Corporate Presentation

March 2026

Nasdaq: IONS

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, 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.

Ionis: Pioneered the Field of Oligonucleotide Therapeutics

A Rich History **Discovering** and **Developing** Transformational RNA-Targeted **Medicines**

Miles and family, SMA

- Created **Industry Leading Medicinal Chemistry** and **Manufacturing** Capabilities
- **Optimized** and **Validated Delivery** to Liver and CNS for Human Therapeutics
- **Optimized** and **Validated** Multiple Mechanisms of Action Including RNase H and Splicing
- Led the Way in **Discovering** and **Developing First-in-Class Medicines** for Serious Diseases

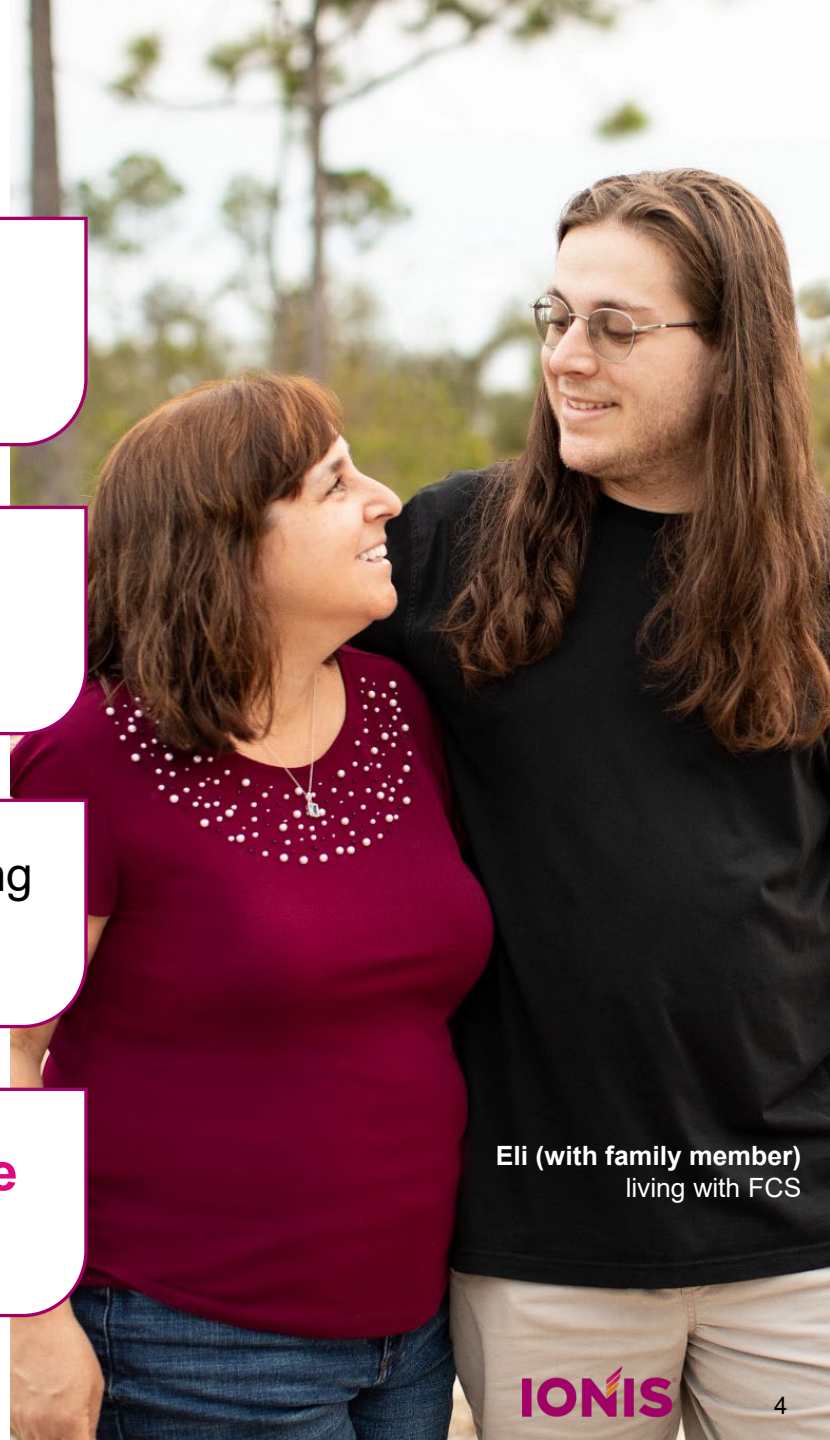
Well Positioned for Accelerating Growth

Fully integrated, commercial-stage biotechnology company

Groundbreaking technology fueling **high-value innovative pipeline**

Consistently delivering breakthrough clinical results enabling **highly successful commercial launches**[1,2]

Clear path to **accelerating revenue growth, sustained positive cash flow** and **substantial value creation**[2]



Eli (with family member) living with FCS

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

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

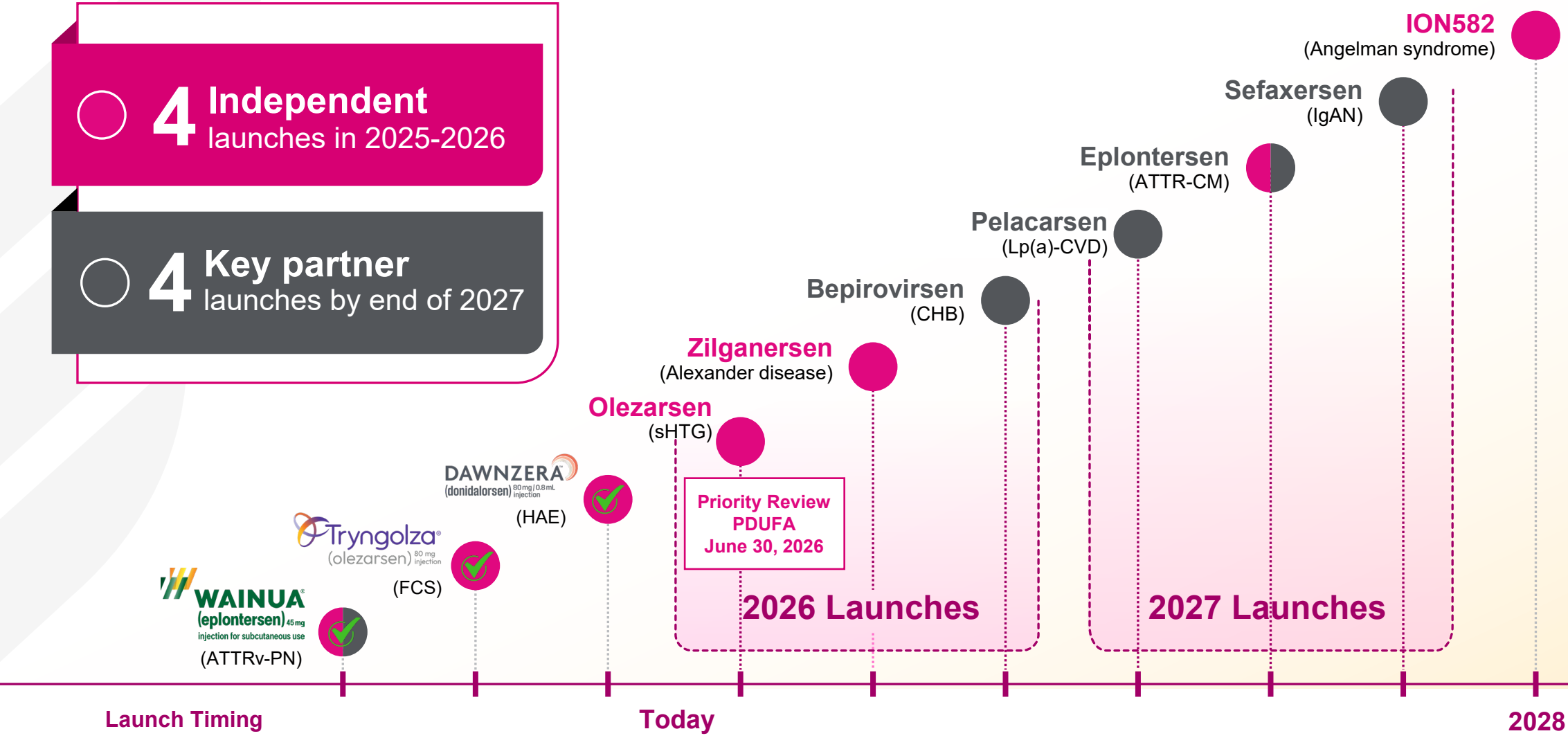
11
Medicines in Late-Stage Development

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.

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.

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.

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.

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

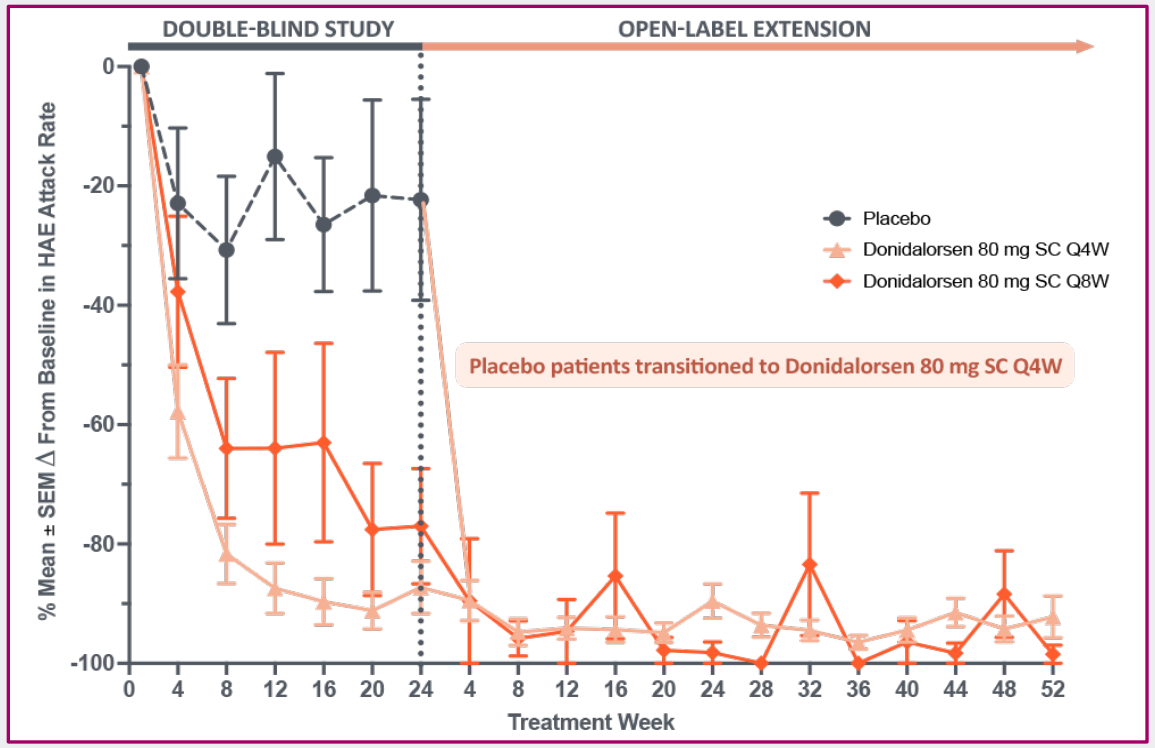
- **~7,000** people with HAE in the U.S.[3]
- **~75%** of people with HAE in the U.S. are on LTPs
- **~1,000** allergists/ immunologists treat **90%** of HAE patients
- **~20%** of people with HAE have historically switched treatments annually
- **>90%** of people with HAE are interested in trying a 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

DAWNZERA's Robust Efficacy Profile[1,2]



94%

Total Mean Reduction in HAE Attack Rates across Q4W and Q8W over 1 year in OLE[2]

Met all Q4W primary and secondary endpoints[3]

81% reduction (p<0.001) in mean HAE attack rate compared to placebo, increased to an 87% reduction (p<0.001) when measured from the second dose

Improved quality-of-life measures[3]

High levels of disease control[4,5]

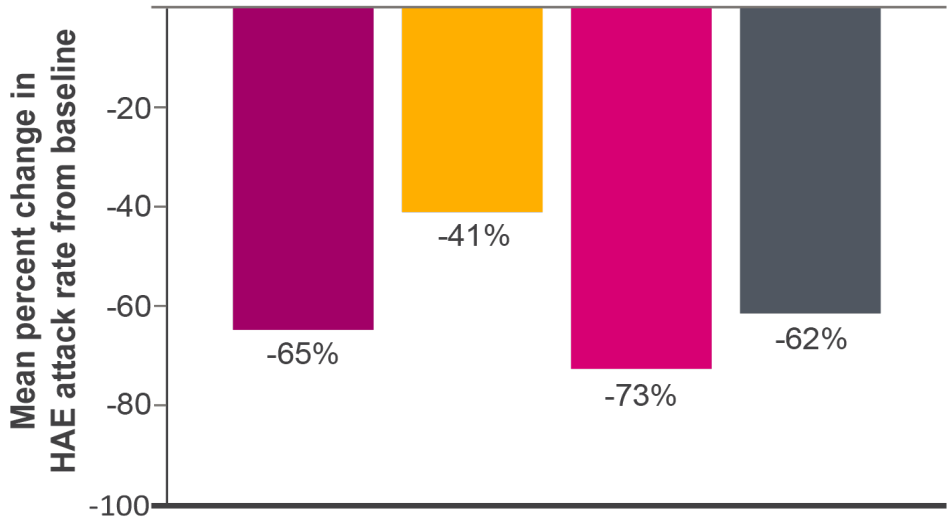
1. DAWNZERA is approved in the U.S. for hereditary angioedema in adults and pediatric patients 12 years of age and older; see Full Prescribing Information. 2.Data on file; HAE attack rate reduction as of data cut-off of January 27, 2025. 3. *N Engl J Med* 2024;391:21-31 DOI: 10.1056/NEJMoa2402478 VOL. 391 NO. 1. 4. Riedl MA, Yarlas A, Bordone L, et al. Patient-reported outcomes in the Phase III OASIS-HAE Study of Donidalorsen for Hereditary Angioedema. *Allergy*. Published online April 19, 2025. doi:10.1111/all.16563. 5. Weller K, Donoso T, Magerl M, et al. Validation of the Angioedema Control Test (AECT)—a patient-reported outcome instrument for assessing angioedema control. *J Allergy Clin Immunol Pract*. 2020;8(6):2050-2057.e4. doi:10.1016/j.jaip.2020.02.038.

IONIS

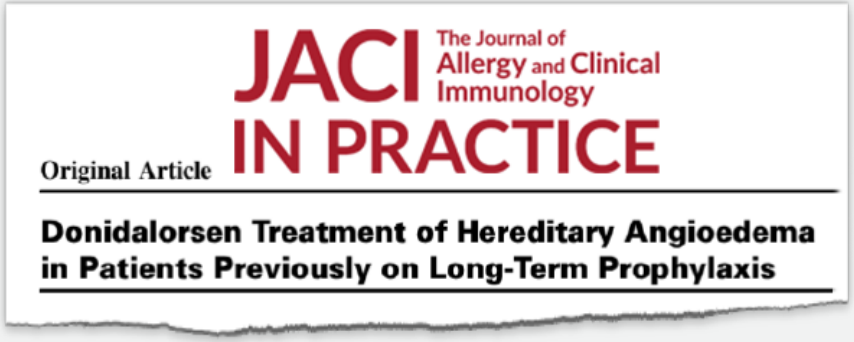
DAWNZERA Substantially Reduced HAE Attack Rates After Switching from Prior Prophylactic Treatment[1,2]

OASIS-Plus Switch Cohort Results

% Reduction in HAE Attack Rate After Switching to DAWNZERA



Prior LTP:	Lanadelumab	C1INH	Berotralstat	Total
n =	31	22	11	64
Baseline, mean ± SD =	0.69 ± 1.09	0.61 ± 0.96	1.80 ± 1.92	0.85 ± 1.28
Week 16 (donidalorsen Q4W), mean ± SD =	0.24 ± 0.33	0.36 ± 0.69	0.48 ± 0.53	0.33 ± 0.51



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.Riedl, Marc A. et al. *The Journal of Allergy and Clinical Immunology: In Practice,* Volume 0, Issue 0.

Switch Data Confirm DAWNZERA's Compelling Profile Resonated with Study Participants[1,2]

of switch patients surveyed **preferred DAWNZERA**

Reasons participants chose for preferring DAWNZERA:

Efficacy
63%
chose **"it works better to control my HAE"**

Tolerability
50%
chose **"less injection-site pain or reaction"**

Convenience
65%
chose **"less time for administration"**

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. Riedl, Marc A. et al. *The Journal of Allergy and Clinical Immunology: In Practice,* Volume 0, Issue 0. 3.

Delivering Transformational Medicines in Focused Therapeutic Areas

Cardiometabolic

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

Rare and prevalent patient populations in focused disease areas

Neurology

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

Potential for Multiple Blockbusters[1]

1. Based on current estimates, subject to change.

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

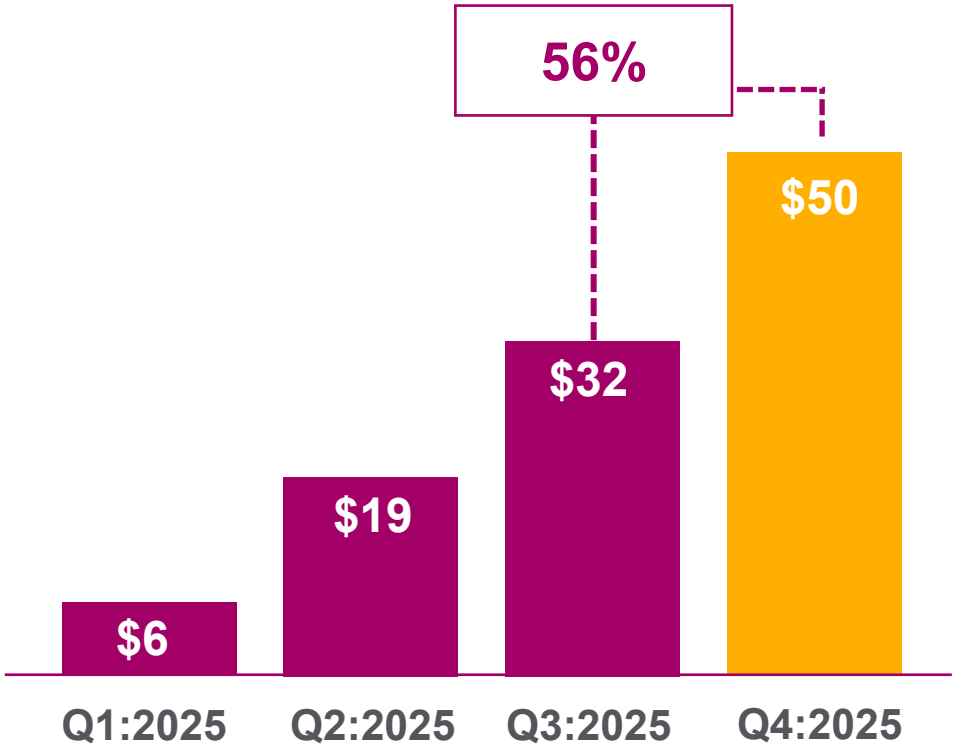
Robust efficacy and safety

- 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.

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 accepted** for **Priority Review;** PDUFA June 30, 2026

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.

Vast Majority of Patients Treated with Olezarsen Achieved Triglyceride Levels Below Risk Threshold for Acute Pancreatitis[2]

Achieved **Highly Statistically Significant Reductions** in **Fasting Triglycerides** at 6 Months

Up to a **72%**

placebo-adjusted mean reduction in fasting triglycerides[1]

(p<0.0001)

86%

achieved TG levels **below 500 mg/dL**[2]

Up to 54%

achieved **normal TG levels** (≤150 mg/dL)[2]

1. *The New England Journal of Medicine*, "Olezarsen for Managing Severe Hypertriglyceridemia and Pancreatitis Risk." Marston, et al. 2. Achievement of triglyceride levels <150 mg/dL, <500 mg/dL and <880 mg/dL at 12 months among patients with baseline levels above these thresholds and available triglyceride levels at month 12 in CORE and CORE2 pooled.

Olezarsen: The First & Only Investigational Treatment to Significantly Reduce Acute Pancreatitis Events in People with sHTG[1]

Achieved **Highly Statistically Significant Reduction** in **Adjudicated Acute Pancreatitis Events**

85%

Reduction in acute pancreatitis events compared to placebo at 12 months[1]

(p=0.0002)

Number Needed to Treat (NNT) over *Just* 1 Year

20 in the **overall** treatment population[2]

4 for those with baseline TGs **≥880 mg/dL** and **history of AP**[2]

1. *The New England Journal of Medicine*, "Olezarsen for Managing Severe Hypertriglyceridemia and Pancreatitis Risk." Marston, et al. 2. Using the mean rates from the binomial regression model, the number of patients needed to treat over one year to prevent one episode of acute pancreatitis was 25 in the overall treatment population (pooled analysis across both doses and studies).

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.

Building a Leading Cardiometabolic Pipeline[1,2]

2 Wholly Owned Medicines in Clinical Development

4 Partnered Medicines in Clinical Development

6 Medicines in Clinical Development

Wholly Owned Medicines

	Indication	Preclinical	Ph1	Ph2	Ph3
Olezarsen (ApoC-III)	sHTG	sNDA accepted for Priority Review			
ION775 (ApoC-III)	sHTG				
ION501 (undisclosed)	Myocardial disease	(TfR1-Targeting)			
ION924 (Apo(a))	Cardiovascular disease				
ION573 (undisclosed)	Cardiovascular disease				

Partnered Medicines

Eplontersen (TTR)[3]	ATTR-CM	
Pelacarsen (Apo(a))	Cardiovascular disease	
Tonlamarsen (Angiotensinogen)	Acute severe hypertension	
ION826/AZD4063 (PLN)[4]	Myocardial disease	(TfR1-Targeting)

1. Timing and expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Co-developing and commercializing WAINUA for ATTRv-PN and ATTR-CM in U.S. with AstraZeneca. 4. In-licensed by AstraZeneca in 2023.

3 Approved Medicines[1]

Leading Neurology Portfolio Positioned to Deliver Accelerating Value

Strong track record in delivering **first-in-class** neurology medicines

Well-positioned to deliver a **steady cadence of medicines**[2]

- **First independent neurology launch** expected **in 2026** with **zilganersen** for Alexander disease
- **Strong pipeline** of wholly owned and partnered medicines in clinical development

Focused strategy for expanding our wholly owned neurology portfolio

Focused on continuous **innovation** and **advancing proven technology**

1. Prescribing information: SPINRAZA.com; QALSODY.com; WAINUA.com. 2. Based on current timing estimates, subject to change.

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.

Zilganersen: First Anticipated Launch from Wholly Owned Neurology Portfolio[1-3]

The Opportunity

- **~1 in 1-3 million people** with **Alexander disease (AxD)**,
- Progressive and often fatal condition
- Accounts for ~2-8% of leukodystrophies, although **likely underreported**[4,5]

Unprecedented Clinical Results

- **First** and **only** investigational medicine to demonstrate **clinically meaningful** and **disease-modifying** impact
- **Granted Breakthrough Therapy designation**

First Mover Advantage

- **Positioned** to **transform** the treatment landscape for **AxD**
- **Expanded Access Program underway** in U.S

Next Steps[3]

- **NDA** submitted **Q1:2026**[3]
- **Launch** in **2026**[3]

Grayson
living with Alexander disease

Reinforces the power of Ionis technology to address neurological diseases by directly targeting the underlying cause

1. Topline pivotal results reported on September 22, 2025. 2. Assuming approval. 3. Based on current timing estimates, subject to change. 4. 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; 5. 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.

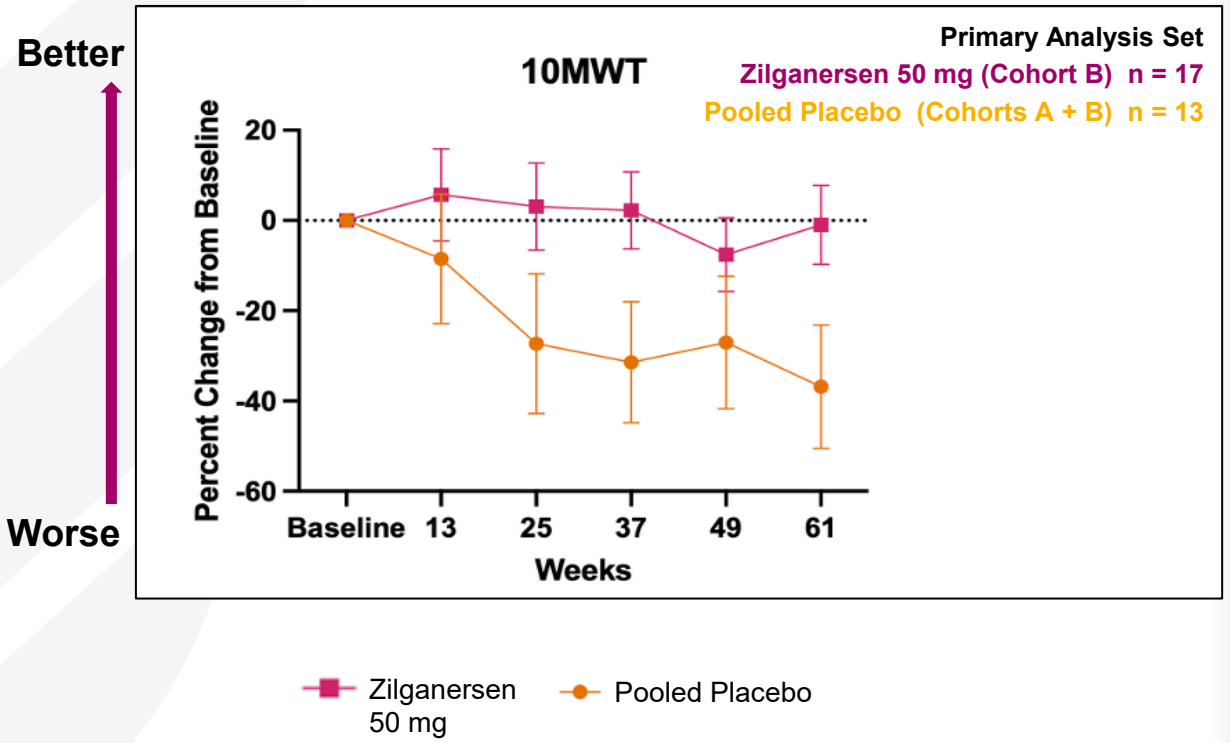
Zilganersen: Patient Disposition and Analysis Sets

	Low Dose 25mg (n=8)	High Dose 50mg (n=24)	Pooled Placebo (n=17)	Infant cohort (n=5)[1]
Mean age at screening, years	20.8	8.9	13.0	1.5
Gender Male (%) Female (%)	 3 (37.5) 5 (62.5)	 7 (29.2) 17 (70.8)	 7 (41.2) 10 (58.8)	 4 (80.0) 1 (20.0)
Primary analysis set, n		**17**	**13**	

Patients enrolled are representative of the broad Alexander disease population

1. One infant patient enrolled after database lock and not included in the topline dataset.

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. Data presented at CNS 2025. 2. Meters per second. 3. ANCOVA model.

Favorable Safety and Tolerability[1]

Zilganersen Demonstrated Favorable Safety and Tolerability at Week 61

- Most TEAEs were mild or moderate
- No TEAEs led to treatment discontinuation in the double-blind treatment period
- Serious TEAEs in >1 patient included seizure, vomiting, influenza, scoliosis
  - 1 TEAE with fatal outcome in the zilganersen group was deemed not related to study drug (attributed to disease progression)[2]
- TEAEs of increased ICP and laboratory CSF protein >45 mg/dL were numerically lower with zilganersen than control
- No zilganersen-related effects on platelet counts, renal or liver function were observed

1. Data presented at CNS 2025. 2. The death was in the 25mg dosing group (not in the primary analysis set) and deemed not related to study drug.

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.

Obudanersen: A Promising Investigational Medicine for Angelman Syndrome

The Opportunity

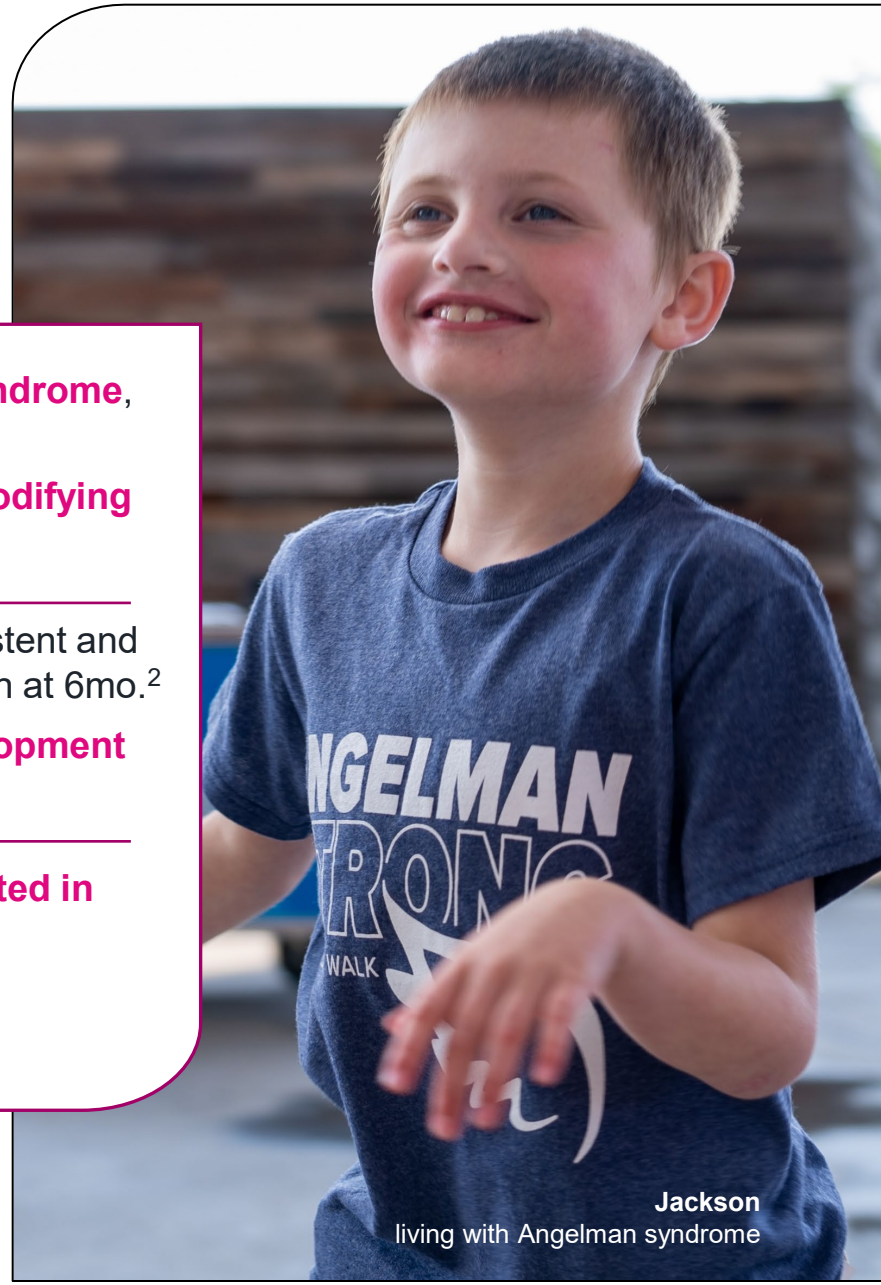
- **>100k people** in major geographies with **Angelman syndrome**, a severe, rare neurodevelopmental disorder[1]
- **Significant unmet need** with **no approved disease-modifying treatments**

Key Clinical Highlights

- **Positive results seen in the HALOS study**, with consistent and meaningful improvements in key areas of clinical function at 6mo.[2]
- **Long-term extension data** continues to **support development**
- **Granted Breakthrough Therapy designation**

Next Steps

- Full enrollment of pivotal Phase 3 REVEAL study **expected in 2026**[3]
- Phase 3 **data expected in 2027**[3]
- UPD/ID CHAMPION **study initiation expected in 2026**

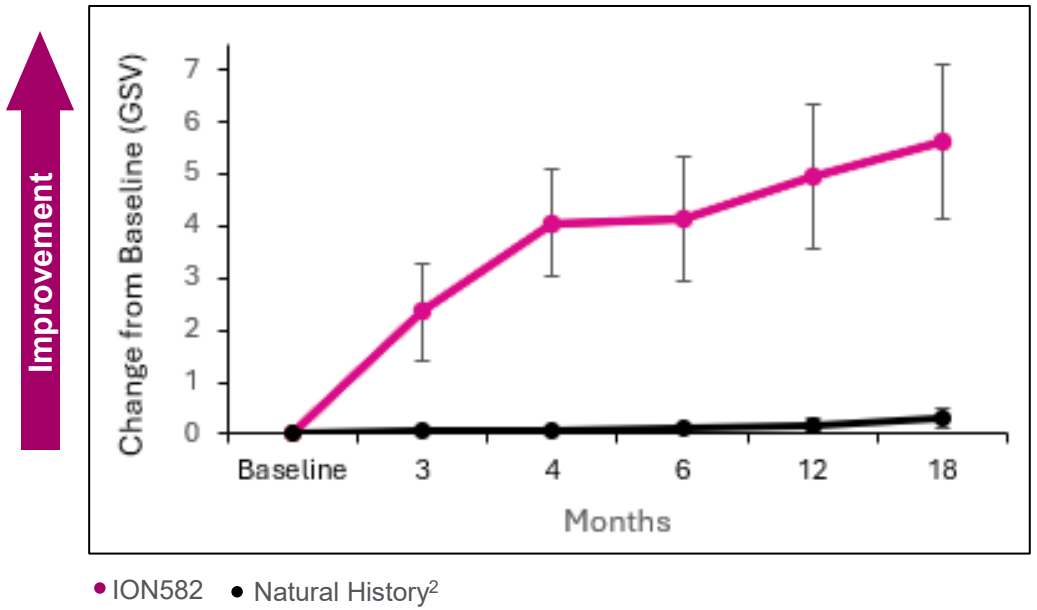


Jackson
living with Angelman syndrome

1. Luk. *Eur. J. Méd. Genet*. (2016). 2. Based on data generated to date from the Phase 1/2a HALOS study of ION582. 3. Based on current assumptions, subject to change.

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

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.

Responder Analysis: Continued Benefit in Multiple Domains Assessed in the HALOS Study[1-3]

HALOS

	Responders on Bayley-4 Expressive Communication	Responders on ≥ 1 Bayley-4 Domains	Responders on ≥ 2 Bayley-4 Domains	Responders on ≥ 3 Bayley-4 Domains
6 months	61%	95%	84%	68%
12 months	64%	97%	89%	75%
18 months	71%	97%	83%	71%

Responders are defined as having a change from baseline of >20% the standard deviation plus the expected change for growth from natural history[4]

Nearly All Study Participants Responded to ION582 Treatment on ≥ 1 Bayley-4 Domains through 18 Months

1. Medium and high dose groups,≥2 years of age, n=35-38. Excludes patients who dose escalated or had a gap in dosing between MAD and LTE. 2. Bayley N. Aylward GP. *Bayley Scales of Infant and Toddler Development-Fourth Edition*. NCS Pearson. (2019). 3. Analysis reflects data from participants in the ION582 HALOS study aged 2-34 years old who received either 40mg or 80mg ION582 for the entirety of the study. Participant data for those who dose-escalated during the study and with data from out-of-window visits are excluded. 4. Natural history studies: www.clinicaltrials.gov/study/NCT04507997 and www.clinicaltrials.gov/study/NCT00296764 and includes Bayley-3 to Bayley-4 conversion by Pearson.4.

IONIS

Extending the SMA Franchise

SPINRAZA® (nusinersen) injection 12 mg/5 mL

Nusinersen High Dose

- Now approved in EU and Japan
- April 3, 2026 PDUFA[1]

Salanersen

- Designed with a novel Ionis chemistry to achieve strong efficacy & once-yearly dosing
- Interim Phase 1 data showed that once-yearly dosing with both doses tested was well tolerated and led to substantial slowing of neurodegeneration
- Biogen advancing into Phase 3
- Improved economics over SPINRAZA[2]

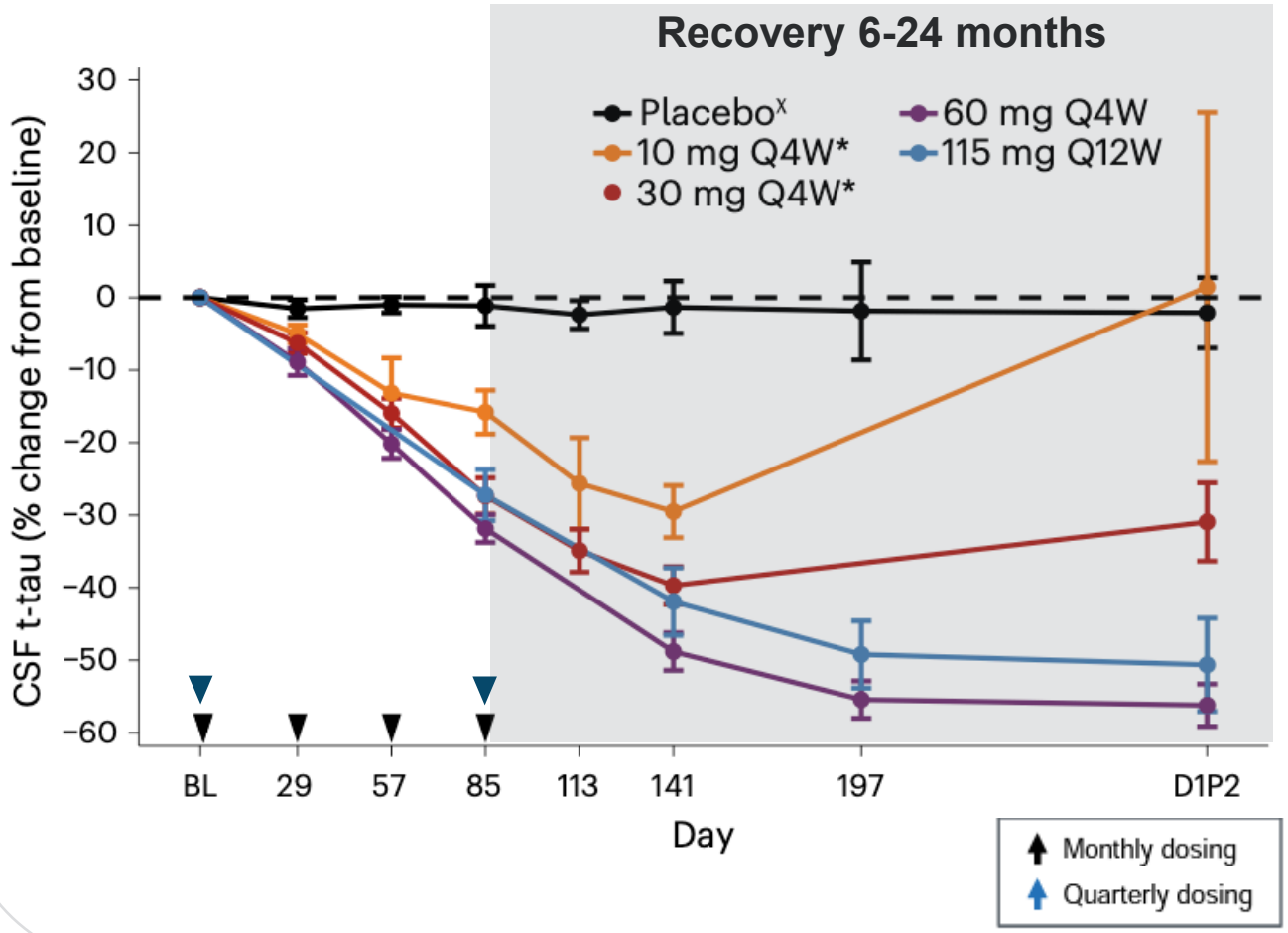
1. Timing expectations based on current assumptions and subject to change. 2. SPINRAZA is approved in the U.S. for or the treatment of spinal muscular atrophy in pediatric and adult patients; see Full Prescribing Information.

IONIS-MAPT$_{Rx}$: Rapid, Substantial and Sustained Reduction in Tau in CSF in Phase 1b Study[1]

MAPT$_{Rx}$ (BIIB80) is designed to **reduce production and thus aggregation of tau protein** associated with disease in Alzheimer's disease

Total tau in the CSF **continued to decline 16 weeks post-last dose** of BIIB080 in 4-and 12-week cohorts

Generally well-tolerated at all doses and dose frequencies



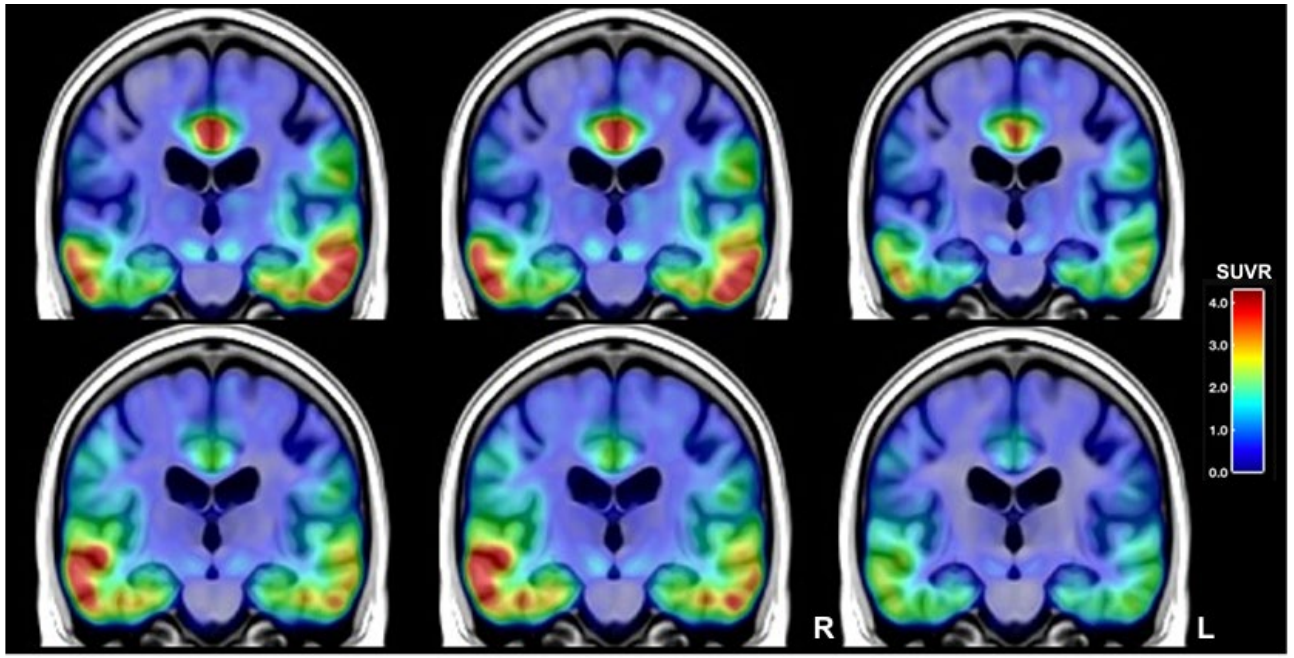
1. Mummery et al., Nat Med, 2023; AD = Alzheimer's disease; CSF = cerebrospinal fluid; Q4W = every 4-week dosing; Q12W = every 12-week dosing; t-tau = total tau

IONIS-MAPT$_{Rx}$: Consistent Reduction in Tau Burden Across All Brain Regions

Screening → Placebo → **Week 25** → 115mg Q12W → **Week 100**

2380-4011
67 y/o
Male
CDR= 0.5
MMSE= 26

2176-4009
71 y/o
Male
CDR= 0.5
MMSE= 26



CELIA Phase 2 Study in patients with early AD fully enrolled; Data expected mid-2026[2,3]

Phase 1b Tau PET Results[1]

Patients initially on placebo then MAPT$_{Rx}$ (BIIB080) showed **reduced tau burden following treatment**

Reduced tau burden at all doses and dose frequencies in the long-term extension study

Generally **well-tolerated at all doses and dose frequencies**

1. Collins et al., AD/PD 2023 CDR Clinical Dementia Rating scale; MMSE Mini Mental State Examination; SUVR standard uptake valueratio; CELIA Study (Biogen conducting): Clinialtrials.gov/NCT05399888 2. Timing based on current estimates and subject to change. 3. Biogen disclosed CELIA trial update reducing number of patients in August 2024.

Accelerating Innovation to Strengthen Leadership in RNA-Targeted Medicines

Expanding Technology Platform

Broad Range of Technologies

ASO | siRNA | MsPA
NMA | DNA Editing

Optimized Potency and Durability

Systemic and Local Applications

Advancing Targeted Delivery

Cardiac Muscle

Skeletal Muscle

Blood Brain Barrier

Expanding Therapeutic Opportunities

Established Franchises

Cardiometabolic

Neurology

New Therapeutic Areas

Pulmonary | Renal

Partnered Medicines Amplify Our Opportunities

Multiple Phase 3 Readouts in 2026[1]

	Bepirovirsen (HBV) H1:26	Pelacarsen (Lp(a)-CVD) H1:26	Eplontersen (ATTR-CM) H2:26	Sefaxersen (IgAN) 2026
Addressable Population[2]	**~300M patients** worldwide	**>8M patients** with CVD and elevated Lp(a) worldwide	**~300-500k patients** worldwide	**>400k patients** worldwide
Value Proposition	**1st** and **only investigational medicine** shown potential to achieve clinically meaningful functional cure[3] **U.S. Fast Track Designation**	**First-in-class potential** to address a major independent risk factor for CVD	Potential to be the **treatment of choice** for people with ATTR On track to **deliver the richest data set** in growing ATTR market	**1st investigational RNA-targeted medicine** to treat IgAN by addressing the underlying pathophysiology of alternative complement pathway activation[4]

1. Based on current assumptions, subject to change. 2. Market data on file. 3. That is currently in Phase 3 development and when combined with oral nucleoside/nucleotide analogues (NAs). 4. That is in Phase 3 development.

Pelacarsen: Addressing a Major Independent Risk Factor for CVD[1]

Lp(a) Driven Cardiovascular Disease

- Lp(a): independent, genetic, causal risk factor for CVD, mediating MI, stroke and peripheral artery disease
- Lp(a) levels determined genetically, not influenced by diet or lifestyle
- 1 in 5 people worldwide have elevated Lp(a)
- Currently no approved therapies to treat elevated Lp(a)

Target: Lp(a)

- The root cause of Lp(a)-driven CVD

>8 million

Patients with CVD & elevated Lp(a) worldwide[2]

Phase 3 Lp(a) HORIZON Study

- >8,000 patients with high Lp(a) and established CVD
- Study enrolled high-risk, high Lp(a) population with significant CV risk despite stable lipid-lowering treatment[3]
- Baseline demographics support potential for robust data[3]
- **Data expected H1:2026; regulatory filing H2:2026[4]**

Lp(a) Horizon Outcomes Study

Eligible for:

Additional milestone payments

Royalties in the mid-teens to low 20% on net sales[5]

1. Novartis licensed pelacarsen in 2019 and as a result is responsible for development and commercialization, assuming approval. 2. Market data on file. 3. Lp(a) HORIZON study design and baseline demographics published *American Heart Journal*. 4. Timing expectations based on current assumptions and subject to change. 5. Royalty Pharma to receive 25% of any future royalty payments on pelacarsen.

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 H2:2026[1]

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

Driving Accelerating Growth[1,2]

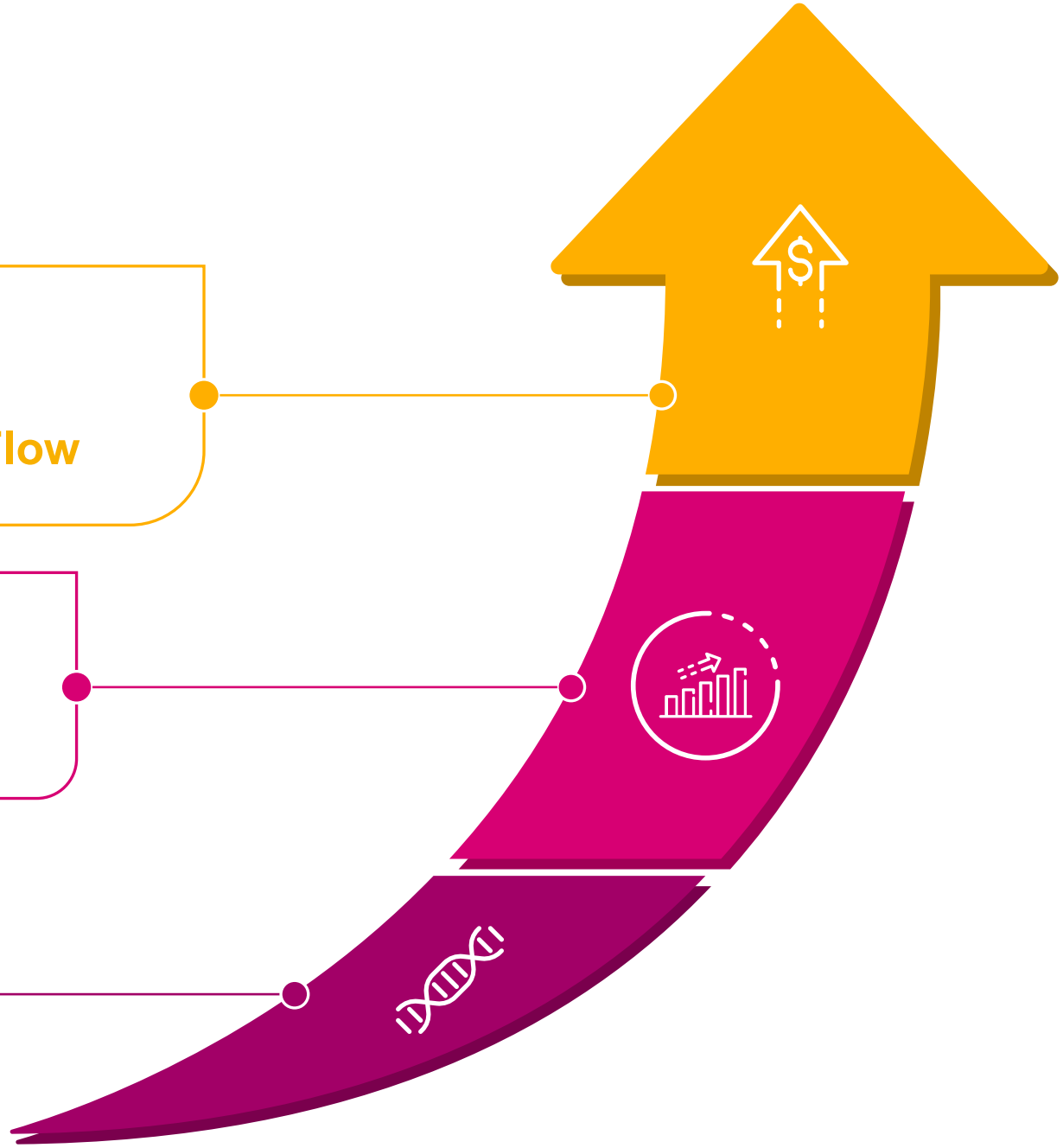
2028 Cash Flow Breakeven

Clear Path to Sustained Positive Cash Flow

Accelerating Revenue Growth

Building a Leading
Cardiometabolic Disease Portfolio

Leading the Way in the Treatment of
Neurological Diseases



1. Based on current estimates, subject to change. 2. Assuming approvals.

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

---

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

---

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[1,4]

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. As a reminder, we plan to provide product level guidance for TRYNGOLZA and DAWNZERA at our first quarter call. The 2026 guidance highlighted on this slide assumes a standard review for TRYNGOLZA. We plan on providing product level guidance for TRYNGOLA that reflects a Priority Review (PDUFA: June 30, 2026) during our first quarter earnings update.

2026 Financial Guidance Reflects Fully Integrated Commercial-Stage Biotech Launching Multiple Medicines[1-4]

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

---

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. 4. As a reminder, we plan to provide product level guidance for TRYNGOLZA and DAWNZERA at our first quarter call. The 2026 guidance highlighted on this slide assumes a standard review for TRYNGOLZA. We plan on providing product level guidance for TRYNGOLA that reflects a Priority Review (PDUFA: June 30, 2026) during our first quarter earnings update.

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

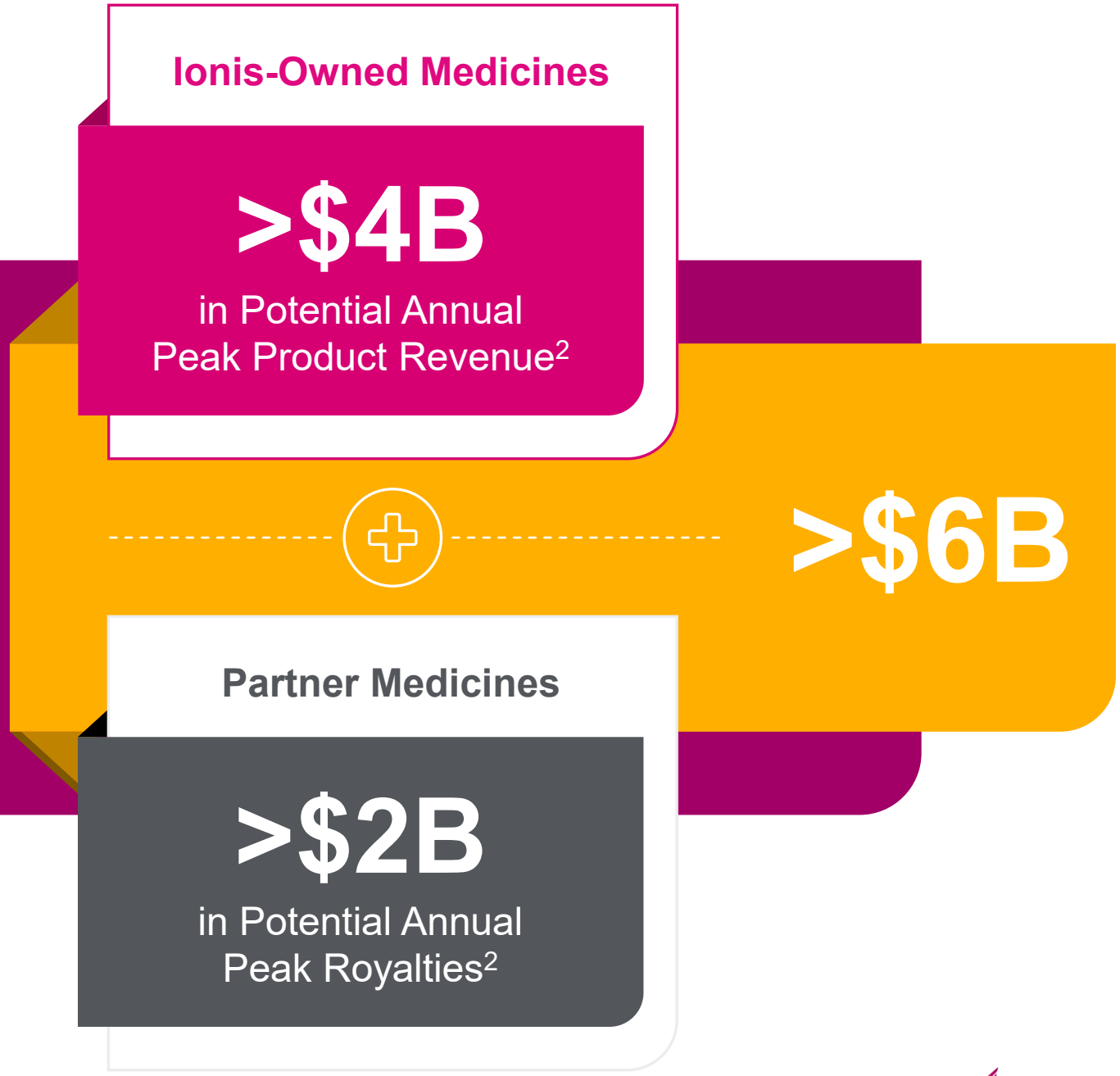
- Olezarsen
- Zilganersen
- Bepirovirsen

Multiple Phase 2 Data Readouts

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

1. Based on current assumptions, subject to change.

Marketed Products and Planned Launches Provide Substantial Revenue Growth Opportunity[1]



1. Assumes additional approvals through 2028. 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.

Accelerating Revenue from Steady Cadence of Independent Launches[1,2]

>$4B

in Potential Annual Peak Product Revenue from Recent Launches and Late-Stage Medicines

Launch Timing

Today

Olezarsen
(sHTG)

>$2B

Zilganersen
(Alexander disease)

>$100M

2026 Launches

ION582
(Angelman syndrome)

>$1B

2028+

5 Additional medicines

in mid-stage development

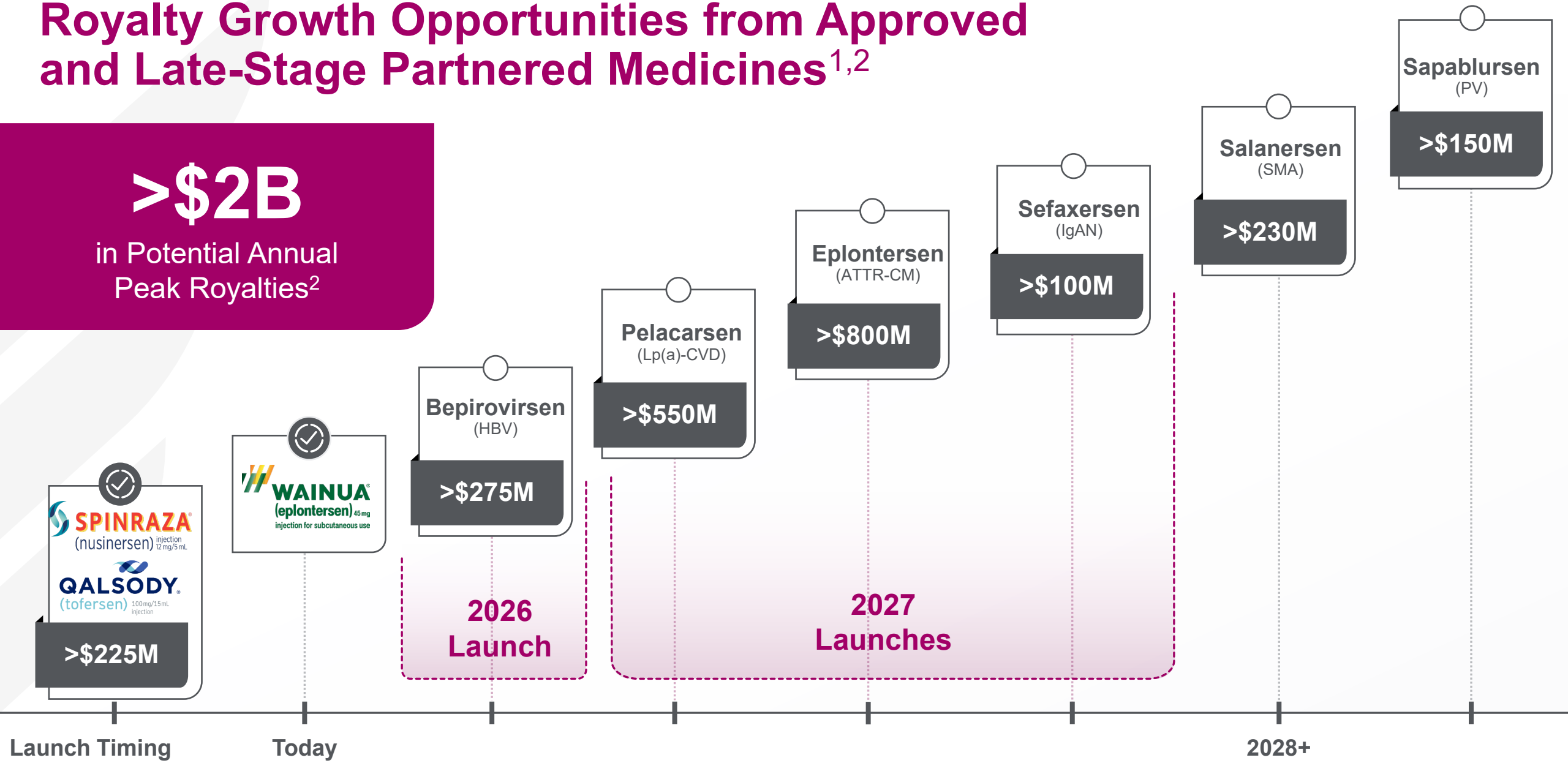
Multi-Billion-Dollar

Multiple

Blockbuster Opportunities in our Pipeline Today

Royalty Growth Opportunities from Approved and Late-Stage Partnered Medicines[1,2]

>$2B
in Potential Annual Peak Royalties[2]



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.

Significant Upside Potential from Late-Stage Partnered Programs

>$6B

in Remaining Partner Payments

>50% anticipated to be earned by 2030[1]

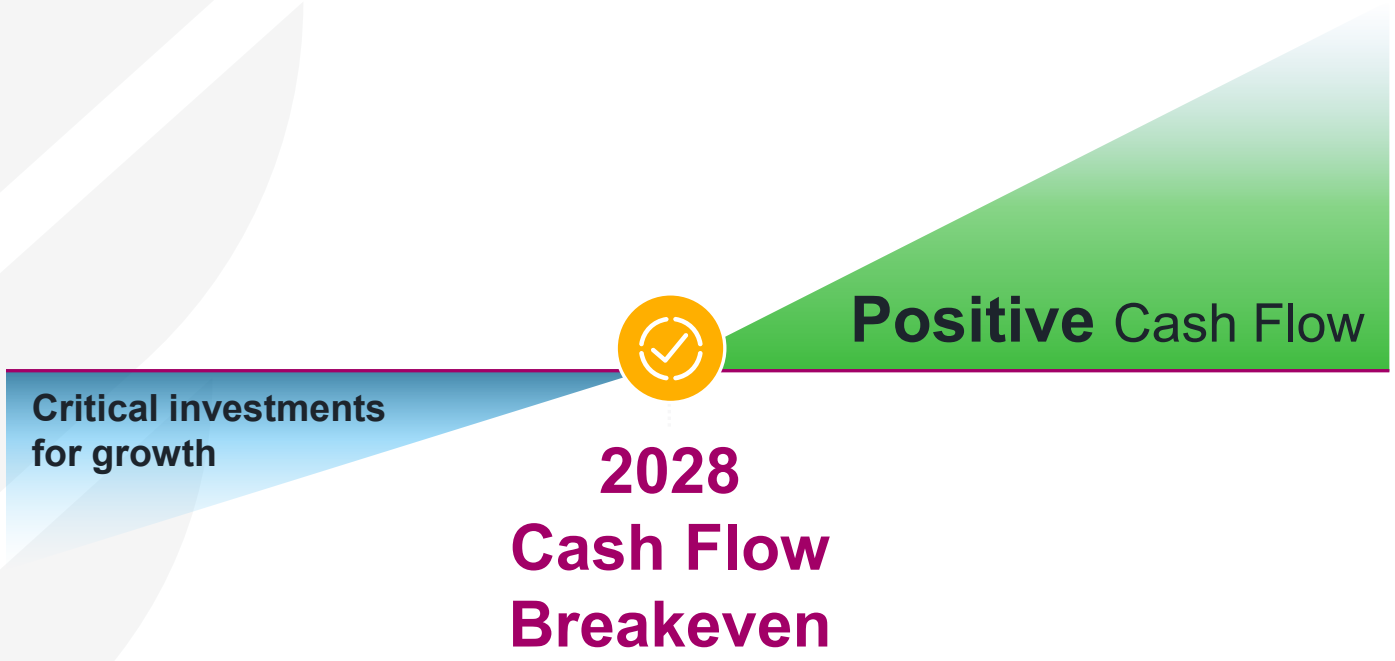
Royalties

Nearly All Partner Revenue Drops to the Bottom Line as Profit

	Total Remaining Milestone Payments	Royalties
Bepirovirsen HBV	**~$200M**	Tiered, 10-12% on net sales
Pelacarsen[2,3] Lp(a)-CVD	**$1.3B**	Tiered, mid-teens to low 20%
WAINUA ATTRv-PN ATTR-CM	**$3.3B**	US: mid-20% OUS: Tiered up to high teens
Sefaxersen IgAN	**>$390M**	Tiered, high-teens to 20%
Salanersen SMA	**>$550M**	Tiered, mid-teens to mid-20%
Sapablursen PV	**$660M**	Mid-teens

1. Based on current timing assumptions, subject to change. 2. Under Royalty Pharma agreement, 25% of pelacarsen royalties payable to Royalty Pharma. 3. Total payments include $900M from Novartis and $625M in milestone payments from Royalty Pharma.

Clear Path to Sustained Positive Cash Flow[1]



Key Drivers

- New product launches
- Growing royalty revenue
- Strong financial foundation
- Disciplined expense management

1. Based on current assumptions, subject to change.

Ionis Corporate Responsibility Strategy Supports Long-term Value Creation

Ionis Corporate Responsibility Strategic Pillars

Innovate to improve the lives of people with serious disease

We innovate across the business and work tirelessly to discover, develop and deliver important new medicines for people with serious diseases.

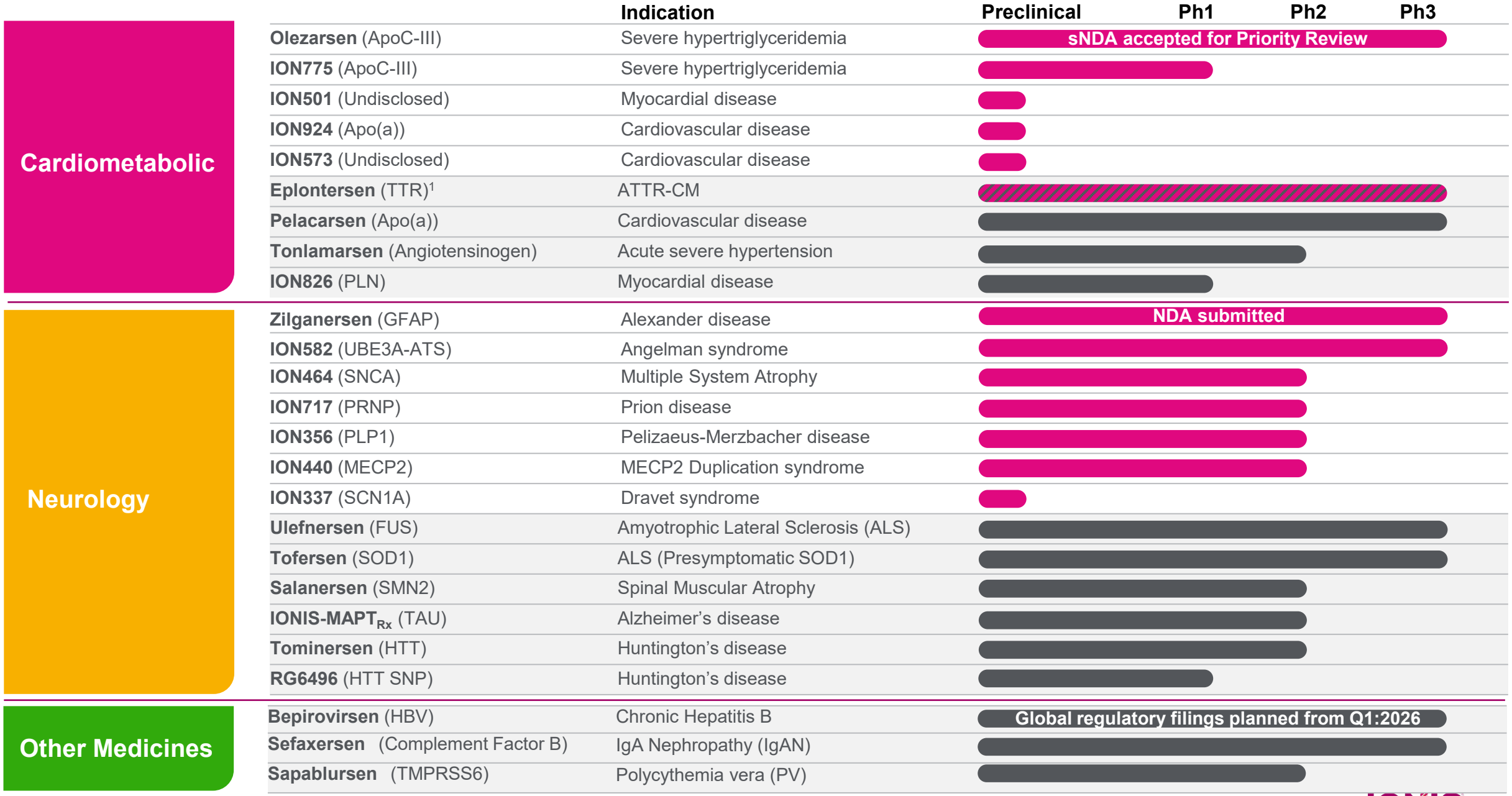
Empower our people and communities

We are committed to fostering an inclusive culture that drives excellence, embraces diversity and supports our communities.

Operate responsibly and sustainably

We operate with integrity to help create a better, more sustainable future for all through environmental stewardship and responsible business practices and stakeholder interactions.

Focused High-Value Pipeline to Drive Continued Growth



1. Co-developing and commercializing WAINUA for ATTRv-PN and ATTR-CM in U.S. with AstraZeneca

Wholly Owned Partnered Co-Commercialized

IONIS

Accelerating Growth through Life-Changing Medicines