

Q1 2018 Financial Results and Highlights

May 4, 2018



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

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 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, 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, which is 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 trademark of Akcea Therapeutics, Inc. TEGSEDI™ is a trademark of Akcea Therapeutics, Inc. WAYLIVRA™ is a trademark of Akcea Therapeutics, Inc. SPINRAZA® is a registered trademark of Biogen.

Q1 2018 Highlights

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



Q1 2018 Highlights

Strongest financial position ever as a result of the power of antisense technology



>\$2 billion*
in cash

New Biogen Collaboration

\$1 billion upfront



Investment

commercialize through
Akcea



\$144 million
in revenue

\$25 million
in operating profit**



*Upon the close of the collaboration with Biogen

**Pro forma

Power and Productivity of Platform Drives Ionis' Development and Commercialization Strategy

3 to 5 New Drugs Per Year Requires Multiple Approaches

EXAMPLES

Strategic Research Collaborations



- ✓ Highly specialized knowledge
- ✓ Experience with complex disease models and clinical testing paradigms
- ✓ Non-dispositive Phase 2 studies
- ✓ Large, costly development/commercialization infrastructure

Commercialize through Affiliates



- ✓ Dispositive Phase 2 studies
- ✓ Manageable pivotal studies
- ✓ High-touch patient support – as in rare disease
- ✓ Therapeutic areas that match our expertise

Maximizes value to patients + optimizes Ionis' participation in commercial opportunity

Q1 2018 Earnings Webcast Agenda

Topic

Speaker

- **Welcome and Introductions**

Stan Crooke, M.D., Ph.D., CEO, Ionis

- **Financial Performance**

Beth Hougen, CFO, Ionis

- **Commercial Preparations for
TEGSEDI and WAYLIVRA**

Sarah Boyce, President, Akcea

- **Key Pipeline Accomplishments**

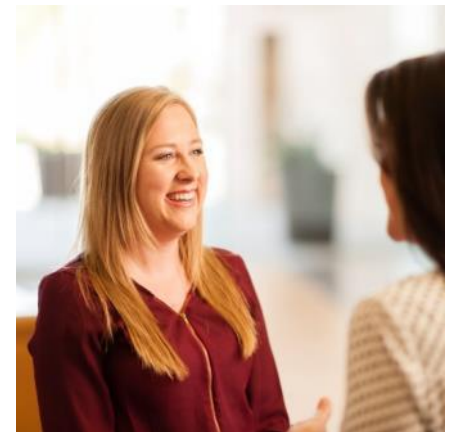
Brett Monia, Ph.D., COO, Ionis

- **Conclusion and Q&A**

Stan Crooke, M.D., Ph.D., CEO, Ionis

Financial Performance

Beth Hougen, Chief Financial Officer



Q1 2018 Financials at a Glance

On track for third consecutive year of pro forma operating income

**\$144 million in
revenue**

25% increase over Q1 2017

**\$25 million in
operating income***

7th consecutive quarter of
operating income*



\$41 million
in royalties

**>\$2 billion
cash**

upon the close of Biogen
transaction

Impact of New Biogen Collaboration on Ionis' Financials

\$1 billion upfront payment

- \$500 million to access our technology for neurological disease
- \$500 million for fair market value of Ionis stock

Substantial payments for each program

- Up to \$270 million for each drug that successfully gets to the market
- Tiered royalties from the mid-teens up to 20%

Biogen conducting all development and commercial activities

- Hundreds of millions of dollars in “in kind” contribution to be paid by Biogen
- Milestone payments and license fees drop directly to our bottom line as profit
- Enhances our ability to make strategic investments like investing in the commercialization of TEGSEDI through our affiliate, Akcea

Benefits from Investment in TEGSEDI Commercialization Through Akcea

With successful launch of TEGSEDI, Ionis will see...



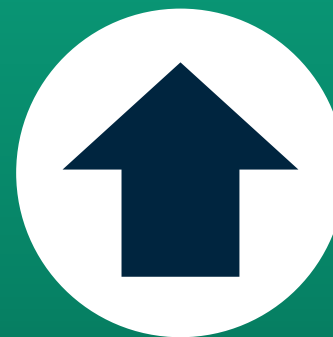
Commercial Revenue

100% of TEGSEDI product sales reflected on Ionis' P&L



Earnings Growth

High value rare disease drug



Cash

\$1.5B in milestone payments and 60% profit share

75% Ownership of Akcea Requires Consolidated Financial Reporting

Commercial Preparations for TEGSEDI™ and WAYLIVRA™

Sarah Boyce, President of Akcea Therapeutics



Akcea on Track to Launch Two Drugs in 2018

Final stages of
regulatory review
for marketing
approval

Industry-leading
commercial team in
place

Monitoring
process accepted
by investigators and
patients

Team driving
disease education,
patient ID and
efficient diagnosis

Enrolling EAP



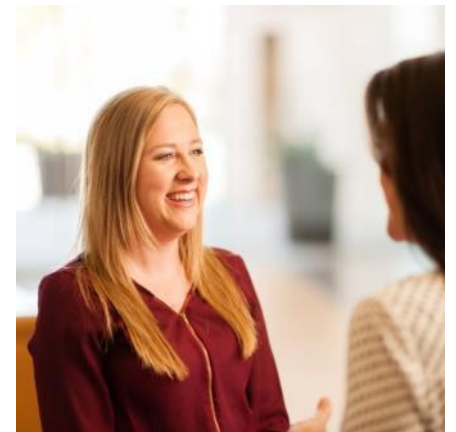
TegsediTM
(inotersen) injection
284 mg/1.5 mL



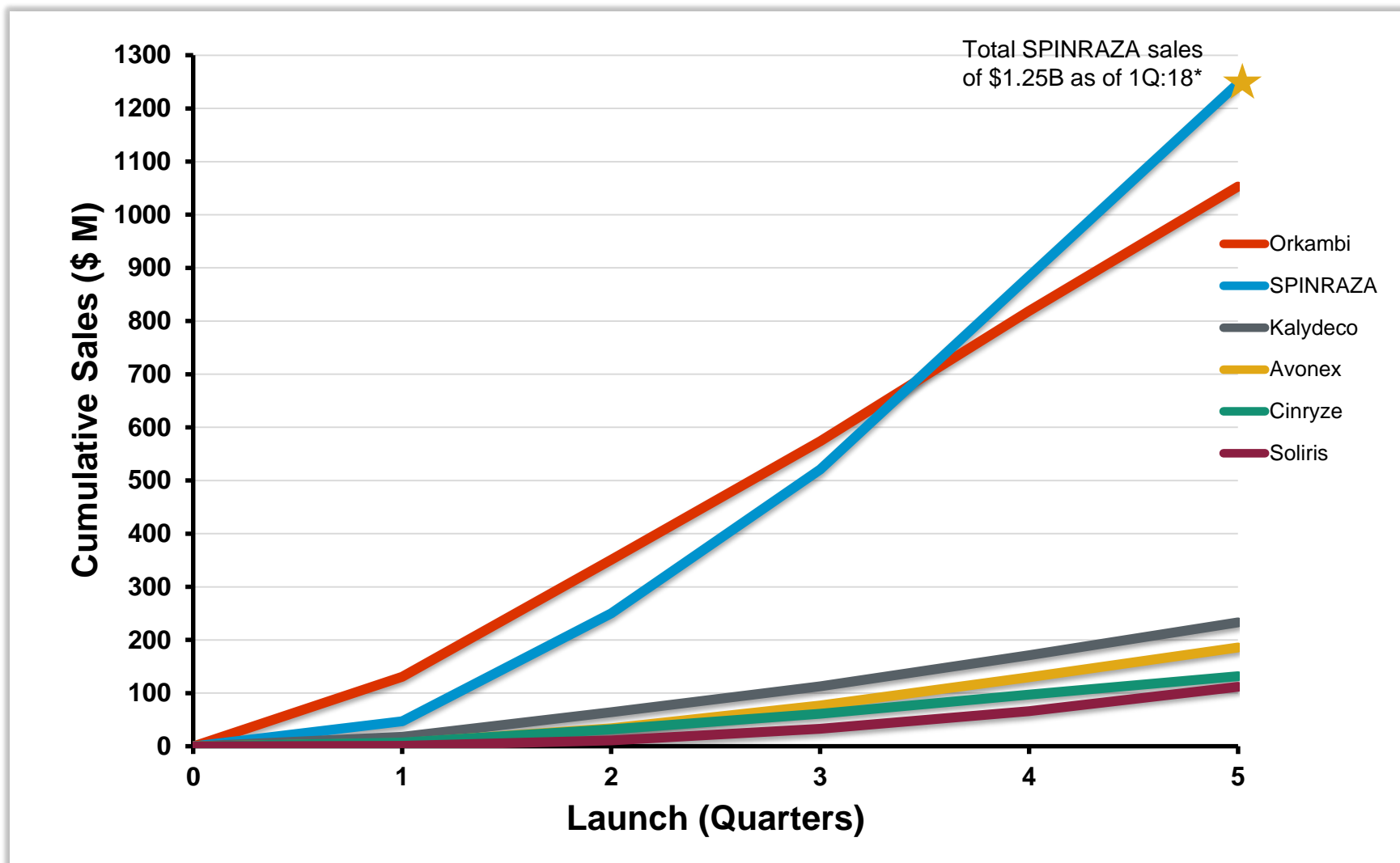
waylivraTM
(volanesorsen sodium)
Injection 300mg in 1.5mL

Key Pipeline Accomplishments

Brett Monia, Chief Operating Officer



SPINRAZA is One of the Most Successful Rare Disease Drug Launches in History



*As reported by Biogen

Note: Sales data obtained from Biomedtracker or Company SEC filings

The Opportunity in Neurological Diseases is Very Broad

Broad opportunity regardless of the disease cause

Broad opportunity for a variety of neurological diseases

Broad opportunity to exploit different antisense mechanisms

Ionis is Independently Advancing a Neurological Disease Portfolio

Our antisense technology is well-suited to treat a broad range of diseases, including neurological diseases

Drug	Indication	Late-stage Research	Preclinical	Phase I	Phase II	Phase III	Registration	Commercial
TEGSEDI™ (inotersen)	hATTR							
AKCEA-TTR-L _{Rx}	ATTR							
IONIS	Lafora Disease							
IONIS	Alexander Disease							
IONIS	Charcot-Marie-Tooth							

Expect to add several new wholly owned programs in the next 12-18 months

For multiple rare neuro diseases

Ionis is Continuing to Advance Industry-Leading Neurological Disease Franchise

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Highly Successful Neurological Drug on the Market

SPINRAZA – “One of the most successful rare disease drug launches in history”

1

Neurological Drug Under Regulatory Review

TEGSEDI (inotersen) – “Potential to transform the lives of patients with hATTR”

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Neurological Drugs in Development

- IONIS-HTT_{Rx} (RG6042)
- IONIS-SOD1_{Rx}
- IONIS-MAPT_{Rx}
- ATL1102

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Neurological Drugs in Preclinical

- AKCEA-TTR-L_{Rx}
- IONIS-C9_{Rx}
- IONIS-BIIB6_{Rx}
- IONIS-BIIB7_{Rx}
- IONIS-BIIB8_{Rx}
- IONIS-DNM2-2.5_{Rx}

**More than 20 wholly owned and
partnered drug discovery programs**

For Alzheimer's, Parkinson's, ALS, pain and multiple rare neurological diseases

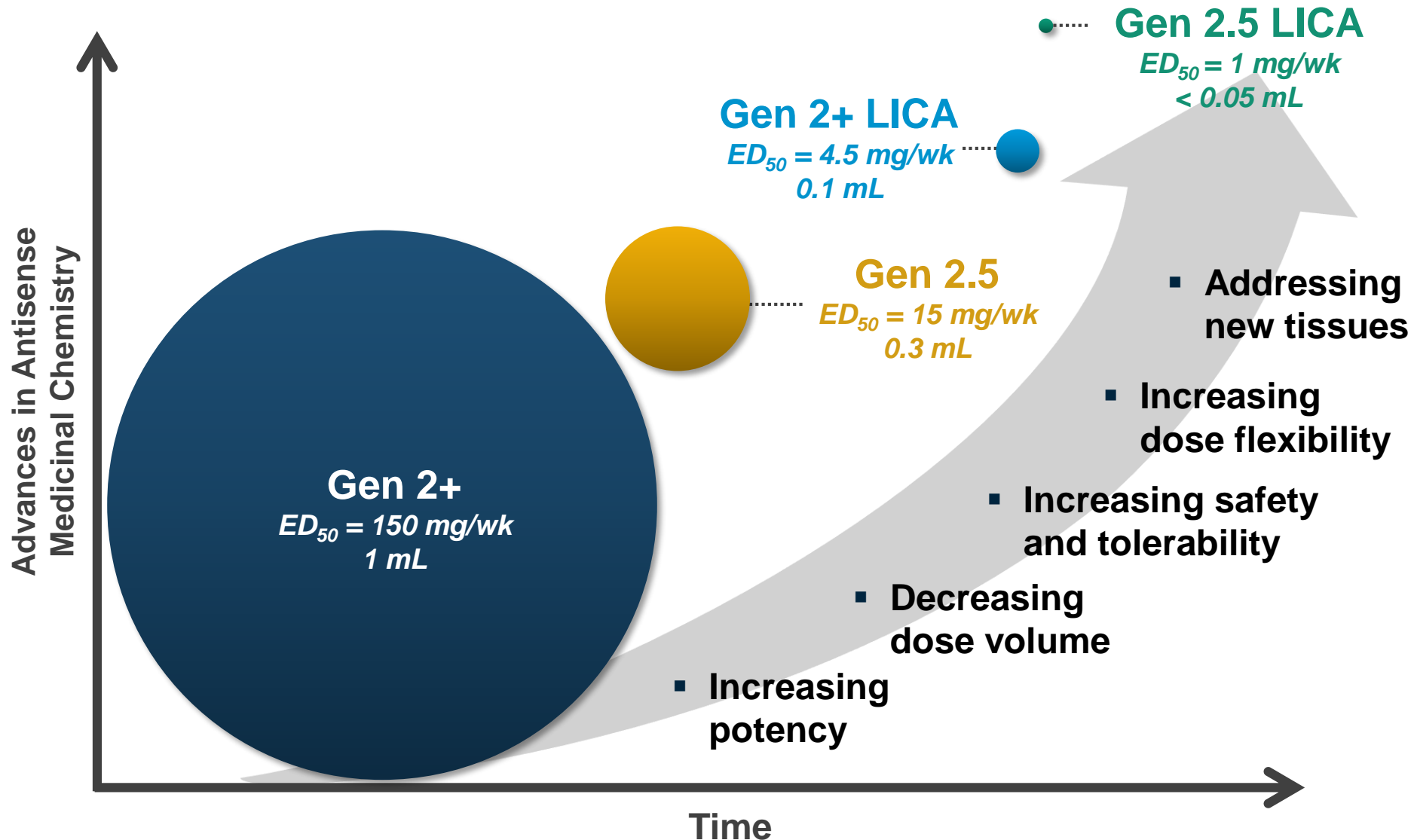
We Have Also Advanced Our Technology in Oncology, Cardiac, Renal and Metabolic Diseases

Drug	Indication	Preclinical	Phase I	Phase II	Phase III	Registration	Commercial
Danvatirsen (IONIS-STAT3-2.5 _{Rx})	Cancer						
IONIS-KRAS-2.5 _{Rx}	Cancer						
IONIS-AZ4-2.5-L _{Rx}	CVD						
IONIS-AZ5-2.5 _{Rx}	Kidney Disease						
IONIS-AZ6-2.5-L _{Rx}	NASH						

AstraZeneca Strategic Collaboration:

- Completing study of Danvatirsen + Imfinzi in people with head and neck cancer
- Licensed 2nd and 3rd antisense drugs under cardiac, renal and metabolic collaboration for a total of \$60 million
 - Ionis may receive \$300 million each in additional development and regulatory milestone payments, as well as tiered royalties from sales of each drug

Advances in Our Technology Substantially Improve the Utility of Antisense Drugs



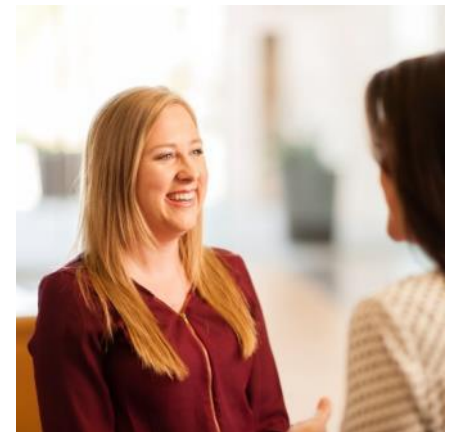
ED_{50} 's and dose volumes are representative of liver targets

Next Potential Commercial Opportunities

Drug	Indication	Partner
Plazomicin	Severe Bacterial Infection	Achaogen
IONIS-HTT _{Rx} (RG6042)	Huntington's disease	Roche
IONIS-GHR-L _{Rx}	Acromegaly	Ionis
IONIS-TMPRSS6-L _{Rx}	B-Thalassemia	Ionis
AKCEA-APO(a)-L _{Rx}	CVD	Akcea/Novartis
Danvatirsen (IONIS-STAT3-2.5 _{Rx})	Cancer	AstraZeneca

2018 and Beyond

Stan Crooke, Chief Executive Officer



Financial Strength Gives Ionis Ability to Make Strategic Investments



>\$2 billion*
in cash



**\$144 million in
revenue**

25% increase over Q1 2017



**\$25 million in
operating income***

7th consecutive quarter of
operating income*



*Upon the close of the collaboration with Biogen

**Q1 2018 pro forma

Looking Ahead to 2018

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Drugs Potentially On the Market

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Phase 2 Readouts

- AKCEA-APO(a)-L_{Rx}
- AKCEA-ANGPTL3-L_{Rx}
- IONIS-DGAT2_{Rx}
- IONIS-HTT_{Rx} ✓
- IONIS-SOD1_{Rx}
- IONIS-PKK_{Rx}

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Phase 2/3 Initiations

- IONIS-STAT3-2.5_{Rx}
- IONIS-HTT_{Rx}
- IONIS-GHR-L_{Rx}
- IONIS-FB-L_{Rx}
- IONIS-AR-2.5_{Rx}
- IONIS-KRAS-2.5_{Rx}

Multiple POC Initial Clinical Trial
Readouts

Q&A

Revolutionizing Medicine. Saving Lives.

