YE:2025 Business Update and Financial Results

February 25, 2026

Nasdaq: IONS

Yajaira (with family)
Living with sHTG

On Today's Earnings Call

Brett Monia, Ph.D.
Chief Executive Officer

Holly Kordasiewicz, Ph.D.
Chief Development Officer

Kyle Jenne
Chief Global Product Strategy Officer

Beth Hougen
Chief Financial Officer

Eugene Schneider, M.D.
Chief Clinical Development 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 and our expectations regarding development and regulatory milestones. Any statement describing Ionis' goals, expectations, financial or other projections or guidance, 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, 2024, 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

Strong Track Record of Industry-Leading Success[1-4]

Key Recent Achievements

6
Positive Phase 3 Data Readouts

4
Approved Medicines

Tryngolza® (olezarsen) 80 mg injection

DAWNZERA™ (donidalorsen) 80 mg/0.8 mL injection

WAINUA® (eplontersen) 45 mg injection for subcutaneous use

QALSODY® (tofersen) 100 mg/15 mL injection

2
Independent Launches

Tryngolza® (olezarsen) 80 mg injection

DAWNZERA™ (donidalorsen) 80 mg/0.8 mL injection

11
Medicines in Late-Stage Development

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome (FCS) in adults as an adjunct to diet; see Full Prescribing Information; Approved in the EU as an adjunct to diet in adult patients for the treatment of genetically confirmed FCS. 2. DAWNZERA is approved in the U.S. for hereditary angioedema in adults and pediatric patients 12 years of age and older; see Full Prescribing Information. 3. QALSODY.com. 4. WAINUA.com.

Strong Momentum Across the Business

Providing multi-billion-dollar revenue potential for Ionis[1]

First Independent Launch Exceeding Expectations

Tryngolza® (olezarsen) 80 mg injection

First FDA-approved treatment for FCS

YE:25 net sales of $108M

EU Launch underway[2]

Second Independent Launch Underway

DAWNZERA™ (donidalorsen) 80 mg/0.8 mL injection

Positioned to transform the HAE Treatment Paradigm

Early excitement seen with DAWNZERA from physicians and patients

Recently approved in the EU[3]

Preparations on Track for First Broad Patient Population Launch

Olezarsen in sHTG

Groundbreaking Phase 3 results position olezarsen to be the new standard of care for sHTG

sNDA submitted

On track to be launch ready by June 2026[4]

Preparations on Track for First Independent Neurology Launch

Zilganersen in AxD

First ever investigational medicine to show a disease-modifying effect in Alexander disease

NDA submitted

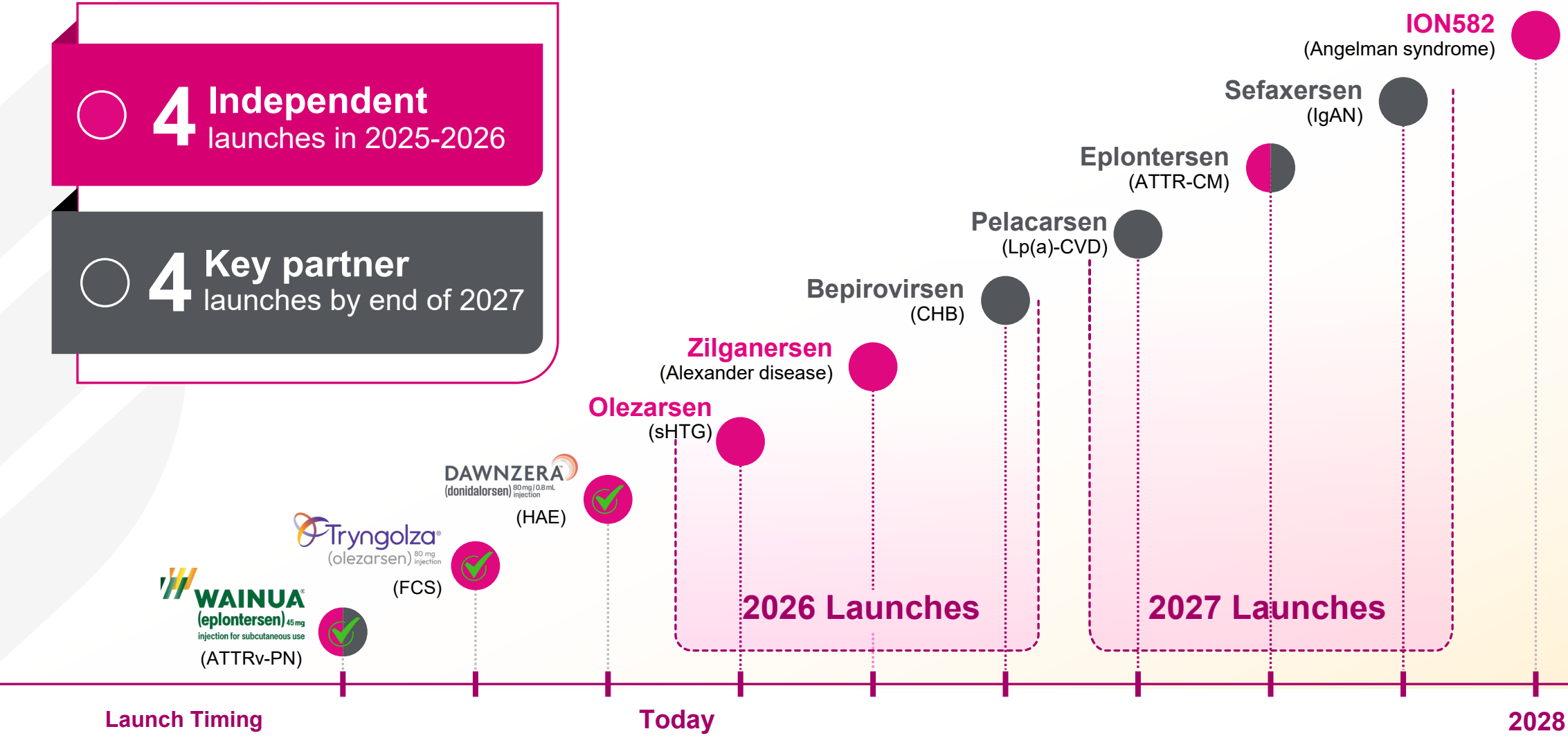
Launch on track for H2:2026

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. Sobi is responsible for commercializing TRYNGOLZA in the EU. 3. Otsuka is responsible for commercializing DAWNZERA in the EU. 4. Approval anticipated in June 2026 under Priority Review or October under Standard Review.

Delivering a Steady Cadence of New Medicines[1,2]

4 Independent launches in 2025-2026

4 Key partner launches by end of 2027



1. Assuming approval. 2. Based on current timing assumptions, subject to change.

Delivering Important Pipeline Achievements

Holly Kordasiewicz, Ph.D.

Chief Development Officer

Olezarsen:

Positioned to be the New Standard of Care for Severe Hypertriglyceridemia[1]

Groundbreaking clinical results[2]:

- **Highly statistically significant** and **clinically meaningful mean reductions** in **fasting triglycerides** of **up to 72% on top of standard of care**
  - 86% of olezarsen-treated patients achieved triglyceride levels below 500 mg/dL
  - Up to 54% of olezarsen-treated patients achieved normal triglyceride levels
- **First and only** investigational treatment to **significantly reduce acute pancreatitis** events in people with sHTG
  - 85% reduction in acute pancreatitis events compared to placebo
- **Favorable safety** and **tolerability**

sNDA submitted; On track to be launch ready by June 2026[1,3]

1. Timing expectations based on current assumptions and subject to change. 2. Marston NA, Bergmark BA, Alexander VJ, et al. Olezarsen for managing severe hypertriglyceridemia and pancreatitis risk. *N Engl J Med.* 2026;394(5):429-441. doi:10.1056/NEJMoa2512761. 3. Approval anticipated in June 2026 under Priority Review or October under Standard Review.

IONIS

Late-Stage Ionis-Owned Neurology Opportunities: Zilganersen and Obudanersen[1]

Zilganersen
for the Treatment of Alexander Disease

First and **only** investigational **medicine** to demonstrate **clinically meaningful disease-modifying impact**

Prevalence: ~1 in 1-3 million; accounts for ~2-8% of leukodystrophies, although likely underreported[2]

U.S. and EU Orphan designation; U.S. Fast Track designation

NDA submitted; Launch H2:2026; EAP underway[3]

Obudanersen
for the Treatment of Angelman Syndrome

Significant unmet need with no approved disease-modifying treatments

HALOS long-term extension data continues to support development

>100k people in major geographies[4]

Granted Breakthrough Therapy designation

Full enrollment of pivotal Phase 3 REVEAL study expected in **2026**; **data** expected in **2027**[3]

1. Formerly ION582. 2. Yoshida T, Sasaki M, Yoshida M, et al. Nationwide survey of Alexander disease in Japan and proposed new guidelines for diagnosis. J Neurol. 2011;258(11):1998-2008. 3. Based on current timing assumptions, subject to change. 4. Luk HM, Lo IFM. *Eur J Med Genet.* 2016;59:315–319.

Leading the Way in the Treatment of Neurological Diseases

6 Wholly Owned Medicines in Clinical Development

6 Partnered Medicines in Clinical Development

12 Medicines in Clinical Development

Approved Medicines[1-3]

SPINRAZA® (nusinersen) injection 12 mg/5 mL

QALSODY® (tofersen) 100 mg/15 mL injection

WAINUA® (eplontersen) 45 mg injection for subcutaneous use

Wholly Owned Medicines

	Indication	Preclinical	Ph1	Ph2	Ph3
Zilganersen (GFAP)	Alexander disease	NDA submitted			
ION582 (UBE3A-ATS)	Angelman syndrome				
ION464 (SNCA)	Multiple System Atrophy				
ION717 (PRNP)	Prion disease				
ION356 (PLP1)	Pelizaeus-Merzbacher disease				
ION440 (MECP2)	MECP2 Duplication syndrome				
ION337 (SCN1A)	Dravet syndrome				

Partnered Medicines

Ulefnersen (FUS)	Amyotrophic Lateral Sclerosis (ALS)	
Tofersen (SOD1)	ALS (Presymptomatic SOD1)	
Salanersen (SMN2)	Spinal Muscular Atrophy	
IONIS-MAPT$_{Rx}$ (TAU)	Alzheimer's disease	
Tominersen (HTT)	Huntington's disease	
RG6496 (HTT SNP)	Huntington's disease	

1. SPINRAZA.com 2. QALSODY.com. 3. WAINUA.com.

2026 Key Value-Driving Events[1]

Clinical Events

Phase 3

Bepirovirsen
B-Well data
(CHB)

Eplontersen
CARDIO-TTRansform data
(ATTR-CM)

Sefaxersen
IMAGINATION data
(IgAN)

ION582
Enrollment completion
(Angelman syndrome)

Pelacarsen
Lp(a) HORIZON data
(Lp(a)-CVD)

Ulefnersen
FUSION data
(FUS-ALS)

Sapablursen
Phase 3 initiation
(PV)

Salanersen
Phase 3 initiation
(SMA)

Phase 2

IONIS-MAPT$_{Rx}$
CELIA data
(Alzheimer's disease)

Tominersen
GENERATION HD2 data
(Huntington's disease)

Tonlamarsen
Phase 2 data
(Uncontrolled hypertension)

Regulatory Actions

Donidalorsen
EU approval
(HAE)

Olezarsen
U.S. approval
EU submission
(sHTG)

Zilganersen
U.S. submission
U.S. approval
(AxD)

High Dose Nusinersen[2]
U.S. approval
EU approval
(SMA)

Bepirovirsen
Submission & approval
(CHB)

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

Eplontersen
U.S. submission
(ATTR-CM)

Product Launches

DAWNZERA
EU
(HAE)

Olezarsen
U.S.
(sHTG)

Zilganersen
U.S.
(Alexander disease)

Bepirovirsen
U.S. & Japan
(CHB)

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. 2. Refiled with the FDA.

Building on our Commercial Success

Kyle Jenne

Chief Global Product Strategy Officer

TRYNGOLZA Outperforms Expectations in First Year of Launch as the First FDA-Approved Treatment for FCS[1]

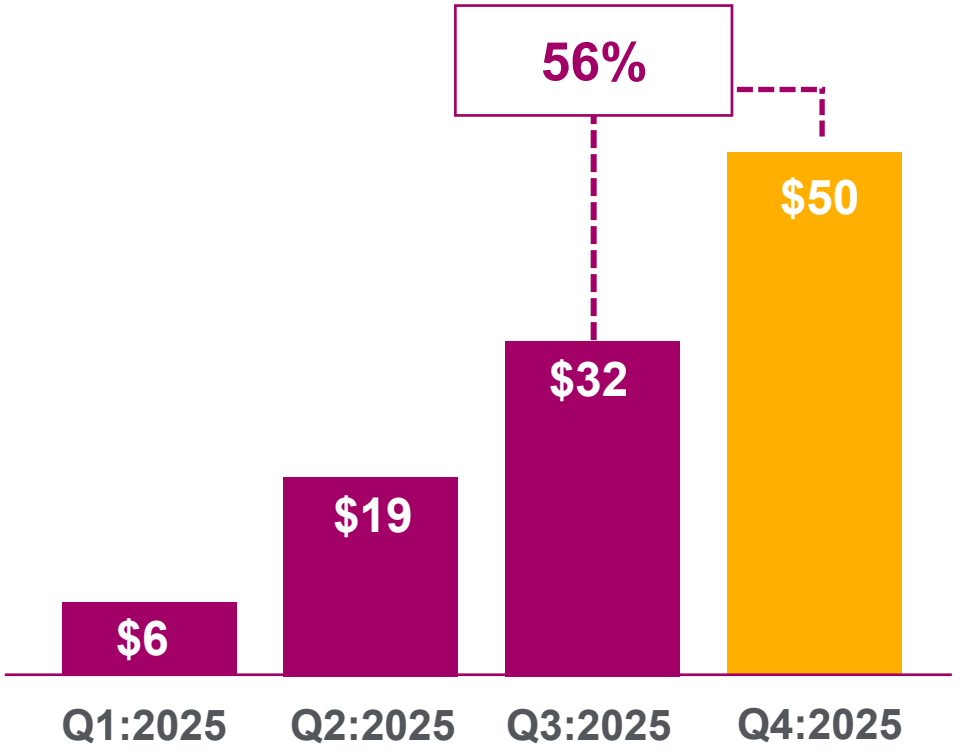
Robust efficacy and safety

- Significant and sustained triglyceride reductions
- Substantial reduction in acute pancreatitis events

Convenience of once-monthly self-administration with an autoinjector

EU launch now underway[2]

Generated $108 million in 2025



TRYNGOLZA, U.S. Product Sales, net (millions)

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see Full Prescribing Information. 2. Approved in the EU as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).

Strong Commercial Execution and Compelling Product Profile Driving Increasing TRYNGOLZA Demand[1,2]

Strong Uptake

Effective patient identification efforts; strong referral and patient growth

No meaningful impact on cancellations or discontinuation rates following new market entrant

Breadth and depth of unique physicians prescribing TRYNGOLZA growing

Robust Physician Engagement

Targeting ~20,000 physicians with expanded field team

Leveraging omnichannel capabilities to reach >30k HCPs

TRYNGOLZA awareness gaining traction

High satisfaction with prescribing experience and overall TRYNGOLZA profile

Broad Patient Access

Broad FCS access and coverage

Effectively managing evolving pricing dynamics to preserve access and coverage

Coverage split: ~60% commercial, ~40% government

>90% of patients had $0 out-of-pocket costs in commercial setting

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see Full Prescribing Information. 2 On-label patients with FCS.

sHTG Launch Preparations Confirm Strong Enthusiasm for Olezarsen

Groundbreaking Pivotal sHTG Results[1]

Highly statistically significant and clinically meaningful reductions in fasting triglycerides

First and only investigational treatment to significantly reduce acute pancreatitis events in people with sHTG

Robust HCP Demand

Strong enthusiasm for olezarsen and its potential to address the unmet needs of people with sHTG

Ongoing Payer Engagement

Educating on clinical and economic burden of disease and associated budget impact

Maximizing value with broad access

1. Marston NA, Bergmark BA, Alexander VJ, et al. Olezarsen for managing severe hypertriglyceridemia and pancreatitis risk. *N Engl J Med.* 2026;394(5):429-441. doi:10.1056/NEJMoa2512761.

Olezarsen: Poised to Become Ionis' First Blockbuster Medicine

>3 million people with sHTG in the U.S.[1]

- Includes >1 million people with high-risk sHTG[1]
- Early launch focus on high-risk sHTG with >880 mg/dL or ≥500 mg/dL + AP history and/or comorbidities

- **Highly statistically significant** and **clinically meaningful** reductions in fasting **triglycerides**[2]
- **First and only** investigational treatment to **significantly reduce acute pancreatitis** events in **people with sHTG**[2]

Simplicity of **monthly self-administration** with a patient-friendly **autoinjector**

- **First mover advantage**
- **Full field team onboard** and **deployed**
- **sNDA submitted; On track to be launch ready by June 2026**[3]

Annual Peak Product Revenue Opportunity[3]

Increased to

>$2B

(Previous: >$1 billion)

1. Saadatagah S, et al. J Clin Lipid 2025;19:432-441; Sanchez RJ, et al. Lipids Health Dis 2021;20:72; Sikora Kessler A, et al. Lipids Heath Dis 2025;24:252. 2. Marston NA, Bergmark BA, Alexander VJ, et al. Olezarsen for managing severe hypertriglyceridemia and pancreatitis risk. *N Engl J Med.* 2026;394(5):429-441. doi:10.1056/NEJMoa2512761. 3. Timing and peak sales expectations based on current assumptions and subject to change.

DAWNZERA Launch off to Encouraging Start[1]

Delivering on What HAE Patients Need Most

First and **Only RNA-Targeted Treatment** to **Prevent HAE Attacks**

Indicated for prophylaxis to prevent attacks of HAE in adult and pediatric patients ≥12 years old

The Opportunity

- ~7,000 people with HAE in the U.S.[2]
- Substantial patient dissatisfaction

Compelling Product Profile

- Substantial and durable efficacy, with favorable safety and tolerability
- Switch study demonstrated strong patient preference for DAWNZERA
- Longest dosing interval option[3]
- Self-administration with an autoinjector

Encouraging Early Launch Momentum

Prescriptions written for all patient segments:

- Switches from other long-term prophylactic treatments
- Previously on-demand treatment only
- Treatment naïve

Growing number of repeat prescribers

Approved in U.S. and EU[4]

1. DAWNZERA is approved in the U.S. for hereditary angioedema in adults and pediatric patients 12 years of age and older; see Full Prescribing Information. 2. Christiansen SC, Wilmot J, Castaldo AJ, Zuraw BL. The US Hereditary Angioedema Association Scientific Registry: hereditary angioedema demographics, disease severity, and comorbidities. Ann *Allergy Asthma Immunol*. 2023 Dec;131(6):766-774.e. 3. Market data on file. 4. Otsuka is responsible for commercializing DAWNZERA in the EU.

Zilganersen: Our First Anticipated Neurology Launch on Track for H2:2026[1,2]

Substantial Unmet Need

Alexander disease is a **rare**, **progressive** and **often fatal** neurological condition

No approved disease-modifying treatments

Groundbreaking Phase 3 Data

First time an investigational **medicine** has shown a **positive disease-modifying impact in Alexander disease**

Demonstrated **statistically significant** and **clinically meaningful stabilization** on the **primary endpoint**

Well-Established Patient Community

Strong partnership with the Alexander disease **patient community**

Strategy to Reach Patients

Evaluation and **diagnosis**

Treatment management

Access and **adherence**

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

Innovative Commercial Organization with Proven Ability to Bring Medicines to People with Serious Diseases

Top-Tier Team

Demonstrated Strong Initial Launch Execution

Scaling Capabilities for Upcoming Launches

YE:2025 Financial Performance and 2026 Financial Guidance

Beth Hougen

Chief Financial Officer

YE:2025 Financial Highlights[1]

Exceeded 2025 Guidance

Revenues $944M

Commercial Revenue: $436M

- $108M in TRYNGOLZA product sales
- Total commercial revenues increased ~49% YoY

R&D Revenue: $508M

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

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Operating Expenses[2] $1,192M

R&D Expenses[2]: $826M

- Large majority funding late-stage programs

SG&A Expenses[2]: $352M

- YoY increase fueling ongoing and planned launches

Operating Loss[2] ($248M)

- Reflects strong revenue generation from multiple sources and disciplined expense management

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Cash & Short-term Investments $2.7B

- Enables investments in launches and Ionis-owned pipeline
- Includes $433M earmarked to repay the 2026 convertible notes

1. For the year ended December 31, 2025. 2. Non-GAAP – please see reconciliation to GAAP in YE:2025 press release.

2026 Revenue Guidance Reflects Growing Commercial Revenue and Substantial Partner Revenue[1]

Revenue: $800-$825 million[2]

+ ~20% vs 2025[3]

Assumes olezarsen standard review

TRYNGOLZA

Strong FCS patient demand expected to continue

Engaging with payers to ensure broad access

Meaningful revenue decline expected ahead of anticipated sHTG approval[2]

Accelerating growth following sHTG launch[2]

DAWNZERA

Strong launch fundamentals in place: increasing demand, high referral-to-start conversion rate

Meaningful contribution to total commercial revenue growth

Royalties

SPINRAZA to remain resilient; H1 to reflect annual tiered royalty reset

WAINUA expected to continue upward trajectory

R&D Revenue

Multiple opportunities to generate R&D revenue

$65M in milestone payments already achieved

1. Based on current assumptions; subject to change. 2. Assumes standard review and approval in late October 2026. 3.Excludes the $280 million license fee for sapablursen in 2025.

2026 Financial Guidance Reflects Fully Integrated Commercial-Stage Biotech Launching Multiple Medicines[1-3]

Revenue
$800-$825 million
+ ~20% vs 2025[4]

Numerous diverse revenue sources

TRYNGOLZA and DAWNZERA product level guidance to be provided at Q1:26 Earnings[4]

Operating Loss
$500-550 million[3]
Similar level to 2025[4]

Investing in multiple launches, including broad sHTG indication

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Investing in advancing pipeline

Improved operating leverage

Cash
~$1.6 billion

Investments for launches, pipeline and technology

Reflects use of $433M to repay 2026 Convertible Notes

On track to achieve cash flow breakeven in 2028

1. Based on current assumptions, subject to change. 2. Assumes standard review and approval in late October 2026. 3. Excluding the $280 million license fee for sapablursen in 2025. 4. Non-GAAP – please see reconciliation to GAAP in YE:2025 press release.

Conclusion

Brett Monia, Ph.D.

Chief Executive Officer

Well Positioned to Continue Driving Accelerating Growth

Key Catalysts in 2026[1]

5 Phase 3 Data Readouts

- ✔ Bepirovirsen
- Pelacarsen
- Eplontersen
- Sefaxersen
- Ulefnersen

4 NDA Submissions

- Zilganersen
- Bepirovirsen
- Pelacarsen
- Eplontersen

3 Launches

- Olezarsen
- Zilganersen
- Bepirovirsen

Multiple Phase 2 Data Readouts

Alzheimer's Disease (TAU) | Huntington's Disease (HTT)
Uncontrolled Hypertension (AGT)

1. Based on current assumptions, subject to change.

Q&A

Breakthrough Therapies Driving Accelerating Growth