Q3:24 Business Update and Financial Results

November 6, 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, 2023, 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.ionis.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

Realizing the Promise of our Wholly Owned Innovative Medicines[1,2]

Olezarsen

First-mover Advantage for Two Patient Populations: FCS and sHTG

Independent U.S. Launch in FCS expected by YE:2024

Blockbuster sHTG opportunity on track for Phase 3 data in H2:2025

Donidalorsen

Potential Preferred Prophylactic Treatment for HAE

August 21st, 2025 PDUFA Date
MAA submission expected soon[3]

Independent U.S. launch in HAE expected in 2025

ION582

Potential Transformational Medicine for Angelman Syndrome

Positive end of Phase 2 FDA discussion; aligned on Phase 3 design

Phase 3 development for Angelman Syndrome expected start in H1:2025

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions.

Numerous Important Achievements in 2024 To Date

2
New Product Launches

WAINUA™ (eplontersen) 45 mg injection for subcutaneous use

U.S launch (ATTRv-PN)[1]

QALSODY® (tofersen) 100 mg/15 mL injection

EU launch (SOD1-ALS)[2]

4
Positive Phase 3 Readouts[3]

Olezarsen
Familial Chylomicronemia Syndrome (FCS)

Donidalorsen
(OASIS-HAE & OASISplus Studies)
Hereditary Angioedema (HAE)

Nusinersen
(DEVOTE)
Spinal Muscular Atrophy (SMA)

6
Phase 3 Studies Fully Enrolled[4]

Olezarsen
(CORE, CORE2 & ESSENCE Studies)
Severe hypertriglyceridemia (sHTG)

Zilganersen
Alexander disease

Bepirovirsen
(B-Well 1 & B-Well 2 Studies)
Chronic HBV

4
Positive Phase 2 Readouts[5]

Donidalorsen
(OLE study)
Hereditary Angioedema (HAE)

IONIS-FB-L$_{Rx}$
IgAN

ION582
(HALOS study)
Angelman Syndrome

ION224
MASH

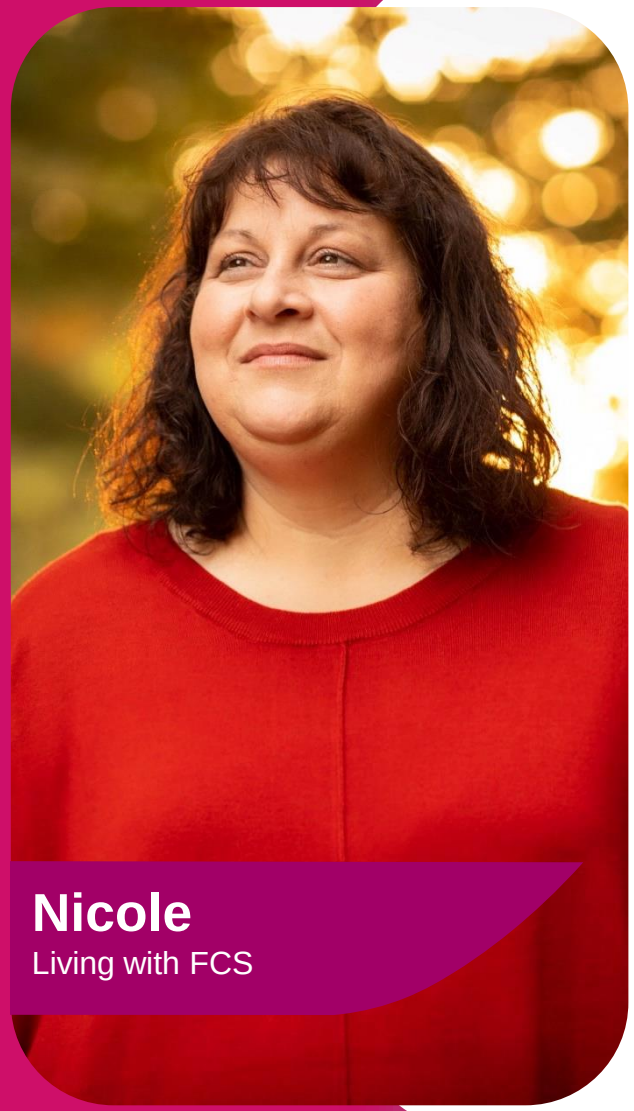
1. WAINUA: www.wainua.com. 2. QALSODY: www.ema.Europa.eu; Biogen is responsible for commercializing QALSODY. 3. Balance (olezarsen for FCS), DEVOTE (higher dose nusinersen for SMA), OASIS-HAE and OASISplus (donidalorsen for HAE). 4. CORE, CORE2 and Essence (olezarsen for sHTG). B-Well 1 & B-Well 2 (chronic HBV). Phase 3 study for zilganersen (Alexander disease) 5. Phase 2 readouts of: donidalorsen for HAE, ION224 for MASH, IONIS-FB-L$_{Rx}$ for IgAN and ION582 for Angelman syndrome.

Delivering Important Pipeline Achievements

Eugene Schneider, M.D.
Chief Clinical Development Officer

Olezarsen:

Wholly Owned Blockbuster Opportunity with potential to become the **Standard-of-Care** for People with **Severely Elevated Triglycerides**[1-3]



Two planned indications:
- Starting with rare disease opportunity in FCS
- Expanding to broader sHTG population

Substantial unmet need

Positive Balance (FCS) study results[4]:
- Robust reductions in apoC-III, TGs & favorable safety and tolerability
- Markedly lower rate of acute pancreatitis vs. placebo

December 19, 2024 PDUFA;
EU filing under review

1st independent launch

Phase 3 sHTG program enrollment complete; data expected in H2:2025

1. Based on data generated to date. 2. Timing based on current estimates and subject to change. 3. Assuming approval 4. Due to statistical hierarchy, reductions in apoC-III and acute pancreatitis are considered exploratory.

Donidalorsen:

A **Wholly Owned** Potential **Preferred Treatment** for People with **Hereditary Angioedema**[1,2]

New prophylactic treatments needed[3]

Donidalorsen's clinical results include[1]:

- Substantial and sustained reductions in HAE attacks
  - New positive Phase 2 OLE data in patients treated up to three years
- Improved QoL measures
- High levels of disease control
- >80% preference for donidalorsen over other prophylactic treatments[4]
- Favorable safety and tolerability
- Patient-friendly monthly or every two-month self-administration with an autoinjector

August 21, 2025 PDUFA; EU submission planned for this year[5]

1. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 2. Assuming approval. 3. Sandra C. Christiansen MD, Joyce Wilmot MS, Anthony J. Castaldo MPA, Bruce L. Zuraw MD, For the US HAEA Medical Advisory Board members, The US HAEA Scientific Registry: Hereditary Angioedema Demographics, Disease Severity, and Comorbidities, Annals of Allergy, Asthma Immunology (2023); HAEI (https://haei.org/hae/faq/ accessed May 2024). 4. Switch preference data represents percentage of switch patients surveyed with total n=55 assessed at week 17 and as of February 28, 2024 who indicated donidalorsen preference over their prior prophylactic treatment. 5. Timing based on current estimates and subject to change.

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

Positioned to deliver the richest 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 Expected in H2:2026[1]

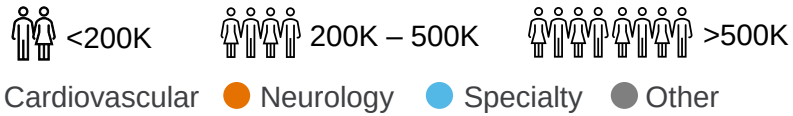
1. Timing expectations based on current assumptions and subject to change.

Positioned to Deliver Steady Cadence of Potentially Transformational Medicines[1]

9 investigational medicines in Phase 3 for 11 indications

		Indication	Prevalence[2]	Anticipated Next Event[3]
WAINUA (eplontersen)	IONIS / AstraZeneca	ATTRv-PN		**OUS approvals (2024)**
		ATTR-CM		**Ph3 data (2026)[4]**
Olezarsen	IONIS	FCS		**FDA approval (2024)[5]**
		sHTG		**Ph3 data (2025)[6]**
Donidalorsen	IONIS[7]	HAE		**MAA filing (2024)**
Zilganersen	IONIS	Alexander disease		**Ph3 data (2025)**
Ulefnersen	IONIS	FUS-ALS		**Ph3 data (2026)**
Pelacarsen	NOVARTIS	Lp(a) CVD		**Ph3 data (2025)**
Bepirovirsen	GSK	HBV		**Ph3 data (2026)**
IONIS-FB-L$_{Rx}$	Roche	IgA nephropathy		**Ph3 data (2026)**
Tofersen	Biogen	Presymptomatic SOD1-ALS		**Ph3 data (2028)**

1. Assuming approval. 2. Market data on file. 3. Timing expectations are based on current assumptions and are subject to change. 4. Data expected in H2:2026. 5. MAA filing planned for Q4:2024. 6. Data expected in H2:2025. 7. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions.



Leading Neurology Franchise

3

Approved Medicines[1]

13

Medicines in Clinical Development

7

Wholly Owned Medicines in Clinical Development[2]

SPINRAZA® (nusinersen) injection 12 mg/5 mL

QALSODY® (tofersen) 100 mg/15 mL injection

WAINUA™ (eplontersen) 45 mg injection for subcutaneous use

Zilganersen
Alexander disease
(GFAP)

Ulefnersen
FUS-ALS
(FUS)

ION582
Angelman syndrome
(UBE3A-ATS)

ION717
Prion disease
(PRNP)

ION356
Pelizaeus-Merzbacher
Disease (PLP1)

ION440
MECP2 duplication
syndrome (MECP2)

ION269
Alzheimer's disease
(APP)

Tofersen
Presymptomatic SOD1-ALS
(SOD1)

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

ION859
Parkinson's disease
(LRRK2)

Tominersen
Huntington's disease
(HTT)

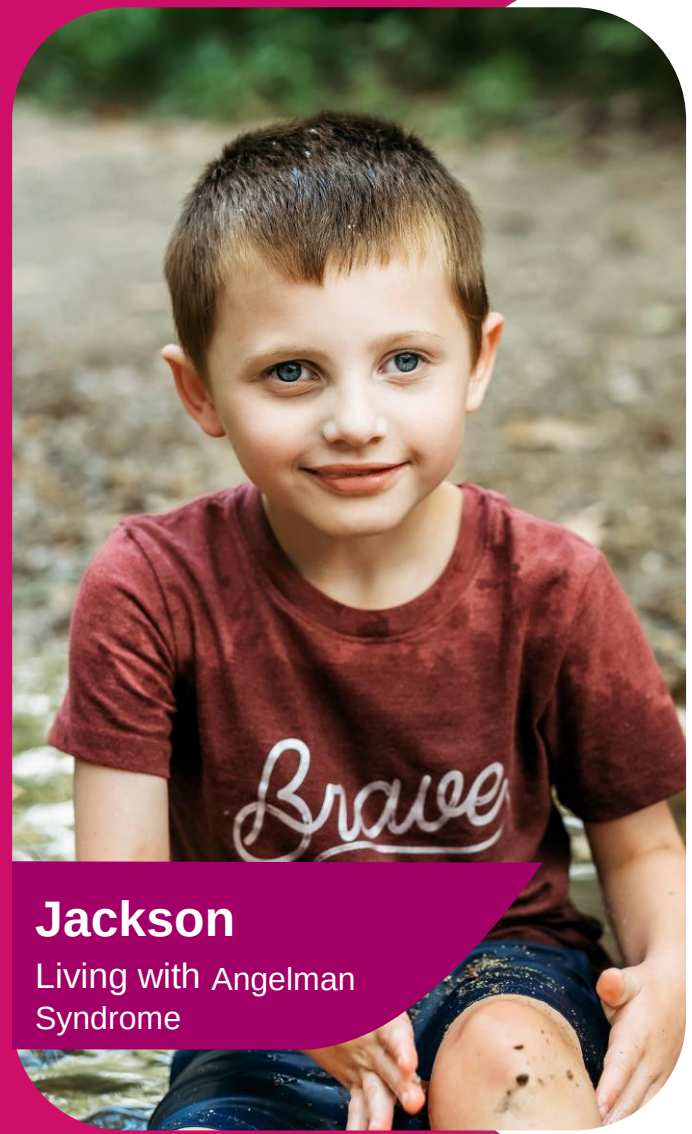
ION464
Multiple System Atrophy
(alpha-synuclein)

ION306
SMA (SMN2)

1. SPINRAZA: www.spinraza.com; QALSODY: www.qalsody.com; Biogen is responsible for commercializing SPINRAZA and QALSODY; WAINUA: www.wainua.com. 2. Wholly owned programs include: zilganersen (Alexander disease), Ulefnersen (FUS-ALS), ION582 (Angelman syndrome), ION717 (Prion disease), ION356 (PMD), ION440 (MECP2 Duplication syndrome) and ION269 (APP).

ION582:

A **Promising** New Investigational Medicine for **Angelman Syndrome** from Ionis' **Wholly Owned** Neurology P**ipeline**[1]



Jackson
Living with Angelman Syndrome

Positive Early Results Seen in the HALOS Study[1]

- Consistent and meaningful improvements in key areas of clinical function, including communication, cognition and motor function
- Evidence of consistent improvements across age groups and genotypes
- Favorable safety and tolerability profile

Phase 3 Study Start Planned for H1:2025[2]

- Totality of data generated to date support advancing to pivotal development
- FDA alignment on Phase 3 study design

Priority Wholly Owned Opportunity

- Significant transformational potential
- Strengthens Ionis' wholly owned neurology pipeline

1. Based on data generated to date from the Phase 1/2a HALOS study of ION582. 2. Timing expectations based on current assumptions and subject to change.

Upcoming Key Value-Driving Events[1]

Q4:2024 and 2025

Phase 2 Clinical Data Events

Sapablursen
Polycythemia vera

—

ION464
Multiple System Atrophy

Phase 3 Clinical Data Events

Olezarsen
CORE, CORE2,
ESSENCE data
sHTG

—

Zilganersen
Alexander disease

—

Pelacarsen
HORIZON data
Lp(a) CVD

Regulatory Actions

Eplontersen
OUS approvals,
ATTRv-PN

—

Olezarsen
FDA approval, FCS
EU approval, FCS

—

Donidalorsen
FDA approval, HAE
EU filing, HAE
EU approval, HAE

—

Nusinersen
(higher dose)
FDA filing, SMA
OUS filings, SMA

New Product Launches

WAINUA
EU + other countries
ATTRv-PN

—

Olezarsen
U.S. FCS
EU FCS

—

Donidalorsen
U.S. HAE
EU HAE

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.

Preparing to Bring Important Ionis Medicines to Patients

Kyle Jenne
Chief Global Product Strategy and Operations Officer

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

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

Substantial and sustained Q-o-Q growth of 44% driven by strong demand[2]

Encouraging patient mix and breadth of prescribers

Physicians report positive patient experience:

- Quality-of-life improvements
- Ability to access treatment
- Self-administration via an autoinjector

High unmet need remains with <20% of ATTRv-PN patients on treatment

1. WAINUA: www.wainua.com; co-developing and commercializing in the U.S. with AstraZeneca. 2.Q3:2024 compared to Q2'2024 WAINUA product sales.

Olezarsen:

Designed to Address Two Patient Populations with Urgent Unmet Need[1,2]

Familial Chylomicronemia Syndrome

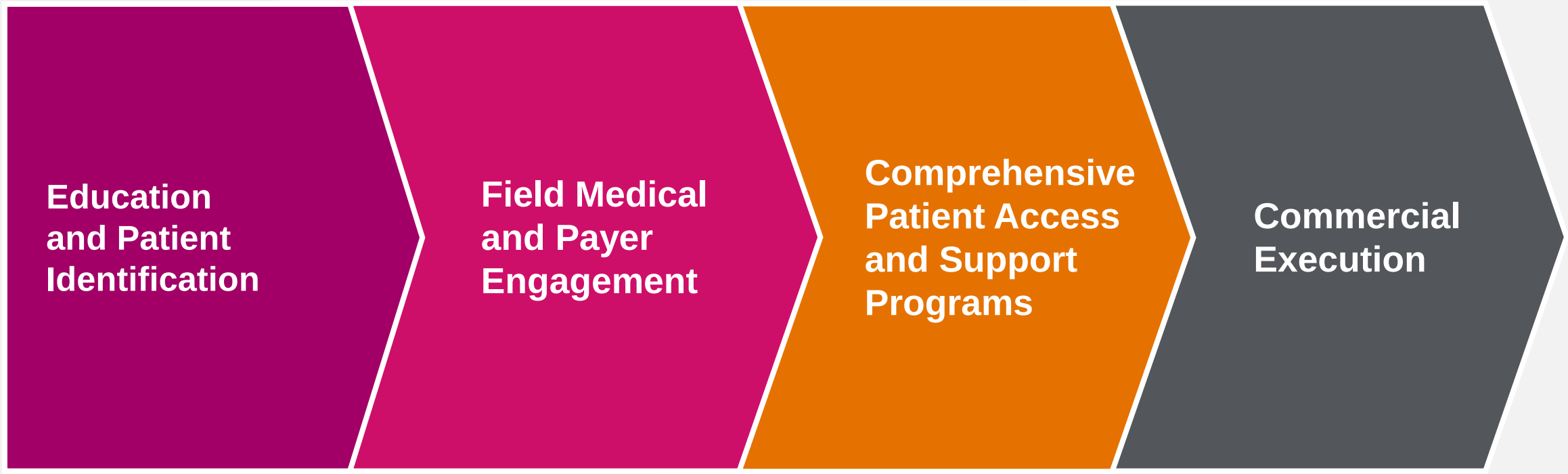
- **Rare disease opportunity**[3-5]
- **No approved treatments** in the U.S.
- **Significant risk** for acute, potentially fatal pancreatitis
- **Planned first indication** launch with **high margin potential**

Severe Hypertriglyceridemia

- **Large addressable** market[6-9]
- **Limited benefit** from current standard of care
- **Treatment guidelines** recommend preventative treatment
- **Blockbuster potential**

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 4. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6. 5. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 6. Sanchez et al. *Lipids in Health and Disease* 2021;20:72. 7. Berberich et al. *Lipids in Health and Disease* 2021;20:98. 8. Fan et al., *J Clin Lipidology* 2019; 13:100-108. 9. Christian et al., *Am J Cardiol* 2011;107:891-897.

Comprehensive Launch Approach Focused on Targeted Education, Engagement and Patient Support



Our Second Planned Independent Launch: Donidalorsen for HAE

HAE Landscape Dynamics Underscore Donidalorsen's Potential[1,2]

Well Defined Population with **>20K People with HAE** in U.S. & EU

Growing Global Market

New Treatment Options Needed

People with HAE Have Shown **Willingness to Switch**

Concentrated Prescriber Base in the US

Efficient Commercial Model

1. Market data on file. 2. Lumry et al. "Hereditary Angioedema: The Economics of Treatment of an Orphan Disease. Front. Med. 16 February 2018 Sec. Hematology Volume 5 – 2018.

Donidalorsen: Clinical Results Support Potential to be a Preferred Choice for People with HAE[1,2]

Lauren & Lindsey
Sisters Living with HAE

- **Potential first-in-class RNA-targeted medicine**
- **Substantial and sustained attack rate reduction with long-term durability and disease control demonstrated in the studies**
- **Strong patient preference results with data to inform potential switching**
- **Favorable safety and tolerability profile in the studies**
- **Data support monthly or every two-month self-administration with an autoinjector**

1.Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 2. Assuming approval.

Delivering Medicines to People in Need

WAINUA (eplontersen) 45 mg injection for subcutaneous use

Co-Developing and Co-Commercializing in the U.S. with AstraZeneca

Launched in ATTRv-PN January 2024[1]

Leading patient engagement program

AstraZeneca leading other customer-facing commercial and medical affairs teams

Pre-commercialization activities and investments underway to support potential ATTR-CM opportunity

Olezarsen

Independent U.S. Launch in FCS expected by YE:2024[2,3]

Building on WAINUA infrastructure

FCS field team hired and trained

Patient and caregiver support team

Further scale capabilities to realize blockbuster potential in sHTG

Donidalorsen

Independent U.S. Launch in HAE expected in 2025[2,3]

Building on WAINUA and olezarsen infrastructure

Established market with concentrated prescriber base

Otsuka to bring to people with HAE in Europe and Asia Pacific Regions[4]

1. WAINUA: www.wainua.com. 2. Assuming approval. 3. Timing expectations based on current assumptions and subject to change. 4. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions.

Q3 2024 Financial Performance

Beth Hougen
Chief Financial Officer

Q3:2024 YTD Financial Highlights[1]

On Track to Achieve 2024 P&L Guidance; Increased Cash Guidance to ~$2.2 Billion

$479M

Revenue

Commercial Revenue: $207M

- SPINRAZA comprised largest component
- New stream of royalty revenue from WAINUA launch with substantial and sustained sequential quarterly growth

R&D Revenue: $272M

- Reflects the value Ionis' pipeline and technology create as programs advance

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$749M

Operating Expenses[2]

R&D Expenses[2]: $589M

- Flat YoY as several late-stage studies have ended and other late-stage studies are now fully enrolled

SG&A Expenses[2]: $154M

- Increased YoY from launch of WAINUA and advancing go-to-market activities for multiple near-term independent launches

1. For the nine months ended September 30, 2024. 2. Non-GAAP – please see reconciliation to GAAP in Q3 2024 press release.

On Track to Achieve 2024 P&L Financial Guidance

Increased Cash Guidance to ~$2.2B Reflects Equity Offering Proceeds

Revenue	Operating Loss	Cash
>$575 million	**<$475** million[1]	**~$2.2** billion
		Prior: $1.7 billion

Expectations for 2024:

Revenue: Substantial and sustained

- **Commercial:** Significant SPINRAZA royalties; growing WAINUA royalties
- **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 Q3 2024 press release.

Clear Path to Drive Value Creation

Foundation

Robust Innovative Pipeline Positions Ionis to Drive Value

Invest

Invest to Bring Important Medicines to Patients

—

Advancing Pipeline and Technology to Drive Steady Cadence of New Medicines

Growth

Positive Cash Flow Powered by Substantial Revenue Growth

Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

Ionis is Well-Positioned for Substantial Growth

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

Key Value-Driving Events Planned For 2024[1]

Phase 2 Clinical Data Events

Donidalorsen
3-year OLE, HAE

IONIS-FB-L$_{Rx}$
IgA nephropathy (>1yr OLE)
Geographic Atrophy

ION224
MASH (NASH)

ION582
Angelman syndrome

ION541
ALS

Phase 3 Clinical Data Events

Donidalorsen
OASIS-HAE topline data

OASIS-HAE full data

OASISplus OLE
+
Switch data

Olezarsen
Balance study full data, FCS

CORE & CORE2 studies fully enrolled, sHTG

SPINRAZA
DEVOTE (higher dose) study data, SMA

Regulatory Actions

Eplontersen
OUS approvals, ATTRv-PN
OUS filings, ATTRv-PN

Olezarsen
NDA filing, FCS
FDA approval, FCS
EU filing, FCS

Donidalorsen
NDA filing, HAE
MAA submission, HAE

QALSODY
EMA approval, SOD1-ALS
China approval, SOD1-ALS

New Product Launches

WAINUA
U.S. ATTRv-PN[2]

Olezarsen
U.S. FCS

QALSODY
EU, SOD1-ALS[3]
China, SOD1-ALS[3]

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. Green checkmarks indicate positive outcome. Red checkmarks indicate program is not moving forward. 2. WAINUA: www.wainua.com 3. QALSODY: www.ema.Europa.eu; Biogen is responsible for commercializing QALSODY.