Corporate Presentation

May 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

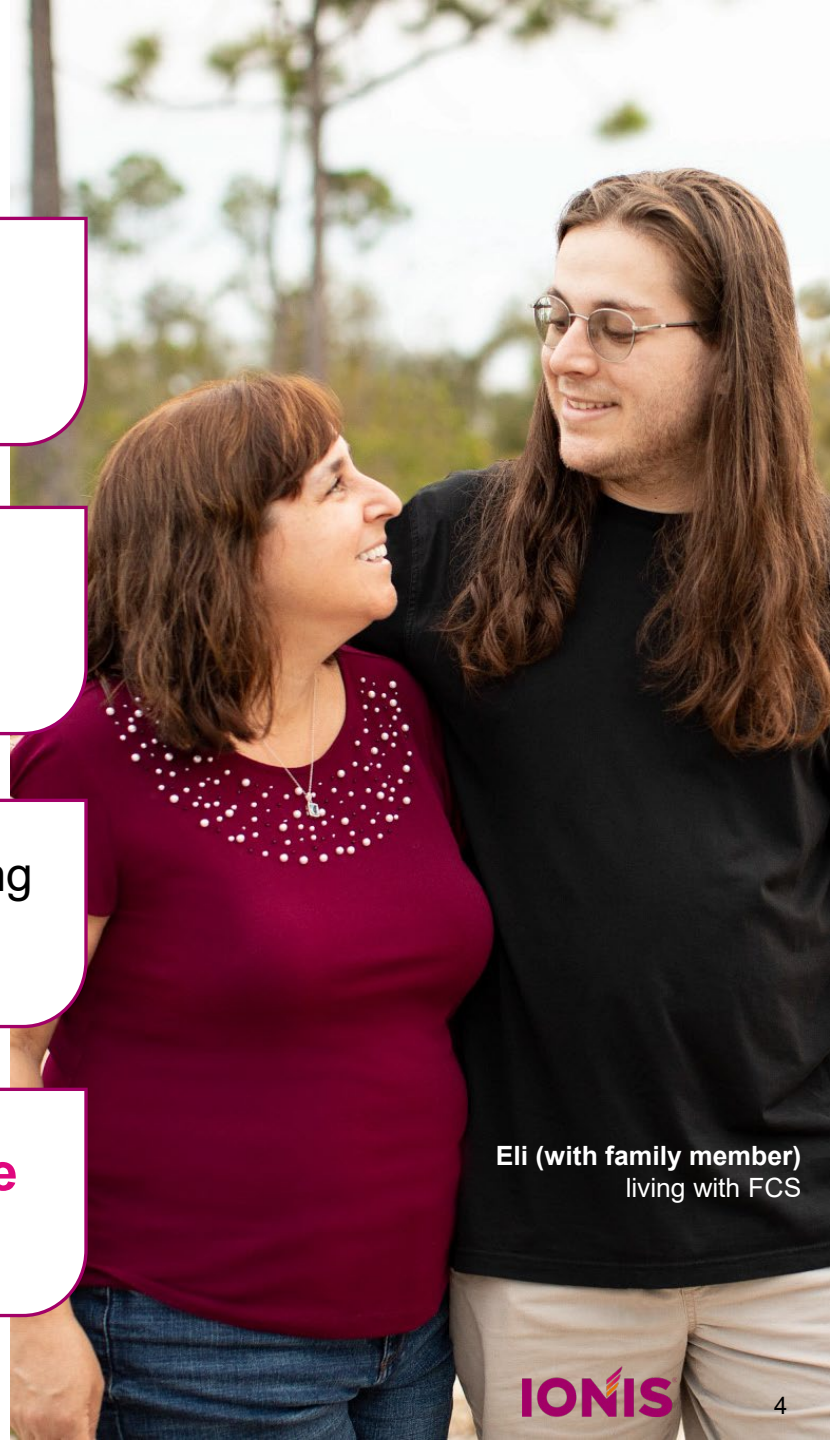
Well Positioned for Accelerating Growth

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.

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.

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

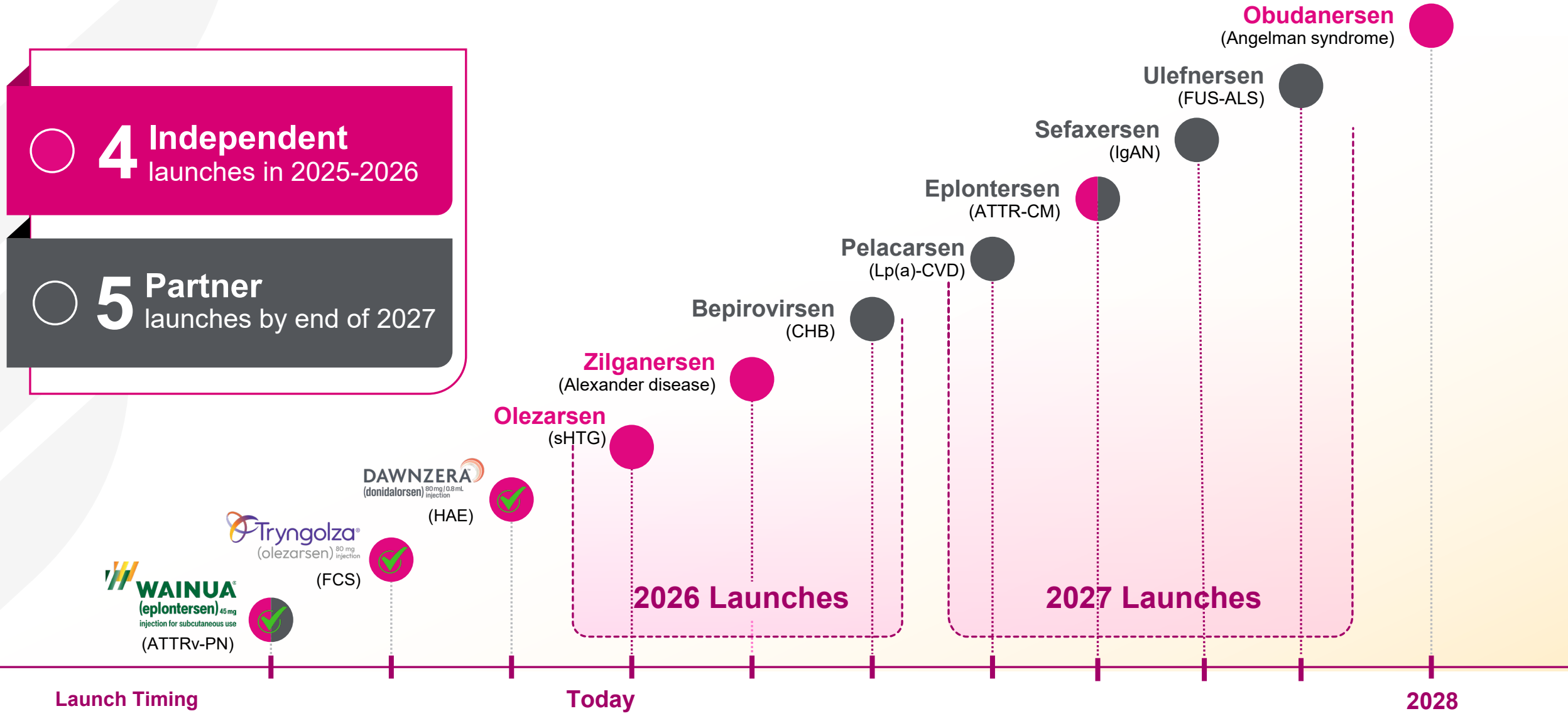
Tryngolza® (olezarsen) 80 mg injection

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]



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

IONIS

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)
- **Obudanersen**
  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.

Focused Commercial Execution Building Sustainable TRYNGOLZA Demand[1]

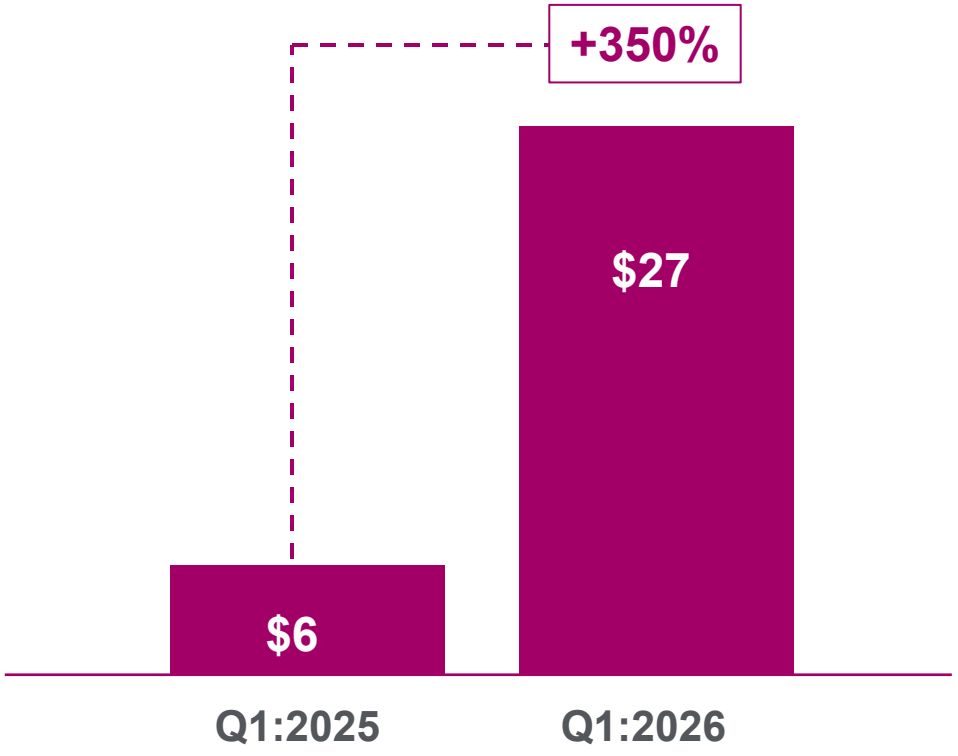
Robust efficacy and safety

- 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: 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.

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.

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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).

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.

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 with 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.

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

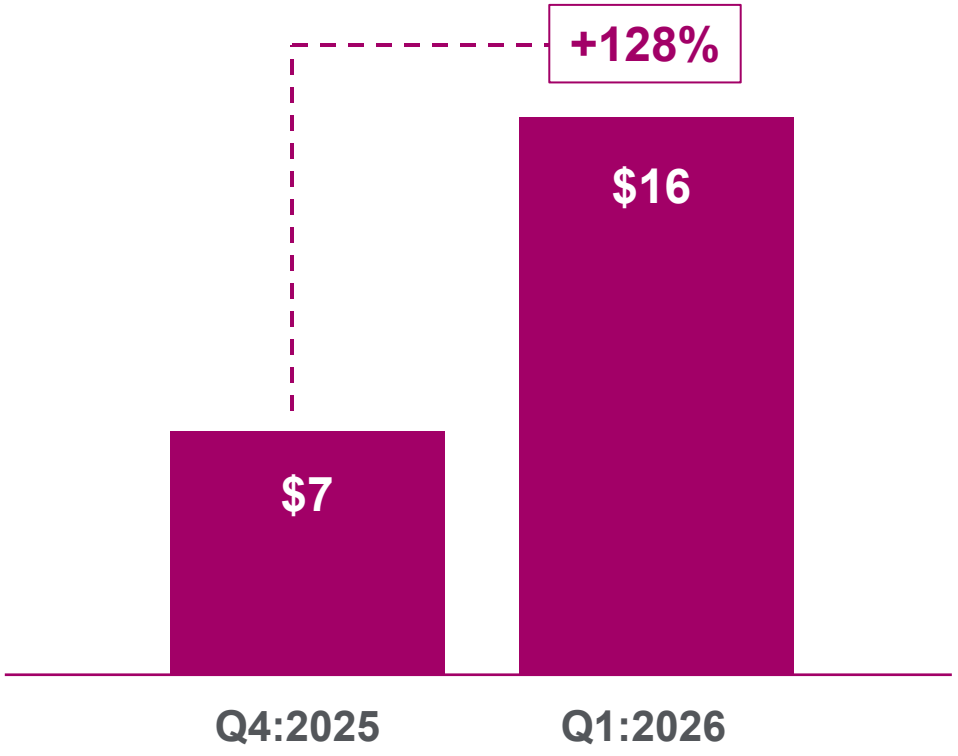
Prescriptions written for all patient segments:

- 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.

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

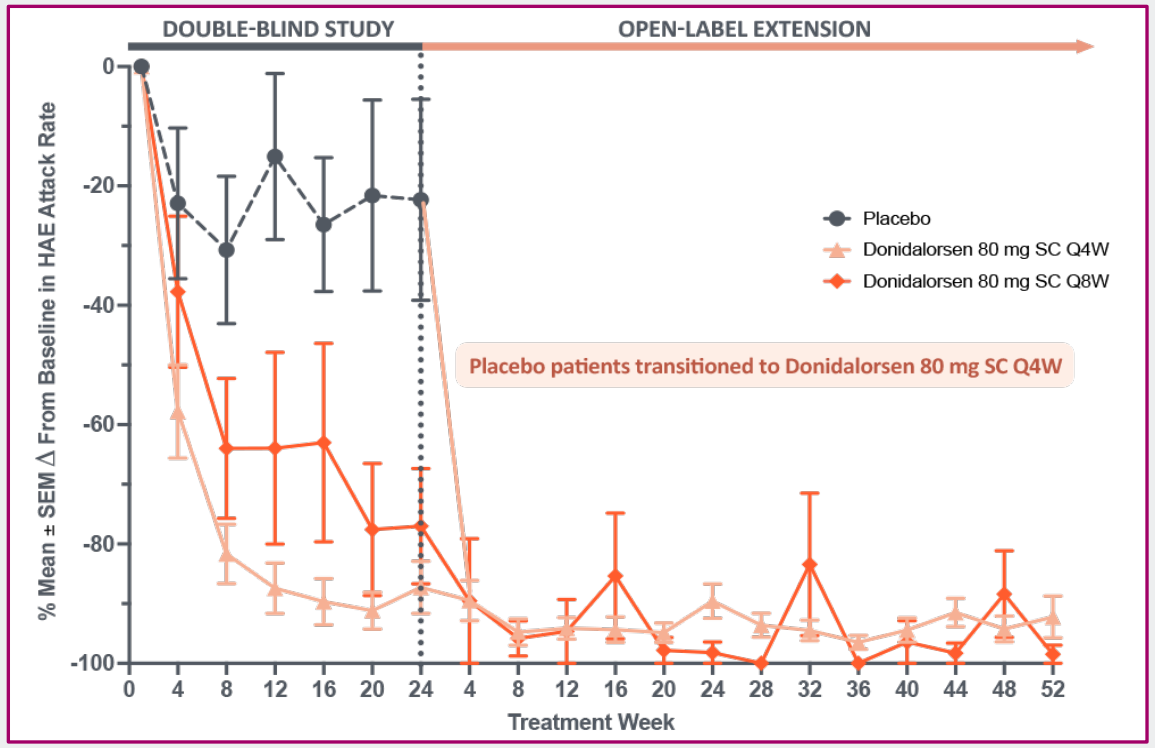
~20% of people with HAE have historically switched treatments annually

>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.

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]

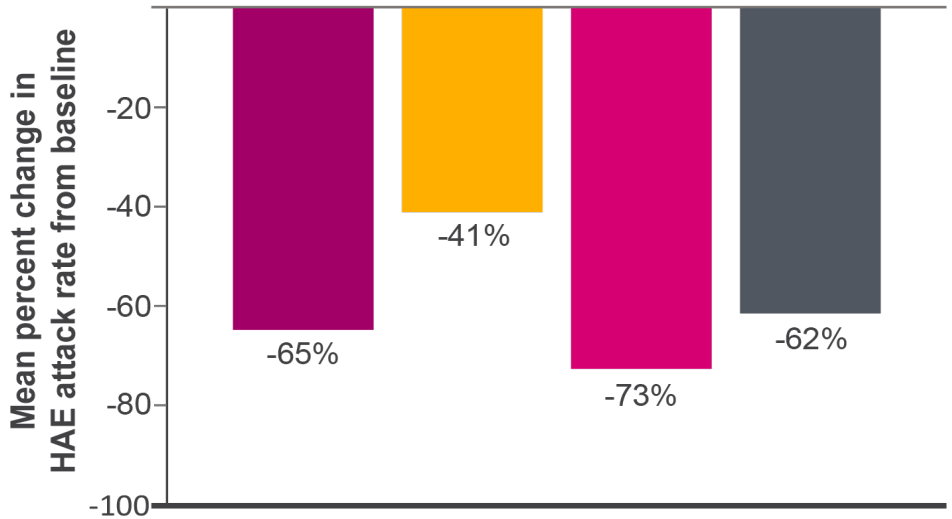
High levels of disease control[4,5]

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.

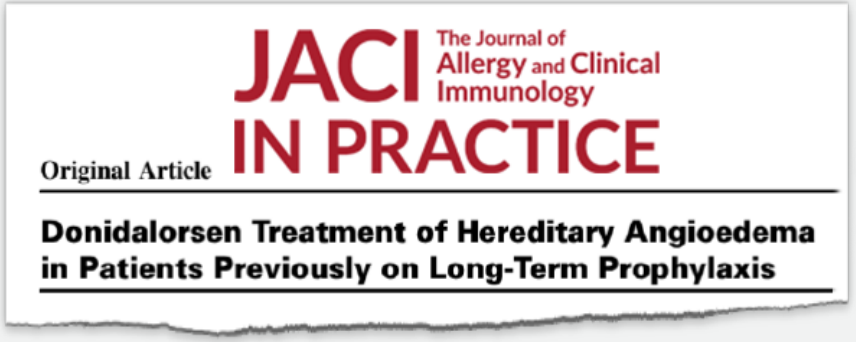
DAWNZERA Substantially Reduced HAE Attack Rates After Switching from Prior Prophylactic Treatment[1,2]

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.

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 accepted with Priority Review			
Obudanersen (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: 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, potentially underestimated[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.

Baseline Demographics and Clinical Characteristics Were Generally Comparable Between Treatment Groups

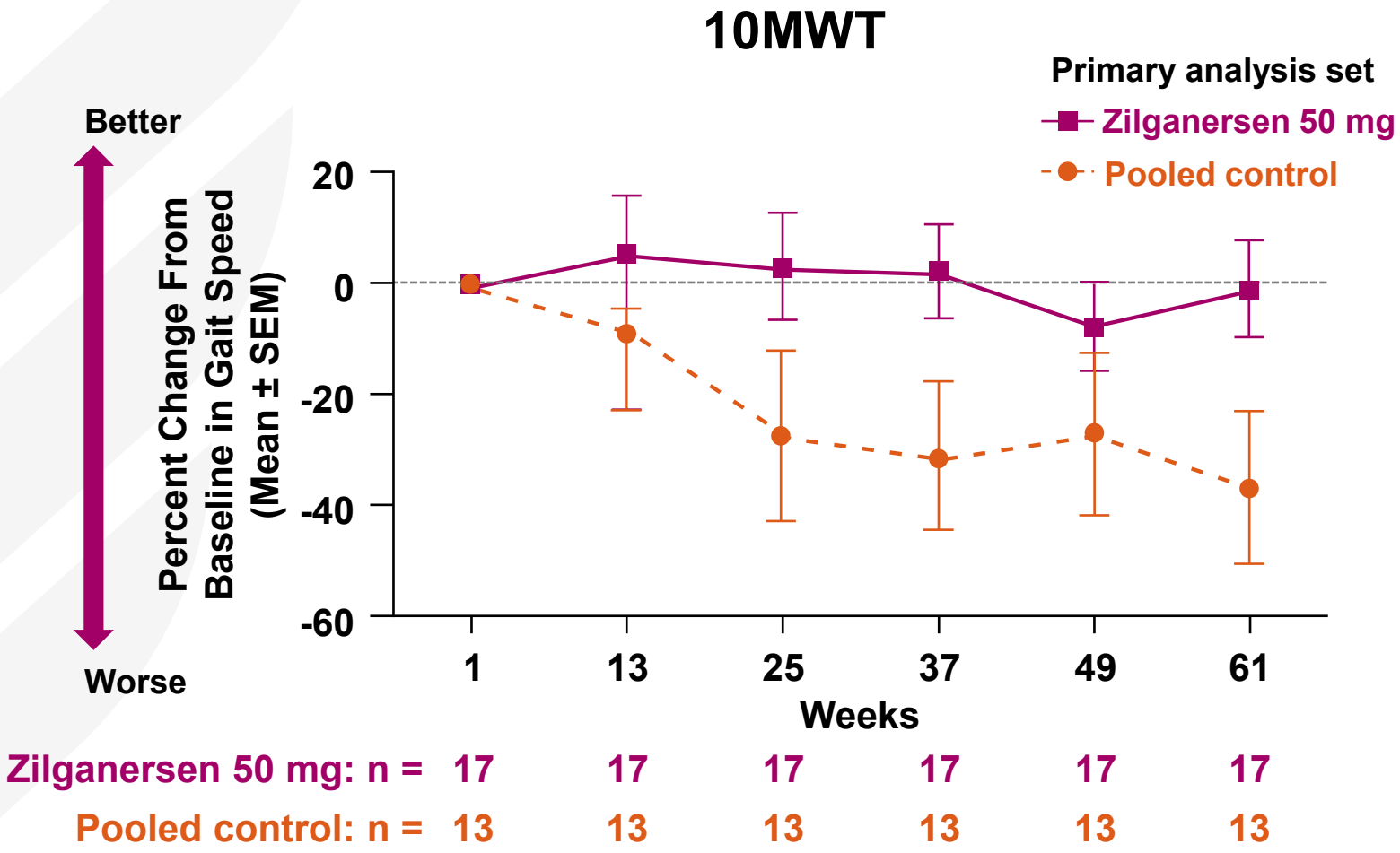
- A total of 49 participants were randomized in the double-blind treatment period:
  - Zilganersen 50 mg (n = 24)
  - Zilganersen 25 mg (n = 8)
  - Control (n = 17)
- The primary analysis set includes[a]
  - Zilganersen 50 mg (n = 17)
  - Control (n =13)

- **Enrolled patients who are representative of the broad AxD population**
- **All eligible patients who completed the double-blind treatment period enrolled into the OLE**

All participants n (%)	Zilganersen 25 mg or 50 mg n = 32	Pooled control n = 17
Age, years, median (range)	11.0 (2.0–53.7)	10.3 (3.0–53.0)
2–18 years	29 (90.6)	15 (88.2)
19–65 years	3 (9.4)	2 (11.8)
Sex		
Female	22 (68.8)	10 (58.8)
Male	10 (31.3)	7 (41.2)
Race		
Asian	2 (6.3)	1 (5.9)
Multiple	1 (3.1)	1 (5.9)
Other	2 (6.3)	0
White	27 (84.4)	15 (88.2)
10MWT, m/s, ≥5 years, mean ± SD (primary analysis set)[a]	1.20 ± 0.63	1.05 ± 0.52

[a]The primary analysis set includes all participants in stratum 1 ([i] ≥5 years of age; and [ii] if ≥18 years of age, had onset of AxD motor symptoms/signs within 5 years of screening; and [iii] demonstrate an abnormality in gross motor skills) who were randomized, received at least 1 dose of the study drug (zilganersen or control), and have at least 1 postbaseline primary efficacy assessment.
The cohort D open-label substudy in participants <2 years of age is not shown.
10MWT, 10-Meter Walk Test; AxD, Alexander disease; SD, standard deviation.

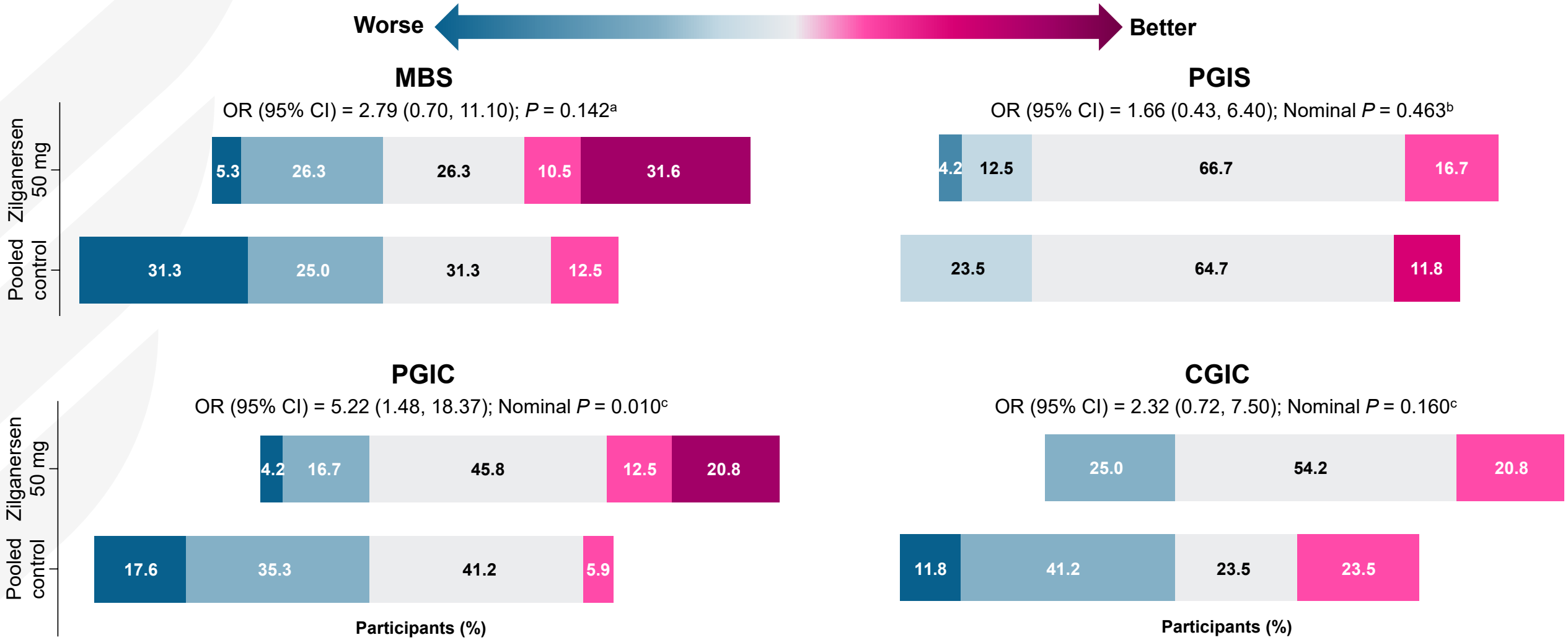
Zilganersen Resulted in Significant and Clinically Meaningful Stabilization of Gait Speed vs Control (Primary Endpoint)



- There was a **statistically significant 33.3% LSM difference** at Week 61 between zilganersen 50 mg and control (*P* = 0.041)
- The positive treatment effect of zilganersen exceeded the threshold of a **clinically meaningful difference*[1-4]**

The primary analysis set includes all participants in stratum 1 ([i] ≥ 5 years of age; and [ii] if ≥18 years of age, had onset of AxD motor symptoms/signs within 5 years of screening; and [iii] demonstrate an abnormality in gross motor skills) who were randomized, received at least 1 dose of the study drug (zilganersen or control), and have at least 1 postbaseline primary efficacy assessment.
*Due to lack of sufficient literature in AxD, MCID was based on multiple sclerosis literature.
10MWT, 10-Meter Walk Test; AxD, Alexander disease; LSM, least square mean; MCID, minimal clinically important difference; SEM, standard error of the mean.
1. Kaufman M, et al. *Mult Scler*. 2000;6(4):286-90. 2. Hobart J, et al. *Neurology*. 2013;80:1509-17. 3. Cohen JA, et al. *JAMA Neurol*. 2014;71:1386-93. 4. Kragt J, et al. *Mult Scler*. 2006;12:594-8.

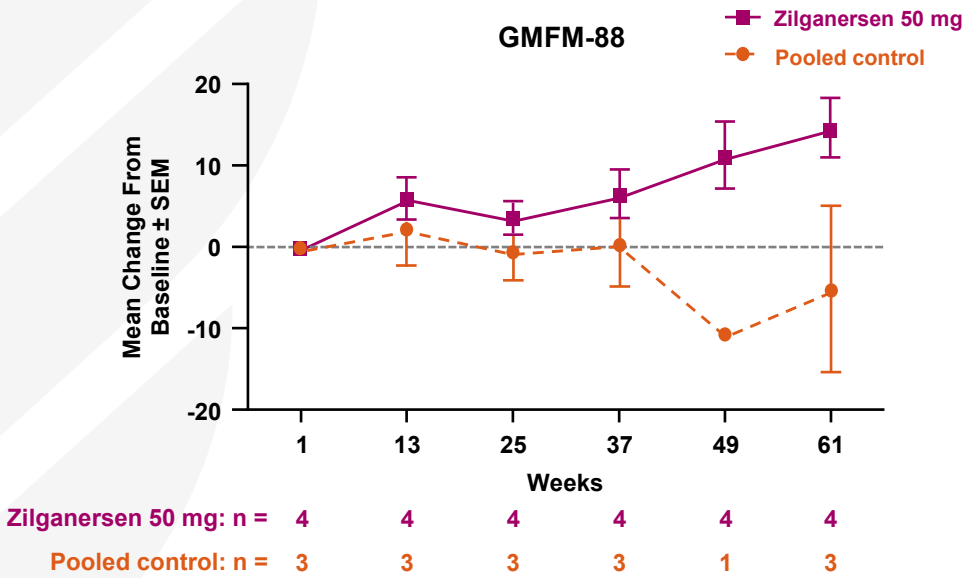
Key Secondary Endpoints Capturing Disease Severity and Global Health Status Favored Zilganersen at Week 61



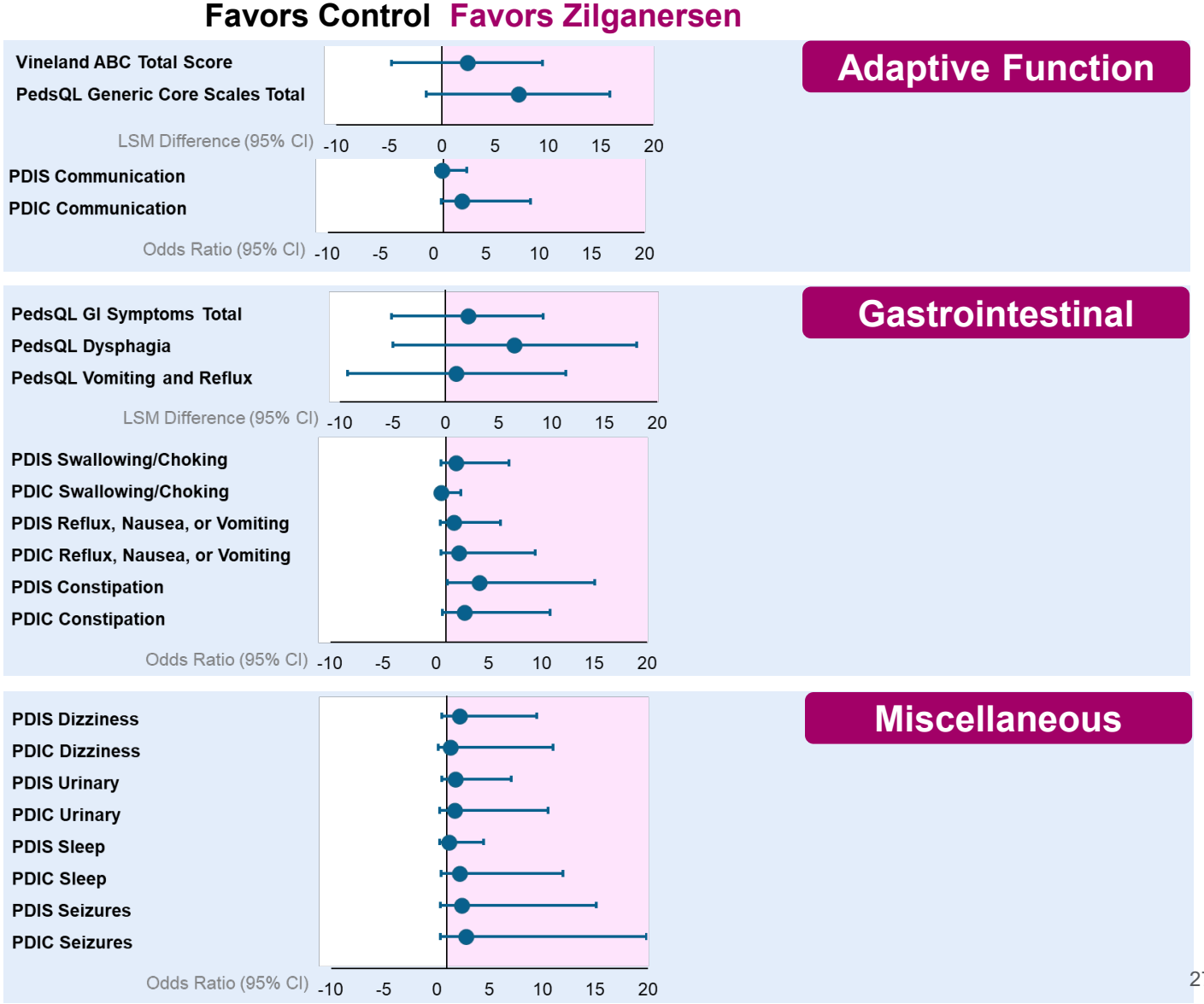
[a]*P*-values were from a chi-square test. If any cell from the 2-by-2 table was <5, then Fisher's exact test was used. [b]Proportional odds model with treatment group and baseline as covariates. [c]Proportional odds model with treatment group as a factor. Key secondary endpoints were assessed in the full analysis set (all participants who were randomized, received at least 1 dose of the study drug [zilganersen or control], and had at least 1 postbaseline efficacy assessment in the double-blind treatment period). MBS was measured on a 5-point scale from 5 (much worse) to 1 (much better). Change from baseline at Week 61 in PGIS was measured on a scale from 4 (worse) to −4 (better). PGIC and CGIC were measured on a 5-point scale from 4 (much worse) to 0 (much better). CGIC, Clinical Global Impression of Change; CI, confidence interval; MBS, Most Bothersome Symptom; OR, odds ratio; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity.

Most Efficacy Endpoints, Evaluating Motor, Adaptive Function, Gastrointestinal, and Autonomic Symptoms, Favored Zilganersen

Motor



22.9 least square mean difference at Week 61 between zilganersen 50 mg and control (nominal *P* = 0.034)



CI, confidence interval; GI, gastrointestinal; GMFM-88, Gross Motor Function Measure-88; LSM, least square mean; PDIC, Patient Domain Impression of Change; PDIS, Patient Domain Impression of Severity; PedsQL, Pediatric Quality of Life Inventory; SEM, standard error of the mean; Vineland ABC, Vineland Adaptive Behavior Composite.

Zilganersen Demonstrated Acceptable Safety and Tolerability at Week 61

- Most TEAEs were mild or moderate in severity
- No TEAEs led to study drug discontinuation
- No effects of zilganersen on platelet counts or renal or liver function were identified
- One participant had TEAEs[a] consistent with potential aseptic meningitis that required interruption of treatment during the OL period without leading to permanent discontinuation
- One participant (zilganersen 25 mg) experienced a serious TEAE of disease progression (onset in the double-blind period) resulting in death during the OL period

All participants n (%)	Zilganersen 25 mg or 50 mg n = 32	Pooled control n = 17
Any TEAE	32 (100)	17 (100)
Mild	7 (21.9)	3 (17.6)
Moderate	18 (56.3)	11 (64.7)
Severe	7 (21.9)	3 (17.6)
TEAEs leading to		
Treatment discontinuation	0	0
Treatment interruption	4 (12.5)	4 (23.5)
Any serious TEAE	12 (37.5)	8 (47.1)
Seizure	2 (6.3)	2 (11.8)
Vomiting[a]	1 (3.1)	2 (11.8)
Influenza	2 (6.3)	0
Scoliosis	2 (6.3)	0
Increased ICP[b]	1 (3.1)	3 (17.6)
CSF protein >ULN[c]	6 (18.8)	5 (29.4)

The table includes all participants who were randomized and received ≥1 dose of the study drug. [a]A single participant presented with serious vomiting accompanied by headache, elevated CSF protein, and CSF WBC count >ULN. [b]Increased ICP includes TEAEs with preferred terms within a predefined MedDRA search strategy (CSF pressure increased, intracranial pressure increased, brain herniation, hydrocephalus, idiopathic intracranial hypertension, papilloedema, and vomiting projectile). In addition, Cushing's triad, defined as hypertension, bradycardia, and irregular breathing or dyspnea reported simultaneously, was included. [c]CSF protein >ULN (or >45 mg/dL when ULN was not provided).
CSF, cerebrospinal fluid; ICP, intracranial pressure; MedDRA, Medical Dictionary for Regulatory Activities; OL, open-label; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; WBC, white blood cell.

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.

Obudanersen: A Promising Investigational Medicine for Angelman Syndrome

The Opportunity

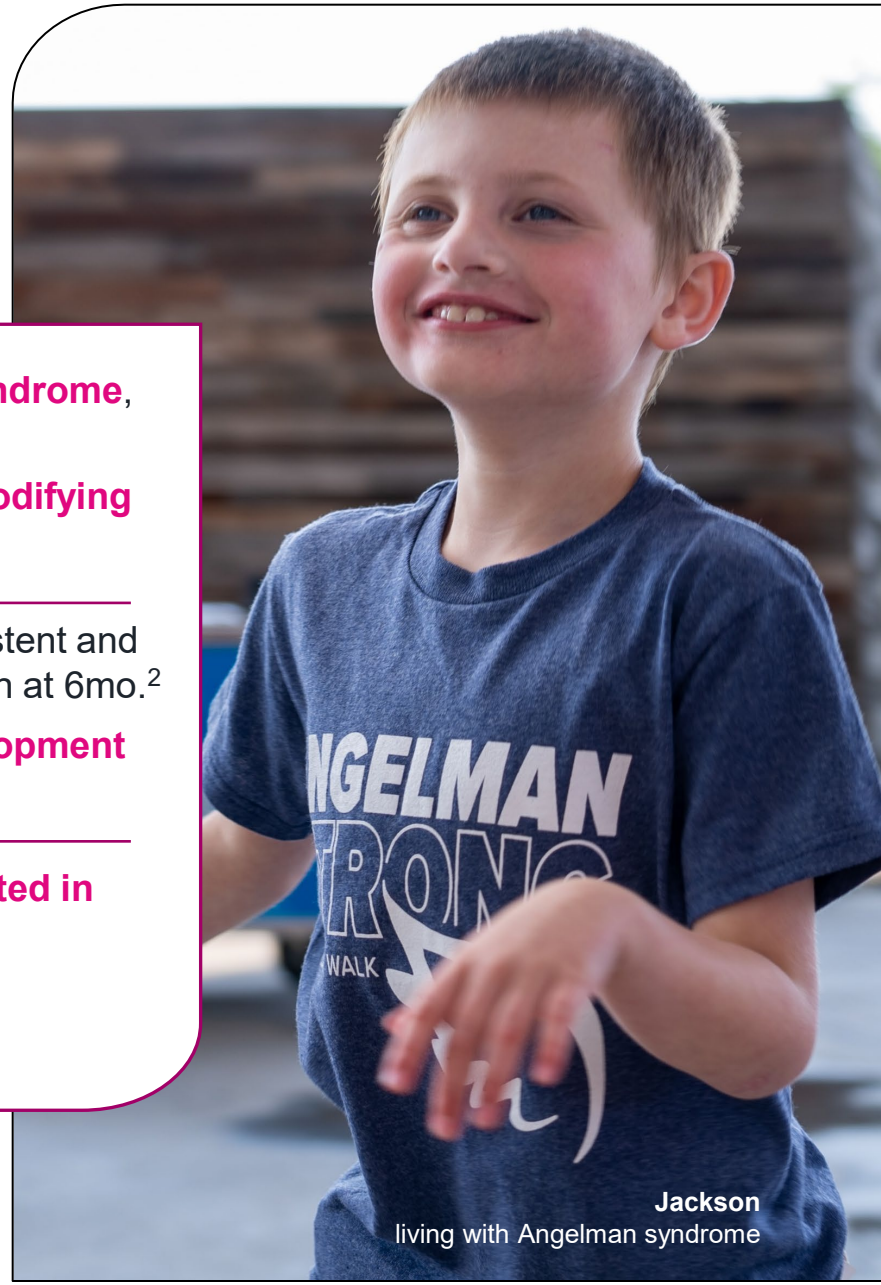
- **>100k people** in major geographies with **Angelman syndrome**, a severe, rare neurodevelopmental disorder[1]
- **Significant unmet need** with **no approved disease-modifying treatments**

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**

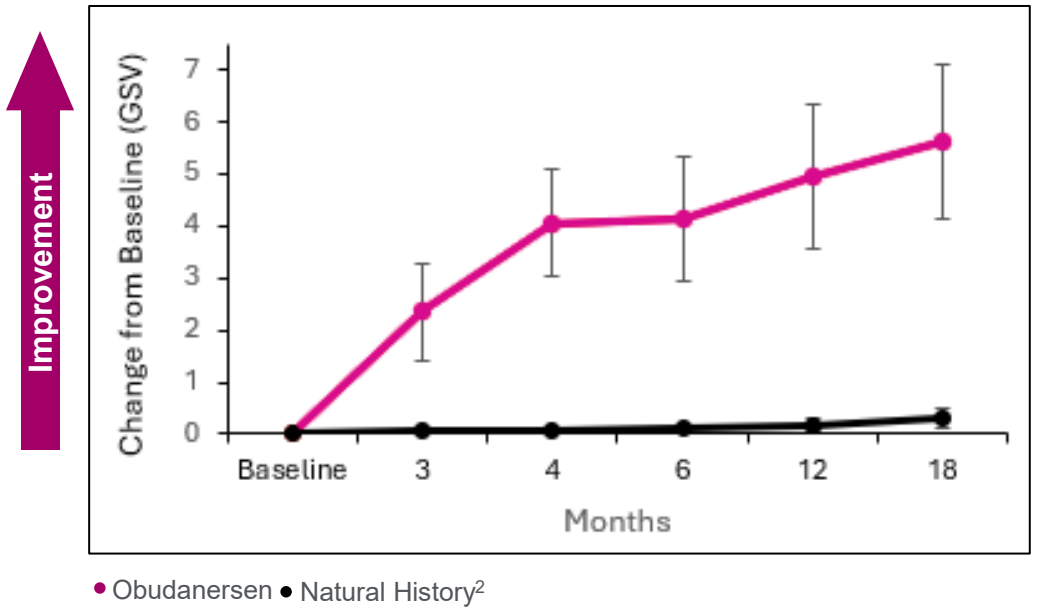


Jackson
living with Angelman syndrome

1. Luk. *Eur. J. Méd. Genet*. (2016). 2. Based on data generated to date from the Phase 1/2a HALOS study of obudanersen. 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 Obudanersen 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 obudanersen 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 Obudanersen 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 obudanersen HALOS study aged 2-34 years old who received either 40mg or 80mg obudanersen 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 U.S., EU and Japan**

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
- Improved economics over SPINRAZA[2]

Salanersen Phase 3 program underway

- First patient dosed in STELLAR-1 in presymptomatic infants genetically diagnosed with SMA

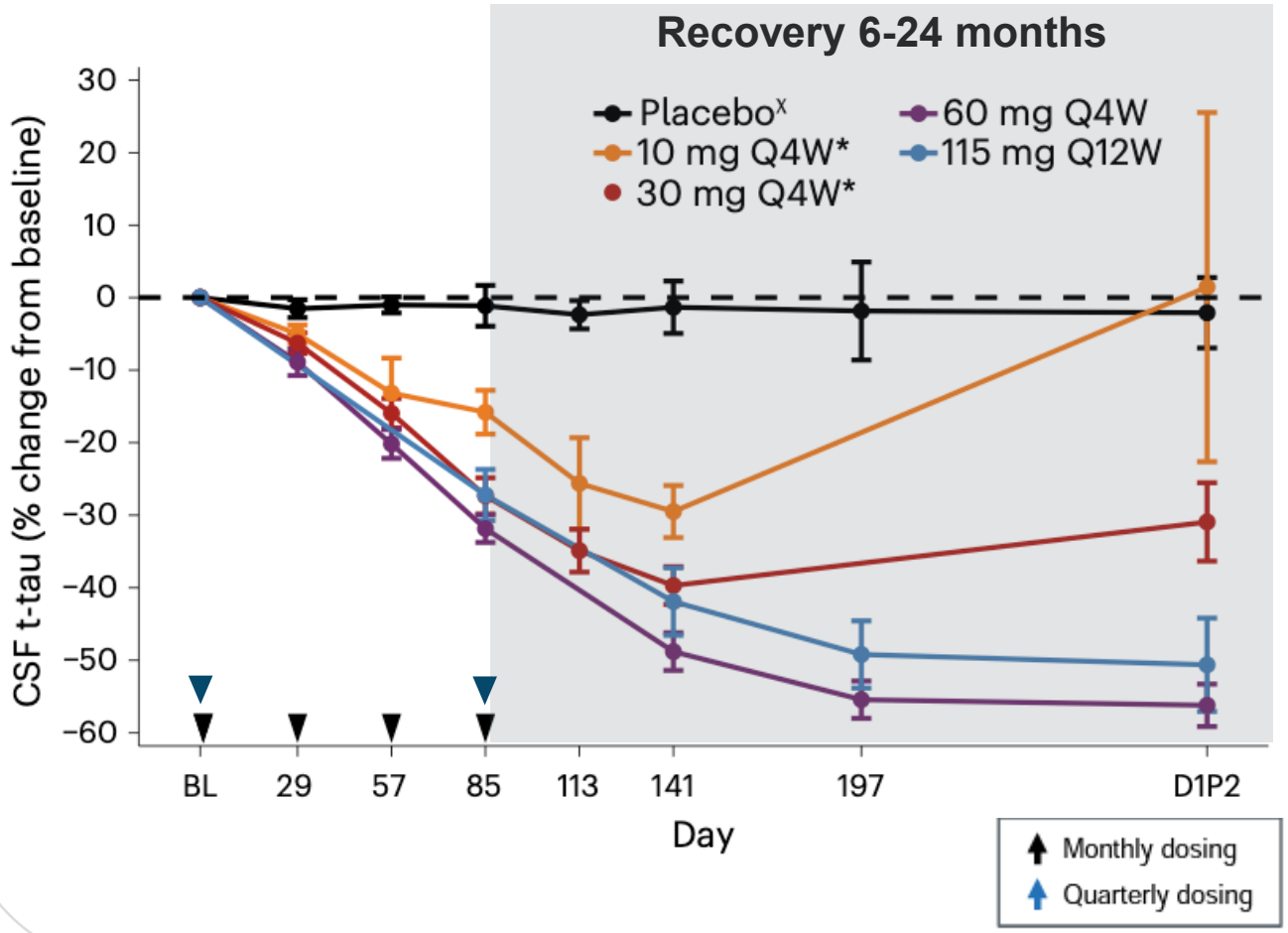
1. Timing expectations based on current assumptions and subject to change. 2. SPINRAZA is approved in the U.S. for or the treatment of spinal muscular atrophy in pediatric and adult patients; see Full Prescribing Information.

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



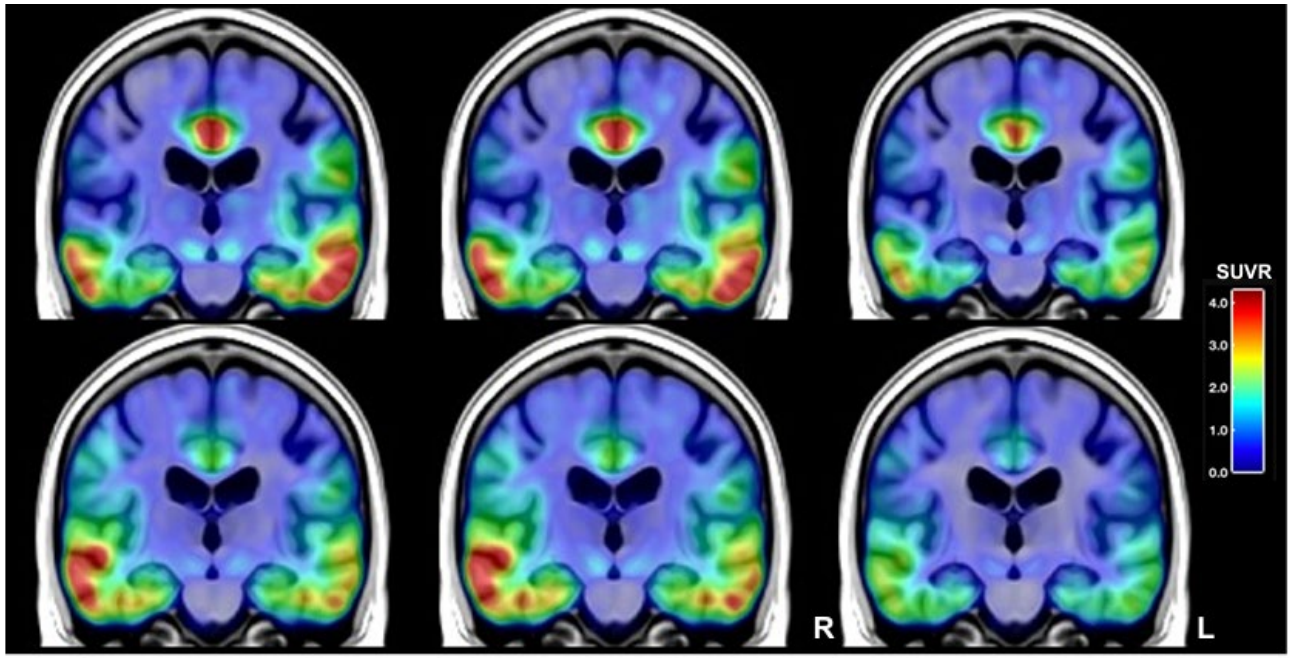
1. Mummery et al., Nat Med, 2023; AD = Alzheimer's disease; CSF = cerebrospinal fluid; Q4W = every 4-week dosing; Q12W = every 12-week dosing; t-tau = total tau

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) H2:26	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] **Granted Priority Review**; PDUFA October 26, 2026	**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 mid-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.

IONIS

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]

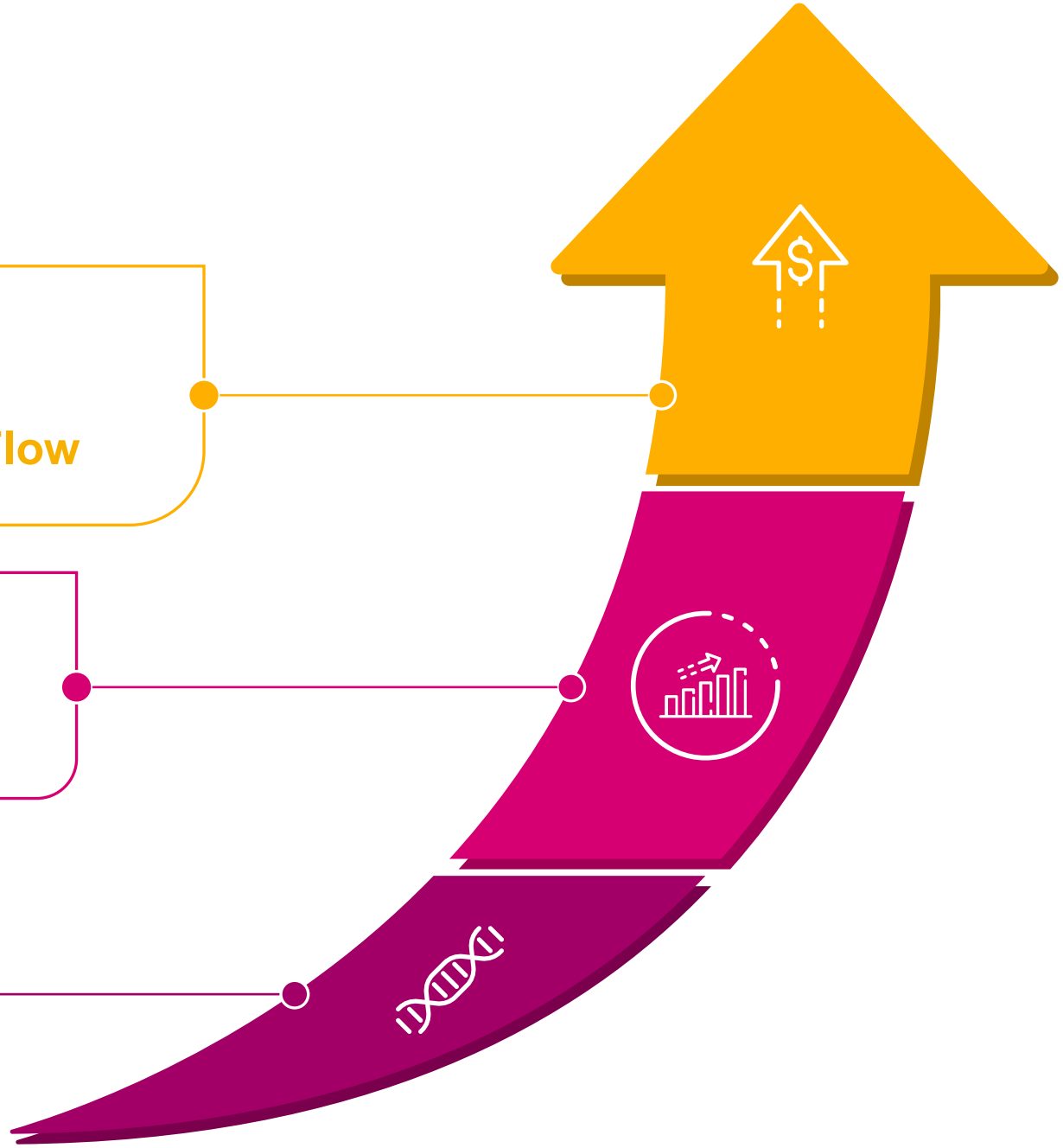
2028 Cash Flow Breakeven

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.

Q1:2026 Financial Highlights[1]

Revenues $246M

Commercial Revenue: $108M

- $27M in TRYNGOLZA product sales
- $16M in DAWNZERA product sales
- Total commercial revenues ~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.

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]

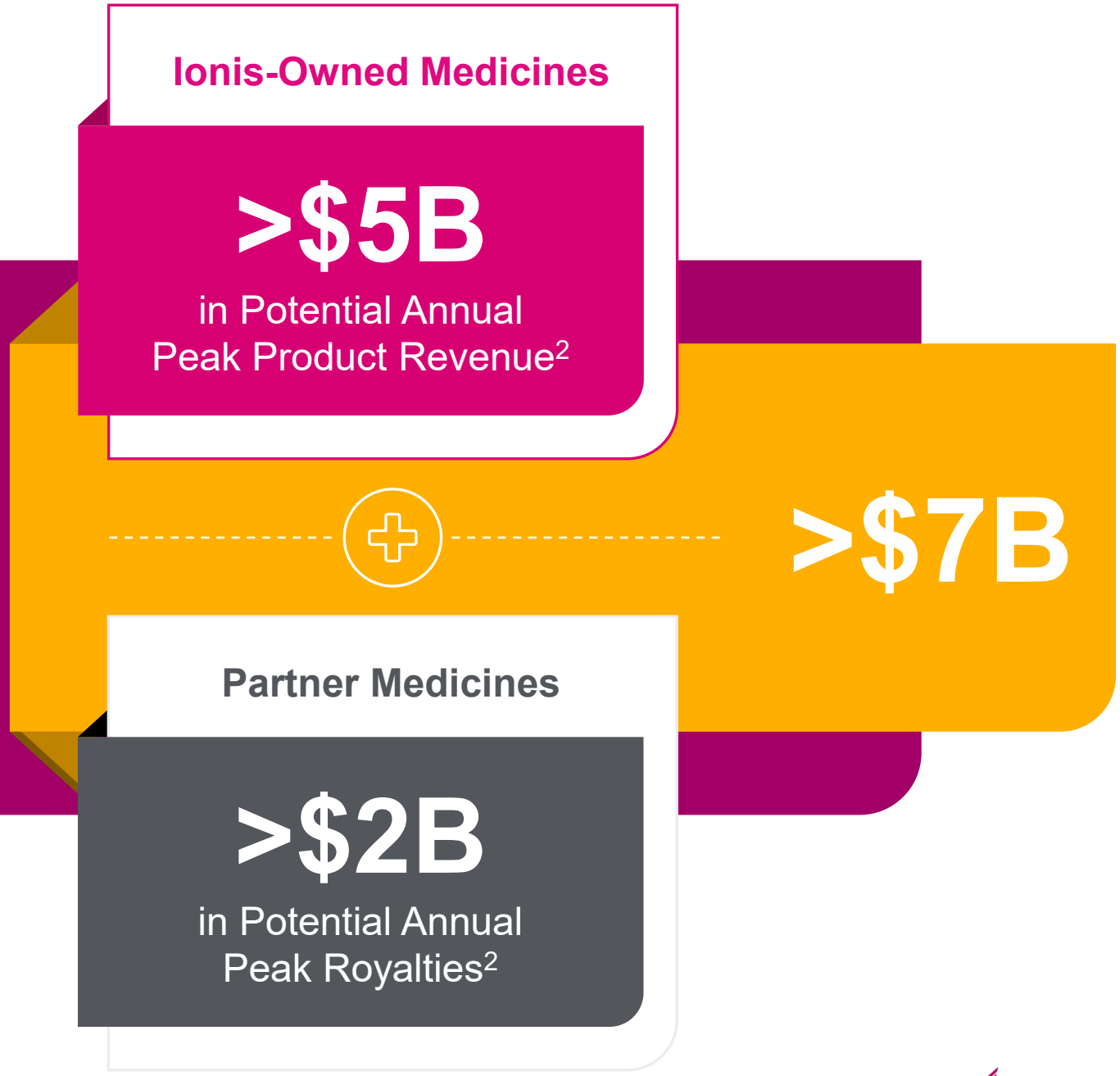
First ever investigational medicine to show a disease-modifying effect in Alexander disease

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

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]

>$5B

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

Launch Timing

Today

Olezarsen
(sHTG)

>$3B

Zilganersen
(Alexander disease)

>$100M

2026 Launches

Obudanersen
(Angelman syndrome)

>$1B

2028+

5 Additional medicines

in mid-stage development

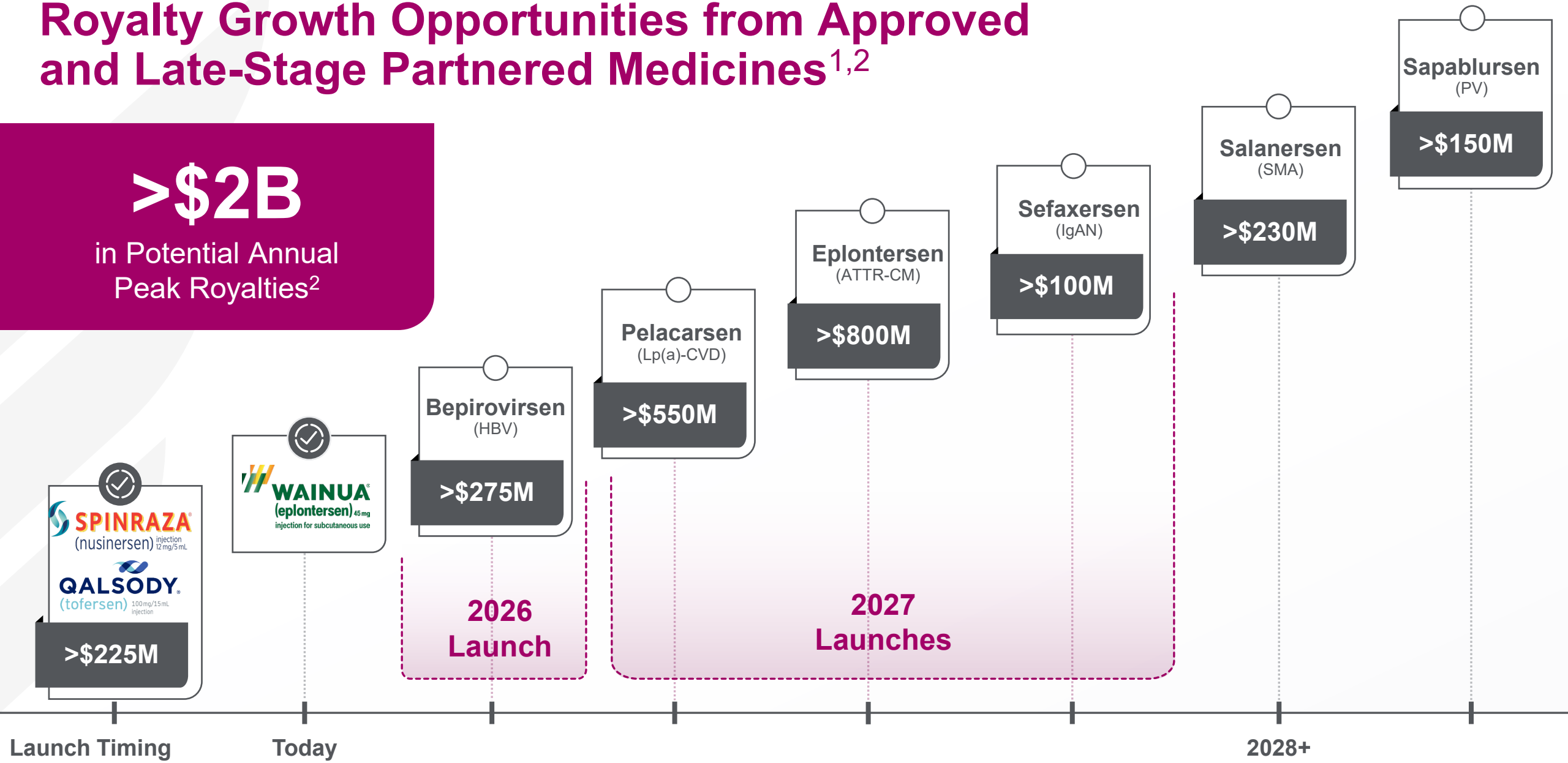
Multi-Billion-Dollar

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]

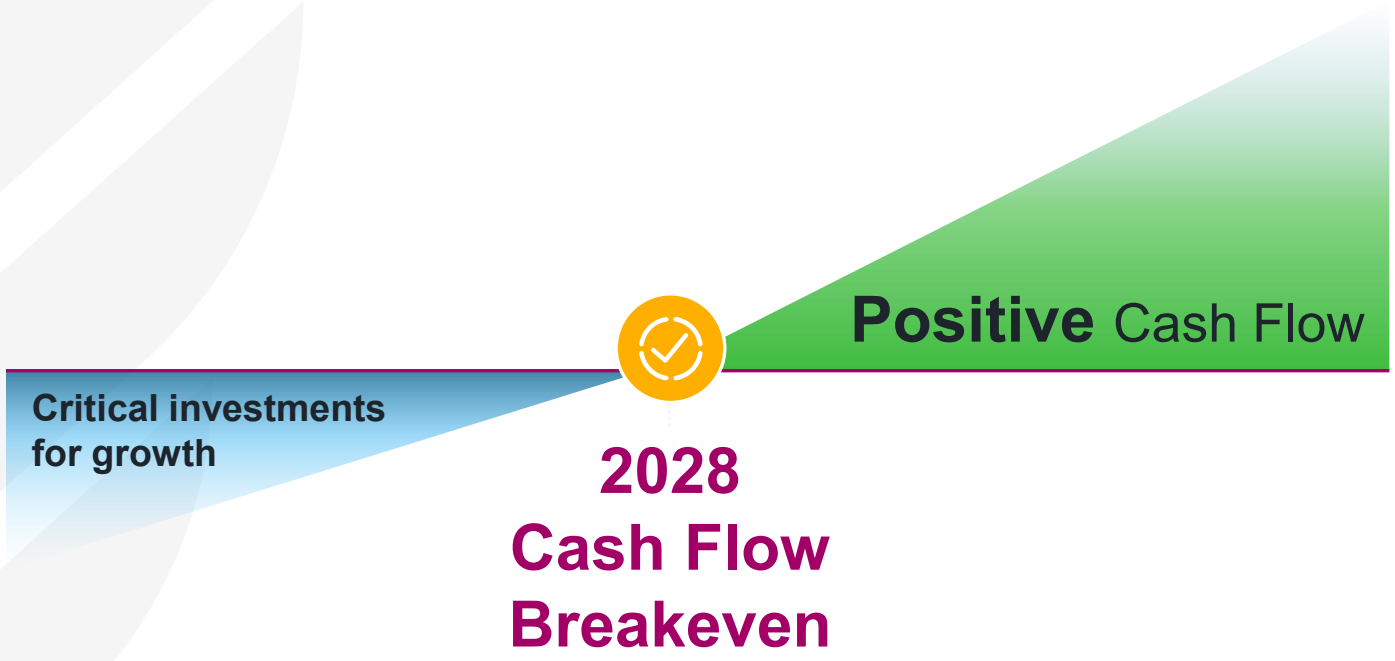
Royalties

Nearly All Partner Revenue Drops to the Bottom Line as Profit

	Total Remaining Milestone Payments[4]	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	**>$500M**	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. 4. As reported in Q1 2026 Form 10-Q.

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.

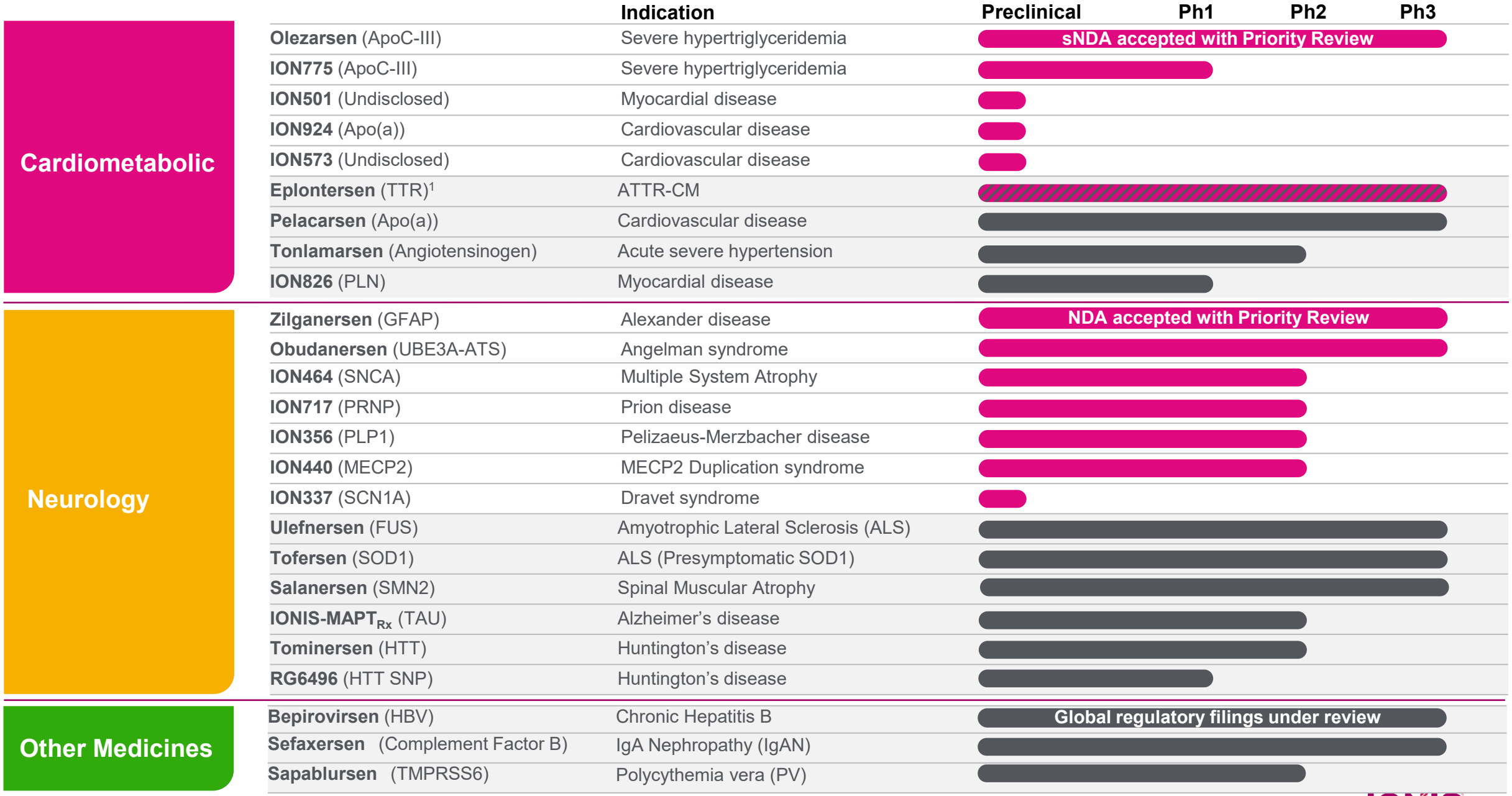
Empower our people and communities

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