Q3:2025 Business Update and Financial Results

October 29, 2025

Nasdaq: IONS

Eli (with family member)
Living with FCS

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

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, 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

Delivering Transformational Medicines in Focused Therapeutic Areas

Neurology

First- or best-in-class medicines to address a broad range of diseases with high unmet need

Rare and prevalent patient populations in focused disease areas

Cardiometabolic

First- or best-in-class medicines that target cardiometabolic diseases, the leading causes of death globally

Potential for Multiple Blockbusters[1]

1. Based on current estimates, subject to change.

Q3:2025: 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 and only FDA-approved treatment for FCS

Q3'25 net sales of **$32M**

Approved in the EU

Second Independent Launch Underway

DAWNZERA™ (donidalorsen) 80 mg/0.8 mL injection

Positioned to transform the HAE Treatment Paradigm

U.S. launch underway

Early excitement seen with DAWNZERA from physicians and patients

Positive Phase 3 Data
Olezarsen in sHTG

Statistically significant & clinically meaningful mean reductions of up to 72% in PBO-adjusted fasting triglycerides

Highly statistically significant 85% reduction in adjudicated acute pancreatitis events

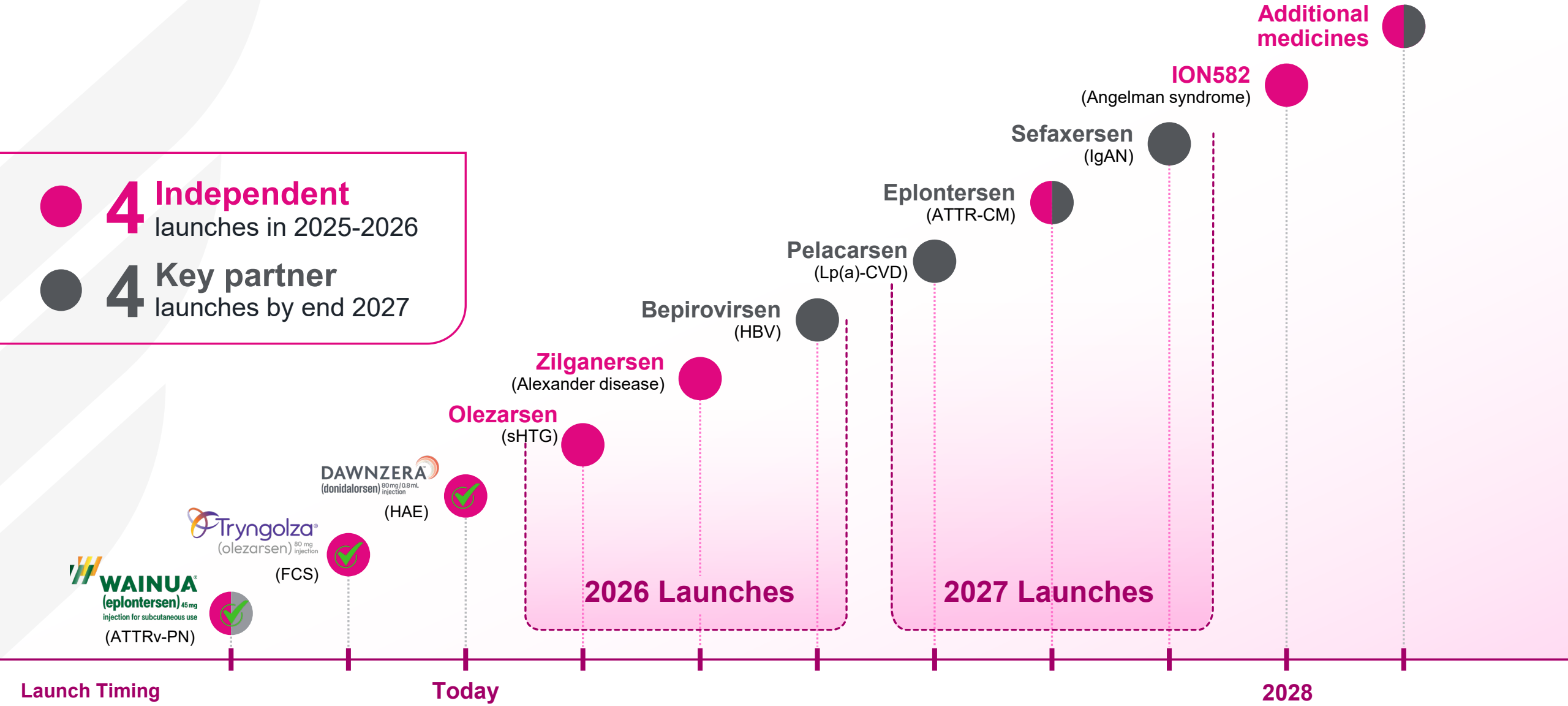
Positive Phase 3 Data
Zilganersen in AxD

Statistically significant & clinically meaningful stabilization on the primary endpoint of gait speed

Consistent benefit across key secondary endpoints observed

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

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



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

Delivering Important Pipeline Achievements

Richard Geary, Ph.D.

Chief Development Officer

Olezarsen Achieved Highly Statistically Significant Reductions in Fasting Triglycerides at 6 Months[1]

Primary Endpoint	Placebo	Olezarsen 50 mg	Olezarsen 80 mg
CORE			
% Reduction from baseline[2]	0.5%	63%	73%
% Placebo-adjusted reduction[4]		63%	72%
P-value[3]		p<0.0001	p<0.0001
CORE2			
% Reduction from baseline[2]	14%	63%	68%
% Placebo-adjusted reduction[4]		49%	55%
P-value[3]		p<0.0001	p<0.0001

Up to a **72%** placebo-adjusted mean reduction in fasting triglycerides[1]

1. Results from the CORE and CORE2 pivotal studies. 2. Least-squares mean. 3. P-values are based on comparison between each olezarsen group and placebo group in percent reduction in fasting triglycerides. 4..Least-squares mean difference of percent reduction in fasting triglycerides

Olezarsen Demonstrated a Highly Statistically Significant Reduction in Acute Pancreatitis Events [1-3]

85%

(p=0.0002)

Reduction in acute pancreatitis events compared to placebo[1-3]

Secondary endpoint, pooled olezarsen (50 mg and 80 mg) from CORE and CORE2 compared to pooled placebo at 12 months

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

1. All AEs and SAEs consistent with acute pancreatitis that occurred during the study were adjudicated by a blinded, independent committee according to the revised Atlanta classification of acute pancreatitis.
2. Banks et al. *Gut* 2013;62:102–111. 3. Results from the CORE and CORE2 pivotal studies

Olezarsen: Poised to be the New Standard of Care for sHTG[1]

Groundbreaking Clinical Results[2]:

Highly statistically significant and clinically meaningful mean reductions in fasting triglycerides of up to 72%

First and only medicine to significantly reduce acute pancreatitis events in people with sHTG with an 85% reduction compared to placebo

Favorable safety and tolerability

AHA data presentation and webcast on November 8[1]

sNDA submission on track by YE:2025[1]

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. Results from the CORE and CORE2 pivotal studies

Zilganersen for the Treatment of Alexander Disease

First and Only Investigational Medicine to Demonstrate Clinically Meaningful and Disease-Modifying Impact[1]

Grayson and family
living with Alexander disease

Alexander Disease (AxD)[2-5]
Fatal and Progressive Ultra-Rare Childhood Neurological Disorder

Characterized by gross/fine motor and cognitive impairment, speech difficulties, ataxia and seizures

Caused by mutations in *GFAP*

~65% of cases occur in childhood

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

Zilganersen

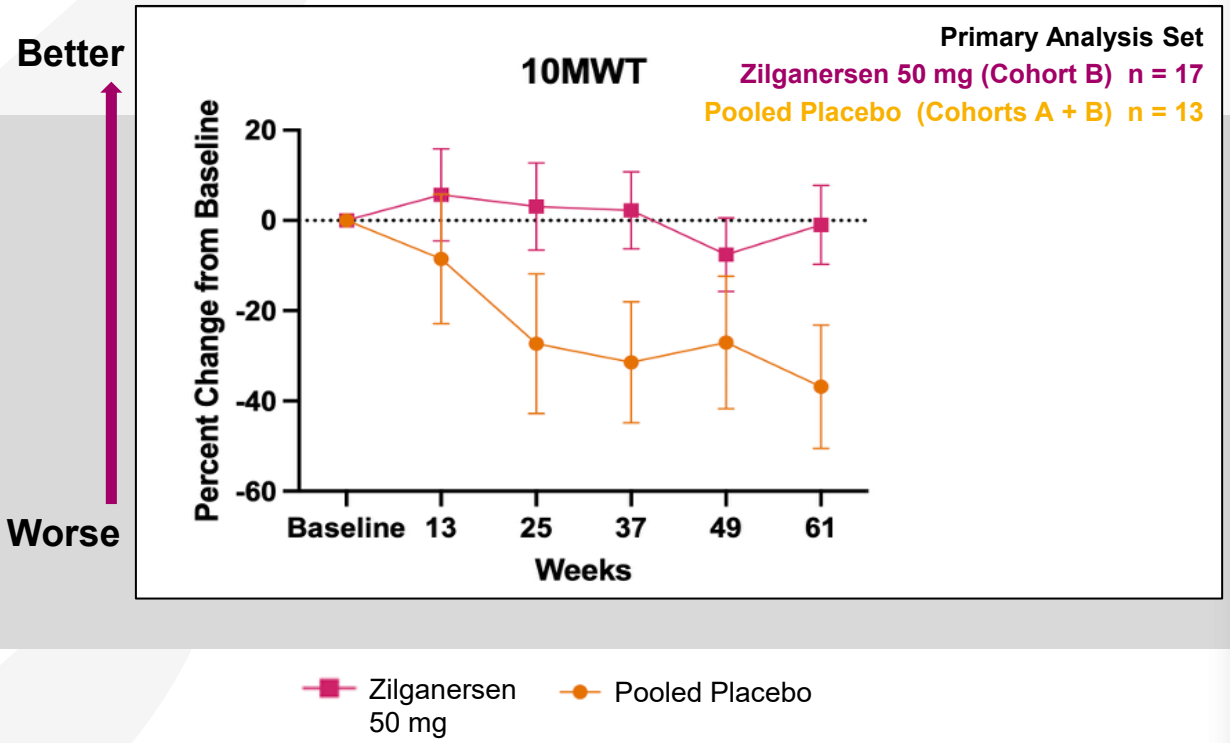
Unprecedented pivotal results position zilganersen to potentially transform the AxD treatment landscape[6]

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

First anticipated launch from our wholly owned neurology portfolio: NDA submission Q1:2026; **Launch H2:2026**[6,7]

1. Topline pivotal results reported on September 22, 2025. 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. Heim et al., Am J Med Genet 1997; 71:475-478 and Cohen et al., Ann Hum Genet 2020; 84:11–28. Messing, Albee. Alexander Disease: A Guide for Patients and Families. Colloquium Series on Neuroglia in Biology and Medicine: From Physiology to Disease. Vol. 3. No. 1. Morgan & Claypool Life Sciences, 2017; 4. Prust M, et al. GFAP mutations, age at onset, and clinical subtypes in Alexander disease. Neurology. 2011;77(13):1287-1294. 5. Srivastava et al., 1993. 6. Assuming approval. 7. Based on current timing estimates, subject to change.

Zilganersen Improves Gross Motor Function[1]



Primary Endpoint (10MWT)		Zilganersen (50mg) n=17	Pooled Placebo n=13
Baseline			
$(m/s)^2$	Mean	1.2	1.1
% Change at Week 61			
	Mean	-1.0%	-36.9%
	Least Squares Mean (LSM) (95% CI)	-2.1% (-23.0, 18.8)	-35.4% (-59.3, -11.5)
	LSM Difference (95% CI)	**33.3%** (1.4, 65.3)	
P-value[3]		**p=0.0412**	

Key secondary endpoints consistently favored zilganersen

All eligible patients who completed the double-blind treatment period enrolled into the OLE

1. Topline pivotal results reported on September 22, 2025. 2. Meters per second. 3. ANCOVA model.

ION582: A Promising New Investigational Medicine for Angelman Syndrome

Jackson
living with Angelman syndrome

ION582

Potential to address a significant unmet need with no approved disease-modifying treatments

U.S. Breakthrough, Fast Track, Rare Pediatric and Orphan designations; EU Orphan designation

Positive Results Seen in the HALOS Study[1]

Consistent and meaningful improvements in key areas at 6 months: **Clinical function** including **communication**, **cognition** and **motor function**

Evidence of consistent improvements across age groups and genotypes at 6 months

Infant cohort recently added, with first patient dosed

Long-term data suggests meaningful, disease-modifying potential

Robust Pivotal Phase 3 REVEAL Study Now Underway[2]

Full enrollment expected next year[3]

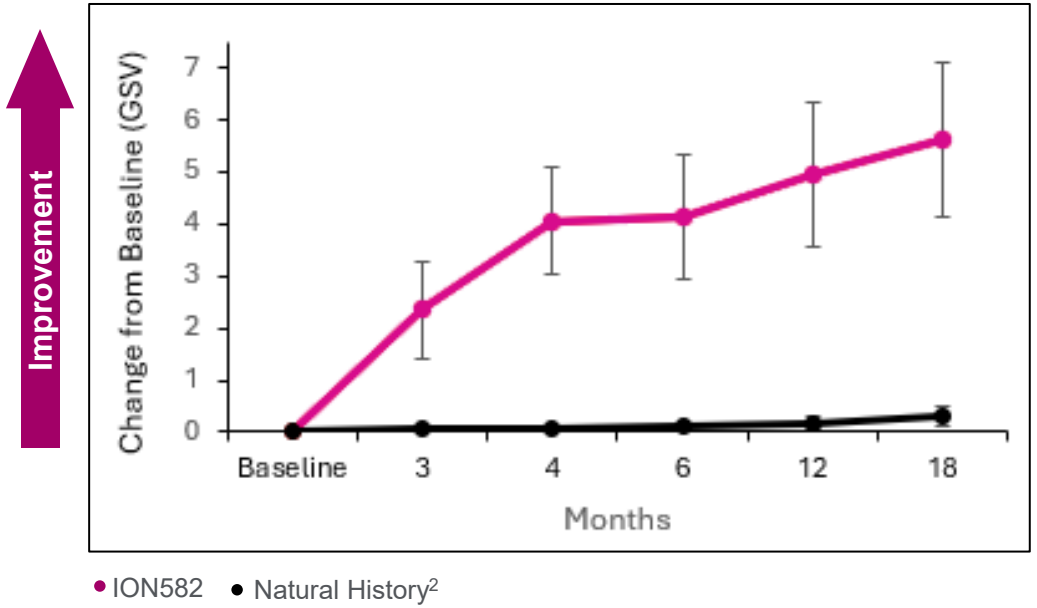
Global, randomized, ION582 quarterly vs. placebo in children and adults and both deletion and mutation genotypes

1. Based on data generated to date from the Phase 1/2a HALOS study of ION582. 2. REVEAL Trial, clinicaltrials.gov/NCT06914609. 3 Based on current timing estimates, subject to change.

Expressive Communication: Continued Improvement Observed on Bayley-4 at 18 Months[1]

HALOS

Change on Bayley-4 Expressive Communication ION582 vs. Natural History



Improvements on Bayley-4 measure of expressive communication exceed natural history[2]

Consistent improvements across additional assessment tools measuring expressive communication

GSV, Growth scale values 1. ≥2 years of age medium (40mg) and high (80mg) dose groups, n=35-40 for ION582 treatment. Excludes patients who dose escalated or had a gap in dosing between MAD and LTE. 2. Natural history data compiled from two studies: www.clinicaltrials.gov/study/NCT04507997 and www.clinicaltrials.gov/study/NCT00296764 and includes Bayley-3 to Bayley-4 conversion by Pearson.

Focused High-Value Wholly Owned Pipeline to Drive Continued Growth

		Indication	Prevalence[1]	Next Events[2]	
Cardiometabolic	**Olezarsen** (ApoC-III)	Severe hypertriglyceridemia	3	**FDA approval and launch**	**2026**
	ION775 (ApoC-III)	Severe hypertriglyceridemia	3	**Ph2 start**	**2026**
	ION501 (Undisclosed)	Myocardial disease	3	**Complete IND TOX**	**2026**
Neurology	**Zilganersen** (GFAP)	Alexander disease	1	**FDA approval and launch**	**2026**
	ION582 (UBE3A-ATS)	Angelman syndrome	2	**Ph3 complete enrollment**	**2026**
	ION464 (SNCA)	Multiple System Atrophy	1	**Ph1/2 data**	**2026**
	ION717 (PRNP)	Prion disease	1	**Ph1/2 data**	**2026**
	ION356 (PLP1)	Pelizaeus-Merzbacher disease	1	**Ph 1/2 complete enrollment**	**2026**
	ION337 (SCN1A)	Dravet syndrome	1	**First-in-patient study start**	**2026**
	ION440 (MECP2)	MECP2 Duplication syndrome	1	**Ph1/2 complete enrollment**	**2027**

1 <50K 2 50K – 500K 3 >500K

1. Prevalence data on file. 2. Based on current assumptions, subject to change.

Building on the Commercial Success of TRYNGOLZA

Kyle Jenne

Chief Global Product Strategy Officer

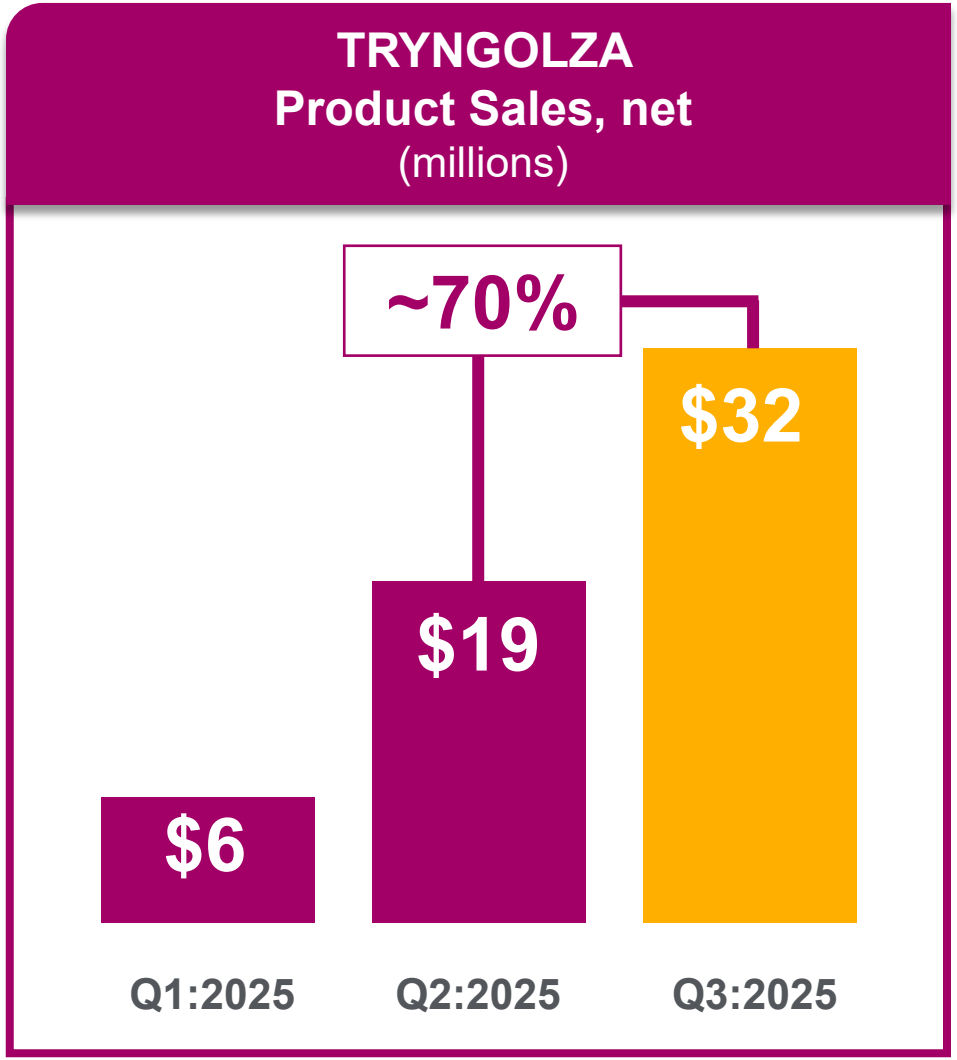
TRYNGOLZA: First and Only FDA-Approved Treatment for FCS[1]

Robust efficacy and safety

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

Convenience of once-monthly self-administration with an autoinjector

Now approved in the EU[2]



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 Robust Uptake[1-3]

Strong Initial Uptake

Effective patient identification efforts

Breadth and depth of unique physicians prescribing TRYNGOLZA continues to grow

70% cardiologists and endocrinologists
30% lipidologists and internal medicine

Robust Physician Engagement

Targeting over 3,000 physicians

Leveraging omnichannel capabilities to reach >30K HCPs

TRYNGOLZA awareness gaining traction

Highly favorable feedback

Positive Access Dynamics

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

Clinically diagnosed and genetically confirmed patients gaining access

>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. For the quarter ended September 30, 2025. 3 On-label patients with FCS.

Building on TRYNGOLZA Early Launch Momentum for Sustained Success[1]

Patient Finding is Critical

Most of the **3,000** estimated U.S. FCS **patients remain unidentified** and **undiagnosed**[2-6]

Targeted HCP Education is Essential

Targeting over 3,000 physicians to **increase FCS awareness** with customer facing field team

Further extending reach with omnichannel and targeted marketing

Establishing Broad, Durable Access is Key

Majority of formal policies **support clinical scoring, genetic testing**, or indeterminant genetic test plus scoring

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see Full Prescribing Information. 2. Dron JS, et al. *BMC Med Genomics* 2020;13(1):23. 3. Hegele RA. *Nat Rev Genet* 2009;10(2):109-21. 4. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 5. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 6. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6.

Severe Hypertriglyceridemia: Prevalent Condition with Significant Unmet Medical Need

Substantial Unmet Need

Fasting triglycerides **≥500 mg/dL** and **increased risk** of potentially life-threatening acute pancreatitis

Limited benefit from currently available treatments, including **fibrates** and **omega-3s**

Market Poised for New Treatment

HCPs and patients dissatisfied with current sHTG treatments

Payors **recognize value** in treating people with **TGs ≥500 mg/dL**

Significant Market Opportunity[1-3]

>3 million people with sHTG in the U.S.

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

1. Sanchez et al. *Lipids in Health and Disease.* 2021;20:72. 2. Christian et al., *Am J Cardiol.* 2011;107:891-897. 3. Saadatagah et al. *J Am Heart Assoc.* 2021;10(11):e019343.

Strategy to Realize the Blockbuster Potential of Olezarsen in sHTG[1,2]

Targeting Key HCPs

Specialty focused, **~20,000 cardiologists, endocrinologists** and **lipidologists** in the U.S.

Actively treating high-risk sHTG patients with standard of care

Expanding Disease Awareness[3]

Conducting sHTG **disease state education with key HCPs**

Engaging >30K HCPs in disease state education

Building a Right-Sized Field Team

~200-person cardiometabolic field team to effectively target HCPs at launch

Flexibility to scale as the market evolves

Attractive Payer and Access Dynamics[4]

Payers recognize value in **treating people with TGs ≥500 mg/dL**

Engaging payers to ensure **broad olezarsen access** to people with sHTG

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. Assuming approval. 3. TRYNGOLZA (olezarsen) is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information. 4. U.S. Payer Research.

DAWNZERA Launch Off to Encouraging Start[1]

> “I don’t think about having HAE until my next injection.”
>
> - Person with HAE on DAWNZERA for four years

Launch Underway

FDA approval on August 21st

First patient self-administered DAWNZERA within 10 days of approval

Exceptional initial commercial execution

Positive Physician Engagement

Prescriptions written for all patient segments: switches from long-term prophylactic (LTP) treatments, acute-only and treatment naïve

Repeat prescribers

Positive response to DAWNZERA profile, including MoA, switch data and dosing profile

Encouraging Early Launch Signals

Free trial program operating smoothly to provide new patients with initial DAWNZERA dose

Patient starts across the U.S.

Strong initial payer engagement

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.

U.S. HAE Market Dynamics Underscore DAWNZERA's Potential[1,2]

~7,000 people with HAE in the U.S.[3]

~75% of people with HAE in the U.S. are on LTPs

~1,000 allergists/ immunologists treat **90%** of HAE patients

~20% of people with HAE have historically switched treatments annually

>90% of people with HAE are interested in trying a new prophylactic therapy[4]

DAWNZERA Peak Sales Potential: >$500M[5]

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. Market data on file. 3. Riedl et al. 2023 *J ALLERGY CLIN IMMUNOL PRACT* VOLUME 11, NUMBER 8; Sylvestre et al 2021 *J ALLERGY CLIN IMMUNOL PRACT* VOLUME 9, NUMBER 12; Nieto et al 2023 World Allergy Organization Journal. 4. Ionis-sponsored Harris Poll results. 5. Based on current estimates.

IONIS

IONIS EVERY STEP: Innovating to Meet the Needs of the HAE Community[1]

IONIS EVERY STEP™ SUPPORT SERVICES

- Dedicated personal support from Patient Education Managers
- Disease education, injection training and connection to additional resources
- DAWNZERA Direct digital companion
- Free trial program
- Financial support programs[2]

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. For commercially-covered patients only. Medicare, Medicaid, TRICARE, Department of Defense, or Veterans Administration, or any other state or federal government-funded patients are not eligible.

Zilganersen: Our First Anticipated Neurology Launch[1,2]

Substantial Unmet Need

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

No approved disease-modifying treatments

Well-Established Patient Community

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

Strategy to Reach Patients

Evaluation and **diagnosis**

Treatment management

Fulfillment 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

Scalable Capabilities for Future Launches

Q3:2025 Financial Performance

Beth Hougen

Chief Financial Officer

Q3:2025 Financial Highlights[1]

Revenues $157M

Commercial Revenue: $116M

- $32M in TRYNGOLZA product sales
- Royalty revenues increased ~13% YoY

R&D Revenue: $41M

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

Operating Expenses[2] $286M

R&D Expenses[2]: $197M

- Decreased slightly YoY, while strategically funding our advancing pipeline
- Large majority funding late-stage programs

SG&A Expenses[2]: $87M

- Increased YoY to fuel ongoing and planned launches

Operating Loss[2] ($129M)

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

Cash & Short-term Investments $2.2B[3]

- Enables investments in launches and Ionis-owned pipeline

1. For the quarter ended September 30, 2025. 2. Non-GAAP – please see reconciliation to GAAP in Q3:2025 press release.

Increasing 2025 Financial Guidance[1]

Revenue

$875-$900 million

Includes: $85-95 million of TRYNGOLZA net revenues

Prior $825-850 million

Operating Loss

$275-300 million[2]

Prior $300-325 million

Cash

>$2.1 billion

Prior ~$2.0 billion

1. Based on current assumptions, subject to change. 2. Non-GAAP – please see reconciliation to GAAP in Q3:2025 press release.

Conclusion

Brett Monia, Ph.D.

Chief Executive Officer

Well-Positioned to Build on Strong Momentum

Key Upcoming Catalysts[1]

2
NDA Submissions in Next Few Months

2
Independent Launches Next Year[2]

5
Phase 3 Data Readouts in 2026

Multiple
Phase 2 Data Readouts in 2026

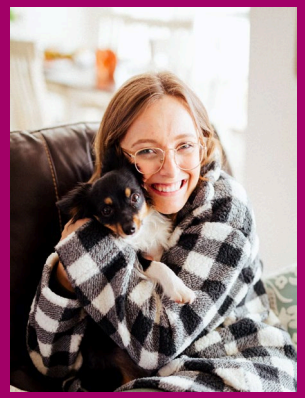
≥2
Phase 3 Study Starts in 2026

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

Q&A

Transforming Human Health through RNA-Targeted Medicines













2025 and 2026 Key Value-Driving Events[1]

Phase 3 **Clinical Events**

2025

ION582
✓ Study start
(Angelman syndrome)

Olezarsen
✓ CORE & CORE2 Data
(sHTG)

Olezarsen
✓ Essence Data
(HTG)

Zilganersen
Data
(Alexander disease)

2026

Pelacarsen
Lp(a) 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
FUSION data
(FUS-ALS)

Regulatory **Actions**

2025

DAWNZERA
✓ U.S. approval
(HAE)

TRYNGOLZA
✓ EU approval
(FCS)

WAINZUA
✓ EU approval
(ATTRv-PN)

Olezarsen
U.S. Submission
(sHTG)

Higher Dose Nusinersen[2]
✓ 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

TRYNGOLZA
✓ U.S.
(FCS)

TRYNGOLZA
✓ EU
(FCS)

Donidalorsen
✓ U.S.
(HAE)

WAINZUA
✓ EU
(ATTRv-PN)

2026

Olezarsen
U.S.
(sHTG)

Bepirovirsen
U.S.
(HBV)

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. 2. Refiling process on track