



# Q3:23 Business Update and Financial Results

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November 2, 2023

Nasdaq: IONS



# On Today's Earnings Call



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



**Onaiza Cadoret**  
*Chief Global Product Strategy and  
Operations Officer*



**Richard Geary, Ph.D.**  
*Executive Vice President, Development*



**Beth Hougen**  
*Chief Financial Officer*



**Eugene Schneider, M.D.**  
*Chief Clinical Development Officer*



**Eric Swayze, Ph.D.**  
*Executive Vice President, Research*

# Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of QALSODY™ (tofersen), SPINRAZA® (nusinersen), TEGSEDI® (inotersen), WAYLIVRA® (volanesorsen), eplontersen, olezarsen, donidalorsen, zilganersen, ulefnersen, pelacarsen, bepirovirsen, IONIS-FB-L<sub>Rx</sub>, Ionis' technologies, and Ionis' other products in development. 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 including but not limited to those related to our commercial products and the medicines in our pipeline, and 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, 2022, and most recent Form 10-Q, which are on file with the SEC. Copies of these and other documents are available at [www.ionispharma.com](http://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 registered trademark of Ionis Pharmaceuticals, Inc. Akcea Therapeutics® is a registered trademark of Akcea Therapeutics, Inc. TEGSEDI® is a trademark of Akcea Therapeutics, Inc. WAYLIVRA® is a registered trademark of Akcea Therapeutics, Inc. QALSODY™ is a trademark of Biogen. SPINRAZA® is a registered trademark of Biogen.

# Introduction

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Brett Monia, Ph.D.  
Chief Executive Officer

# Important Achievements in 2023<sup>1</sup>

Positioned for Next-Level Growth

## Late-Stage Pipeline

- Eplontersen:
  - PN: December 2023 PDUFA date; under review in EU and Canada
  - CM: largest ATTR-CM study fully enrolled; data as early as H1:2025
- Olezarsen: Positive Ph3 data in patients with FCS; U.S. & EU filing early 2024
- Donidalorsen: Ph3 study fully enrolled; data expected H1:24

## Commercial Readiness

- Eplontersen ready for launch in the U.S. with AstraZeneca
- Olezarsen and donidalorsen go-to-market activities on track
- Preparing for next wave of wholly owned medicines

## Financial Foundation

- On track to achieve 2023 financial guidance
- \$2.2 billion<sup>2</sup> in cash enables investment to drive increasing value

1. Timing expectations based on current assumptions and subject to change 2. Cash, cash equivalents and short-term investments at September 30, 2023.

# Preparing to Bring Important Ionis Medicines to Patients

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Onaiza Cadoret  
Chief Global Product Strategy and Operations Officer

# Poised to Deliver Ionis Medicines to Patients in Need<sup>1,2,3</sup>

## Eplontersen

**Strong efficacy and safety** data with **self-administration** profile for the global ATTR market

**On track** for ATTRv-PN launch & go-to-market plans for ATTR-CM

Well positioned with Ionis' **ATTR market knowledge & AstraZeneca's global scale**

Estimated peak sales: **Multibillion<sup>4</sup>**

## Olezarsen

Expected to be a **first-in-class** US treatment for patients with **severely elevated triglycerides**

**On track** for first independent launch in FCS

**Independent launch** in larger SHTG indication to follow

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## Donidalorsen

Potential **advance in prophylactic treatment** for patients with HAE

**On track** for independent launch in HAE

Attractive **market** with **concentrated prescriber base**

Estimated peak sales: **>\$500 Million**



## Preparing for Next Wave of Wholly Owned Medicines

1. Global peak sales estimates are based on current assumptions and are subject to change. 2. Profile based on data generated to date. 3. Assuming approval. 4. Estimated global peak sales includes ATTRv-PN and ATTR-CM.

# Eplontersen: Positioned to Address the High Unmet Need in ATTR<sup>1,2,3,4</sup>



Potential to be the **treatment of choice** for the **global ATTR population** with monthly **self-administered** auto-injector profile



Our goal is to become the **preferred choice** for **patients who are new to treatment**

## Expanding Patient Population

	Indication	Patients <sup>3,4</sup>
	ATTR	~500K
<b>CM</b>	wtATTR & ATTRv	300K-500K
<b>PN</b>	ATTRv-PN + Mixed	40K

**Currently <20% of ATTR patients are treated<sup>2</sup>**

Ocular Manifestation

Lumbar Spinal Stenosis

GI Manifestations

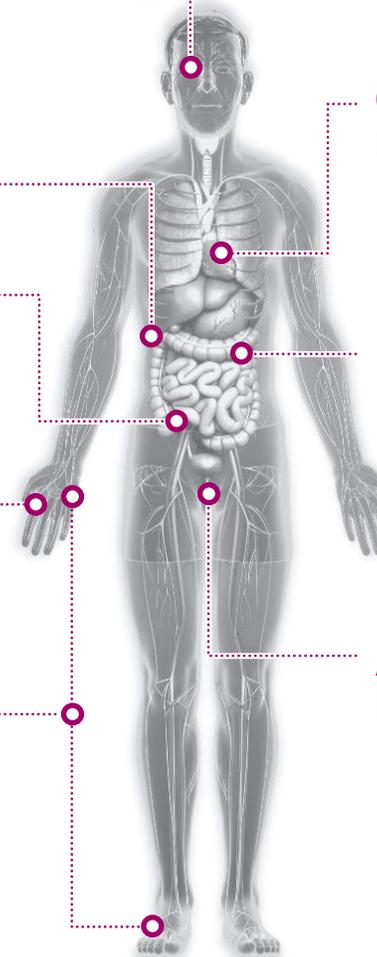
Bilateral Carpal Tunnel Syndrome

Peripheral Sensory-motor Neuropathy

Cardiovascular Manifestations

Nephropathy

Autonomic Neuropathy



amyloidosis.org (<https://amyloidosis.org/facts/familial/>; <https://amyloidosis.org/facts/wild-type/>)  
 NOTE: For illustrative purposes only. 1. ATTRv-PN potential approval this year. 2. Market data on file. 3. Conceição I et al. *J Peripher Nerv Syst.* 2016;21:5-9. 4. Ando Y et al. *Orphanet J Rare Dis.* 2013;8:31.

# Building Launch Momentum with Campaigns to Broaden Disease and Brand Awareness

... About ATTR ATTR Symptoms Diagnosing ATTR Treatment Approaches **SEE THE PATTRNS**



A systemic disease with a constellation of signs and symptoms

## SEE THE PATTRNS.

**TAKE ACTION.**

Multisystem organ dysfunction due to deposition of transthyretin amyloid (ATTR) fibrils often goes unrecognized.

Recognizing the pattern of symptoms is a critical aspect of early intervention, which may help halt disease progression and preserve patients' quality of life.

- ATTR: Not As Simple As Polyneuropathy and Cardiomyopathy
- ATTR: More Than Polyneuropathy and Cardiomyopathy
- ATTR: Beyond Polyneuropathy and Cardiomyopathy

## ATTR Disease State Awareness Deck

**Extensive HCP Education**

AstraZeneca IONIS

**SEE THE PATTRNS**

### EXPLORE THE PATHS TO ACCURATE ATTR DIAGNOSIS

As a rare disease with a seemingly unrelated constellation of symptoms, transthyretin amyloidosis (ATTR) is often underdiagnosed and/or misdiagnosed. ATTR can be debilitating for patients, which is why it's important to catch and treat it as early as possible.<sup>1,4</sup> For more information on the disease's impact on your patients, keep reading and visit our website below.

Learn more at [seetheATTRns.com](http://seetheATTRns.com)

**A MISDIAGNOSIS OR DELAYED DIAGNOSIS CAN HAVE LASTING CONSEQUENCES<sup>1,2</sup>**

Patients with ATTR often face diagnostic challenges due to low clinical suspicion and nonspecific symptoms, resulting in underdiagnosis, misdiagnosis, and/or delayed treatment.<sup>1,3</sup>

<p>PATIENTS WITH ATTR FACE A MEDIAN DIAGNOSTIC DELAY OF</p> <p><b>&gt;3 YEARS</b></p> <p>REGARDLESS OF PHENOTYPIC PRESENTATION<sup>4</sup></p>	<p>~60% OF PATIENTS SAW</p> <p><b>&gt;3 PHYSICIANS</b></p> <p>BEFORE RECEIVING THE CORRECT DIAGNOSIS OF ATTR<sup>5</sup></p>
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**The importance of a timely and correct diagnosis<sup>1,3</sup>**



THE LATER AN ATTR DIAGNOSIS IS MADE → THE LATER TREATMENT IS INITIATED → THE MORE DEBILITATING SYMPTOMS CAN BECOME → CREATING A HIGHER BURDEN OF DISEASE FOR PATIENTS

**Timely diagnosis is critical to avoid rapid disease progression of untreated ATTR<sup>1</sup>**

Learn how to diagnose ATTR.

Explore diagnostic paths

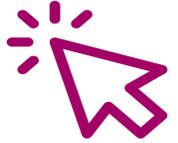
References: 1. Nalvi-Nicolau JN, Karam C, Khalifa S, Maurer MS. Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multigenic awareness. Heart Fail Rev. 2022;27(3):785-795. 2. Anon Y, Colombo T, Berk JL, et al. Guidelines of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2019;14:1. 3. Garcia MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Medeg Care. 2017;23(suppl 7):S107-S112. 4. Adams D, Aguilarrondo V, Polyzakis M, Saravel N, Sierra MS, Nalvi-Nicolau J. Expert opinion on monitoring symptomatic hereditary transthyretin-mediated amyloidosis and assessment of disease progression. Orphanet J Rare Dis. 2021;16(1):411. 5. Loucaas I, Maurer MS, Warner M, Guthrie S, Hu X, Grogan M. Amyloidosis Research Consortium Cardiac Amyloidosis Survey: results from patients with AL and ATTR amyloidosis and their caregivers. Poster presented at: 63rd Annual Heart Failure Society of America, September 13-16, 2019, Philadelphia, PA.

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**seethepatterns**

**comingsoon**



**WAINUA (epilontersen) 45 mg**  
injection for subcutaneous use

## A NEW WAY FORWARD



**COMING SOON**

**WAINUA (epilontersen) 45 mg**  
injection for subcutaneous use

AstraZeneca IONIS

**Sign up to learn more**

Fields marked with an \* are required

First name\*  Last name\*

Work email\*

NPI number\*

Specialty

**Submit**

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# Poised to Deliver Ionis Medicines to Patients in Need<sup>1,2,3</sup>

## Eplontersen

Strong efficacy and safety data with self-administration profile for the global ATTR market

On track for ATTRv-PN launch & go-to-market plans for ATTR-CM

Well positioned with Ionis' ATTR market knowledge & AstraZeneca's global scale

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## Donidalorsen

Potential advance in prophylactic treatment for patients with HAE

On track for independent launch in HAE

Attractive market with concentrated prescriber base

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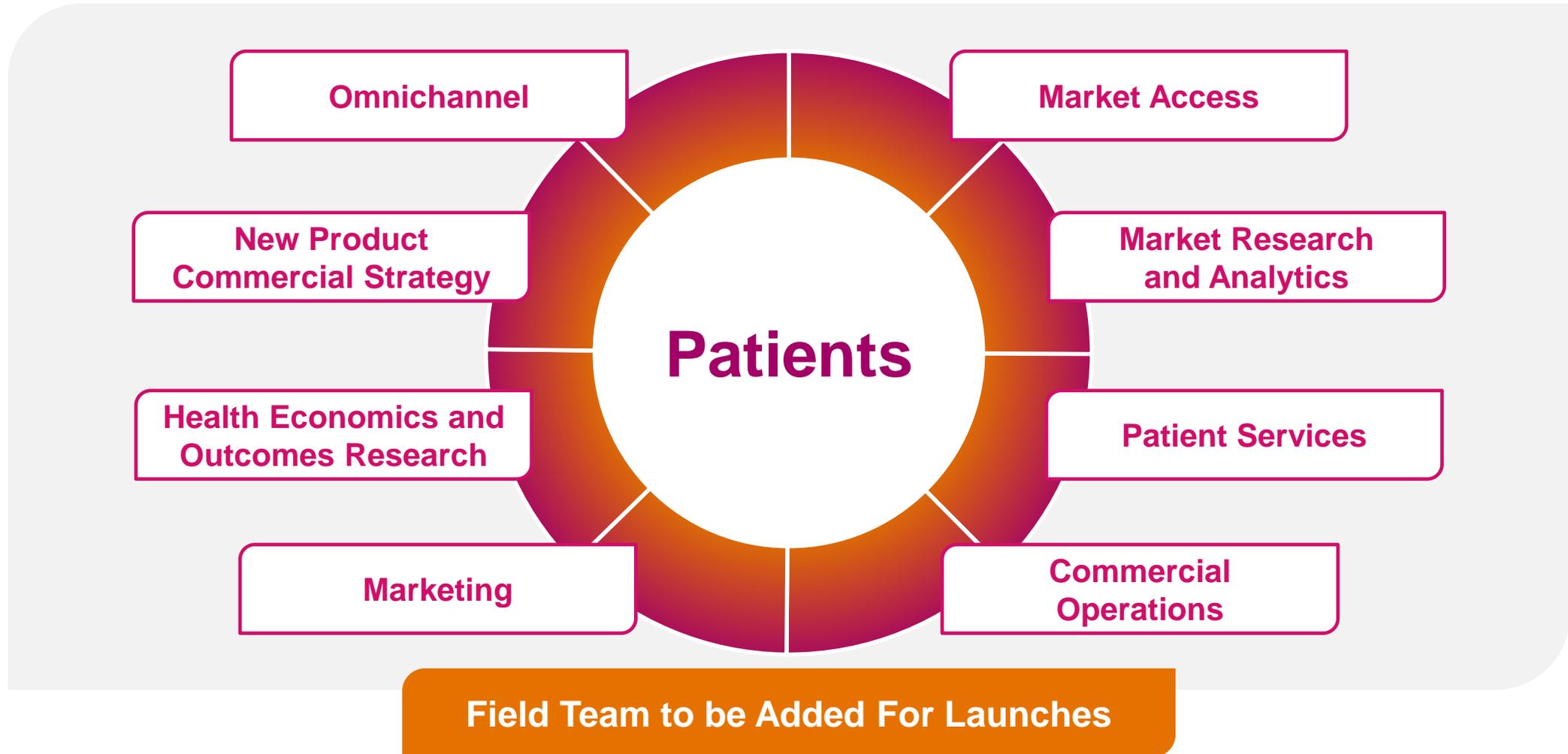
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# Commercial Infrastructure in Place: Ready to Deliver Medicines to People in Need



# Pipeline Performance

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Richard Geary, Ph.D.  
Executive Vice President, Development

# Eplontersen's Development Program is Delivering Robust Results to Address Underserved ATTR Patients Globally<sup>1</sup>

## ATTRv POLYNEUROPATHY



- Met co-primary + secondary endpoints in Phase 3 with favorable safety and tolerability
- NDA accepted, PDUFA date December 22, 2023
- Currently under review in the EU and Canada
- On track for additional OUS submissions in 2023+

## ATTR CARDIOMYOPATHY



- Most comprehensive ATTR-CM study to date
- Positioned to deliver most robust data in broad patient population
- Largest study conducted in ATTR-CM now fully enrolled with >1,400 patients
- On track for data as early as H1:2025

## ATTR Amyloidosis



- Open-label extension studies in patients with ATTRv-PN and ATTR-CM enrolling
- Imaging sub-studies in ATTR-CM to assess the effects on cardiac structure and function underway
- Additional profile-enhancing studies underway

1. Timing expectations and peak sales estimates are based on current assumptions and are subject to change.

# Olezarsen is Delivering Robust Data Supporting its Potential as a Breakthrough Treatment for FCS and SHTG<sup>1</sup>

## **Balance** a familial chylomicronemia syndrome study

- Significant reductions in TGs, clinically meaningful reductions in AP, favorable safety and tolerability
- OLE progressing well
- Ph 2b study supporting FCS NDA exposure database, on track to complete H2:2023
- On track for US and EU filings early 2024
- Launch preparations underway

## **CORE** a hypertriglyceridemia study

- First pivotal study in patients w/ TGs  $\geq 500$  mg/dL enrolling
- Pivotal registrational study
- ~540 patients

## **CORE<sub>2</sub>** a hypertriglyceridemia study

- Confirmatory study in patients w/ TGs  $\geq 500$  mg/dL enrolling
- Pivotal registrational study
- ~390 patients

## **Essence** TIMI-73b

- Supportive Ph3 study in patients w/ TGs  $\geq 200$  mg/dL
- Adds to patient exposure database
- ~1,300 patients

----- Data expected in late 2024/early 2025 -----

1. Timing expectations are based on current assumptions and are subject to change.

# Donidalorsen is Delivering Robust Data Supporting its Potential to Advance Prophylactic HAE Treatment<sup>1,2</sup>

## Hereditary Angioedema

### Phase 2

- Positive Phase 2 data published in *New England Journal of Medicine*
- Positive Phase 2 1-year OLE data, including positive QoL data reported
- New 2-year Phase 2 OLE data reinforce donidalorsen's compelling profile



- Phase 3 OASIS-HAE study fully enrolled
- Data expected H1:2024



- Switch study underway in patients previously treated with other prophylactic therapies
- Phase 3 OLE study underway in patients who have completed OASIS-HAE
- Data expected mid-2024

1. Based on double blind Phase 2 study data published in NEJM in 2022 and Phase 2 OLE data. 2. Timing expectations based on current assumptions and subject to change.

# Well Positioned to Deliver Steady Cadence of Potentially Transformational Medicines

## Phase 3 Pipeline

		Indication	Prevalence <sup>1</sup>	Next Event <sup>2</sup>
Eplontersen		ATTRv-PN		US approval (2023) OUS submissions (2023)
		ATTR-CM		Ph3 data (2025)
Olezarsen		FCS		NDA filing (2024)
		SHTG		Ph3 data (2024)
Donidalorsen		HAE		Ph3 data (2024)
Zilganersen		Alexander disease		Ph3 data (2025)
Ulefnersen		FUS-ALS		Ph3 data (2025)
Pelacarsen		Lp(a) CVD		Ph3 data & filing (2025)
Bepirovirsen		HBV		Ph3 B-Well 1 & 2 data (2025)
IONIS-FB-L <sub>Rx</sub>		IgA nephropathy <sup>3</sup>		Ph2 data (2024)
Tofersen		Presymptomatic SOD1-ALS		Ph3 data (2027)

1. Market data on file. 2. Timing expectations are based on current assumptions and are subject to change.  
3. IONIS-FB-L<sub>Rx</sub> is also in the Phase 2 GOLDEN study in patients with Geographic Atrophy, with topline data expected in 2024.



# Leading and Validated Neurology Franchise

2

Approved Medicines<sup>1</sup>

12

Medicines in Clinical Development

4

New Medicines Entering the Clinic by YE:2024

**SPINRAZA**  
SMA (SMN2)

**QALSODY**  
SOD1-ALS (SOD1)

**Eplontersen**  
ATTR (TTR)

**Tofersen**  
Presymptomatic SOD1-ALS (SOD1)

**IONIS-MAPT<sub>Rx</sub>/BIIB080**  
Alzheimer's disease (Tau)

**ION859/BIIB094**  
Parkinson's disease (LRRK2)

**Tominersen**  
Huntington's disease (HTT)

**ION306/BIIB115**  
SMA (SMN2)

**ION582/BIIB121**  
Angelman syndrome (UBE3A-ATS)

**Ulefnersen**  
FUS-ALS (FUS)

**ION541/BIIB105**  
ALS (ATXN2)

**ION260/BIIB132**  
Spinocerebellar Ataxia Type 3 (ATXN3)

**Zilganersen**  
Alexander disease (GFAP)

**ION464/BIIB101**  
Parkinson's disease and Multiple System Atrophy (alpha-synuclein)

1. SPINRAZA: [www.spinraza.com](http://www.spinraza.com); QALSODY: [www.qalsody.com](http://www.qalsody.com); Biogen is responsible for commercializing SPINRAZA and QALSODY.

# Q3 2023 Financial Performance

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Beth Hougen  
Chief Financial Officer

# YTD:2023 Financial Results<sup>1</sup>

On Track to Achieve 2023 Guidance

**\$463 million in revenue**

Increased 6% YoY

**\$732 million in operating expenses<sup>2</sup>**

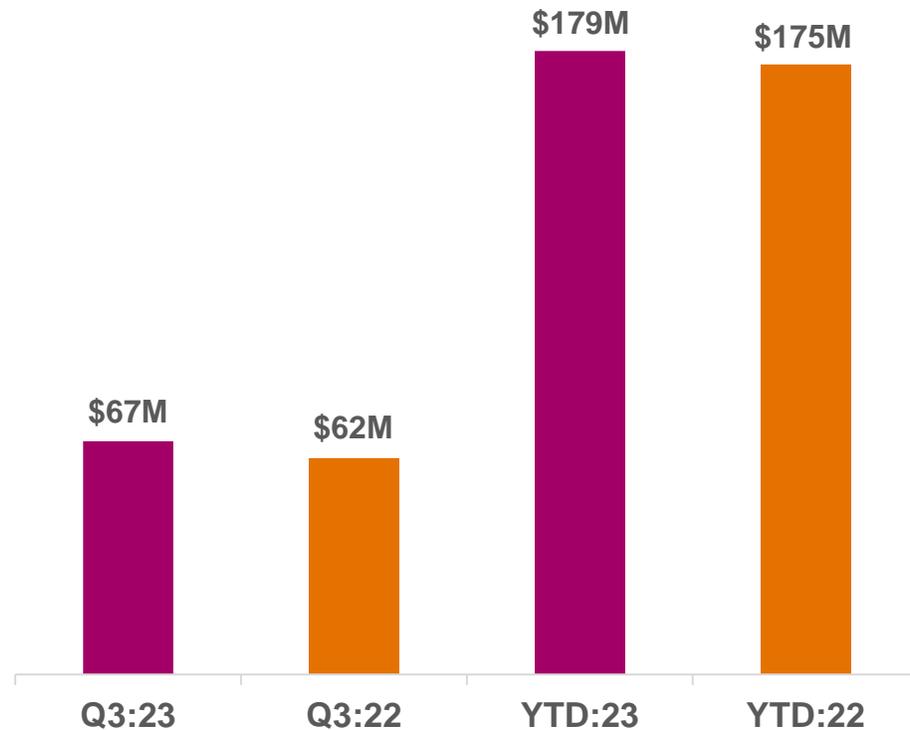
Investing to advance pipeline and go-to-market activities

**\$269 million operating loss<sup>2</sup>**

**\$2.2 billion of cash**  
Deploying financial resources to bring transformational medicines to the market

1. For the nine months ended September 30, 2023. 2. Non-GAAP – please see reconciliation to GAAP in Q3 2023 press release

## \$67M Q3 and \$179M YTD:23 Royalties to Ionis



1. RESPOND: [clinicaltrials.gov/NCT04488133](https://clinicaltrials.gov/NCT04488133); 2. ASCEND: [clinicaltrials.gov/NCT05067790](https://clinicaltrials.gov/NCT05067790); 3. DEVOTE: [clinicaltrials.gov/NCT04089566](https://clinicaltrials.gov/NCT04089566)

- **\$179M in SPINRAZA royalties for Q3 YTD:23**
  - SPINRAZA Q3:23 royalties increased by 9 percent QoQ, driven by a low single digit increase in global product sales
  - Results demonstrate SPINRAZA’s resilience against emerging competition in U.S. and abroad
- **SPINRAZA’s potential growth drivers:**
  - Expansion of existing markets
  - Robust Life Cycle Management program including ongoing RESPOND, ASCEND and DEVOTE studies aim to address remaining unmet need and inform treatment decisions for the SMA community<sup>1-3</sup>
  - Future of SMA franchise includes SPINRAZA follow-on, ION306 (BIIB115)

# YTD 2023 Financial Highlights<sup>1</sup>

On Track to Achieve 2023 Guidance

**\$463M**

## Revenue

**Commercial Revenue: \$230M**

- SPINRAZA comprised largest component

**R&D Revenue: \$233M**

- Reflects the value Ionis' technology creates as partnered programs advance

**\$732M**

## Operating Expenses<sup>2</sup>

**R&D Expenses<sup>2</sup>: \$585M**

- Increased YoY primarily from advancing late-stage programs

**SG&A Expense<sup>2</sup>: \$140M**

- Increased YoY from advancing go-to-market activities for multiple near-term launches

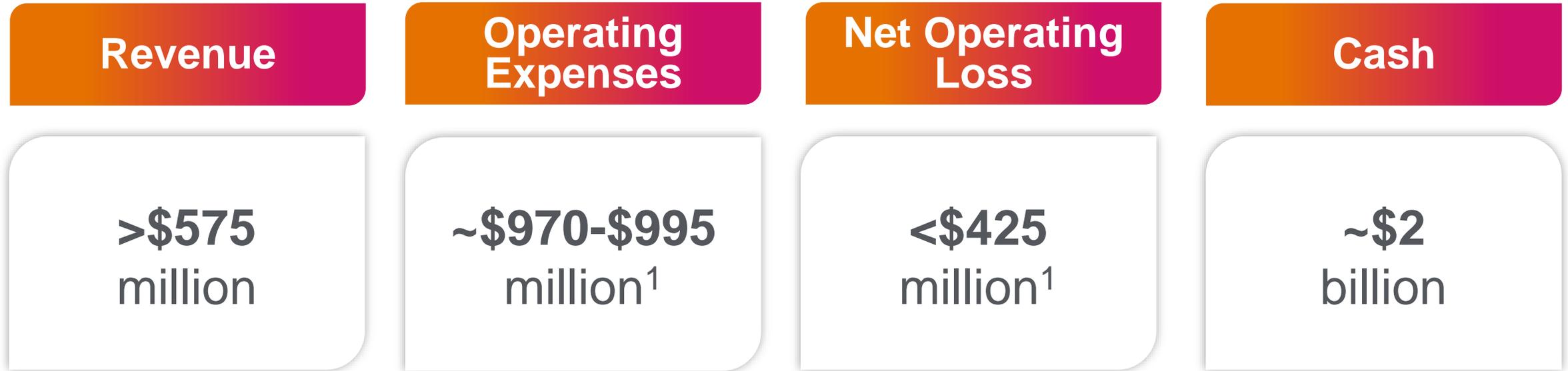
**\$2.2B**

## Cash & short-term investments

Strong financial foundation enables continued investments to drive increasing value

1. For the nine months ended September 30, 2023. 2. Non-GAAP – please see reconciliation to GAAP in Q3 2023 press release.

# On Track to Achieve 2023 Financial Guidance



## Expectations for 2024:

**Revenue:** Substantial and sustained

- **Commercial:** sustained SPINRAZA royalty expected; modest eplontersen royalties commensurate with launch ramp
- **R&D:** multiple sources from numerous advancing programs

**Operating Expenses:** Continue to reflect investments to unlock next-level value

1. Non-GAAP – please see reconciliation to GAAP in Q3 2023 press release.

# Conclusion

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Brett Monia, Ph.D.  
Chief Executive Officer

# Substantial Progress Year to Date<sup>1</sup>

## Clinical Data Events

- ✓ **Eplontersen:** Phase 3, NEURO-TTRansform 35, 66 & 85-week data, ATTRv-PN
- ✓ **Olezarsen:** Phase 3, Balance study data, FCS
- ✓ **Donidalorsen:** Phase 2, OLE 1-year data, HAE
- ✓ **Donidalorsen:** Phase 2, OLE 2-year data, HAE
- ✓ **SPINRAZA:** Phase 4, interim RESPOND data, SMA
- ✓ **Bepirovirsen:** Phase 2, B-Together data, HBV
- ✓ **IONIS-FB-L<sub>Rx</sub>:** Phase 2, IgAN interim data, IgAN

## Enrollment Achievements

- ✓ **Donidalorsen:** Phase 3, OASIS-HAE full enrollment, HAE
- ✓ **Eplontersen:** Phase 3, CARDIO-TTRansform full enrollment, ATTR-CM
- ✓ **IONIS-FB-L<sub>Rx</sub>:** Phase 2, GOLDEN study full enrollment, GA
- ✓ **ION541:** Phase 1/2, HALOS study full enrollment, Angelman syndrome

## Phase 3 Initiations

- ✓ **Bepirovirsen:** chronic HBV
- ✓ **IONIS-FB-L<sub>Rx</sub>:** IgA nephropathy
- ✓ **Zilganersen:** Alexander disease

## Regulatory Actions

- ✓ **QALSODY:** FDA approval SOD1-ALS  
**EU approval<sup>2</sup>**
- ✓ **Eplontersen:** NDA filing acceptance, ATTRv-PN  
**PDUFA: December 22, 2023**
- ✓ **Eplontersen:** EU MAA filing acceptance, ATTRv-PN
- ✓ **Eplontersen:** Health Canada filing acceptance, ATTRv-PN
- ✓ **Orphan Drug Designations:**
  - ✓ Eplontersen (EU)
  - ✓ Donidalorsen (US)
  - ✓ Ulefnersen (US)
  - ✓ ION356 (US)

1. Timing expectations are based on current assumptions and are subject to change. 2. CHMP opinion anticipated in Q4:2023.

# Ionis is Poised to Drive Next-Level Value for Patients and All Ionis Stakeholders

## Substantial progress on key value-driving objectives

01

### Integrated Commercial Capabilities in Place

Steady cadence of new potentially transformational medicines to the market

02

### Established Wholly Owned Pipeline

Advancing and growing our wholly owned pipeline in focused therapeutic areas, including neurology

03

### Leading Technology

Advancing technology to:

- Expand existing franchises
- Address new therapeutic areas

04

### Strong Financial Foundation Poised for Growth

Multi-billion-dollar revenue opportunity will enable positive cash flow



Jackson,  
Angelman Syndrome Patient

# Q&A



# IONIS<sup>®</sup>

