FY 2023 Business Update and Financial Results

February 21, 2024

Nasdaq: IONS

On Today's Earnings Call

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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 our commercial medicines, additional medicines in development and technologies. 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. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. 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 our Form 10-K for the year ended December 31, 2022, and our most recent Form 10-Q quarterly filing, 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

Key Achievements in the Last 12 Months

2

FDA Approvals[1]

QALSODY™ (tofersen) 100 mg/15 mL injection

WAINUA (eplontersen) 45 mg injection for subcutaneous use

3

Positive Phase 3 Readouts[2]

neuro TTRansform

Balance a familial chylomicronemia syndrome study

OASIS

3

Phase 3 Study Starts

Bepirovirsen (HBV)

IONIS-FB-L_{Rx} (IgAN)

Zilganersen (Alexander disease)

4

Key Studies Fully Enrolled[3]

OASIS

cardio TTRansform

GOLDEN

HALOS

5

Additional Positive Clinical Data Readouts

1. WAINUA: www.wainua.com; QALSODY: www.qalsody.com; Biogen is responsible for commercializing QALSODY. 2. NEURO-TTRansform (eplontersen for ATTRv-PN); Balance (olezarsen for FCS). 3. OASIS (donidalorsen for HAE); CARDIO-TTRansform (eplontersen for ATTR-CM), GOLDEN (IONIS-FB-L_{Rx} for GA); HALOS (ION582 for Angelman syndrome)

Pipeline Performance

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

WAINUA Approved for ATTRv-PN: Launch Underway for the First Ionis Co-Commercialized Medicine[1]

FDA Approved on December 21

For ATTR Polyneuropathy, a systemic, progressive and fatal neurological disease

1. WAINUA: www.wainua.com; co-developing and commercializing in the U.S. with AstraZeneca.

WAINUA: Potential to be the Preferred Treatment Option for Patients with ATTR[1,2]

Strong Clinical Profile[3]

Targeted Knockdown

Targeted TTR knockdown at the source with **powerful** and **sustained TTR suppression**

Stops Neuropathy Progression

Demonstrated the power to **stop neuropathy progression**

Sustained Benefit

Significant improvements in measures of **neuropathy** and **quality of life** in a substantial number of patients through **85 weeks**

Largest Data Set

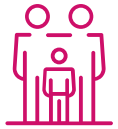
Largest clinical **trial** in **ATTR-CM** which will include **CV outcome data**

Significant Commercial Reach

Global Partnership

Alliance with a global footprint & **industry leader** in CVD medicines

Patient Support



Seamless **patient support** leveraging **Ionis' deep understanding** of these patients and the physicians who treat them

Administration Profile

Monthly **self-administration** with auto-injector

1. WAINUA: www.wainua.com 2. Assuming approval for ATTR-CM. 3. Based on data generated to date and published in *JAMA* in 2023.

WAINUA for ATTR-CM: Global Phase 3 Development Program Designed to Deliver Robust Results

Robust Development Program

cardio TTRansform

Most comprehensive study to date in ATTR-CM, a fatal disease of the heart muscle

Positioned to deliver most robust data in broad patient population

Largest study conducted in ATTR-CM now fully enrolled with >1,400 patients

MRI and scintigraphy sub-studies underway to assess the effects on cardiac structure and function

Next Steps

Data as early as 2025[1]

1. Timing expectations based on current assumptions and 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
- Completed Ph 2b study supporting FCS NDA exposure database
- Granted Breakthrough Therapy designation by FDA
- On track for US and EU filings in 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 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
- Positive Phase 2 2-year OLE data reinforce donidalorsen's compelling profile

OASIS

- Positive Phase 3 topline data, including achieving:
  - Statistically significant reduction in HAE attack rates in patients treated every 4 weeks or 8 weeks
- Data to be presented at upcoming medical congress

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
  - Expanding enrollment
- Data expected mid-2024

Preparing to Submit NDA with US FDA; Otsuka Preparing to Submit MAA in EU[3]

1. Based on Phase 3 data, 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. 3. Licensed European commercialization rights to Otsuka in 2023.

Leading and Validated Neurology Franchise

3

Approved Medicines[1]

11

Medicines in Clinical Development

6

Wholly Owned Medicines in Clinical Development by YE:2024[2]

SPINRAZA
SMA (SMN2)

QALSODY
SOD1-ALS (SOD1)

WAINUA
ATTRv-PN (TTR)

Zilganersen
Alexander disease
(GFAP)

ION717
Prion disease
(PRNP)

Ulefnersen
FUS-ALS
(FUS)

ION541
ALS (ATXN2)

ION582
Angelman syndrome
(UBE3A-ATS)

ION306
SMA (SMN2)

Tofersen
Presymptomatic SOD1-ALS
(SOD1)

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

ION859
Parkinson's disease
(LRRK2)

Tominersen
Huntington's disease
(HTT)

ION464
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; WAINUA: www.wainua.com.2. Timing based on current estimates and subject to change.

Key Value-Driving Events Planned For 2024[1]

Phase 3 Clinical Data Events

Donidalorsen
✓ OASIS-HAE topline data

OASIS-HAE full data

OASIS-PLUS OLE + Switch data

Olezarsen
Balance study full data, FCS

Phase 2 Clinical Data Events

Donidalorsen
3-year OLE, HAE

IONIS-FB-L_{Rx}
Geographic Atrophy

IgA nephropathy

ION224
NASH

ION582
Angelman syndrome

ION541
ALS

Regulatory Actions

Eplontersen
OUS approval decisions, ATTRv-PN

OUS filings, ATTRv-PN

Olezarsen
NDA filing, FCS

FDA approval decision, FCS[2]

EU filing, FCS

Donidalorsen
NDA filing, HAE

QALSODY
EMA approval decision, SOD1-ALS

New Product Launches

WAINUA
✓ ATTRv-PN[3]

Olezarsen
FCS[4]

QALSODY
EU, SOD1-ALS[4]

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. Assuming priority review. 3. WAINUA: www.wainua.com
4. Assuming approval in 2024.

FY 2023 Financial Performance & FY 2024 Financial Guidance

Beth Hougen
Chief Financial Officer

FY 2023 Financial Highlights[1]

Significantly Exceeded Revenue Guidance Leading to Improved Operating Loss

$788M — **Revenue**

Commercial Revenue: $309M

- SPINRAZA comprised largest component

R&D Revenue: $479M

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

$1,035M — **Operating Expenses[2,3]**

R&D Expenses[2]: $822M

- Increased YoY primarily from advancing late-stage programs

SG&A Expenses[2]: $205M

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

$247M — **Operating Loss[2]**

Improved compared to guidance due to substantial revenue earned

$2.3B — **Cash & Short-term Investments**

Enables continued investments to drive increasing value

1. For the year ended December 31, 2023. 2. Non-GAAP – please see reconciliation to GAAP in FY 2023 press release. 3. Operating expenses includes cost of sales, R&D expense and SG&A expenses.

2024 Financial Guidance

Revenue	Operating Loss	Cash
>$575 million	<$475 million[1]	~$1.7 billion

Expectations for 2024:

Revenue: Substantial and sustained

- **Commercial:** sustained SPINRAZA royalties; WAINUA royalties in line with launch ramp
- **R&D:** multiple sources from numerous advancing programs

Operating Loss & Cash: reflects investments toward growth opportunities

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

Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

Well Positioned to Build on Momentum by Executing on Strategic Priorities

01

Wholly Owned Pipeline

Advancing and growing our wholly owned pipeline in focused therapeutic areas (neurology and cardiology)

02

Integrated Commercial Capabilities in Place

Steady cadence of new potentially **transformational medicines** to the **market**

03

Leading Technology

Advancing technology to **expand existing franchises and address new therapeutic areas**

04

Effective Financial Strategy Poised for Growth

Multi-billion-dollar revenue opportunity to enable future **positive cash flow**

Jackson,
Angelman Syndrome Patient

Driving Next-Level Value for Patients and All Ionis Stakeholders

Q&A


IONIS®

Appendix

Delivering Steady Cadence of Potentially Transformational Medicines[1]

9 Medicines in Phase 3 for 11 indications

		Indication	Prevalence[2]	Next Event[3]
WAINUA (eplontersen)	IONIS / AstraZeneca	ATTRv-PN		**Additional OUS submissions (2024)**
		ATTR-CM		**Ph3 data (2025)[4]**
Olezarsen	IONIS	FCS		**NDA filing (2024)**
		SHTG		**Ph3 data (2025)**
Donidalorsen	IONIS	HAE		**NDA filing (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 data (2026)**
IONIS-FB-L_{Rx}	Roche	IgA nephropathy[5]		**Ph2 data (2024)**
Tofersen	Biogen	Presymptomatic SOD1-ALS		**Ph3 data (2027)**

1. Assuming approval 2. Market data on file. 3. Timing expectations are based on current assumptions and are subject to change. 4. Results as early as 2025. 5. IONIS-FB-L_{Rx} is also in the Phase 2 GOLDEN study in patients with Geographic Atrophy, with topline data expected in 2024.