



Q3:23 Business Update and Financial Results

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_{Rx}, 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.

In this presentation, unless the context requires otherwise, “Ionis,” “Company,” “we,” “our,” and “us” refers to Ionis Pharmaceuticals and its subsidiaries.

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Introduction

Brett Monia, Ph.D.
Chief Executive Officer

Important Achievements in 2023¹

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 billion² 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

Onaiza Cadoret
Chief Global Product Strategy and Operations Officer

Poised to Deliver Ionis Medicines to Patients in Need^{1,2,3}

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: **Multibillion⁴**

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

Estimated peak sales: **>\$1 Billion**

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^{1,2,3,4}



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 ^{3,4}
	ATTR	~500K
CM	wtATTR & ATTRv	300K-500K
PN	ATTRv-PN + Mixed	40K

Currently <20% of ATTR patients are treated²

Ocular Manifestation

Lumbar Spinal Stenosis

GI Manifestations

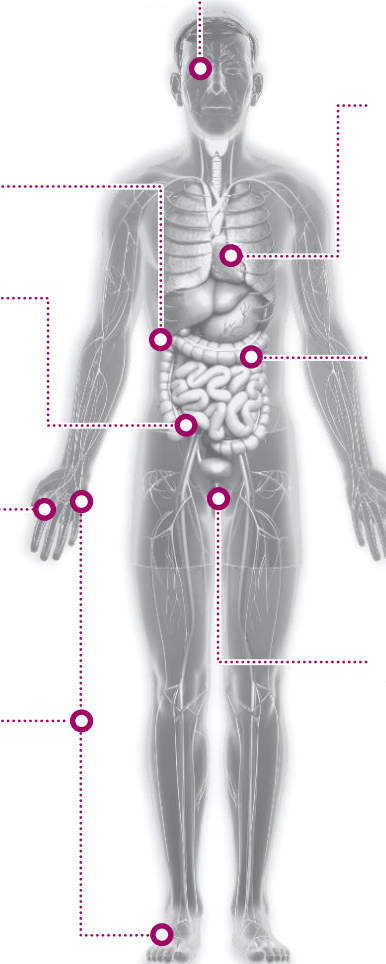
Bilateral Carpal Tunnel Syndrome

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



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.^{1,4} For more information on the disease's impact on your patients, keep reading and visit our website below.


Learn more at seethepatterns.com

A MISDIAGNOSIS OR DELAYED DIAGNOSIS CAN HAVE LASTING CONSEQUENCES^{1,2}

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

PATIENTS WITH ATTR FACE A MEDIAN DIAGNOSTIC DELAY OF	~60% OF PATIENTS SAW
>3 YEARS REGARDLESS OF PHENOTYPIC PRESENTATION ⁴	>3 PHYSICIANS BEFORE RECEIVING THE CORRECT DIAGNOSIS OF ATTR ⁵

The importance of a timely and correct diagnosis^{1,3}



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 ATTR¹

Learn how to diagnose ATTR.

Explore diagnostic paths


References: 1. Nishii-Nicolaou JN, Karam C, Khella S, Maurer MS. Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multigenerational awareness. *Heart Fail Rev*. 2022;27(3):785-795. 2. Aboody T, Bernik JL, et al. Guidelines of transthyretin-related hereditary amyloidosis for clinicians. *Clinchem*. *Pharm*. 2019;13(1). 3. Garcia MA. Hereditary ATTR amyloidosis: burden of disease and diagnostic challenges. *Am J Med*. 2017;130(1):117-124. 4. Adams D, Aguilera V, Polyzaki M, Sarwal N, Sierra MS, Nishii-Nicolaou J. Expert opinion on monitoring symptomatic hereditary transthyretin-mediated amyloidosis and assessment of disease progression. *Clinchem*. *Pharm*. 2021;15(1):411. 5. Louisa L, Maurer MS, Warner M, Guthrie S, Hsu K, Grogan M. Amyloidosis Research Consortium Cardiac Amyloidosis Survey: results from patients with AL and ATTR amyloidosis and their caregivers. Poster presented at 33rd Annual Heart Failure Society of America, September 13-16, 2019, Philadelphia, PA.

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JAMA

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WAINUA
(eplontersen) AS-01
injection for subcutaneous use

A NEW WAY FORWARD



COMING SOON

WAINUA
(eplontersen) AS-01
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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Extensive HCP Education

Poised to Deliver Ionis Medicines to Patients in Need^{1,2,3}

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: **Multibillion⁴**

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

Estimated peak sales: **>\$1 Billion**

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

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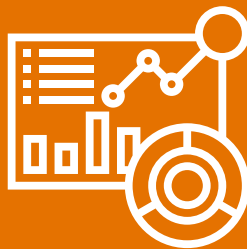
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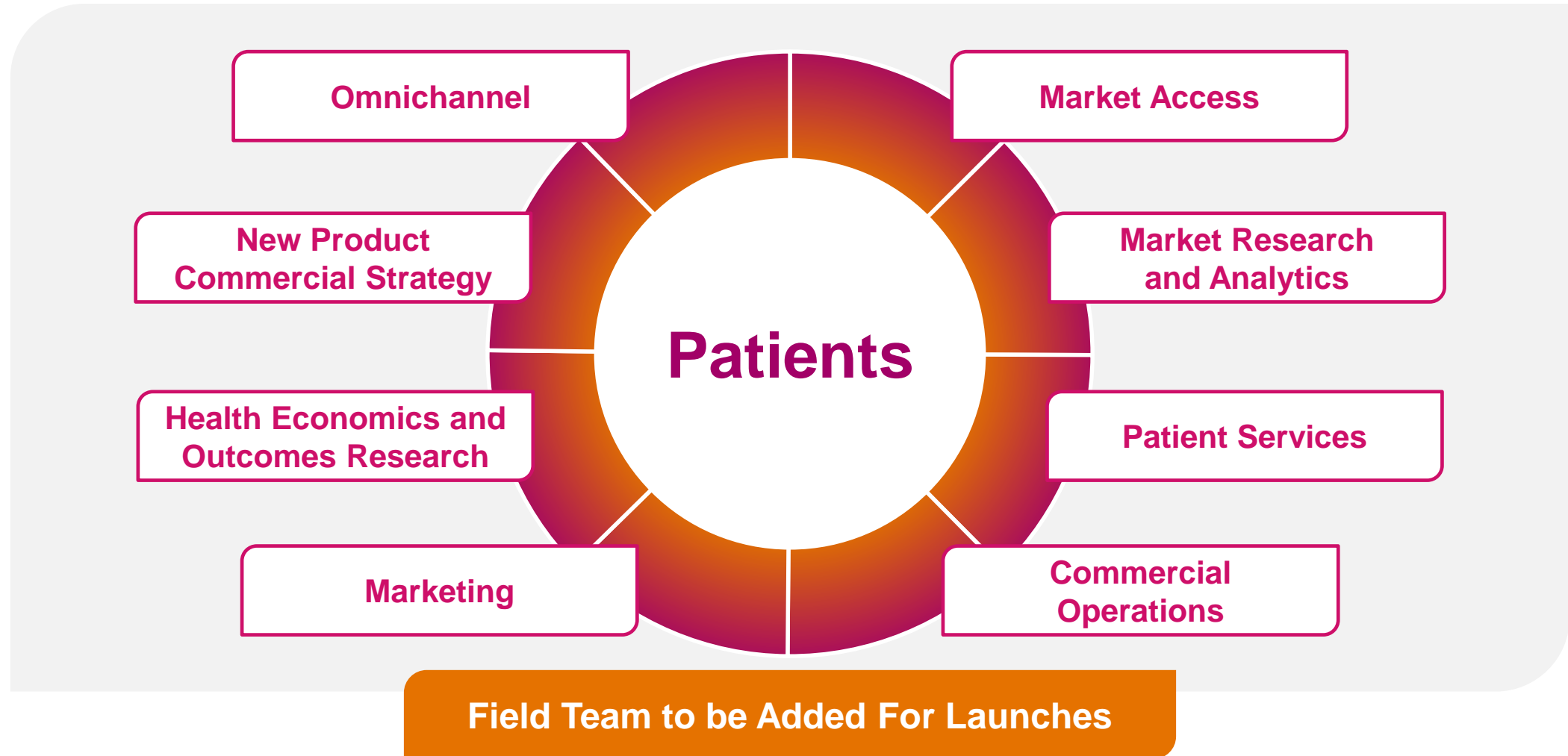
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Preparing for Next Wave of Wholly Owned Medicines

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



Pipeline Performance

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

Eplontersen's Development Program is Delivering Robust Results to Address Underserved ATTR Patients Globally¹

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 SHTG¹

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 ≥ 500 mg/dL enrolling
- Pivotal registrational study
- ~540 patients

CORE₂ a hypertriglyceridemia study

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

Essence TIMI-73b

- Supportive Ph3 study in patients w/ TGs ≥ 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^{1,2}

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.

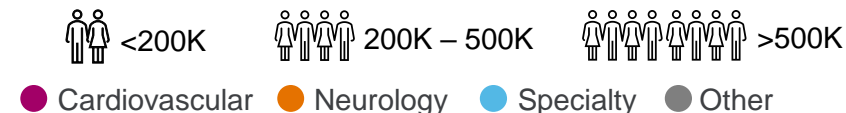
Well Positioned to Deliver Steady Cadence of Potentially Transformational Medicines

Phase 3 Pipeline

		Indication	Prevalence ¹	Next Event ²
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 _{Rx}		IgA nephropathy ³		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_{Rx} 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
Medicines¹

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_{Rx}/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; QALSODY: www.qalsody.com; Biogen is responsible for commercializing SPINRAZA and QALSODY.

Q3 2023 Financial Performance

Beth Hougen
Chief Financial Officer

YTD:2023 Financial Results¹

On Track to Achieve 2023 Guidance

\$463 million in revenue

Increased 6% YoY

\$732 million in operating expenses²

Investing to advance
pipeline and go-to-market activities

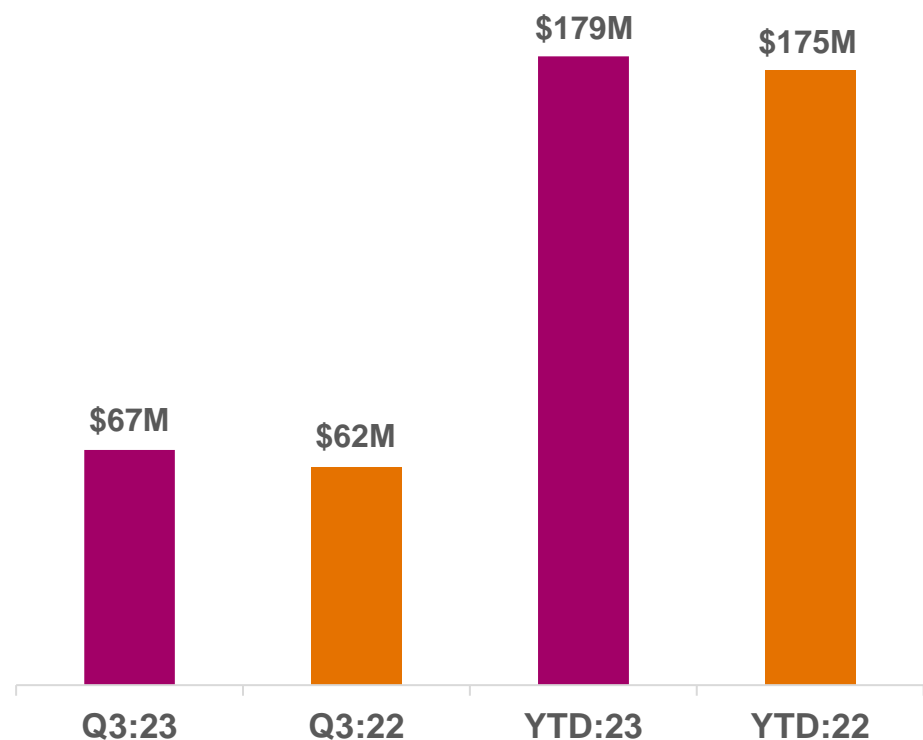
\$269 million operating loss²

\$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; 2. ASCEND: clinicaltrials.gov/NCT05067790; 3. DEVOTE: 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 community¹⁻³
 - Future of SMA franchise includes SPINRAZA follow-on, ION306 (BIIB115)

YTD 2023 Financial Highlights¹

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 Expenses²

R&D Expenses²: \$585M

- Increased YoY primarily from advancing late-stage programs

SG&A Expense²: \$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

Revenue	Operating Expenses	Net Operating Loss	Cash
>\$575 million	~\$970-\$995 million ¹	<\$425 million ¹	~\$2 billion

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

Brett Monia, Ph.D.
Chief Executive Officer

Substantial Progress Year to Date¹

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_{Rx}:** 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_{Rx}:** 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_{Rx}:** IgA nephropathy
- ✓ **Zilganersen:** Alexander disease

Regulatory Actions

- ✓ **QALSODY:** FDA approval SOD1-ALS
EU approval²
- ✓ **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[®]

