Q2:24 Business Update and Financial Results

August 1, 2024

Nasdaq: IONS

On Today's Earnings Call

Brett Monia, Ph.D.
Chief Executive Officer

Richard Geary, Ph.D.
Chief Development Officer

Kyle Jenne
Chief Global Product Strategy Officer

Beth Hougen
Chief Financial Officer

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

Eugene Schneider, M.D.
Chief Clinical Development Officer

Jonathan Birchall
Chief Commercial Officer

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

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]

3
Positive Phase 3 Readouts[3]

Balance — a familial chylomicronemia syndrome study

OASIS — Hereditary Angioedema

OASIS plus — Hereditary Angioedema

6
Phase 3 Studies Fully Enrolled[4]

CORE — Severe hypertriglyceridemia (sHTG)

CORE2 — Severe hypertriglyceridemia (sHTG)

Essence — sHTG-supporting study

Alexander disease

B-Well 1 & B-Well 2 in Chronic HBV

2
Positive Phase 2 Readouts[5]

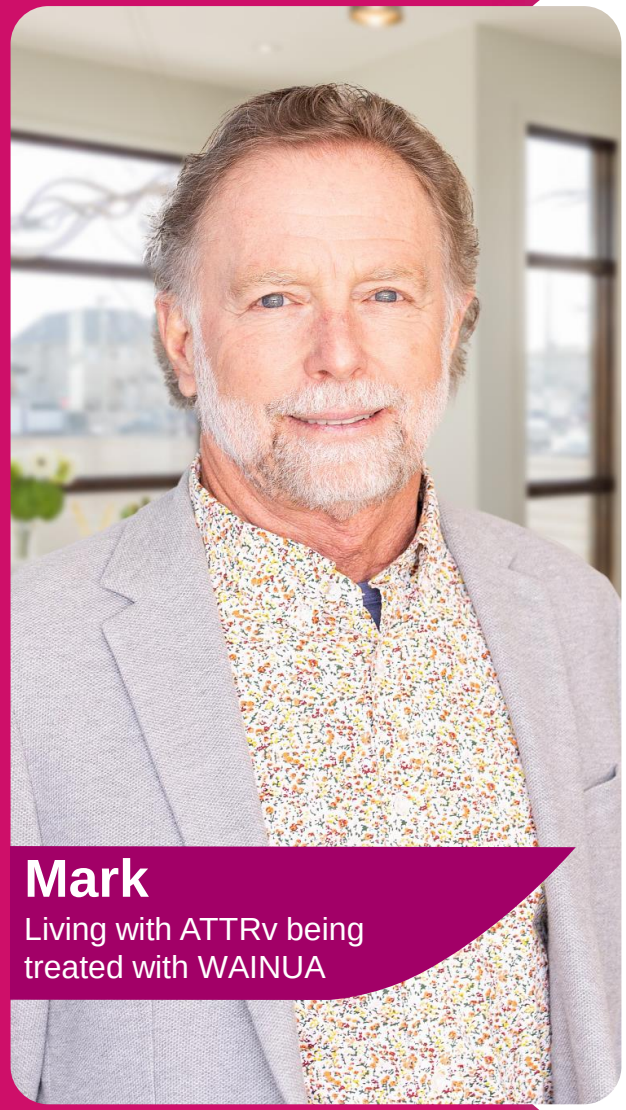
ION224 in MASH

HALOS — ION582 in Angelman syndrome

1. WAINUA: www.wainua.com. 2. QALSODY: www.ema.Europa.eu; Biogen is responsible for commercializing QALSODY. 3. Balance (olezarsen for FCS), OASIS 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 readout of ION224 for MASH; Phase 2 readout of ION582 for Angelman syndrome.

WAINUA:

Potential to be the **Preferred Treatment Option** for **People** with **ATTR**[1]



Poised to deliver benefit to underserved patient population

ATTRv-PN: Approved with strong clinical profile[1,2]

- U.S. launch progressing well for the first Ionis co-commercialized medicine
- EU regulatory decision expected this year[3]

cardio TTRansform

ATTR-CM: Global Phase 3 development program designed to deliver robust results

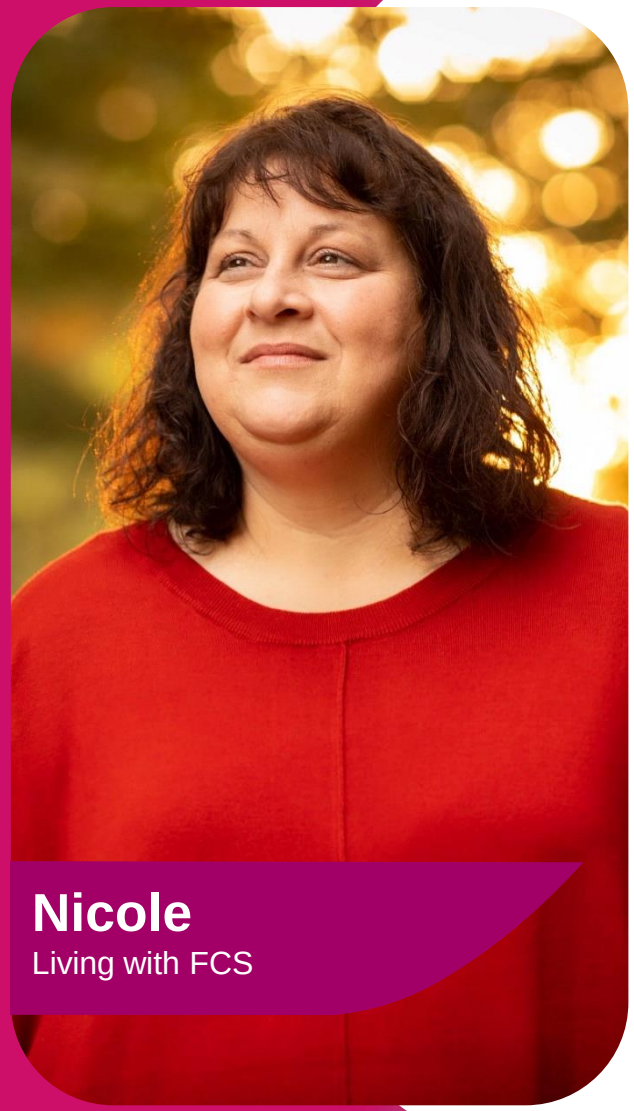
- Largest study conducted in ATTR-CM now fully enrolled with >1,400 patients
- MRI and scintigraphy sub-studies underway to assess the effects on cardiac structure and function
- Data expected in 2026 (base case)[3]

At-home self-administration via an autoinjector

1. Based on data generated to date and published in *JAMA*. 2. WAINUA: www.wainua.com; co-developing and commercializing in the U.S. with AstraZeneca. 3. Timing expectations based on current assumptions and subject to change.

Olezarsen:

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



Two planned indications[2]**:**
- Starting with rare disease opportunity in FCS
- Expanding to broader sHTG population

Substantial unmet need

Positive Balance (FCS) study results[3]**:**
- Robust reductions in apoC-III, TGs & favorable safety and tolerability
- Markedly lower rate of acute pancreatitis vs. placebo

December 19, 2024 PDUFA; EU filing planned for this year[2]

1st independent launch[4]

Phase 3 sHTG program enrollment complete; data expected in 2025[2]

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

Donidalorsen:

A 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
- >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

Plan to reach underserved HAE patients globally

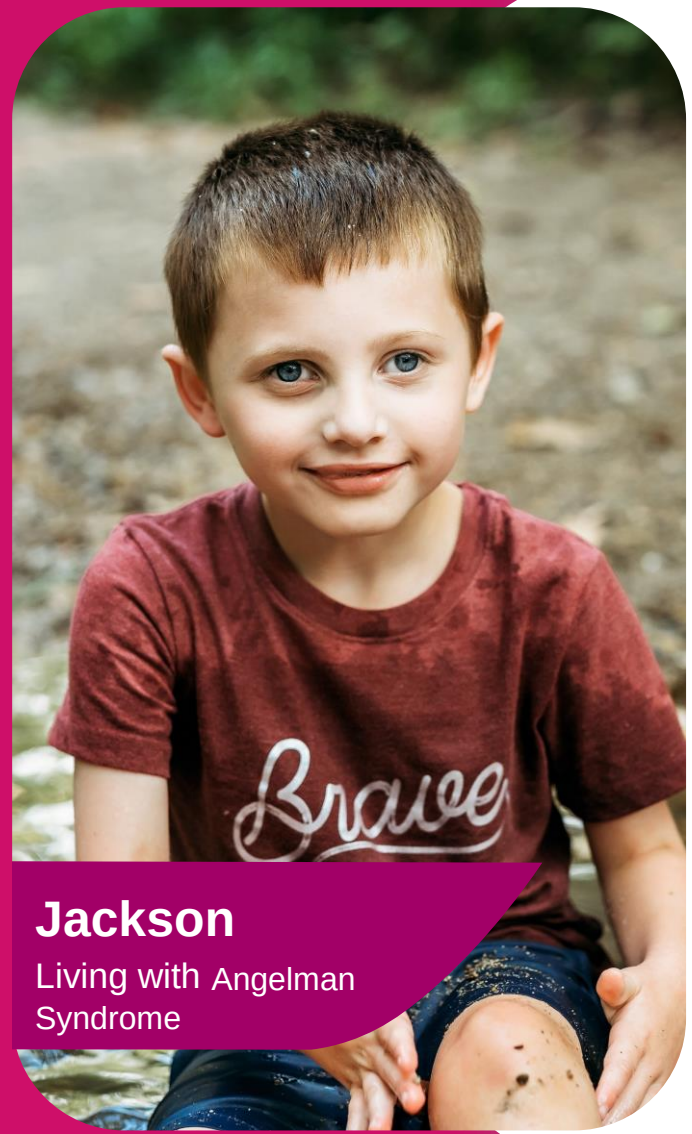
- Ionis to commercialize in the U.S.[2]
- EU and Asia Pacific access through Otsuka (tiered royalties up to 30%)

Launch planned for 2025[2,5]

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.

ION582 for Angelman Syndrome:

Positioned to Become the **Cornerstone** of 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 trial
- Plan to meet with global regulators

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.

Delivering Important Pipeline Achievements

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

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 2026[1,2]

1. Timing expectations based on current assumptions and subject to change. 2. Base case: data expected in 2026.

Olezarsen Delivered Robust Data Supporting its Potential as a Breakthrough Treatment for FCS[1]

Balance
a familial chylomicronemia syndrome study

- **NDA accepted for Priority Review, December 19, 2024 PDUFA**; EU filing on track for this year[2]
- Positive data presented at ACC, published in *NEJM*[1]
  - Olezarsen demonstrated substantial reductions in apoC-III, TGs, marked acute pancreatitis reductions, substantial reduction in hospitalizations and favorable safety and tolerability[3]
- EAP in U.S. for FCS underway, OLE progressing well
- U.S. Breakthrough Therapy and Orphan Drug designations

1. Stroes E, et al. *N Engl J Med*. 2024. 2. Timing expectations are based on current assumptions and are subject to change.3. Due to statistical hierarchy, reductions in apoC-III and acute pancreatitis are considered exploratory.

Olezarsen sHTG Development Program Designed to Support Blockbuster Market Opportunity[1]

Severe Hypertriglyceridemia (sHTG)

CORE
a hypertriglyceridemia study

- Pivotal study in patients w/ TG ≥500 mg/dL (sHTG)
- Registrational study
- >600 patients
- **Enrollment complete**

CORE2
a hypertriglyceridemia study

- Pivotal study in patients w/ TG ≥500 mg/dL (sHTG)
- Confirmatory registrational study
- >400 patients
- **Enrollment complete**

Essence
TIMI-73b

- Supportive Ph3 study in patients w/ TG ≥200-500 mg/dL (HTG)
- Supportive exposure study
- >1,400 patients
- **Enrollment complete**

On Track for Data From All Three Studies in H2:2025

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

Donidalorsen: Robust Data Supports Potential Preferred Treatment for HAE Prophylaxis[1,2]

Hereditary Angioedema

Phase 2

- Positive Phase 2 data published in *New England Journal of Medicine*
- Positive Phase 2, 1-year and 2-year OLE data, including positive QoL data reported
- Presenting Phase 2, 3-year OLE data in H2:24

OASIS

- Substantial reductions in HAE attack rates + favorable safety and tolerability
- Improved QoL measures
- High levels of disease control
- U.S. and EU Orphan drug designations
- Positive data presented at EAACI; published in *NEJM*[3]

OASIS plus

- OLE cohort demonstrated that long-term treatment continued to improve HAE attack rates and QoL measures
- Positive results from Switch cohort in patients previously treated with other prophylactic therapies showed:
  - Improved HAE attack rates, QoL measures and disease control
  - Strong preference for donidalorsen
  - Useful data to inform potential switching
- Positive data presented at EAACI

U.S. and EU filings on track this year; Prepared to launch in 2025[4]

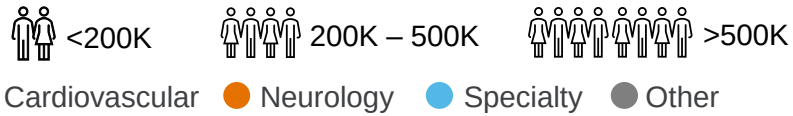
1. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 2. Licensed European and Asia Pacific commercialization rights to Otsuka 3. Riedl, M et al. *N Engl J Med.* 2024. 4. Timing expectations based on current assumptions and subject to change.

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

9 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)**
Donidalorsen (IONIS[6])	HAE		**NDA & 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 (TBD)**
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. Base case: data expected in 2026. 5. MAA filing planned for H2:2024. 6. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions.



Leading Neurology Franchise

3

Approved Medicines[1]

11

Medicines in Clinical Development

7

Wholly Owned Medicines Expected in Clinical Development by YE:2024[2,3]

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)

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. Wholly owned programs include: zilganersen (Alexander disease), Ulefnersen (FUS-ALS), ION582 (Angelman syndrome), ION717 (Prion disease) and ION356 (PMD). ION440 (MECP2 Duplication syndrome) and an undisclosed genetic dementia target are expected to enter clinical development by YE:2024. 3. Timing based on current estimates and subject to change.

ION582:

Important Wholly Owned Program for the Treatment of Angelman Syndrome[1]

A severe neurodevelopmental disorder of significant unmet need

- Estimated 1 in 21,000 people with Angelman syndrome worldwide[2]
  - >100,000 people in major geographies[2]

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

Plan to meet with regulators

On track to initiate Phase 3 development in H1 2025[3]

1. Based on data generated to date from the Phase 1/2a HALOS study of ION582. 2. Luk, H. M. & Lo, I. F. M. *Eur. J. Méd. Genet.* (2016); Yakoreva, M. et al. *A Eur. J. Hum.* Genet. (2019); Mertz, L. G. B. et al. Am. J. Méd. Genet. Part A (2013). Major geographies include U.S., EU, UK, Canada, Brazil, Japan and China. 3. 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
- OASISplus OLE + Switch data

Olezarsen
- Balance study full data, FCS
- CORE & CORE2 studies fully enrolled, sHTG

SPINRAZA
DEVOTE (high dose) study data, SMA

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

Regulatory Actions

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

Olezarsen
- NDA filing, FCS[2]

FDA approval, FCS

EU filing, FCS

Donidalorsen
NDA filing, HAE
MAA submission, HAE

QALSODY
- EMA approval, SOD1-ALS

New Product Launches

WAINUA
- U.S. ATTRv-PN[2]

Olezarsen
U.S. FCS

QALSODY
- EU, 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.

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

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

Olezarsen:

Designed to Address Two Patient Populations with Urgent Unmet Need[1-3]

Familial Chylomicronemia Syndrome

Rare disease opportunity ~1-13 people per million in the U.S.[4-6]

No approved treatments in the U.S.

Significant risk for acute, potentially fatal pancreatitis

Potential first indication launch for olezarsen

Severe Hypertriglyceridemia

Large addressable market, >3 million patients in the U.S.[7-10]

Limited benefit from current standard of care

Treatment guidelines recommend preventative treatment

Clear regulatory path

1. Timing expectations based on current assumptions and subject to change. 2. Assuming approval. 3.Applies to total addressable market. 4. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 5. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6. 6. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 7. Sanchez et al. *Lipids in Health and Disease* 2021;20:72. 8. Berberich et al. *Lipids in Health and Disease* 2021;20:98. 9. Fan et al., *J Clin Lipidology* 2019; 13:100-108. 10. Christian et al., *Am J Cardiol* 2011;107:891-897.

Poised to Deliver Olezarsen to the Market…

Focused on the unique needs of patients, caregivers, physicians and payers

- **Building launch momentum through disease awareness and patient identification**
- **Market research to identify physicians most likely to prescribe olezarsen**
- **Patient & caregiver support to assist patients through their treatment journey**
- **Efficient and targeted commercial team built to address HCP and patient needs**

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.

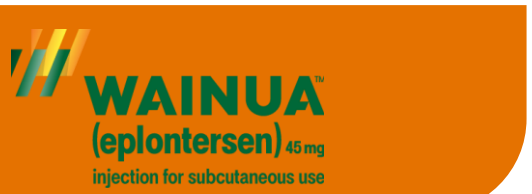
Donidalorsen: Clinical Results Support Potential to be a Preferred Choice for People with HAE[1,2]

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.

Ready to Deliver Medicines to People in Need



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 now in training

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.

Q2 2024 Financial Performance & Clear Path to Positive Cash Flow

Beth Hougen
Chief Financial Officer

H1:2024 Financial Highlights[1]

On Track to Achieve 2024 Guidance

$345M

Revenue

Commercial Revenue: $132M

- SPINRAZA comprised largest component
- New stream of royalty revenue with WAINUA launch

R&D Revenue: $213M

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

---

$498M

Operating Expenses[2]

R&D Expenses[2]: $391M

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

SG&A Expenses[2]: $101M

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

1. For the six months ended June 30, 2024. 2. Non-GAAP – please see reconciliation to GAAP in Q2 2024 press release.

On Track to Achieve 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
- **R&D:** multiple sources from numerous advancing programs

Operating Loss & Cash: reflects strategic investments toward growth opportunities

1. Non-GAAP – please see reconciliation to GAAP in Q2 2024 press release.

Investing Efficiently to Drive Positive Cash Flow

Go-to-Market Activities	Integrated commercial capabilities in place; right-sizing and scaling for successful launches
Late-Stage Medicines	Ionis' current large Phase 3 studies are fully enrolled
Next Wave of Medicines	Investing in advancing our growing wholly owned pipeline
Cutting-Edge Technologies	Continued innovation for future medicines

Modest Expense Growth over the Short- and Mid-Term

SG&A Expenses Ramp In-line with Planned Launches

R&D Expenses Approaching Steady State

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

Q2:2024 Achievements Accelerate Positive Momentum

New Medicines for Patients Today

- Strong **WAINUA** launch continued for hereditary ATTR polyneuropathy[1]
- **QALSODY** approved for SOD1-ALS in the EU[2]

Upcoming Sequential Launches Planned

Olezarsen:

- Positive FCS data presented at ACC, published in *NEJM*
- NDA for FCS accepted for Priority Review; PDFUA December 19th
- Opened Expanded Access Program (EAP) for FCS in U.S.
- Completed enrollment in Phase 3 program for sHTG

Donidalorsen:

- Positive HAE data presented at EAACI, published in *NEJM*
- Positive OLE and switch data presented at EAACI
- Licensed Asia Pacific commercialization rights to Otsuka

Next Wave of Medicines

- Positive **Angelman syndrome** data for **ION582**; preparing for end of Phase 2 FDA meeting in the fall and to advance into Phase 3 development in H1:2025[3]
- Fully enrolled **zilganersen** Phase 3 **Alexander disease study**; data expected 2025[3]

Financials

- Solid Q2 and H1:2024 financial results
- **On track** to achieve **2024 financial guidance**

1. WAINUA: www.wainua.com. 2. QALSODY: www.ema.Europa.eu; Biogen is responsible for commercializing QALSODY.3. Timing expectations based on current assumptions and subject to change.

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®