONIS-FXI-$L_{Rx}$ | Clotting Disorders | Ph. 1 | 2019 |
| AKCEA-TTR-$L_{Rx}$ | ATTR | PC | 2019 |
| IONIS-AZ4-2.5-$L_{Rx}$ | CVD | PC | 2019 |
| IONIS-AZ6-2.5-$L_{Rx}$ | NASH | PC | 2020 |

Severe & Rare  Cardiometabolic & Renal  Other

# We are Strengthening our Position as a Leader in Neurological Diseases

## Neuro

| Partner | Drugs | Indication | PC | Phase I | Phase II | Phase III | Registration | Commercial |
|---|---|---|---|---|---|---|---|---|
| AKCEA THERAPEUTICS | TEGSEDI™ | hATTR | | | | | | |
| IONIS PHARMACEUTICALS | IONIS-TTR-L$_{Rx}$ | ATTR | | | | | | |
| | IONIS-GFAP$_{Rx}$ | Alexander Disease | | | | | | |
| Biogen | SPINRAZA® | SMA | | | | | | |
| | IONIS-SOD1$_{Rx}$ | ALS | | | | | | |
| | IONIS-MAPT$_{Rx}$ | Alzheimer's Disease | | | | | | |
| | IONIS-C9$_{Rx}$ | ALS | | | | | | |
| Roche | IONIS-BIIB6$_{Rx}$ | Neurodegenerative Disease | | | | | | |
| | IONIS-BIIB7$_{Rx}$ | Neurodegenerative Disease | | | | | | |
| | IONIS-BIIB8$_{Rx}$ | Neurodegenerative Disease | | | | | | |
| antisense THERAPEUTICS | IONIS-HTT$_{Rx}$ | Huntington's Disease | | | | | | |
| | ATL1102 | Multiple Sclerosis/DMD | | | | | | |
| Dynacure | IONIS-DNM2-2.5$_{Rx}$ | Centronuclear Myopathy | | | | | | |

## Ionis Wholly Owned Drug Candidates Expected in 2019

IONIS PHARMACEUTICALS

| Indication |
|---|
| Lafora Disease |
| Charcot-Marie-Tooth |

# 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.
- ❑ **WAYLIVRA:** Approval for FCS in the U.S. and EU
- ✓ **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

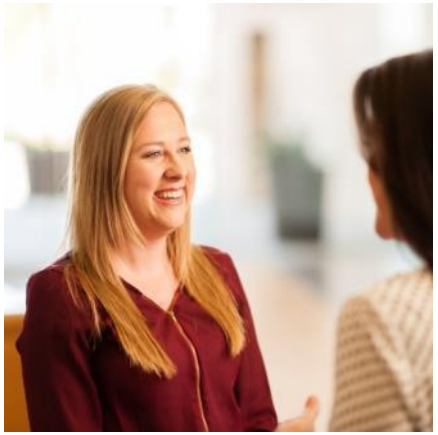
## Pivotal Study Initiations

- ❑ **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 initial clinical trial initiations and readouts**

# 2018 and Beyond

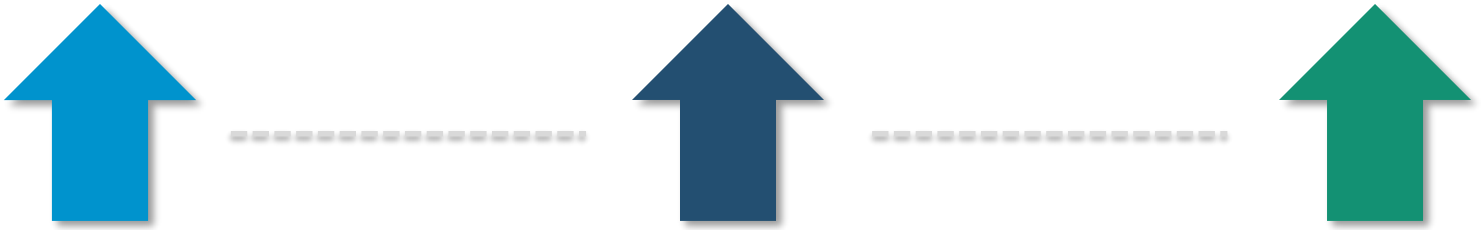
**Stanley Crooke, M.D., Ph.D., Chief Executive Officer and Chairman**



# Ionis: A Multi-Product, Sustainably Profitable Company Delivering Transformational Medicines to Patients

## Positioned for Substantial Growth

DRIVEN BY

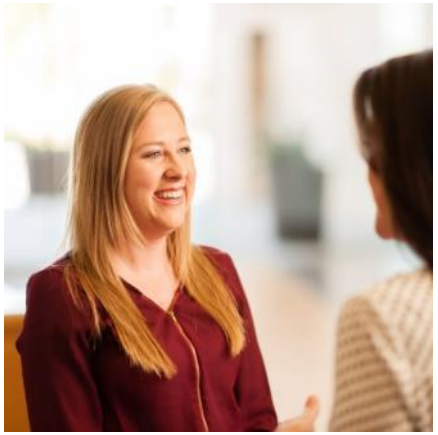


| SHORT-TERM | MID-TERM | LONGER-TERM |
|---|---|---|
| Commercial revenue from SPINRAZA, TEGSEDI, WAYLIVRA | 3+ drugs potentially entering pivotal studies by YE19 | Commercial strategy to maximize the value for each drug |

**Capturing the greatest commercial value for each of our drugs**

# Q&A

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



# Please Join us November 9 in NYC for Investor Day