First Quarter 2026 Business Update & Financial Results

April 29, 2026

Nasdaq: IONS

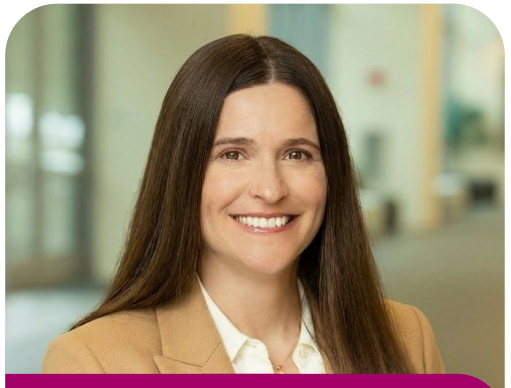
Yajaira (with family)
Living with sHTG

On Today's Earnings Call

Brett Monia, Ph.D.
Chief Executive Officer

Kyle Jenne
Chief Global Product Strategy Officer

Beth Hougen
Chief Financial Officer



Holly Kordasiewicz, Ph.D.
Chief Development 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, 2025, 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

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

2 Phase 3 Study Starts

- Salanersen
- Sapablursen

Multiple Phase 2 Data Readouts

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

1. Based on current assumptions, subject to change.

Strengthening Our Commercial Foundation

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

First Independent Launch Generating Strong Patient Demand

Tryngolza® (olezarsen) 80 mg injection

First FDA-approved treatment for FCS

Q1:26 U.S. net sales of $27M

EU Launch underway[2]

Second Independent Launch Underway

DAWNZERA™ (donidalorsen) 80 mg / 0.8 mL injection

Positioned to transform the HAE Treatment Paradigm

Q1:26 U.S. net sales of $16M

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

Granted Priority Review

PDUFA June 30, 2026

Preparations on Track for First Independent Neurology Launch

Zilganersen in AxD[4]

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

Granted Priority Review

PDUFA September 22, 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. Alexander Disease

Olezarsen: Poised to Become Ionis' First Multi-Billion Dollar 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 **deployed**
- **Granted Priority Review**; PDUFA June 30, 2026

Annual Peak Product Revenue Opportunity[3]

Increased to

>$3B

(Previous: >$2B)

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.

Zilganersen: Preparations on Track for First Independent Neurology Launch[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

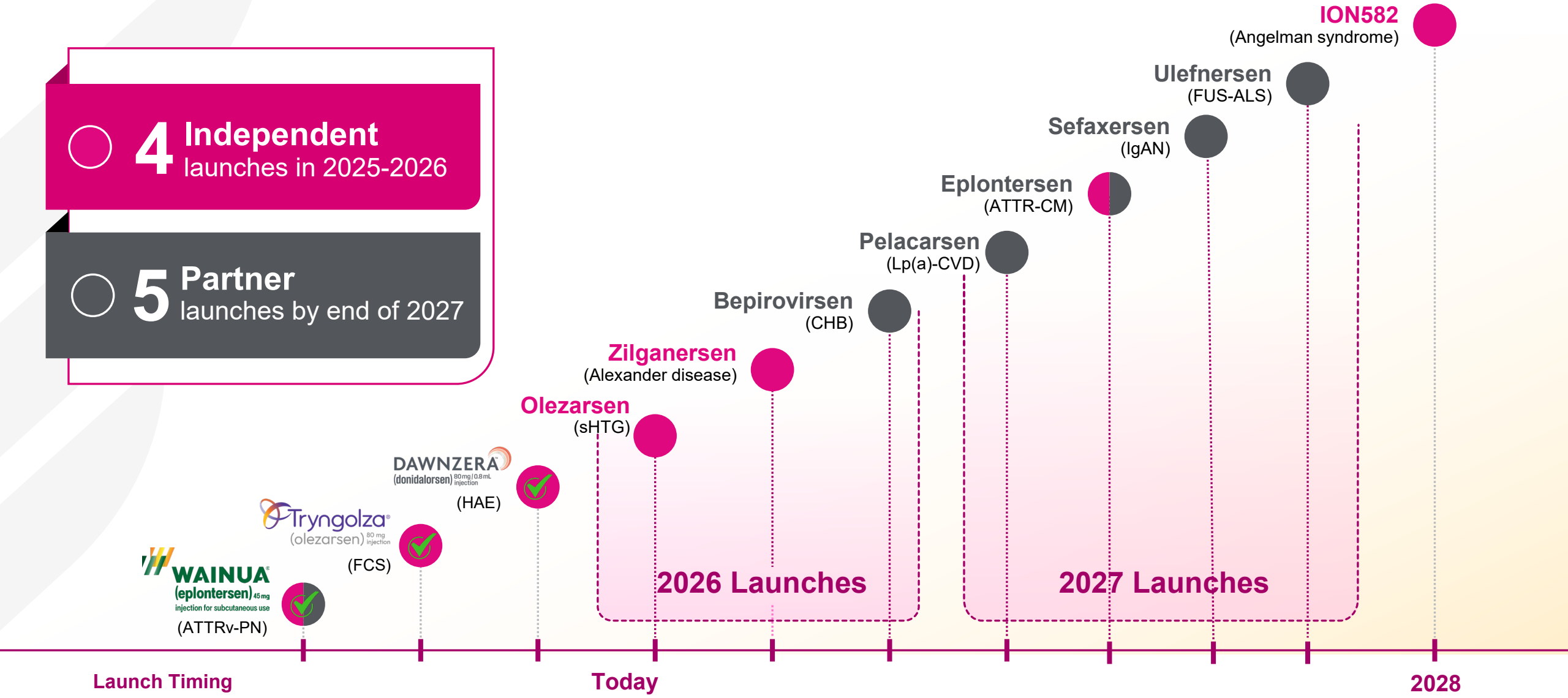
Granted Priority Review; PDUFA September 22, 2026

1. Based on current timing assumptions, subject to change. 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. *Med Genet.* 2016;59:315–319.

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

4 Independent launches in 2025-2026

5 Partner launches by end of 2027



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

Building on our Commercial Success

Kyle Jenne

Chief Global Product Strategy Officer

Focused Commercial Execution Building Sustainable TRYNGOLZA Demand[1]

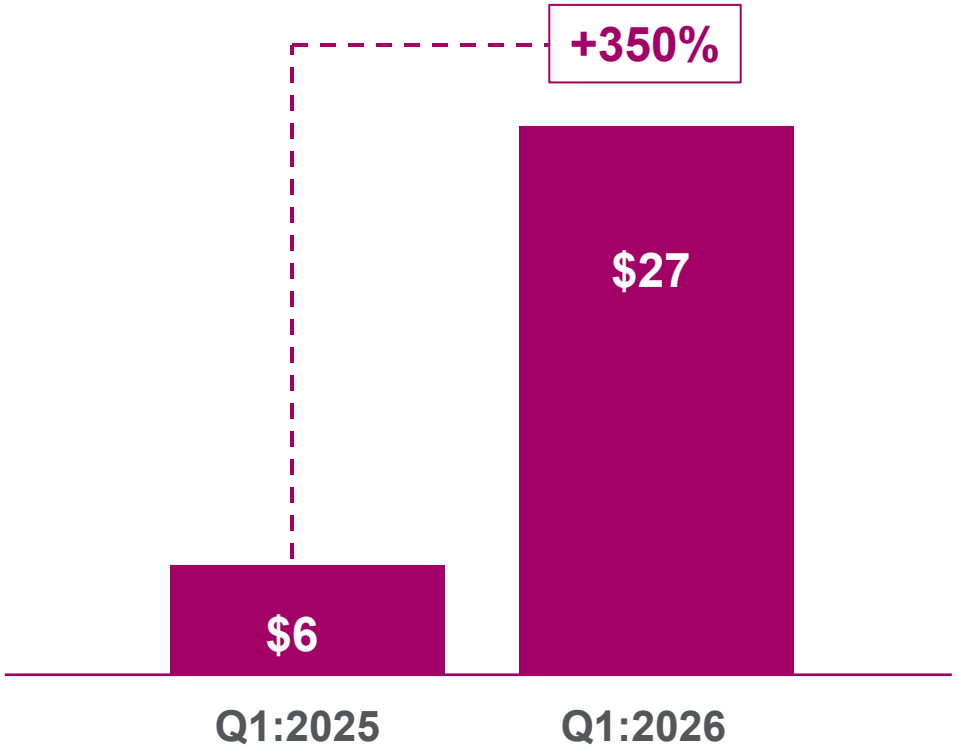
Robust efficacy and safety

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

Convenience of once-monthly self-administration with an autoinjector

EU launch underway[2]

Generated $27 million in Q1:2026



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 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 ~20k 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 managed evolving pricing dynamics in Q1

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.

Olezarsen in sHTG: Launch Readiness and a Larger Opportunity

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

Payer Engagement

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

Maximizing value with broad access

Updated WAC price effective April 1, 2026

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.

DAWNZERA Launch Gaining Significant Momentum[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

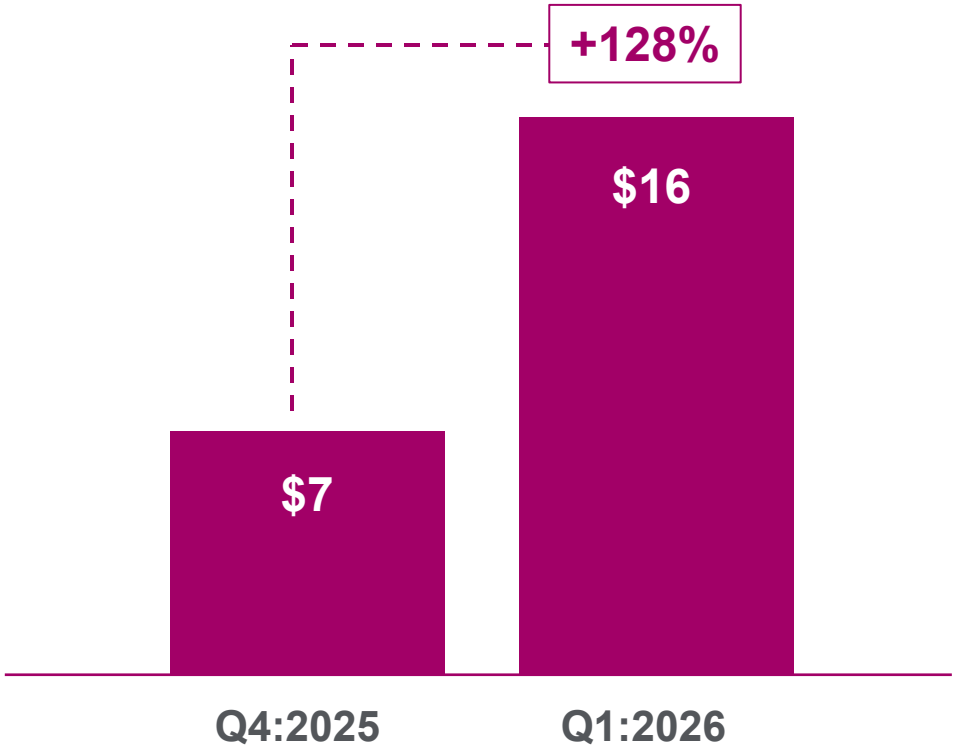
Prescriptions written for all patient segments:

- 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[2]

Generated $16 million in Q1:2026



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

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. Otsuka is responsible for commercializing DAWNZERA in the EU.

Zilganersen: Ionis' First Anticipated Neurology Launch[1,2]

Granted Priority Review

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

Q1:2026 Financial Performance and 2026 Financial Guidance

Beth Hougen

Chief Financial Officer

Q1:2026 Financial Highlights[1]

Revenues $246M

Commercial Revenue: $108M

- $27M in TRYNGOLZA product sales
- $16M in DAWNZERA product sales
- Total commercial revenues increased ~42% YoY

R&D Revenue: $138M

- Includes approximately $95M of milestone payments from multiple partnerships

Operating Expenses[2] $321M

R&D Expenses[2]: $185M

- Large majority funding late-stage programs

SG&A Expenses[2]: $133M

- YoY increase fueling ongoing and planned launches

Operating Loss[2] ($75M)

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

Cash & Short-term Investments $1.9B

- The change in cash and short-term investments from year-end 2025 was primarily related to the $633 million the Company used for the maturity of the 0% convertible notes due on April 1, 2026

1. For the quarter March 31, 2026. 2. Non-GAAP – please see reconciliation to GAAP in Q1:2026 press release.

Improved 2026 Financial Guidance Reflects Growing Contribution from Ionis Launches[1-3]

Revenue

$875-$900M

>30% vs 2025[3]

Previous: $800-825M

Increase of $75M versus prior guidance

TRYNGOLZA net product sales $100-110M

DAWNZERA net product sales $110-120M

Operating Loss

$425-475M[4]

Similar to 2025[3]

Previous: $500-550M

Improved by $75M versus prior guidance

Investing in multiple launches, including broad sHTG indication

Improved operating leverage

Cash

>$1.6B

No Change

Supports investments for launches, pipeline and technology

On track to achieve 2028 cashflow breakeven

1. Based on current assumptions, subject to change. 2. Assumes priority and approval in late June 2026. 3. Excluding the $280 million license fee for sapablursen in 2025. 4. Non-GAAP – please see reconciliation to GAAP in Q1:2026 press release.

Conclusion

Brett Monia, Ph.D.

Chief Executive Officer

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**
  ✓ U.S. approval
  ✓ EU approval
  (SMA)
- **Bepirovirsen**
  ✓ Submission
  Approval
  (CHB)
- **Pelacarsen**
  U.S. submission
  (Lp(a)-CVD)
- **Eplontersen**
  U.S. submission
  (ATTR-CM)

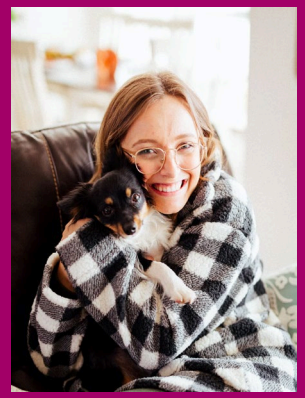
Product Launches

- ✓ **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.

Breakthrough Therapies Driving Accelerating Growth












Q&A