YE:2024 Business Update and Financial Results

February 19, 2025

Nasdaq: IONS

Eli (with family member)
Living with FCS

On Today's Earnings Call

Brett Monia, Ph.D.
Chief Executive Officer

Kyle Jenne
Chief Global Product Strategy Officer

Richard Geary, Ph.D.
Chief Development Officer

Beth Hougen
Chief Financial Officer

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

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

Tryngolza™ (olezarsen) 80 mg injection

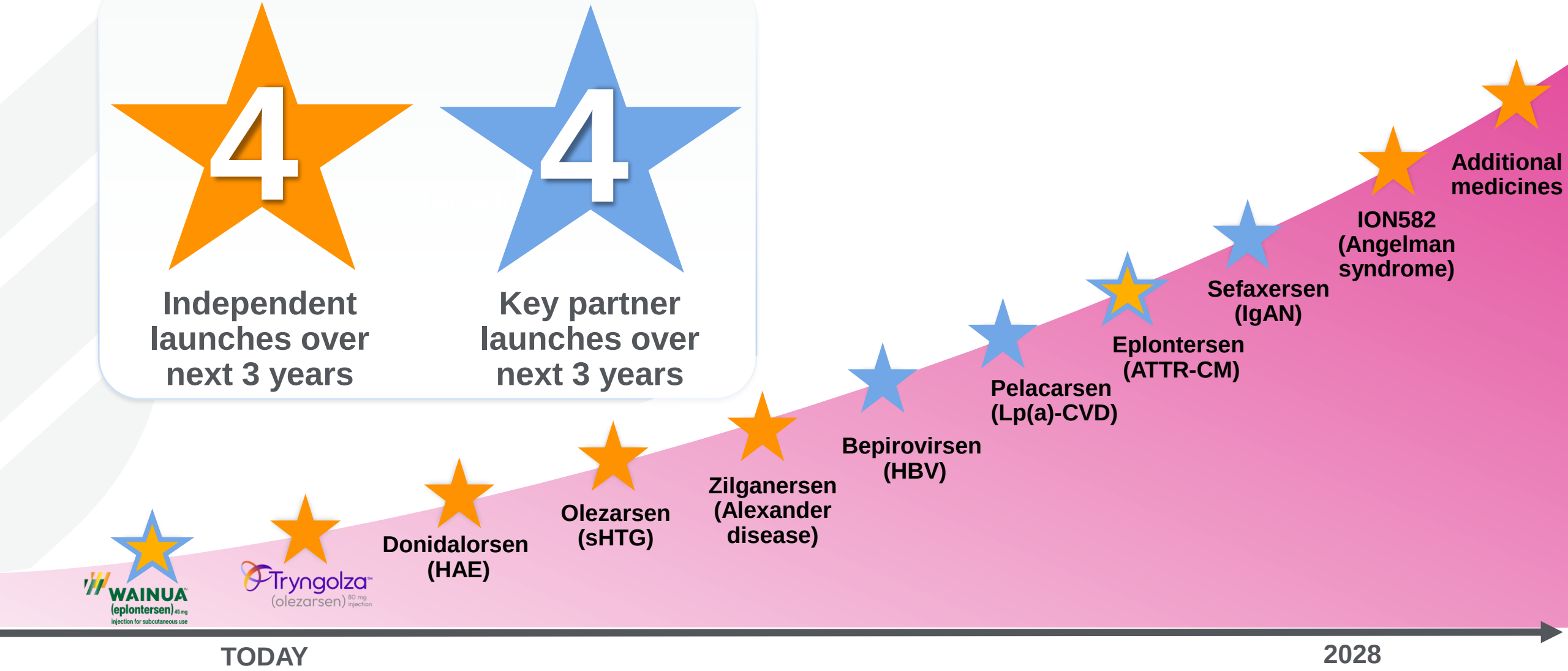
The first FDA-approved therapy for adults with FCS

NOW APPROVED

To reduce triglycerides in adults with FCS as an adjunct to diet

Inflection 2025: Poised to Deliver a Steady Cadence of New Medicines

Numerous Near-Term Growth Drivers[1,2]



1. Assuming approval. 2. Timing expectations are based on current assumptions and are subject to change.

Bringing Important Medicines to Patients

Kyle Jenne

Chief Global Product Strategy Officer

Ionis is Poised for FCS Launch Success with TRYNGOLZA[1]

Compelling Product Profile

- Robust efficacy and safety
  - Significant and sustained triglyceride reductions
  - Substantial reduction in acute pancreatitis events
- Convenience of once-monthly self-administration with an autoinjector

Launch Underway

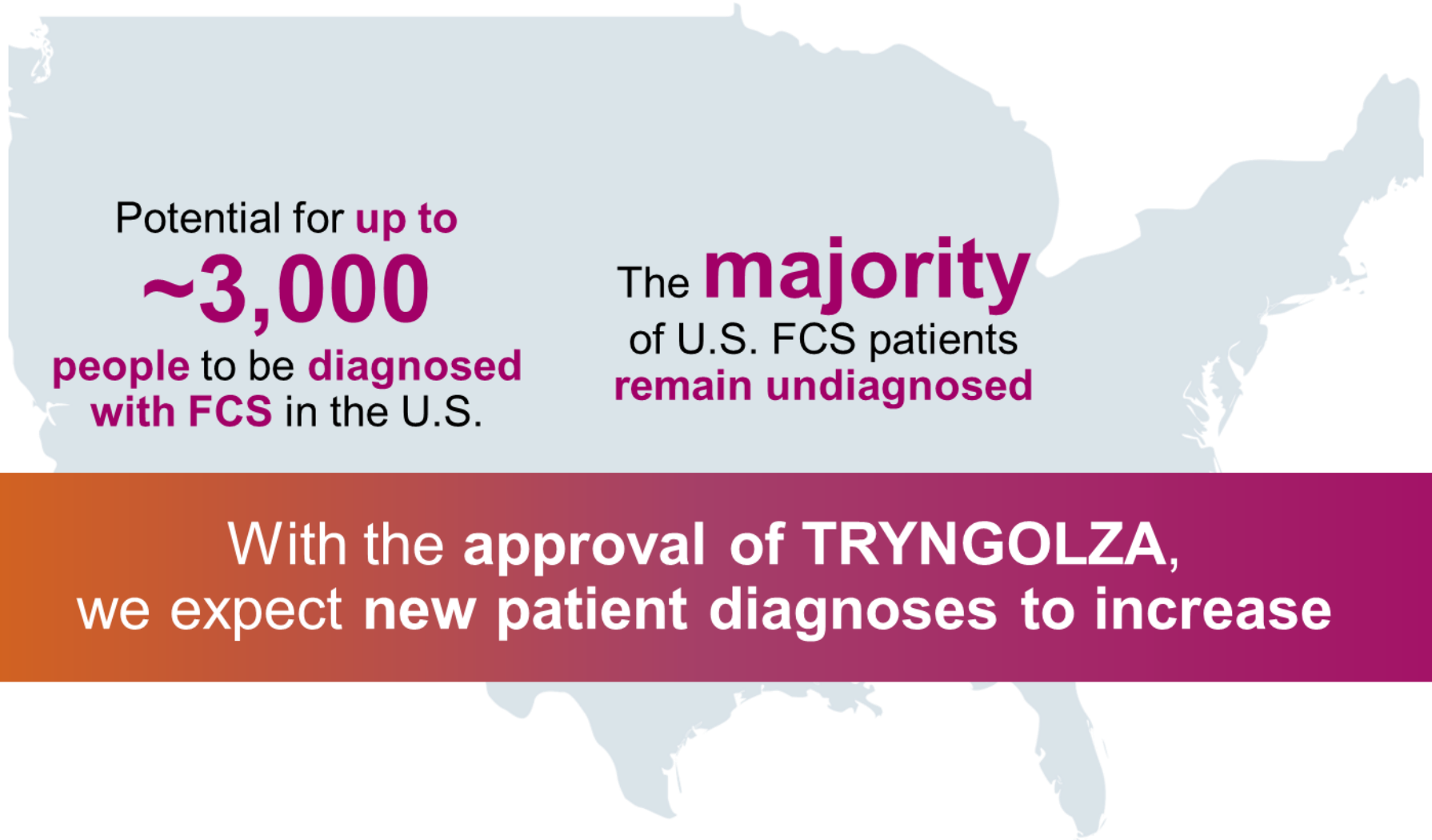
- Highly accomplished team with extensive rare disease experience
- Product in channel before end of 2024

First Mover Advantage

- First FDA-approved treatment for FCS

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information.

TRYNGOLZA Uptake to be Driven by Increasing FCS Awareness[1-5]



Potential for **up to**
~3,000
people to be **diagnosed with FCS** in the U.S.

The **majority** of U.S. FCS patients **remain undiagnosed**

With the **approval of TRYNGOLZA**, we expect **new patient diagnoses to increase**

1. Dron JS, et al. *BMC Med Genomics* 2020;13(1):23. 2. Hegele RA. *Nat Rev Genet* 2009;10(2):109-21. 3. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 4. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 5. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6.

TRYNGOLZA Launch Strategy Designed for Success

Tryngolza™ (olezarsen) 80mg injection

Education & Awareness

Education to support patient identification

HCP engagement, evidence generation, patient advocacy

Commercial Execution

Effective and targeted U.S. commercial team

Now deployed and engaging HCPs in support of U.S. launch

Comprehensive Support Program

Services designed for patients and HCPs

Patient assistance, authorization support, financial support for eligible patients

IONIS EVERY STEP SUPPORT SERVICES

Coverage & Reimbursement

Market access team engaging with payers

To ensure access for people who may benefit from TRYNGOLZA

Omnichannel Engagement

Targeted HCP and patient engagement

Innovative capabilities to identify patients, extend commercial team reach

Olezarsen: Potential to Change the sHTG Treatment Paradigm[1-9]

Severe Hypertriglyceridemia

It is Common

Estimated
>3 million patients in the U.S.

It is Severe

Acute, potentially **fatal pancreatitis** is the most severe manifestation

Patients are Underserved

TG guidelines established; however many patients are **not able to get to goal** with **current treatment** options

Olezarsen

- ✓ **Blockbuster potential**[10]
- ✓ **First Mover Advantage**
- ✓ **Positive data in FCS reinforce our confidence to address sHTG**
- ✓ **Phase 3 Data On Track for This Year**
  - ESSENCE safety study data expected mid-2025
  - CORE, CORE2 study data expected H2:2025
  - Launch planned for 2026

1. Represents those with initial triglyceride levels >500 mg/dL. 2. Sanchez et al. Lipids in Health and Disease 2021;20:72. 3. Berberich et al. Lipids in Health and Disease 2021;20:98. 4. Fan et al., J Clin Lipidology 2019; 13:100-108. 5. Christian et al., Am J Cardiol 2011;107:891-897. 6. Simha V. BMJ. 2020;371:m3109. 7. Yang AL, et al. Pancreatology. 2020;20(5):795-800. 8. Aquest Research, 2021. 9. Assuming approval. 10. Applies to total addressable market.

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WAINUA ATTRv-PN Launch Delivering Accelerated Growth[1]

WAINUA for Hereditary ATTR Polyneuropathy, a systemic, progressive and fatal disease

Substantial and sustained sequential quarterly growth driven by strong demand[2]

Encouraging patient mix and breadth of prescribers

Physicians and patients report positive patient experience:

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

High unmet need; ~80% patients not on treatment[3]

1. WAINUA: www.wainua.com; co-developing and commercializing in the U.S. with AstraZeneca. 2. WAINUA product sales throughout 2024. 3. Based on internal market data.

Our Second Planned Independent Launch: Donidalorsen for HAE

Robust Clinical Data + HAE Landscape Dynamics Underscore Donidalorsen's Potential[1,2]

Robust Clinical Data Set including **Switch Data**[3]

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

Effective Commercial Model

Building on our launch efforts for WAINUA and TRYNGOLZA

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

Innovative, Scalable Commercial Organization for Global Launches

Delivering Important Pipeline Achievements

Richard Geary, Ph.D.

Chief Development Officer

TRYNGOLZA:
First FDA-Approved Treatment for Familial Chylomicronemia Syndrome[1]

Compelling Clinical Results:

- Significant and sustained triglyceride reductions
- Substantial reduction in acute pancreatitis events
- Substantial reduction in all cause hospitalizations and days spent in hospital
- Favorable safety and tolerability profile

First Mover Advantage

U.S. Launch Underway

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information.

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 safety study in patients w/ TG ≥150 (HTG)[2]
- Regulatory requirement for highly prevalent patient population
- >1,400 patients
- Enrollment complete
- **On track for data in mid-2025**

On Track for Data from CORE + CORE2 Studies in H2:2025

1. Timing expectations and peak sales estimates based on current assumptions and subject to change.2. Being conducted in in patients w/ TG ≥150-500 mg/dL (HTG) or TG ≥500 mg/dL (sHTG).

Donidalorsen: Potential Preferred Treatment for People with HAE

Lauren & Lindsey
Sisters Living with HAE

New prophylactic treatments needed[1]

Donidalorsen's clinical results include[2]**:**

- Substantial and sustained reductions in HAE attacks up to three years
- Improved QoL measures
- High levels of disease control
- >80% preference for donidalorsen over other prophylactic treatments[3]
- Favorable safety and tolerability
- Patient-friendly monthly or every two-month self-administration with an autoinjector

August 21, 2025 PDUFA[4]
MAA under review

1. 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). 2. Based on data generated to date including Phase 2, Phase 2 OLE, Phase 3 and Phase 3 OLE + Switch data. 3. 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. 4. Timing based on current estimates and subject to change.

Rich Late-Stage Pipeline with Multi-Billion Dollar Potential[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 (2025)**
		ATTR-CM		**Ph3 data (2026)[4]**
TRYNGOLZA (olezarsen)	IONIS[5]	FCS		**EU approval (2025)**
		sHTG		**Ph3 data (2025)[6]**
Donidalorsen	IONIS[5,7]	HAE		**U.S. approval (2025)[8]**
Zilganersen	IONIS	Alexander disease		**Ph3 data (2025)**
Pelacarsen	NOVARTIS	Lp(a) CVD		**Ph3 data (2026)**
Bepirovirsen	GSK	HBV		**Ph3 data (2026)**
Sefaxersen	Roche	IgA nephropathy		**Ph3 data (2026)**
Ulefnersen	Otsuka	FUS-ALS		**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. Granted Theratechnologies exclusive rights to commercialize olezarsen and donidalorsen in Canda.
6. Olezarsen sHTG data expected in H2:2025. 7. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions. 8. MAA submission completed in Q4'24.

<200K 200K – 500K >500K

Cardiovascular Neurology Specialty Other

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ION582: A Promising New Investigational Medicine for Angelman Syndrome

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]

- FDA alignment on Phase 3 study design
- Robust global 2:1 randomized pivotal study evaluating 2 doses of ION582 compared to placebo in broad AS population

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.

2025 and 2026 Key Value-Driving Events[1]

Phase 3 **Clinical Events**

2025

Olezarsen
Data
(sHTG)

Zilganersen
Data
(Alexander disease)

ION582
Study start
(Angelman syndrome)

2026

Pelacarsen
HORIZON data
(Lp(a)-CVD)

Bepirovirsen
B-Well data
(HBV)

Eplontersen
CARDIO-TTRansform data
(ATTR-CM)

Sefaxersen
IMAGINATION data
(IgAN)

ION582
Enrollment completion
(Angelman syndrome)

Ulefnersen
Phase 3 data
(FUS-ALS)

Regulatory **Actions**

2025

Donidalorsen
U.S. approval
(HAE)

TRYNGOLZA
EU approval
(FCS)

WAINZUA
EU approval
(ATTRv-PN)

Olezarsen
U.S. Submission
(sHTG)

Higher Dose Nusinersen
✓ U.S. & EU submissions
U.S. approval
(SMA)

2026

Donidalorsen
EU approval
(HAE)

Olezarsen
U.S. Approval
(sHTG)

Pelacarsen
U.S. Submission
(Lp(a)-CVD)

Bepirovirsen
Submission(s) & approval(s)
(HBV)

Zilganersen
U.S. submission & approval
(Alexander disease)

Product **Launches**

2025

Donidalorsen
U.S.
(HAE)

✓ **TRYNGOLZA**
U.S.
(FCS)

WAINZUA
EU
(ATTRv-PN)

2026

Olezarsen
U.S.
(sHTG)

Zilganersen
U.S.
(Alexander disease)

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 checkmark indicates event was achieved.

2024 Financial Performance and 2025 Financial Guidance

Beth Hougen

Chief Financial Officer

2024 Financial Highlights[1]

Substantially Exceeded Revenue Guidance, Resulting in Improved Operating Loss and Higher Cash

$705M

Revenue

Commercial Revenue: $293M

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

R&D Revenue: $412M

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

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$1,050M

Operating Expenses[2]

R&D Expenses[2]: $810M

- Flat YoY, while appropriately funded growth opportunities

SG&A Expenses[2]: $230M

- Increased YoY from commercialization efforts

$345M

Operating Loss[2]

Significantly improved compared to guidance due to substantial revenue earned

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$2.3B

Cash & Short-term Investments

Exceeded revised guidance;
Enables investments in launches and Ionis-owned pipeline

1. For the year ended December 31, 2024. 2. Non-GAAP – please see reconciliation to GAAP in YE 2024 press release.

2025 Financial Guidance Reflects Evolution to Fully Integrated Commercial-Stage Biotech

Revenue	Operating Loss	Cash
>$600 million	**<$495** million[1]	**~$1.7** billion

Expectations for 2025:

Revenue: Substantial and sustained

- **Commercial:** Increasing with TRYNGOLZA product sales, potential donidalorsen product sales, growing WAINUA royalties and significant SPINRAZA royalties
- **R&D:** Multiple sources from numerous advancing programs

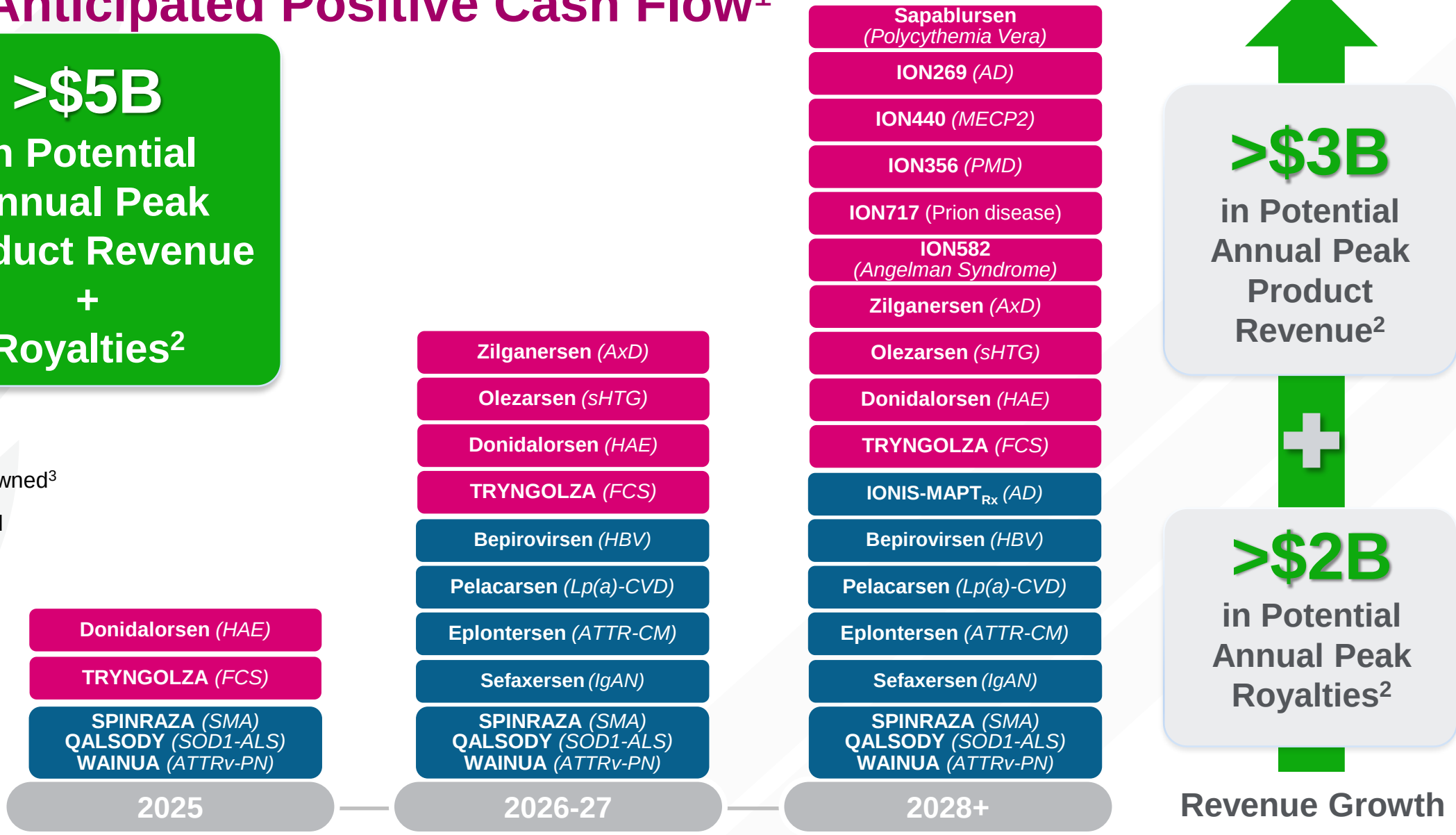
Operating Loss & Cash: Reflects investments to bring our medicines to patients

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

Steady Cadence of Expected Launches to Power Revenue Growth and Anticipated Positive Cash Flow[1]

>$5B
in Potential Annual Peak Product Revenue + Royalties[2]

- Wholly Owned[3]
- Partnered



1. Assuming approval. Estimated timing of potential U.S. approval based on current assumptions and subject to change. 2. Peak sales estimates based on current estimates and subject to change. Partnered royalties based on public disclosure made by the respective partner and Ionis' contractual royalty rates for each medicine. 3. Granted Otsuka exclusive rights to commercialize donidalorsen in Europe and Asia Pacific regions. Granted Theratechnologies exclusive rights to commercialize TRYNGOLZA and donidalorsen in Canada.

Conclusion

Brett Monia, Ph.D.

Chief Executive Officer

Accelerating Value Through Innovation

Proven and **prolific discovery** and **development engine**

Pipeline delivering at all stages

Scalable innovative **commercial organization**

Clear path to **positive cash flow**[1]

Improving the **lives** of **millions of patients** with **transformational medicines**[2]

1. Based on current assumptions and are subject to change. 2. Market data on file, assuming approval.

Q&A


IONIS®
HOPE
HOPE
HOPE
Hope
Hope
Delivering Accelerated Value