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.

Introduction

Brett Monia, Ph.D.
Chief Executive Officer

Important Achievements in 2023[1]

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[2] 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: **Multibillion**[4]

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]

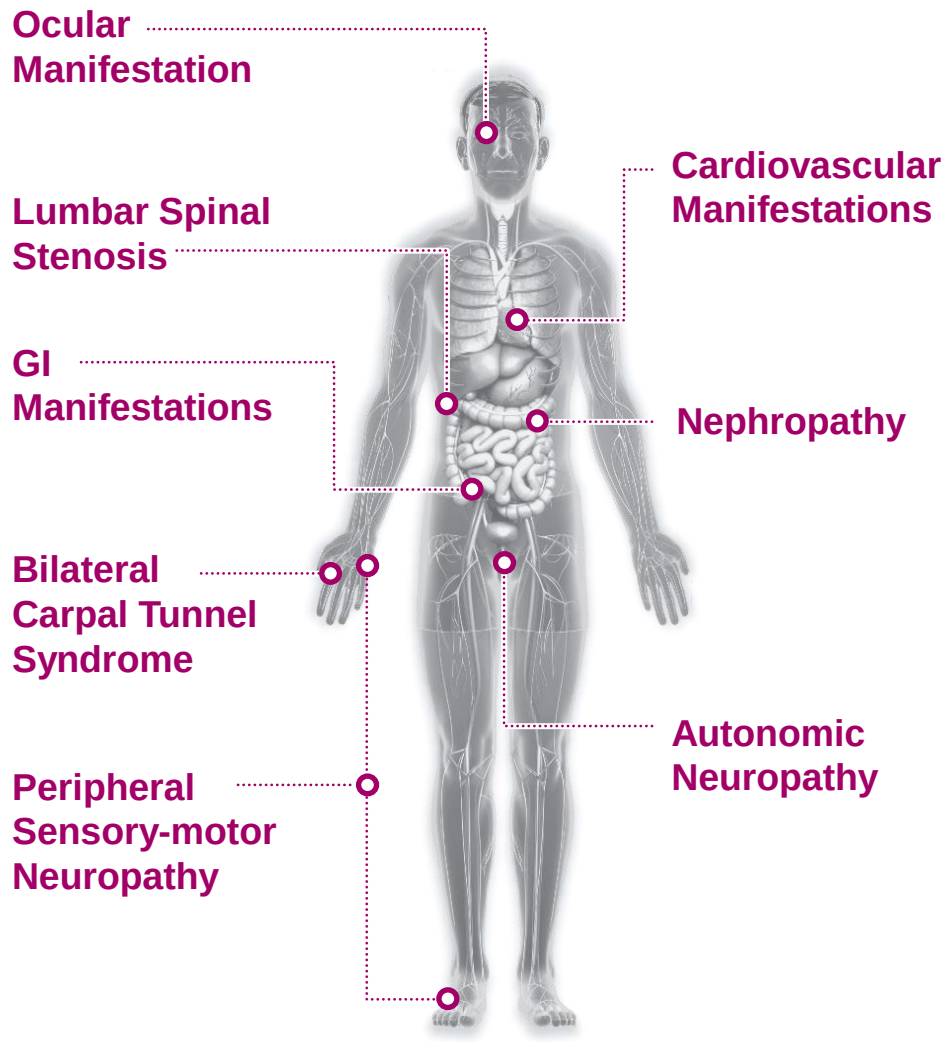
Potential to be the **treatment of choice** for the **global ATTR population** with monthly **self-administered** auto-injector profile

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

Expanding Patient Population

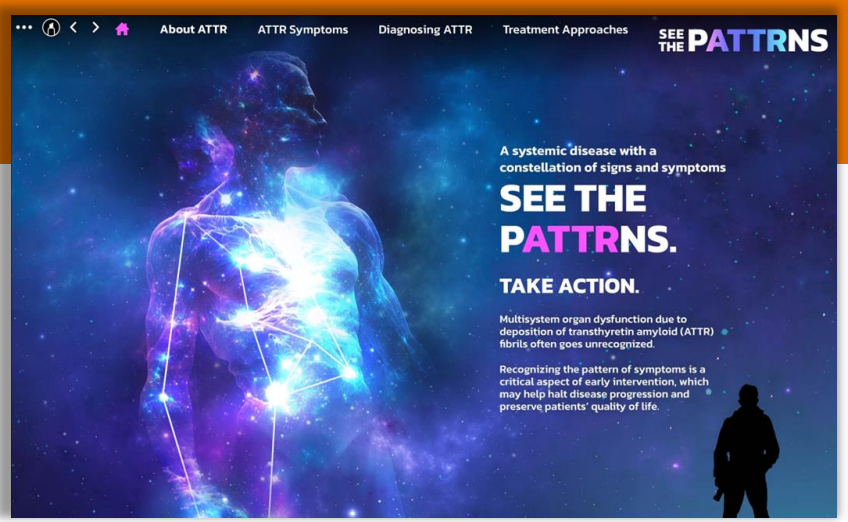
	Indication	Patients[3,4]
	ATTR	~500K
CM	wtATTR & ATTRv	300K-500K
PN	ATTRv-PN + Mixed	40K

Currently <20% of ATTR patients are treated[2]

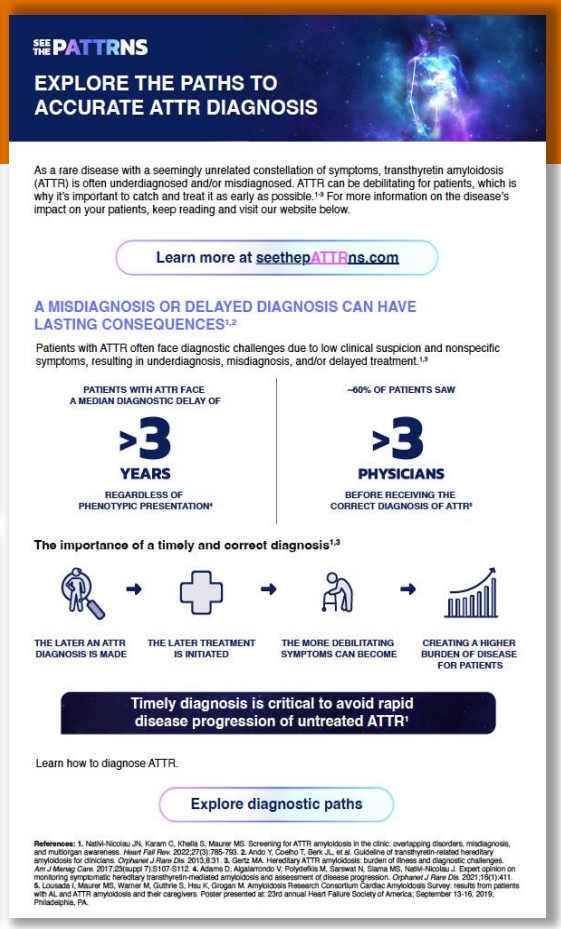


amyloidosis.org (https://amyloidosis.org/facts/familial/; https://amyloidosis.org/facts/wild-type/
NOTE: For illustrative purposes only. 1. ATTRv-PN potential approval this year. 2. Market data on file. 3. Conceição I et al. *J Peripher Nerv Syst*. 2016;21:5-9. 4. Ando Y et al. *Orphanet J Rare Dis*.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

Building Launch Momentum with Campaigns to Broaden Disease and Brand Awareness



Extensive HCP Education



CLICK HERE:
JAMA seethepatterns comingsoon

Poised to Deliver Ionis Medicines to Patients in Need[1,2,3]

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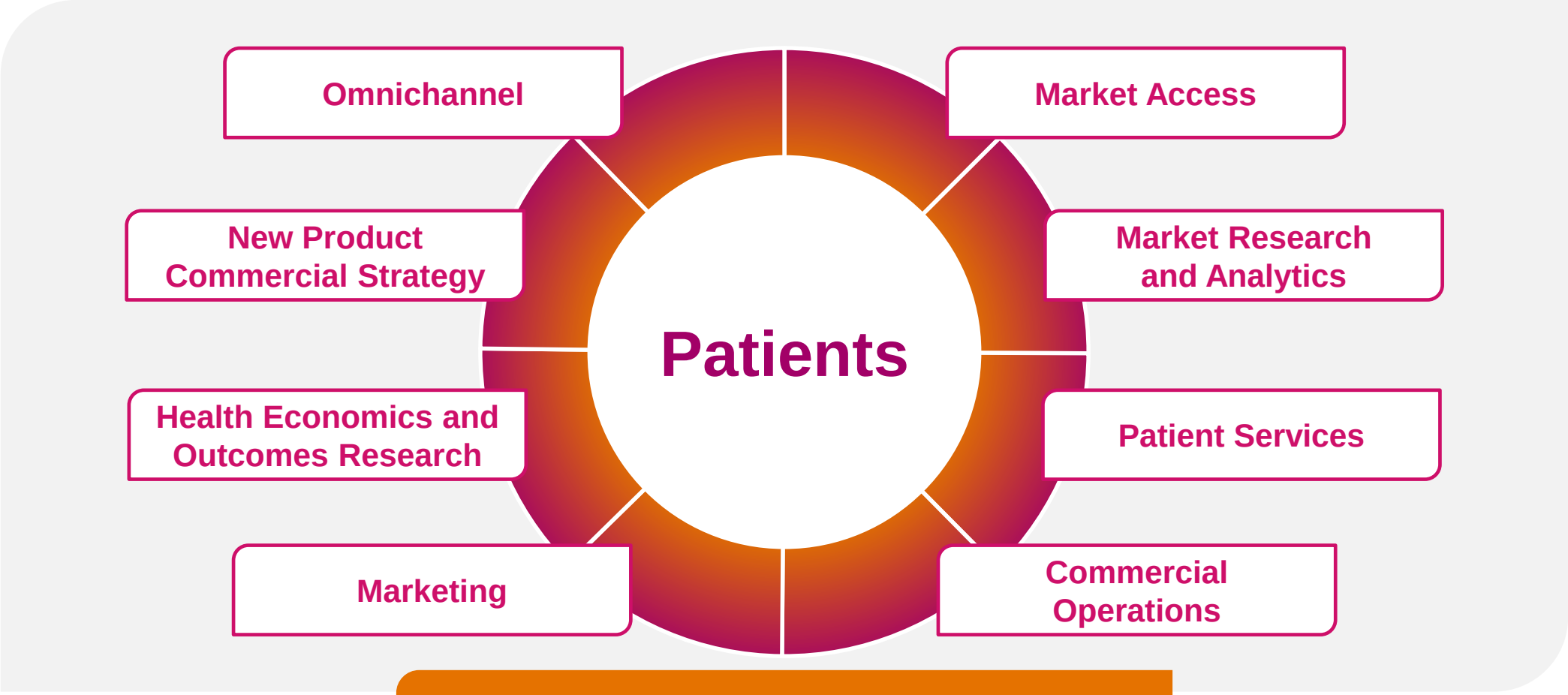
Commercial Infrastructure in Place: Ready to Deliver Medicines to People in Need



Pipeline Performance

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

Eplontersen's Development Program is Delivering Robust Results to Address Underserved ATTR Patients Globally[1]

ATTRv POLYNEUROPATHY

neuro TTRansform

- 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

cardio TTRansform

- 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

TTRansform beyond

- 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[1]

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

OASIS

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

OASIS plus

- 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

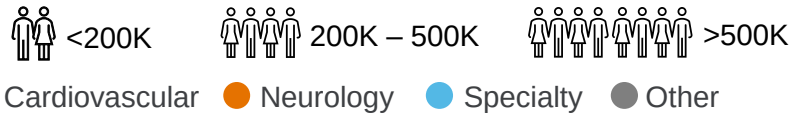
1. Based on double blind Phase 2 study data published in NEJM in 2022 and Phase 2 OLE data. 2. Timing expectations based on current assumptions and subject to change.

Well Positioned to Deliver Steady Cadence of Potentially Transformational Medicines

Phase 3 Pipeline

		Indication	Prevalence[1]	Next Event[2]
Eplontersen	IONIS / AstraZeneca	ATTRv-PN		**US approval (2023)** **OUS submissions (2023)**
		ATTR-CM		**Ph3 data (2025)**
Olezarsen	IONIS	FCS		**NDA filing (2024)**
		SHTG		**Ph3 data (2024)**
Donidalorsen	IONIS	HAE		**Ph3 data (2024)**
Zilganersen	IONIS	Alexander disease		**Ph3 data (2025)**
Ulefnersen	IONIS	FUS-ALS		**Ph3 data (2025)**
Pelacarsen	NOVARTIS	Lp(a) CVD		**Ph3 data & filing (2025)**
Bepirovirsen	GSK	HBV		**Ph3 B-Well 1 & 2 data (2025)**
IONIS-FB-L$_{Rx}$	Roche	IgA nephropathy[3]		**Ph2 data (2024)**
Tofersen	Biogen	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 Medicines[1]

12

Medicines in Clinical Development

4

New Medicines Entering the Clinic by YE:2024

SPINRAZA
SMA (SMN2)

QALSODY
SOD1-ALS (SOD1)

Eplontersen
ATTR (TTR)

ION306/BIIB115
SMA (SMN2)

Tofersen
Presymptomatic SOD1-ALS (SOD1)

ION582/BIIB121
Angelman syndrome (UBE3A-ATS)

IONIS-MAPT$_{Rx}$/BIIB080
Alzheimer's disease (Tau)

Ulefnersen
FUS-ALS (FUS)

ION859/BIIB094
Parkinson's disease (LRRK2)

ION541/BIIB105
ALS (ATXN2)

Tominersen
Huntington's disease (HTT)

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 Results[1]

On Track to Achieve 2023 Guidance

$463 million in revenue
Increased 6% YoY

$732 million in operating expenses[2]
Investing to advance pipeline and go-to-market activities

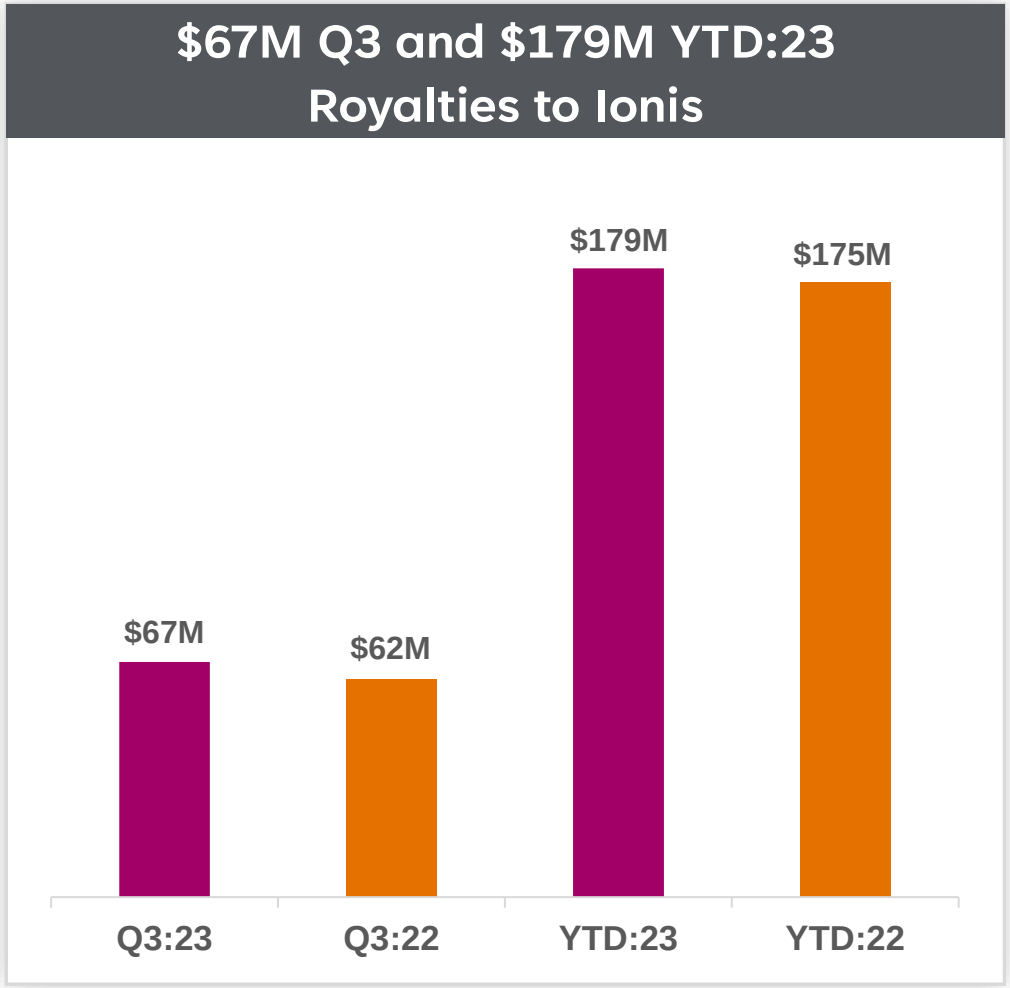
$269 million operating loss[2]

$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

Global Leader for the Treatment of SMA

SPINRAZA® (nusinersen) injection 12 mg/5 mL



- **$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[1-3]
  - Future of SMA franchise includes SPINRAZA follow-on, ION306 (BIIB115)

1. RESPOND: clinicaltrials.gov/NCT04488133; 2. ASCEND: clinicaltrials.gov/NCT05067790; 3. DEVOTE: clinicaltrials.gov/NCT04089566

For important prescribing and safety information, please refer to: www.spinraza.com

YTD 2023 Financial Highlights[1]

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[2]**

R&D Expenses[2]: $585M

- Increased YoY primarily from advancing late-stage programs

SG&A Expense[2]: $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 Date[1]

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 approval[2]

- **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®