IONIS®

A Genetic Medicines Company

Q1:23 Financial Results and Business Update

May 3, 2023

Nasdaq: IONS

Every Moment Matters...
in the Discovery, Development & Delivery
of Life Transforming Genetic Medicines

On Today's Earnings Call

Brett Monia, Ph.D.
Chief Executive Officer

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

Beth Hougen
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Executive Vice President, Research

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Executive Vice President,
Chief Clinical Development Officer

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Executive Vice President,
Chief Global Product Strategy and
Operations Officer

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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, ION363, pelacarsen, bepirovirsen, 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, 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.

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Introduction

Brett Monia, Ph.D.
Chief Executive Officer

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2023 Off to Strong Start with Several Important Achievements[1]

Late-Stage Pipeline

- QALSODY: approved by FDA for SOD1-ALS treatment
- Eplontersen: December 2023 PDUFA date; positive Ph3 data reported; on track for oUS submissions
- Olezarsen: Ph3 FCS data planned for H2:23
- Donidalorsen: on track for full enrollment in Phase 3 OASIS-HAE study soon; latest data reinforce potential competitive profile

Commercial Readiness

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

Financial Foundation

- On track to achieve 2023 financial guidance
- $2.3 billion[2] in cash enables continued investment in creating future growth opportunities

Positioned for Substantial Growth

1. Timing expectations based on current assumptions and subject to change 2. Cash, cash equivalents and short-term investments at March 31, 2023.

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Pipeline Performance

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

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

Met co-primary, secondary endpoints

- Primary endpoints: TTR reduction, mNIS+7 and Norfolk QoL[3]
- Secondary endpoints: mBMI, SF-36 PCS, NSC and PND scores[4]
- Substantial number of patients improved in measures of neuropathy progression and QoL compared to baseline

Favorable safety and tolerability

- Favorable safety and tolerability profile comparable to placebo
- Safety and tolerability consistent with LICA platform

Next steps

- Preparing to launch in the U.S.; PDUFA December 22, 2023
- Preparing for oUS regulatory submissions this year and next year
- Expect full enrollment mid-year for CARDIO-TTRansform in broader ATTR-CM population

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Primary endpoints at week-66, Norfolk QoL was a secondary endpoint at week-35. 4. 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.

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

FAMILIAL CHYLOMICRONEMIA SYNDROME (FCS)

Balance
a familial chylomicronemia syndrome study

- FCS Phase 3 BALANCE study fully enrolled
- Phase 3 data expected H2:2023
- OLE progressing well
- Achieved fast track designation
- Launch preparations underway

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.

Donidalorsen Phase 3 Development Program Designed to Replicate Robust Phase 2 and OLE Results[1]

Hereditary Angioedema

OASIS

- Positive Phase 2 and OLE data, including QoL data reported
- Phase 3 study on track for full enrollment in the near-term
- Phase 3 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

Potential to demonstrate competitive HAE prophylactic profile

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

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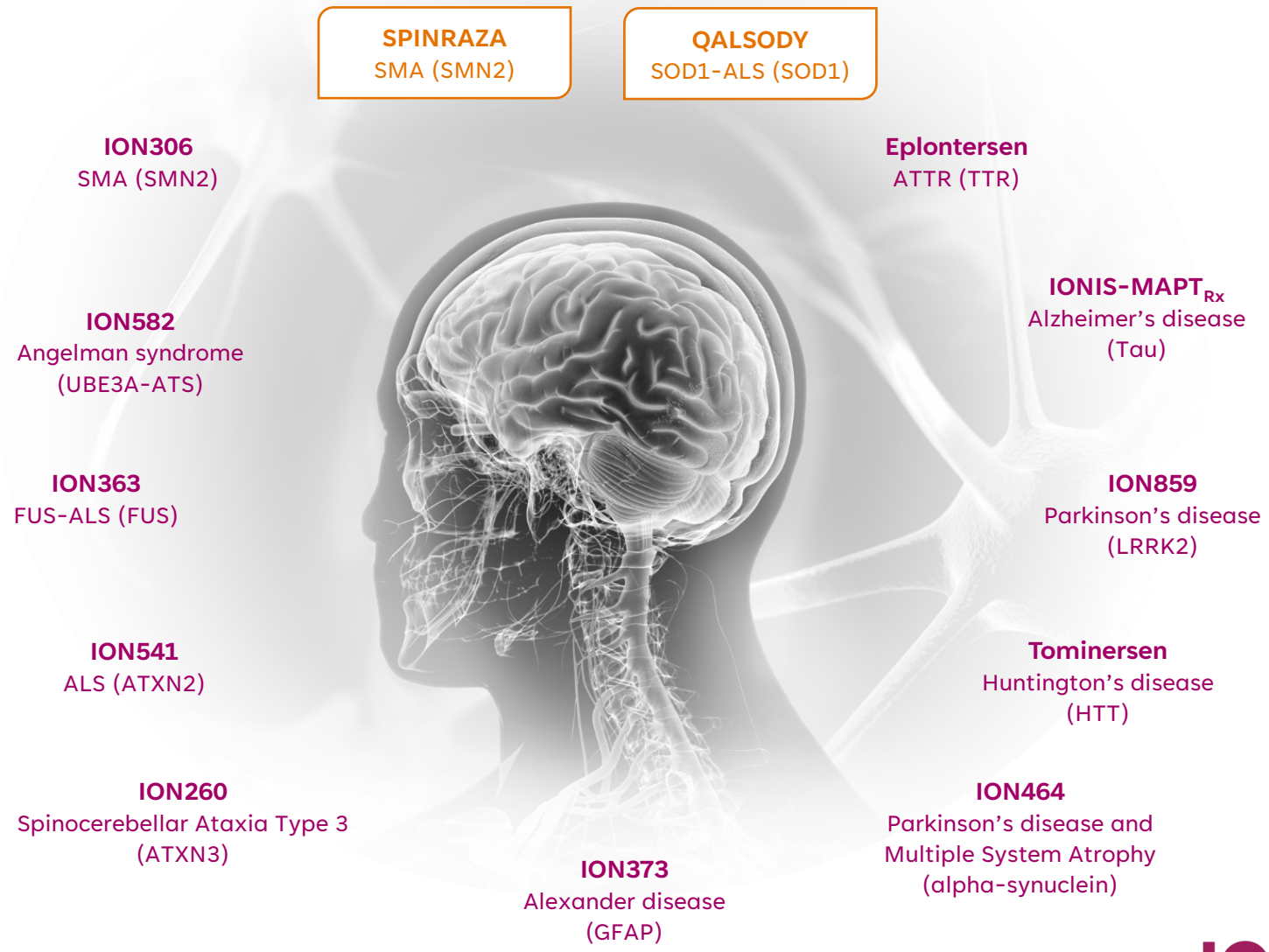
Leading Neurology Franchise: Addressing Major Neurological Diseases

2

Approved Medicines

12

Medicines in Development



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QALSODY: The First Treatment Approved To Target A Genetic Cause of ALS[1,2]

QALSODY to Treat SOD1-ALS

Received Accelerated Approval From FDA

MAA Accepted by EMA

Phase 3 ATLAS Presymptomatic Study Ongoing

FDA approval based on a reduction in neurofilament, a marker of neurodegeneration[1]

Approval supported by 12-month VALOR[3] and OLE integrated data

Data published in the *New England Journal of Medicine*

1. For important prescribing and safety information, please refer to: www.qalsody.com 2. Biogen is responsible for commercializing QALSODY. 3. While statistical significance was not achieved on the primary endpoint of ALSFRS-R at week 28 in the Phase 3 VALOR study, signs of reduced disease progression across multiple secondary and exploratory endpoints were observed.

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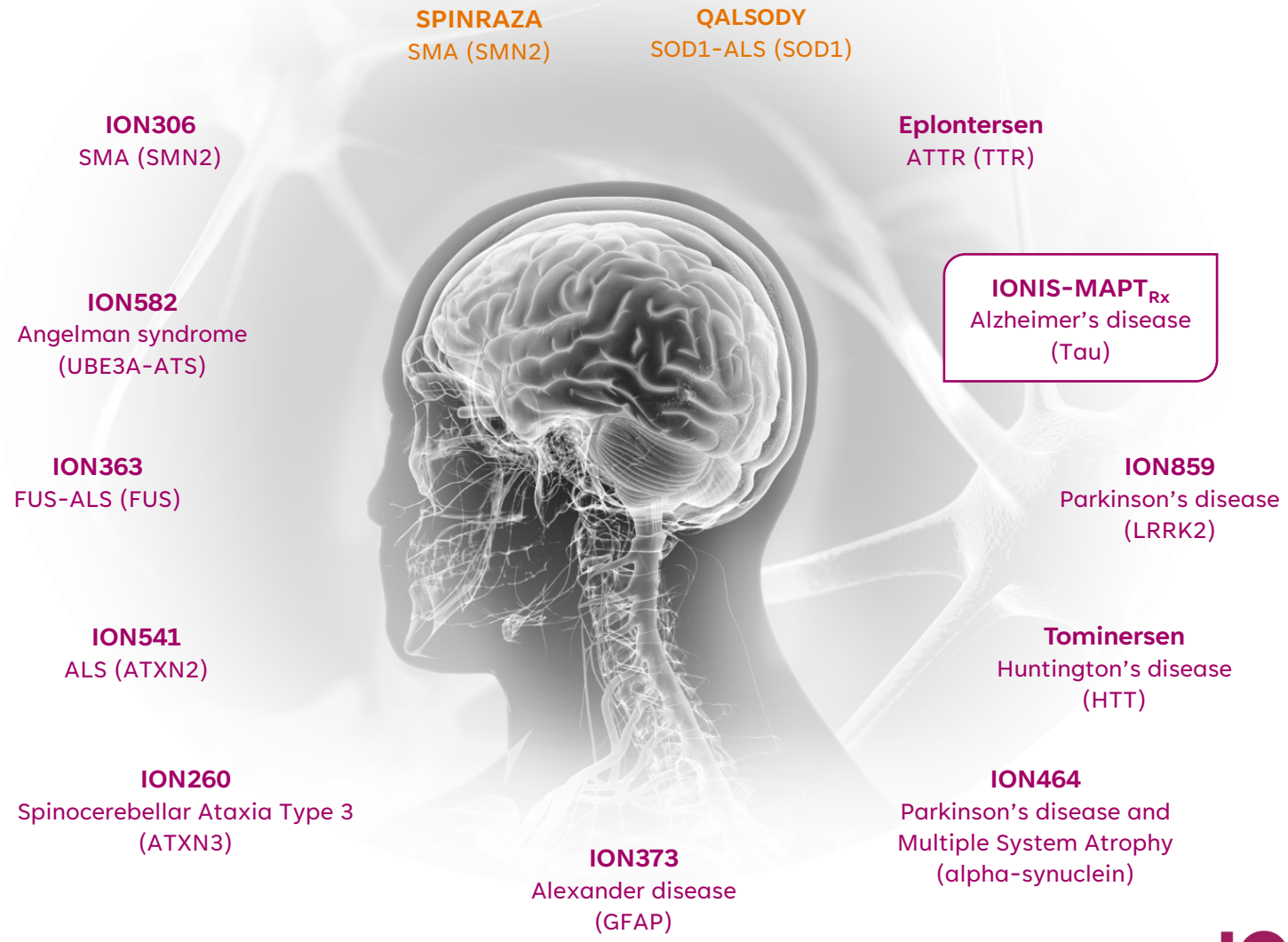
Leading Neurology Franchise: Addressing Major Neurological Diseases

2

Approved Medicines

12

Medicines in Development



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Expanding Robust Late-Stage Pipeline

Positioned to Deliver Steady Cadence of New Drugs to the Market

		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)
ION363	IONIS	FUS-ALS		Ph3 data (2025)
QALSODY	Biogen	SOD1-ALS		EU approval (2023)[3]
		Presymptomatic SOD1-ALS		Ph3 data (2027)
Pelacarsen	NOVARTIS	Lp(a) CVD		Ph3 data (2025)
Bepirovirsen	GSK	HBV		Ph2b B-Together data (2023)

IONIS-FB-L_{Rx} (Roche) expected to enter Phase 3 pipeline in H1:23[2]

1. Market data on file. 2. Timing expectations are based on current assumptions and are subject to change. 3. CHMP opinion anticipated in Q4:2023.

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Key Value Driving Events in 2023[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 Achievements

- ✓ **Eplontersen:** Phase 3, NEURO-TTRansform 35-week & 66-week data, ATTRv-PN
- ❍ **Olezarsen:** Phase 3, BALANCE study data, FCS
- ❍ **Eplontersen:** Phase 3, CARDIO-TTRansform full enrollment, ATTR-CM
- ❍ **Donidalorsen:** Phase 3, OASIS full enrollment, HAE

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.

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Q1 2023 Financial Performance

Beth Hougen
Chief Financial Officer

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Q1:2023 Financial Results

On Track to Achieve 2023 Guidance

$131 million in revenue

Generated from numerous diverse sources

$218 million in operating expenses[1]

Investments in advancing pipeline and go-to-market activities

$87 million [operating loss][1]

$2.3 billion of cash

Deploying financial resources to bring transformational medicines to the market

1. Non-GAAP – please see reconciliation to GAAP in Q1 2023 press release

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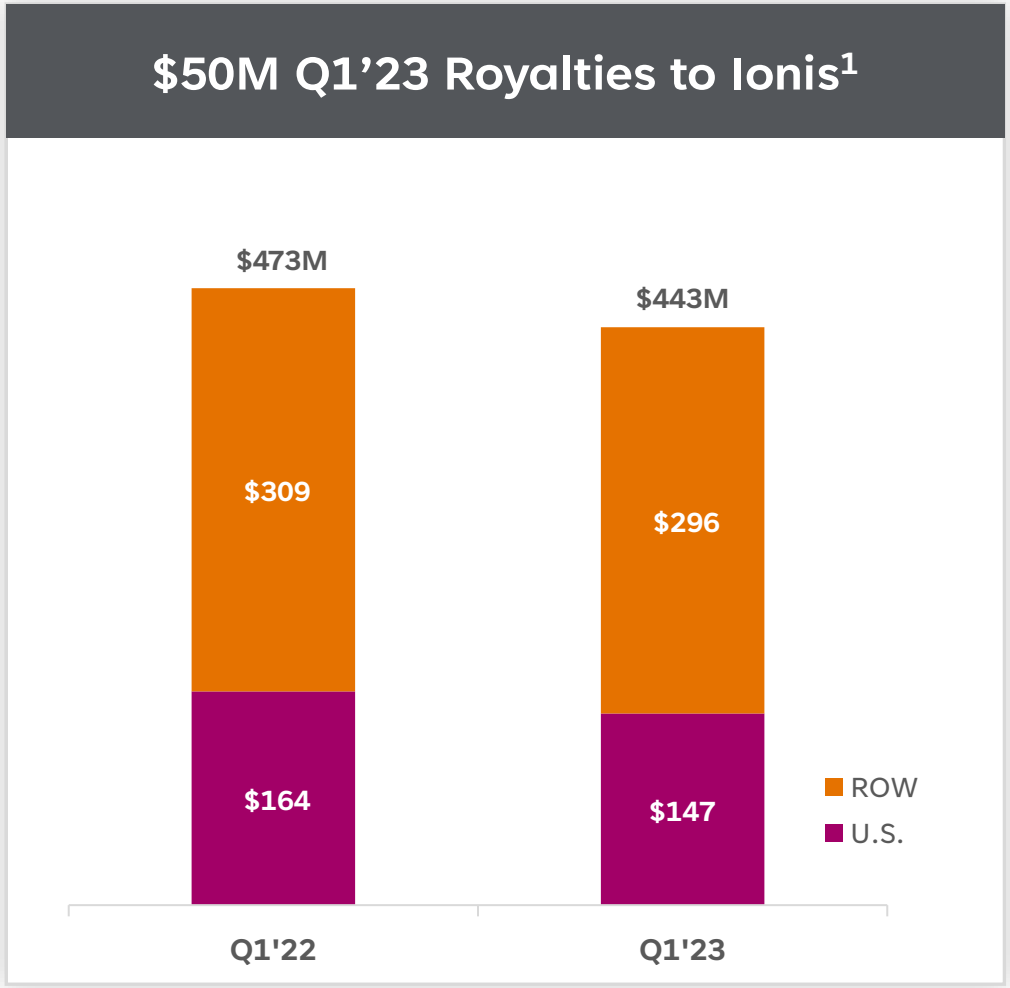
SPINRAZA® (nusinersen) injection 12 mg/5 mL

Global Leader for the Treatment of SMA



- **$50M in SPINRAZA royalties from $443M in product sales**
  - Slightly lower vs Q1'22 primary due to the impact of foreign currency, fewer new patient starts, in the U.S. and channel dynamics
  - Signs of stabilization in patient base
- **SPINRAZA's potential growth drivers:**
  - Market Expansion: Continued geographical expansion & existing market expansion driven by growing adult SMA population
  - Robust Life Cycle Management Program: Ongoing ASCEND[2], RESPOND[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 Q1 2023 Financial Results and Business Update; 1.$ amounts in millions;
2. ASCEND: clinicaltrials.gov/NCT05067790; 3. RESPOND: clinicaltrials.gov/NCT04488133;
4. DEVOTE: clinicaltrials.gov/NCT04089566

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Q1:2023 Financial Highlights

On Track to Achieve 2023 Guidance

$131M **Revenue**

Commercial Revenue: $68M

- SPINRAZA comprised largest component

R&D Revenue: $63M

- Generated from several partners for advancing numerous programs

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$218M **Operating Expenses***

R&D Expenses*: $178M

- Increased YoY primarily from advancing late-stage programs

SG&A Expenses*: $39M

- Increased spend YoY on go-to-market activities

$2.3B **Cash & short-term investments**

Strong financial foundation enables continued investment in creating future growth opportunities

*Non-GAAP – please see reconciliation to GAAP in Q1 2023 press release.

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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 genetic medicines to the market
- **Establish** an integrated commercial organization
- **Expand** and **diversify** our technology platform

*Non-GAAP – please see reconciliation to GAAP in Q1 2023 press release.

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Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

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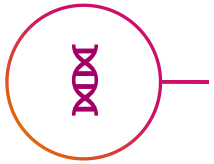
Well Positioned to Capitalize on Our Progress by Executing on Strategic Priorities

Deliver an abundance of genetic medicines to the market

Establish an integrated commercial organization



Expand and **diversify** our technology platform

Strengthen our financial foundation to support our strategic priorities

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Q&A

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