Q2:23 Financial Results and Business Update

August 9, 2023

Nasdaq: IONS

On Today's Earnings Call

Brett Monia, Ph.D.
Chief Executive Officer

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

Beth Hougen
Chief Financial Officer

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

Eugene Schneider, M.D.
Executive Vice President,
Chief Clinical Development Officer

Onaiza Cadoret
Executive Vice President,
Chief Global Product Strategy and Operations Officer

IONIS

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, 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 the First Half of 2023[1]

Late-Stage Pipeline

- QALSODY: approved by FDA for SOD1-ALS[2]
- Eplontersen:
  - PN: December 2023 PDUFA date; on track for oUS submissions
  - CM: largest study in ATTR-CM now fully enrolled; data as early as H1:2025
- Olezarsen: Ph3 FCS data expected H2:23
- Donidalorsen: Ph3 study fully enrolled; data expected H1:24

Commercial Readiness

- On track to launch eplontersen, olezarsen and donidalorsen
  - Co-commercializing eplontersen with AstraZeneca in the US
  - Independently launching olezarsen and donidalorsen
- Key functions in place: global product strategy, market access, brand teams, etc.

Financial Foundation

- On track to achieve 2023 financial guidance
- $2.4 billion[3] in cash enables investment to drive increasing value
- Successfully refinanced 2024 convertible notes to further strengthen balance sheet

Positioned For Substantial Revenue Growth

1. Timing expectations based on current assumptions and subject to change 2. For important prescribing and safety information, please refer to: www.qalsody.com 3. Cash, cash equivalents and short-term investments at June 30, 2023.

Pipeline Performance

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

Eplontersen: Well Positioned to Address Underserved, Global ATTRv-PN Market[1,2]

Attractive Profile

- Met co-primary and key secondary endpoints[3,4,5]
- Halted neuropathy progression and improved QoL through Week-85[6]
- Substantial number of patients improved neuropathy impairment and QoL through week 85[6]
- Favorable safety and tolerability profile

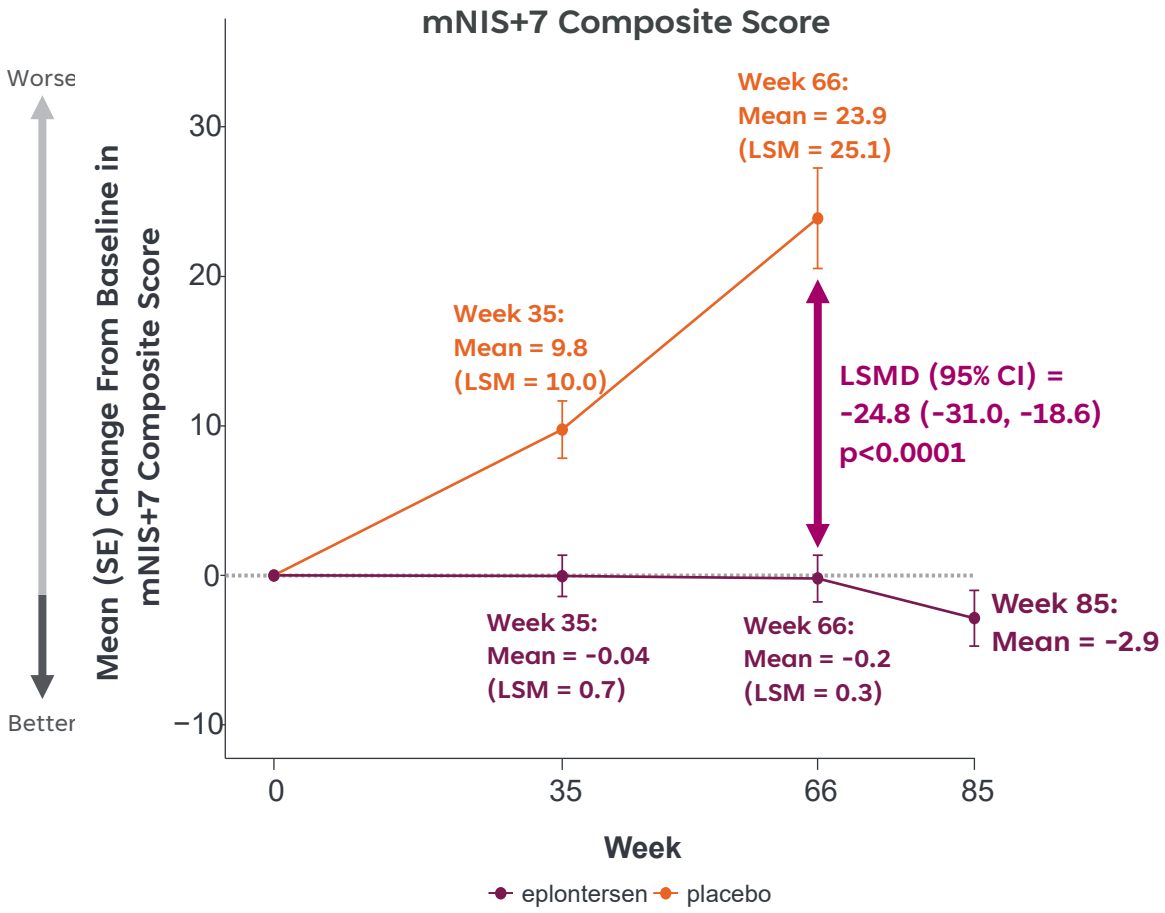
Next steps

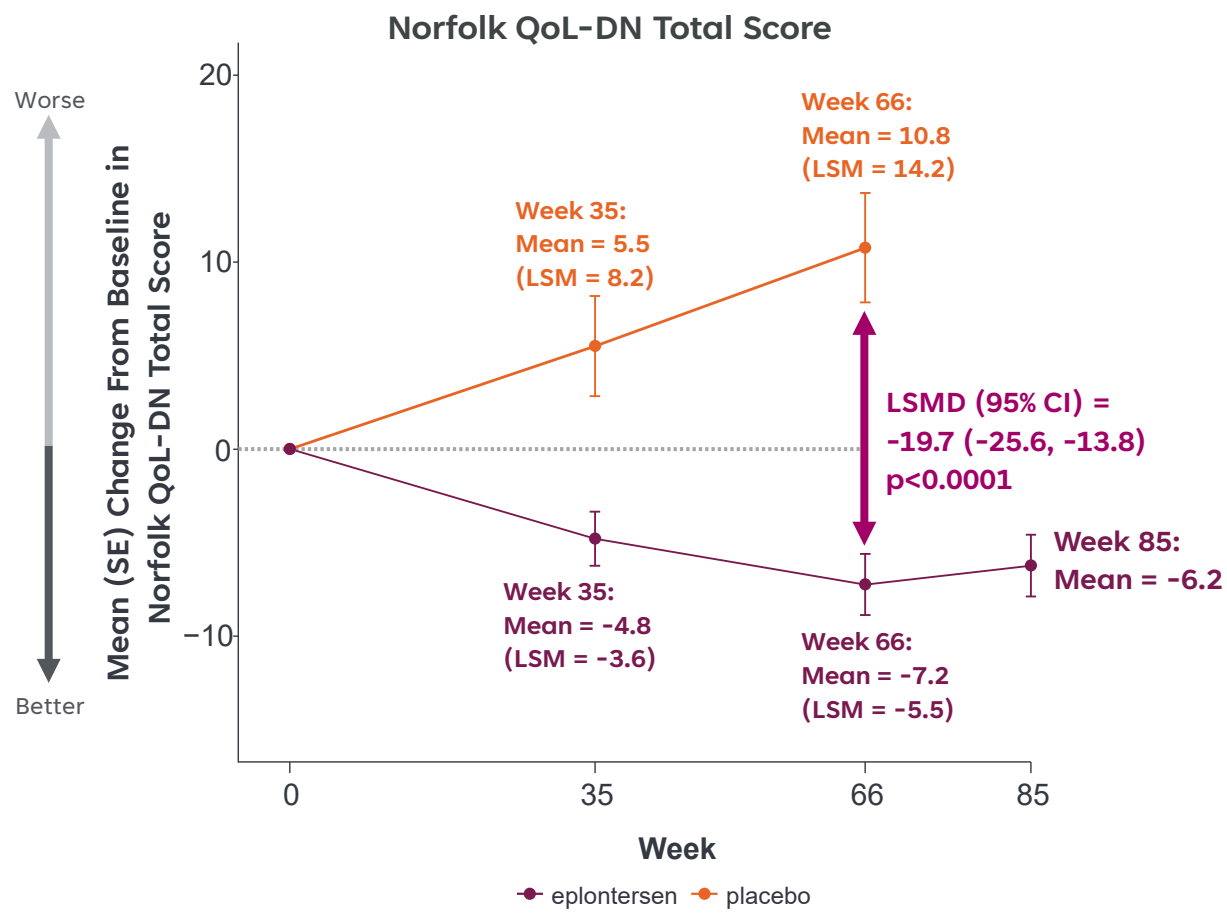
- Planning to launch in the U.S.; PDUFA December 22, 2023
- Preparing oUS regulatory submissions this year and next year
- On track for CARDIO-TTRansform data as early as H1:25 in broad ATTR-CM population with study fully enrolled

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Co-primary and secondary endpoints achieved at week-66 compared to external placebo. 4. Primary endpoints at week-66, Norfolk QoL was a secondary endpoint at week-35. 5. Secondary endpoints at week-66, mBMI, modified body mass index; PCS, Physical Component Summary; SF-36, 36-item Short Form Survey, NCS, neuropathy symptom and change, PND, polyneuropathy disability score. 6. Data reported at week-85 are exploratory.

IONIS

Week-85 Data Further Strengthens Eplontersen's Profile





Substantial number of patients showed improvement in neuropathy impairment and quality of life through 19 months of treatment

SE: Standard Error; LSM: Least Square Mean; LSMD: Least Square Mean Difference

Eplontersen's Development Program is Designed to Deliver Robust Results Supporting Treatment for ATTR[1]

ATTRv POLYNEUROPATHY

- Met co-primary + secondary endpoints in Phase 3 with favorable safety and tolerability
- NDA accepted, PDUFA date December 22, 2023
- On track for oUS submissions in 2023 and 2024

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.

IONIS

Olezarsen Development Program Designed to Support a >$1 Billion Market Opportunity[1,2]

FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS)

Balance
a familial chylomicronemia syndrome study

- Phase 3 data expected H2:2023
- On track to launch in late 2024[3]
- OLE progressing well
- Achieved fast track designation

SEVERE HYPERTRIGLYCERIDEMIA (SHTG)

CORE
a hypertriglyceridemia study

- SHTG Phase 3 study enrolling
- First pivotal study in large SHTG population

CORE2
a hypertriglyceridemia study

- Confirmatory pivotal study enrolling
- Supportive of registration

ESSENCE Plus

- ESSENCE study in patients with mild TGs and CVD risk
- Strengthens safety database necessary for approval
- Additional profile-enhancing studies underway

1. Timing expectations and peak sales estimates are based on current assumptions and are subject to change 2. Estimated peak sales FCS and SHTG. 3. Assuming approval.

IONIS

Donidalorsen Positioned to Demonstrate Competitive HAE Prophylactic Profile[1]

Hereditary Angioedema

OASIS

- Fully enrolled with data expected in H1:2024
- New 2-year Phase 2 OLE data reinforce donidalorsen's competitive profile
- Positive Phase 2 and 1-year OLE data, including QoL data reported

OASIS plus

- SWITCH study underway in patients previously treated with other prophylactic therapies
- Phase 3 OLE study underway in patients who have completed OASIS

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

IONIS

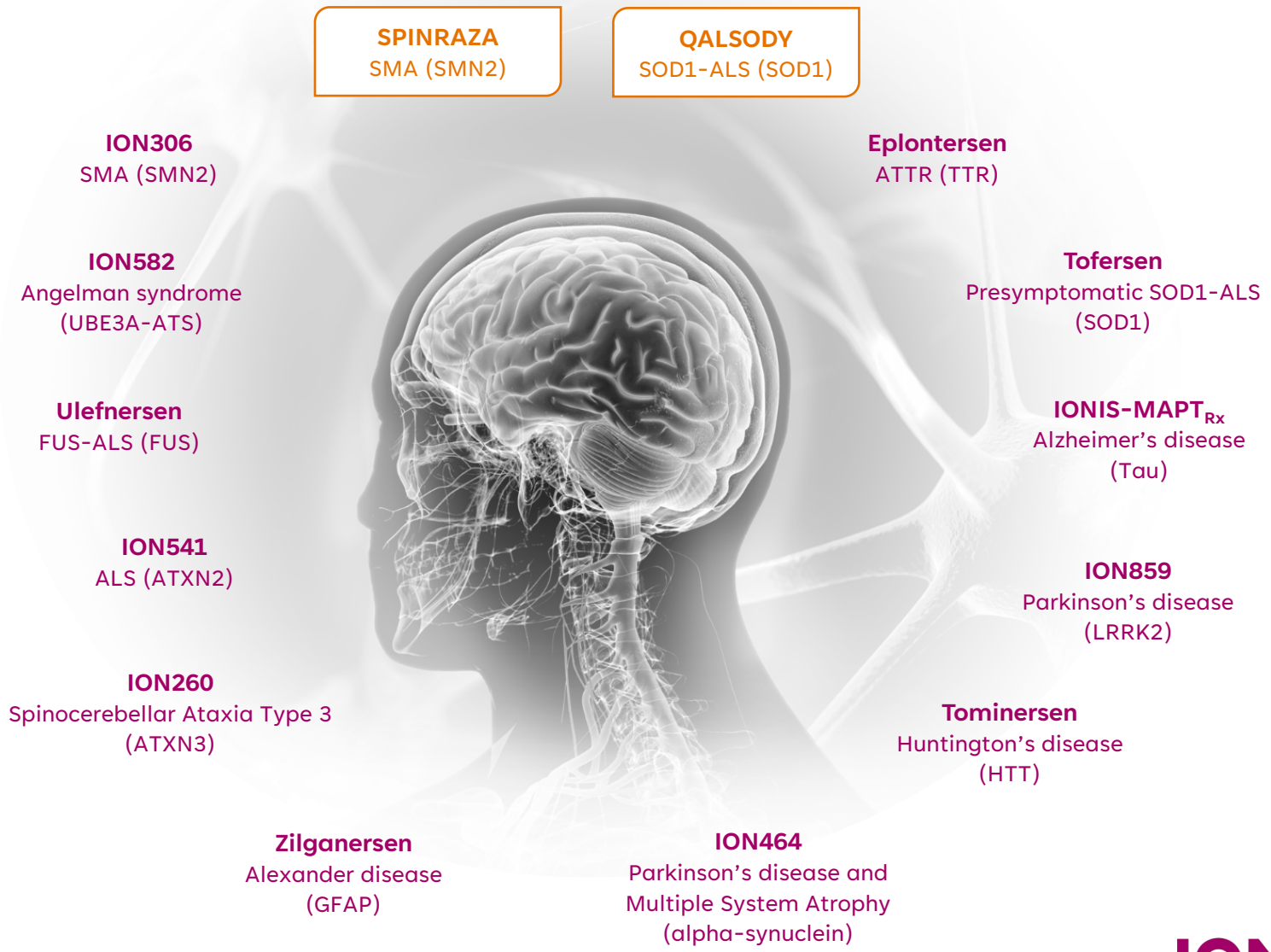
Industry Leading Neurology Franchise: Addressing Major Neurological Diseases

2

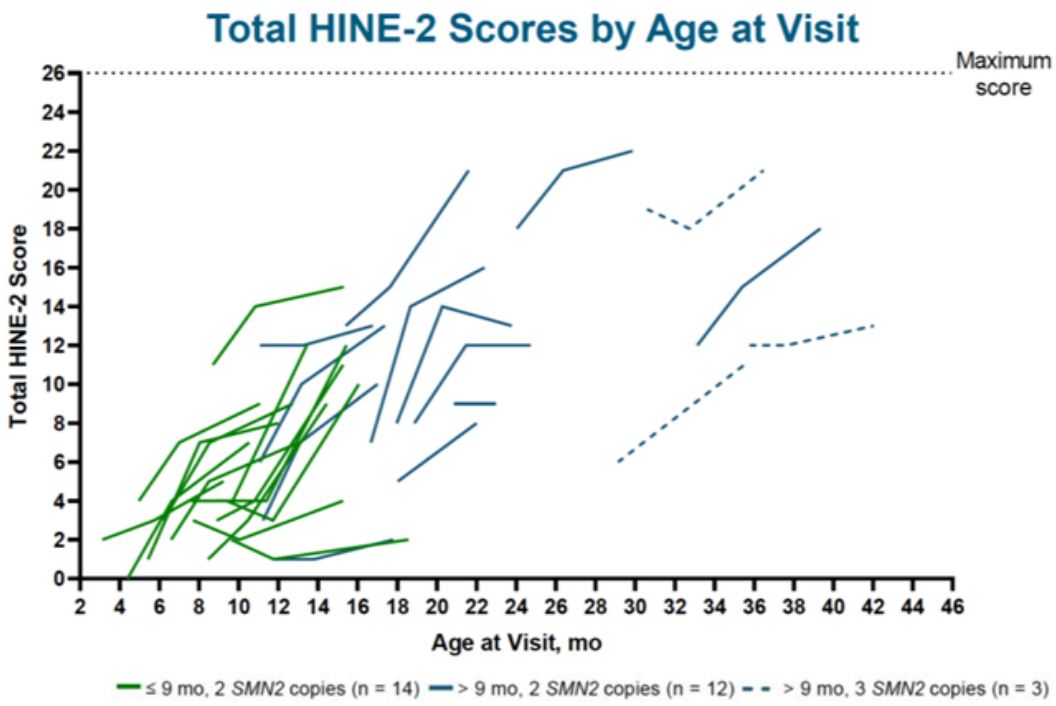
Approved Breakthrough Medicines

12

Medicines in Clinical Development



RESPOND: Interim Results Support SPINRAZA's Potential to Address Remaining Unmet Need[1,2]



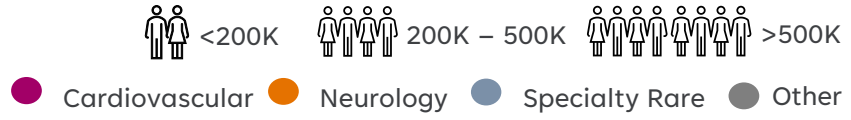
Participants with two SMN2 copies (n=24) improved by a mean of over 5 points on HINE-2

- **Interim results from Phase 4 RESPOND study in SMA patients with suboptimal response to gene therapy showed:**
  - Most participants had investigator and caregiver-reported suboptimal clinical status in multiple domains at baseline
  - Improvements in motor function as measured by increased mean total HINE-2 score from baseline to 6 months
  - No emerging safety concerns
- **Biogen continues to expand upon SPINRAZA's profile through additional ongoing studies:**
  - **ASCEND:** evaluating a higher dose of SPINRAZA in teen and adult SMA patients previously treated with risdiplam[3]
  - **DEVOTE:** evaluating a higher dose of SPINRAZA in a registrational study in infants, children and adult SMA patients[4]

1. Source: Proud et al., CureSMA 2023; must have suboptimal clinical status in > 1 of 4 domains (suboptimal motor function, abnormal swallowing/feeding ability for age; need for respiratory support or other) as determined by investigator at screening and Day 1 of study; #Median of 230.5 days in the study; HINE-2: Hammersmith Infant Neurological Exam - section 2; 2. RESPOND: clinicaltrials.gov/NCT04488133 3. ASCEND: clinicaltrials.gov/NCT05067790; 4. DEVOTE: clinicaltirals.gov/NCT04089566;

IONIS

Late-Stage Pipeline is Advancing and Expanding



		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		Ph3 data (2023)
		SHTG		Ph3 data (2024)
Donidalorsen	IONIS	HAE		Ph3 data (2024)
Ulefnersen	IONIS	FUS-ALS		Ph3 data (2025)
Pelacarsen	NOVARTIS	Lp(a) CVD		Ph3 data & filing (2025)
Bepirovirsen	GSK	HBV		Ph2b B-Together data (2023)
IONIS-FB-L_{Rx}	Roche	IgA nephropathy		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.

IONIS

Key Value Driving Events in 2023- Strong Progress To Date[1]

Regulatory Actions

- **QALSODY:** FDA approval decision, SOD1-ALS
- **QALSODY:** EU approval decision, SOD1-ALS[2]
- **Eplontersen:** FDA approval decision, ATTRv-PN
- **Eplontersen:** oUS filings, ATTRv-PN

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

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

Phase 3 Initiations

- **Bepirovirsen:** Phase 3 initiation, chronic HBV
- **IONIS-FB-L_{Rx}:** Phase 3 initiation, IgA nephropathy

1. Timing expectations are based on current assumptions and are subject to change, timing of partnered program catalysts based on partners' most recent publicly available disclosures. 2. CHMP opinion anticipated in Q4:2023.

IONIS

Q2 2023 Financial Performance

Beth Hougen
Chief Financial Officer

H1:2023 Financial Results

On Track to Achieve 2023 Guidance

$319 million in revenue
Increased 40% QoQ and 16% YoY

$469 million in operating expenses[1]
Investing to advance
pipeline and go-to-market activities

$150 million operating loss[1]

$2.4 billion of cash
Deploying financial resources to bring
transformational medicines to the market

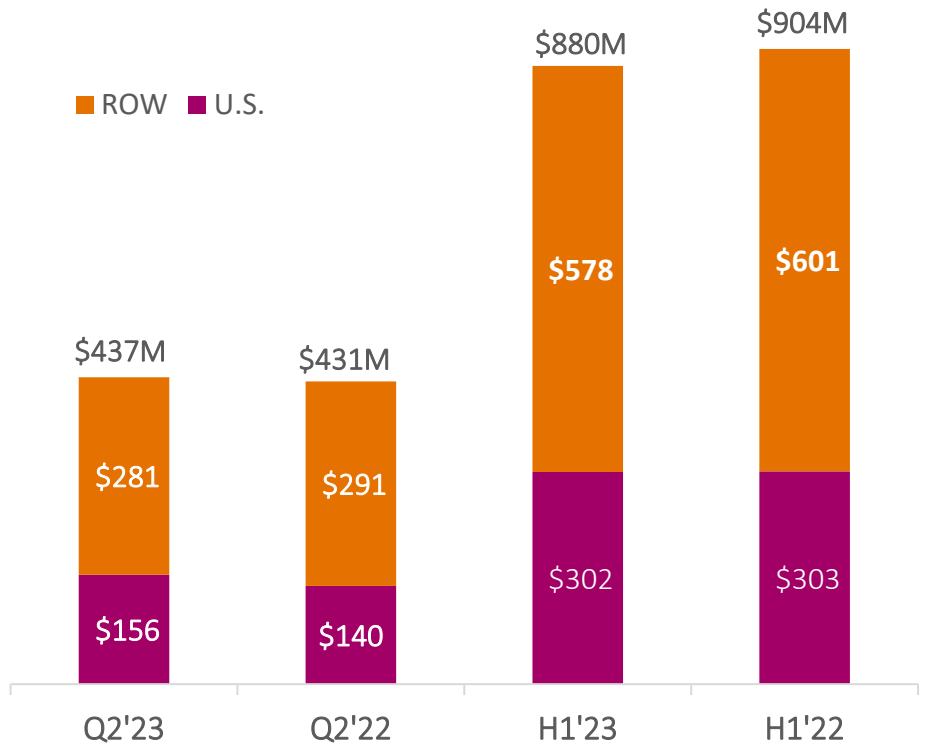
1. Non-GAAP – please see reconciliation to GAAP in Q2 2023 press release

IONIS

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Global Leader for the Treatment of SMA

$61M Q2 and $111M H1'23 Royalties to Ionis[1]



- **$111M in SPINRAZA royalties in H1'23 from $880M in product sales**
  - Global product sales essentially flat QoQ and YoY demonstrating 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: Recent RESPOND[2] interim results add to body of evidence supporting SPINRAZA's efficacy
    - Ongoing ASCEND[3] and DEVOTE[4] studies aim to address remaining unmet need and inform treatment decisions for the SMA community
  - Future of SMA franchise includes SPINRAZA follow-on, ION306 (BIIB115)

Source: Biogen Q2 2023 Financial Results and Business Update; 1.$ amounts in millions;
2. RESPOND: clinicaltrials.gov/NCT04488133; 3. ASCEND: clinicaltrials.gov/NCT05067790;
4. DEVOTE: clinicaltrials.gov/NCT04089566

IONIS®

H1:2023 Financial Highlights

On Track to Achieve 2023 Guidance

$319M — **Revenue**

Commercial Revenue: $146M

- SPINRAZA comprised largest component

R&D Revenue: $173M

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

$469M — **Operating Expenses***

R&D Expenses*: $389M

- Increased YoY primarily from advancing late-stage programs

SG&A Expenses*: $77M

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

$2.4B — **Cash & short-term investments**

Strong financial foundation enables continued investments to drive increasing value

*Non-GAAP – please see reconciliation to GAAP in Q2 2023 press release.

IONIS

On Track to Achieve 2023 Financial Guidance

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

Reflects investments in our strategic priorities:

- **Deliver** an abundance of transformational medicines to the market
- **Establish** an integrated commercial organization
- **Expand** and **diversify** our technology platform

*Non-GAAP – please see reconciliation to GAAP in Q2 2023 press release.

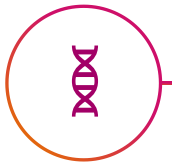
Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

Well Positioned to Capitalize on Our Progress by Executing on Strategic Priorities

Well on our way to achieving our goal of **delivering** an abundance of **new medicines** to the **market**

On track with our go-to-market activities for our **three near-term commercial opportunities**



Enhancing **leadership** position in RNA therapeutics through **technological advancements** to deliver steady cadence of **cutting-edge medicines** well into the future

Strong financial foundation enables us to invest in areas with the greatest potential to drive **increasing value**

IONIS

Q&A

IONIS®

Investor Day

October 4 • New York