IONIS®






44th Annual J.P. Morgan Healthcare Conference 2026

Breakthrough Therapies Driving Accelerating Growth

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Chief Executive Officer

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Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of our commercial medicines, additional medicines in development and technologies and our expectations regarding development and regulatory milestones. Any statement describing Ionis' goals, expectations, financial or other projections or guidance, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on our Form 10-K for the year ended December 31, 2024, and our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these and other documents are available at www.ionis.com.

In this presentation, unless the context requires otherwise, "Ionis," "Company," "we," "our," and "us" refers to Ionis Pharmaceuticals and its subsidiaries.

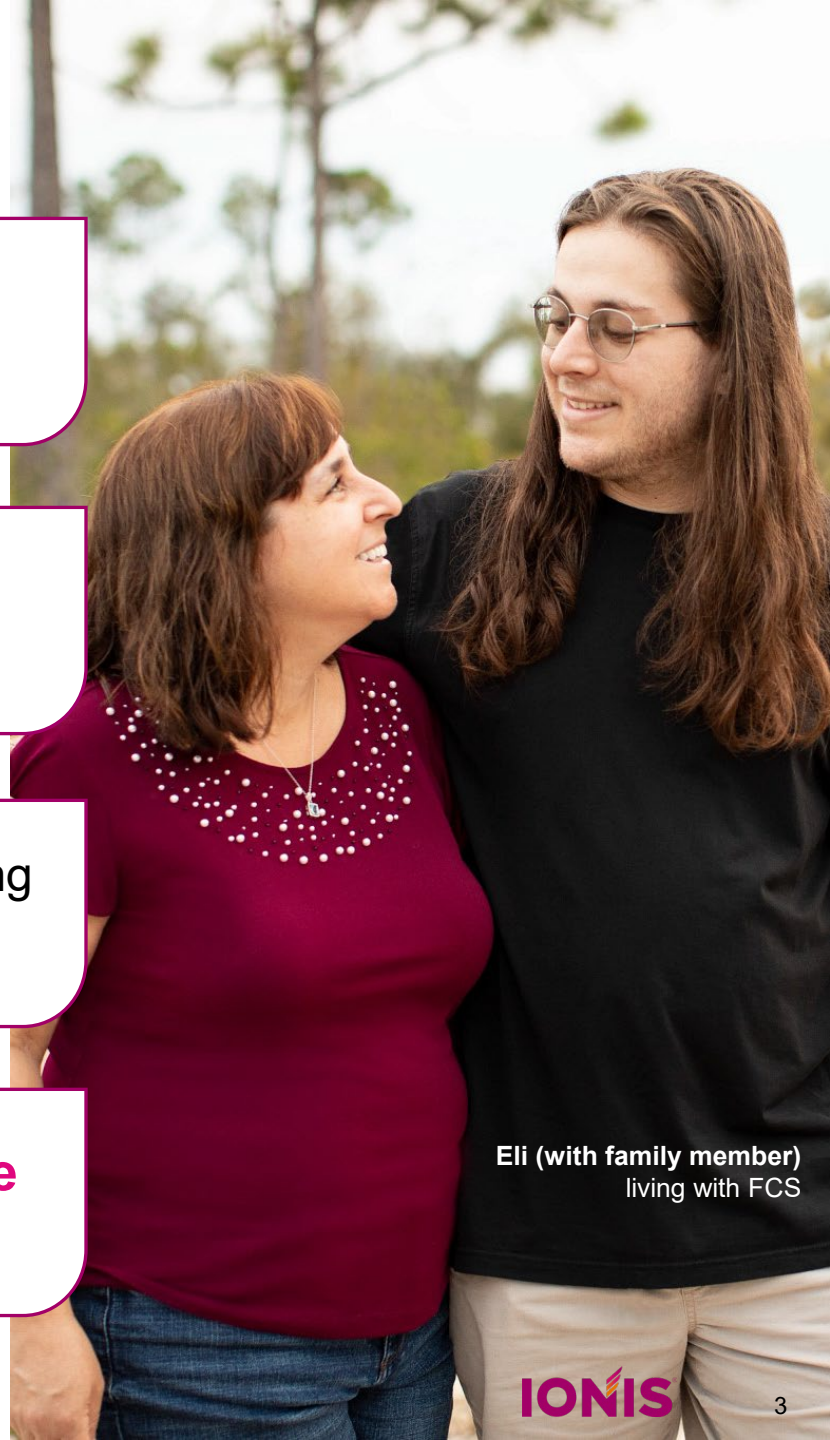
Well Positioned for Accelerating Growth

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.

DAWNZERA: A Novel Therapeutic for HAE Prophylaxis[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

FDA Approval: August 21, 2025

Expect EMA approval and launch in Q1:2026

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.

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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.

Olezarsen: A Transformational Medicine for All sHTG Patients with Urgent Unmet Need[1]

Familial Chylomicronemia Syndrome (FCS)

- **Up to ~3,000** people in the U.S.[2-6]
- **Rare genetic disorder:** Most severe form of sHTG caused by loss of LPL activity[6,7]
- **Significant risk** for acute, potentially fatal pancreatitis[1]

Severe Hypertriglyceridemia (sHTG)

- **>3 million** people with sHTG in the U.S., including **>1 million people with high-risk sHTG**[8]
- Defined by **fasting triglyceride levels ≥500 mg/dL**[9]
- Characterized by **increased risk of acute pancreatitis** and **ASCVD**[9]
- **Limited benefit from currently available treatments**[10-13]

Guidelines **recommend aggressive TG lowering treatment** for all patients with sHTG

1. TRYNGOLZA is currently approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see Full Prescribing Information and the EU , the sNDA for sHTG has been submitted to the FDA. Approved in the EU as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome. 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. Moulin P, et al. Atherosclerosis 2018;275:265-72. 7. Brown EE, et al. J Clin Lipidol 2020;14(4):398-413. 8. Hegele, et al, Lancet Diabetes Endocrinol. 2014 Aug 2(8):655-66. 9. Nawaz H, et al. Am J Gastroenterol. 2015;110(10):1497-1503. 10. Patel SB, et al. Endocr Pract. 2025;31(2):236-262. 11. Santos-Baez, LS et al. Front Endocrinol (Lausanne). 2020;11:616. 12. Skulas-Ray AC, et al. Circulation. 2019;140(12):e673-e691. 13. Aldhaleei WA, et al. Pharmaceuticals (Basel). 2024;17(2):199.

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

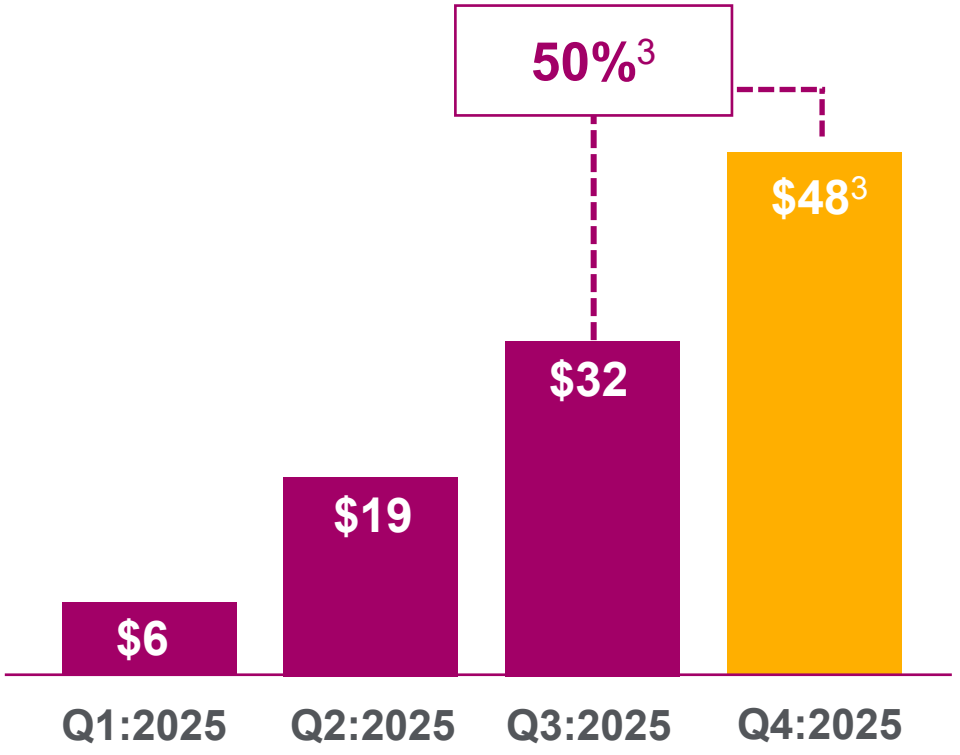
Robust efficacy and safety

- 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 $105 million in 2025[3]



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). 3. Preliminary and unaudited.

Olezarsen Phase 3 Program Designed to Support Opportunity in sHTG

Pivotal Studies in People with sHTG (fasting TG ≥500 mg/dL)

CORE
a hypertriglyceridemia study

CORE2
a hypertriglyceridemia study

Primary Endpoint

Percent change in fasting triglycerides from baseline to month 6

Acute Pancreatitis Secondary Endpoint

Adjudicated event rate between pooled olezarsen compared to pooled placebo at 12 months

Other Secondary and Exploratory Endpoints

Portion of patients who achieved fasting triglycerides <500 mg/dL

Portion of patients who achieved fasting triglycerides <150 mg/dL

Largest Pivotal Program Ever Conducted in sHTG

1,063 participants

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: Poised to Become Ionis' First Blockbuster Medicine

Highly statistically significant and **clinically meaningful** reductions in fasting **triglycerides** with **favorable safety** and **tolerability**[1]

First and only investigational treatment to **significantly reduce acute pancreatitis** events in **people with sHTG**[1]

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

- **First mover advantage**
- **sNDA submitted** to FDA; U.S. Launch expected in **2026**[2]
- **Granted Breakthrough Therapy designation**

Annual Peak Product Revenue Opportunity[2]

Increased to

>$2B

(Previous: >$1 billion)

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

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 Submitted			
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.

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Proven Platform and Capabilities for Delivering Groundbreaking Medicines for Neurological Diseases

Approved Medicines[1-3]

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

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 submission planned for Q1:2026			
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** submission planned for **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.

ION582: A Promising Investigational Medicine for Angelman Syndrome

The Opportunity

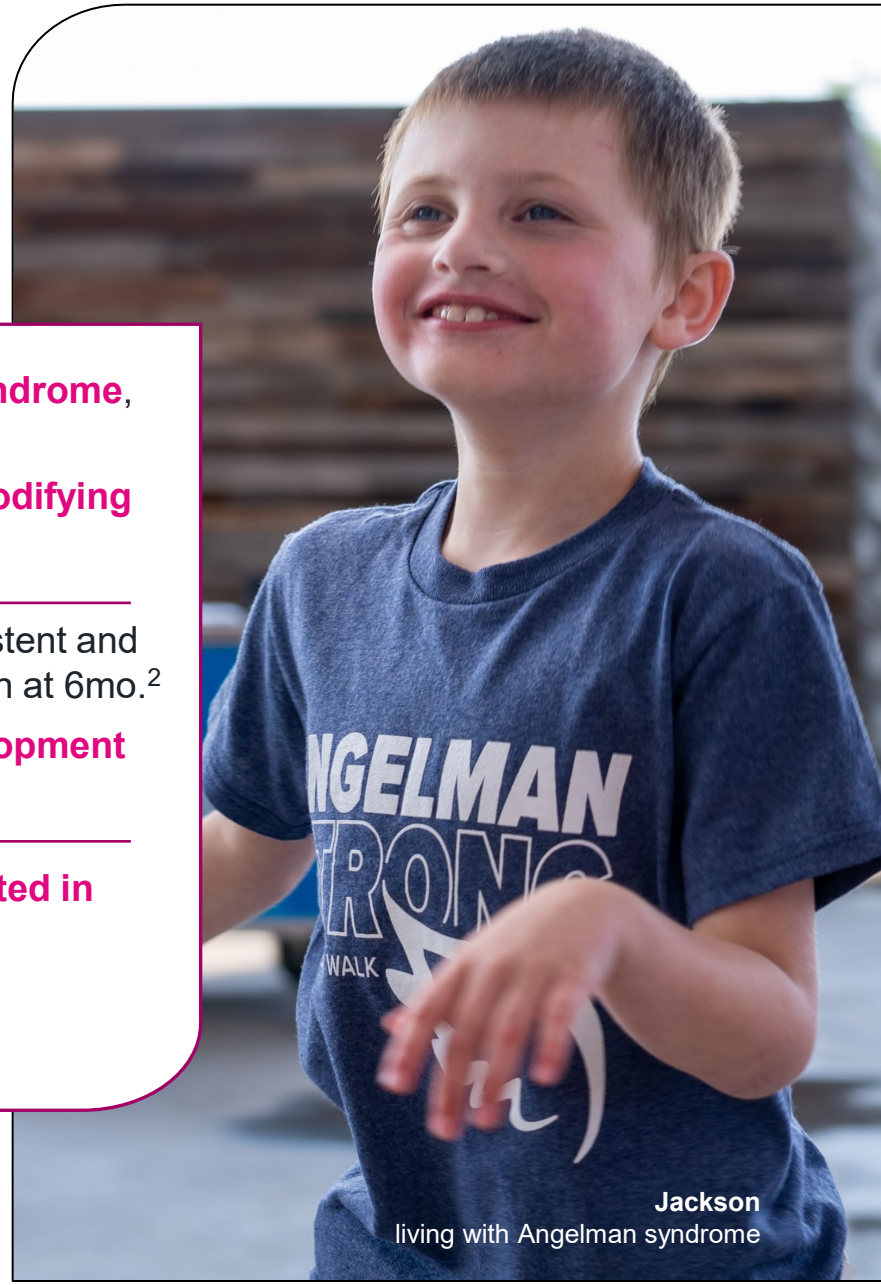
- **>100k people** in major geographies with **Angelman syndrome**, a severe, rare neurodevelopmental disorder[1]
- **Significant unmet need** with **no approved disease-modifying treatments**

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**



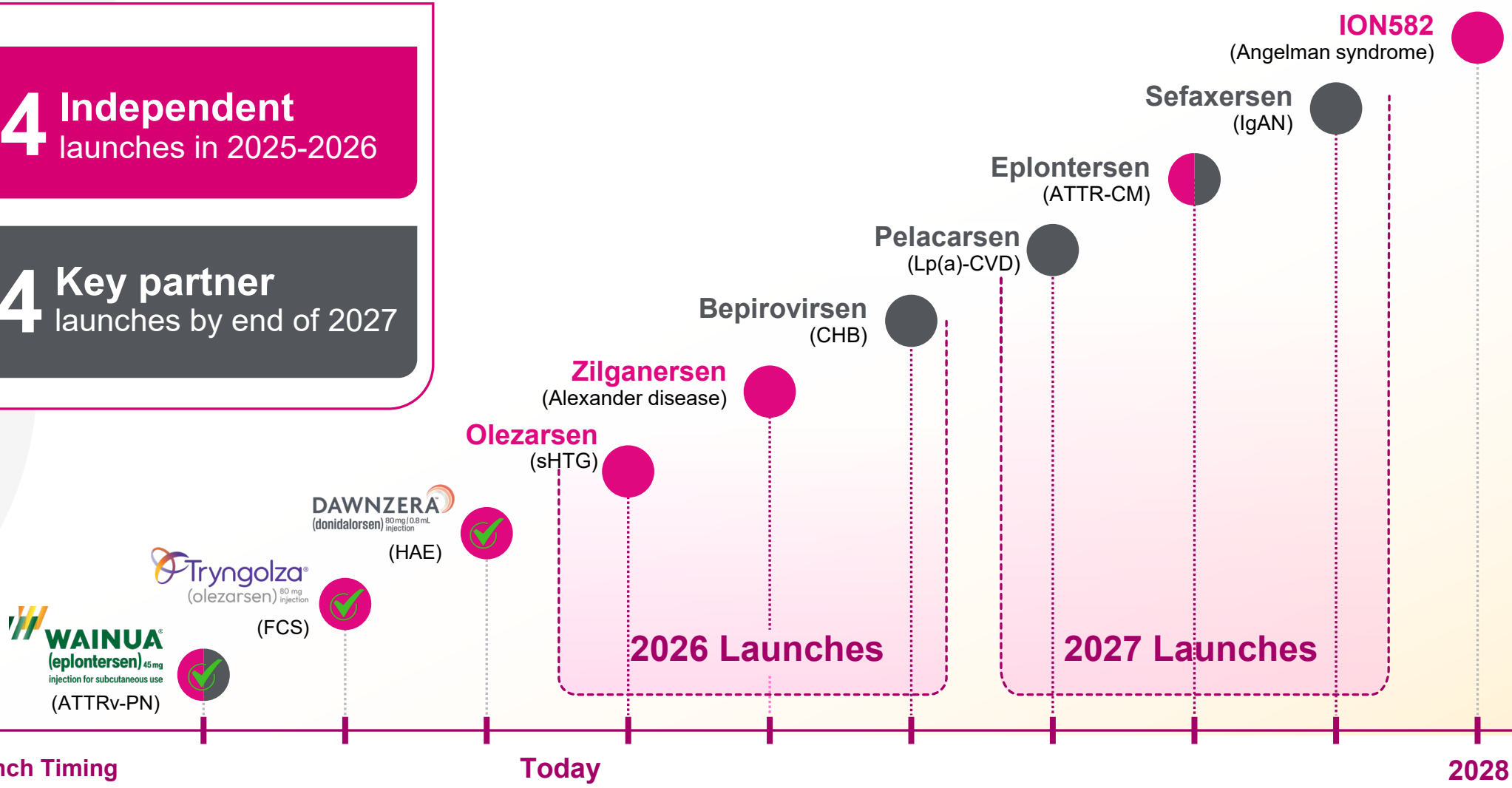
Jackson
living with Angelman syndrome

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.

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

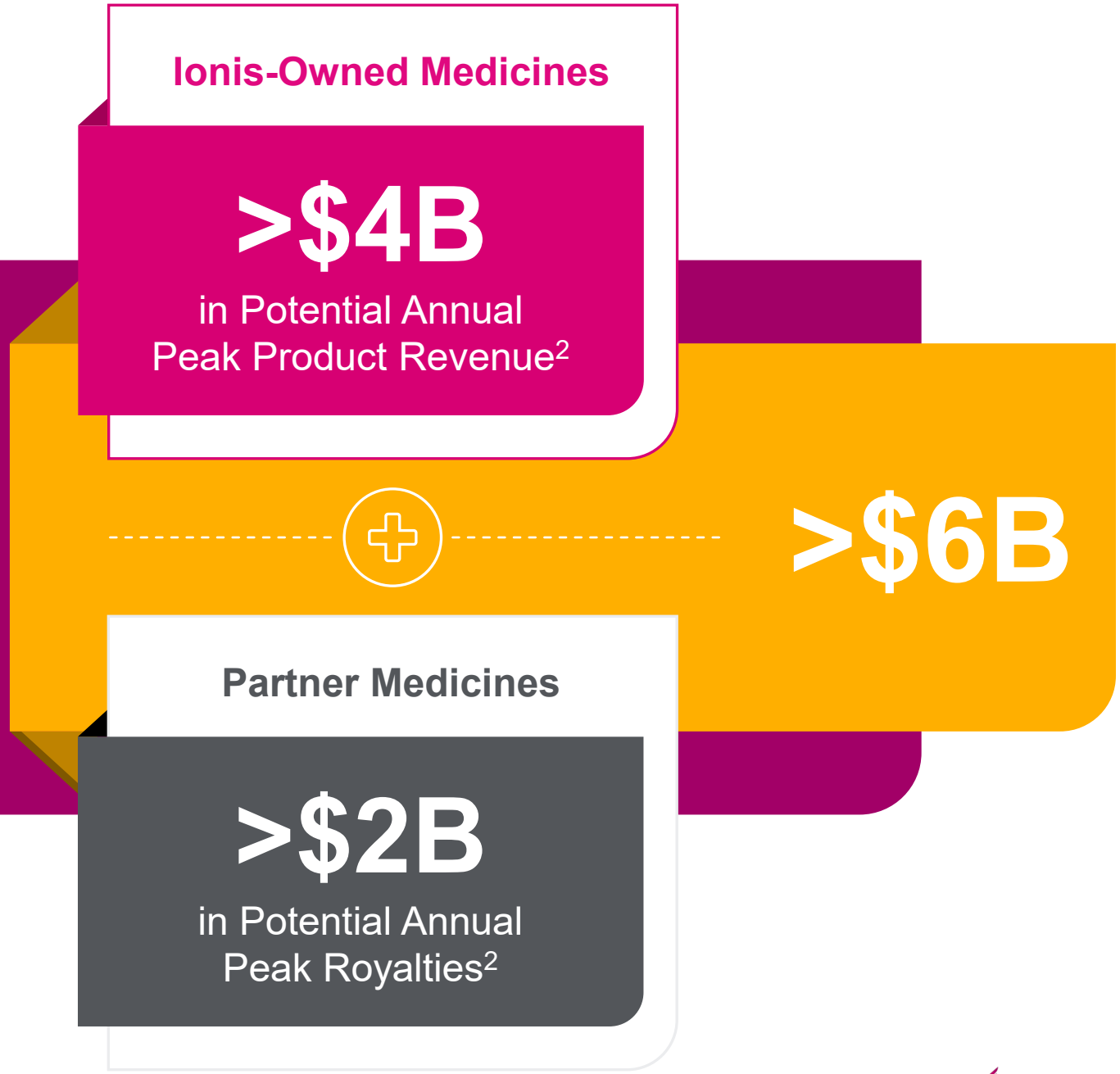
4 Independent launches in 2025-2026

4 Key partner launches by end of 2027



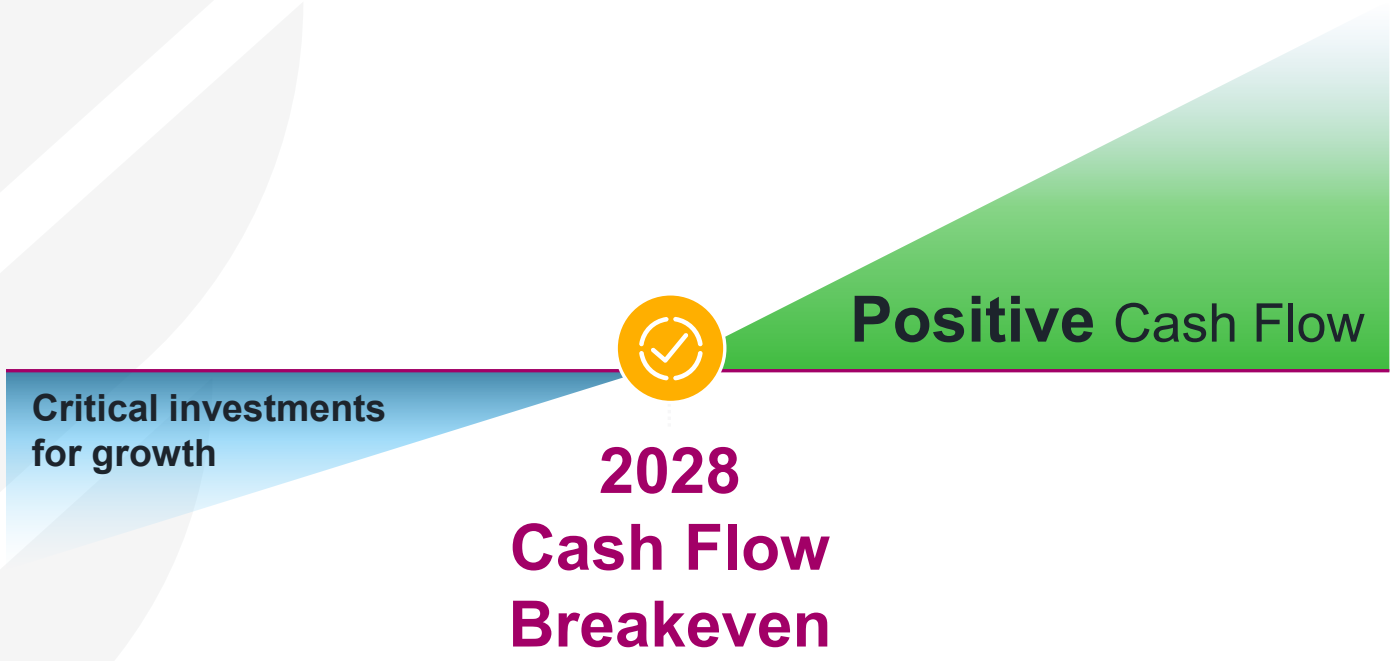
1. Assuming approval. 2. Based on current timing assumptions, subject to change.

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.

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.

Well Positioned to Continue Driving Breakout 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)
Multiple System Atrophy (SNCA) | Prion Disease (PRNP)

1. Based on current assumptions, subject to change.

Driving Accelerating Growth[1,2]

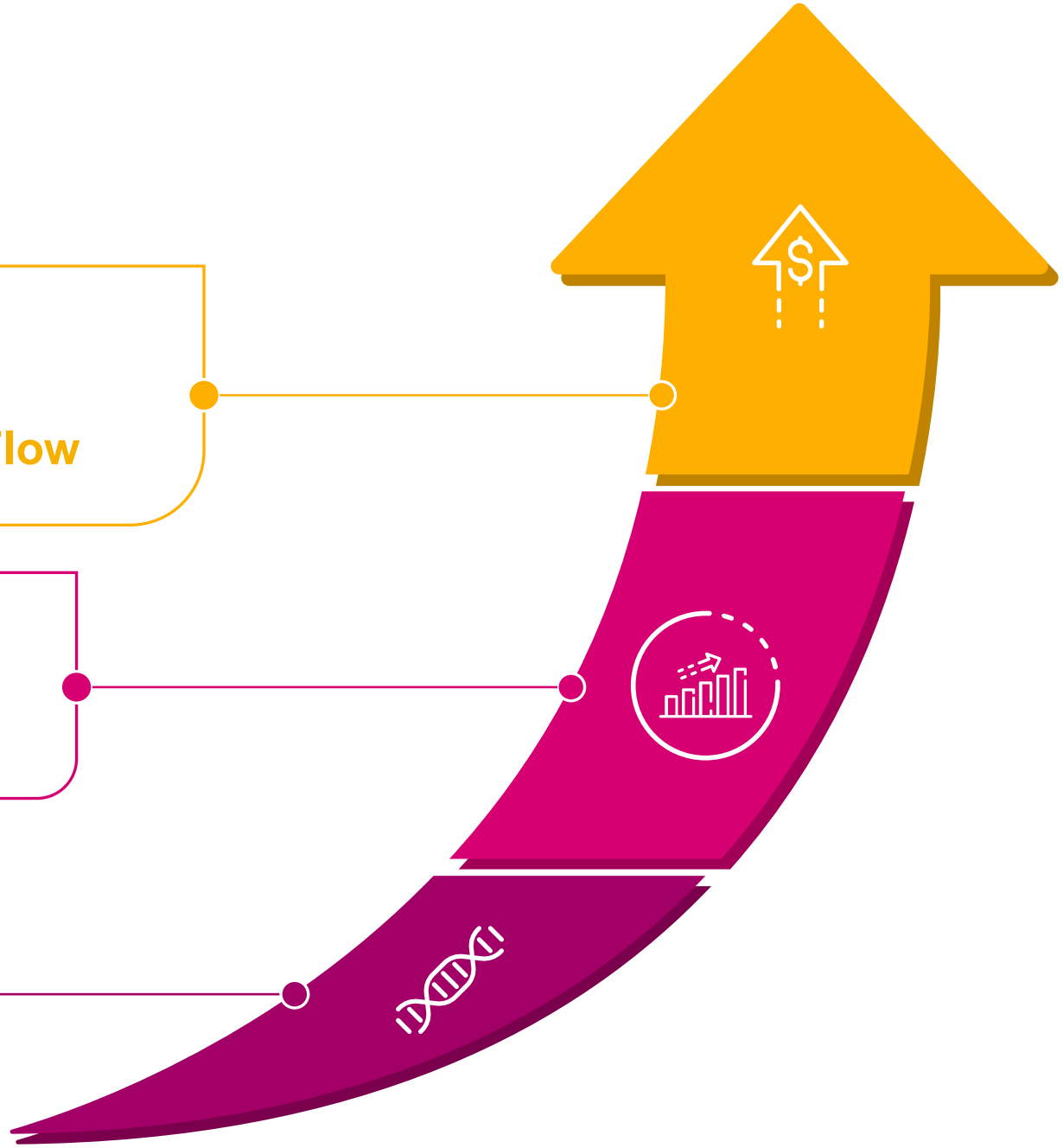
2028 Cash Flow Breakeven

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.

Breakthrough Therapies Driving Accelerating Growth












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)
- **ION464** — HORIZON data (Multiple system atrophy)
- **Tominersen** — GENERATION HD2 data (Huntington's disease)
- **ION717** — PrProfile data (Prion disease)

Regulatory Actions

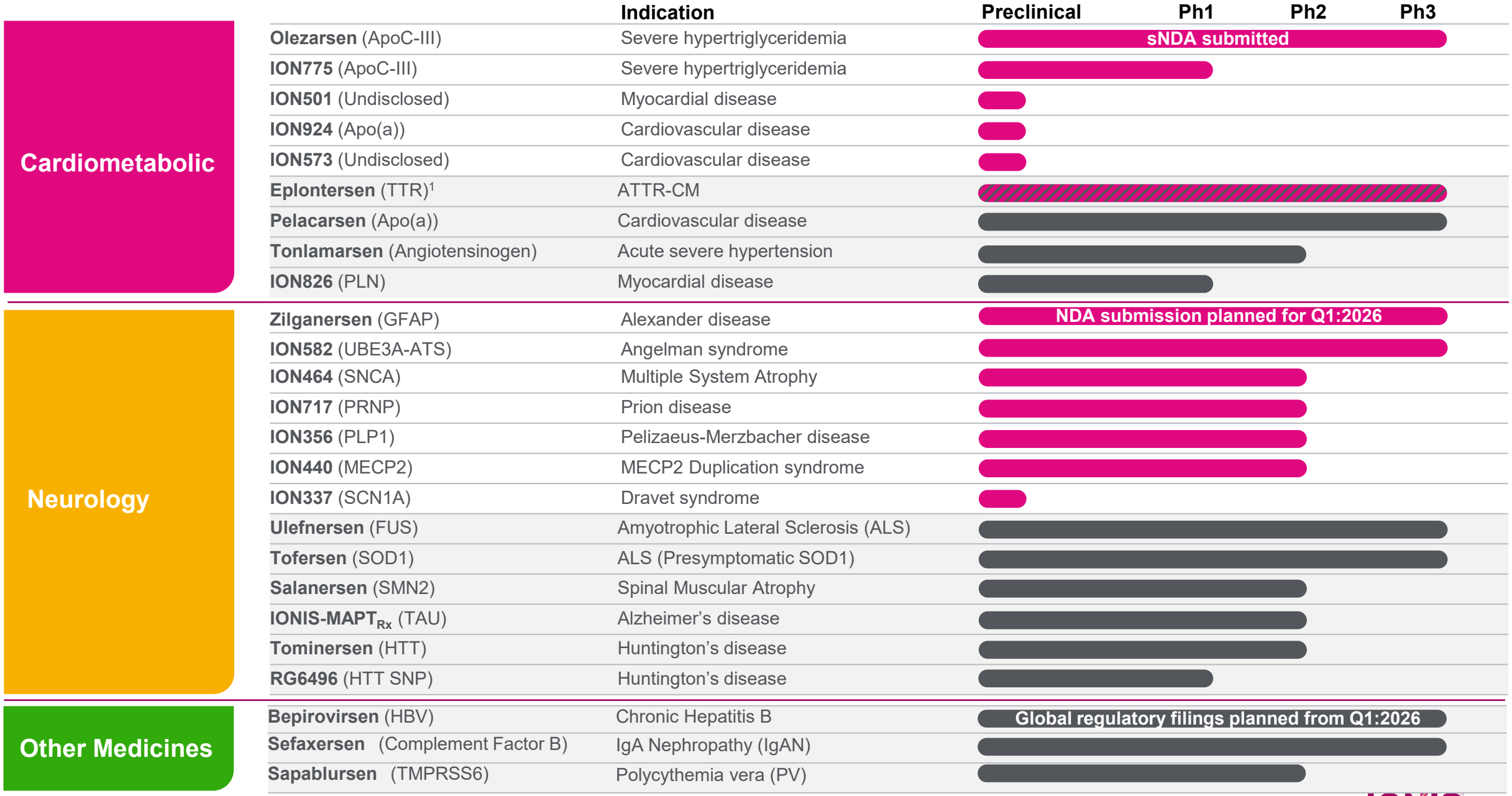
- **Donidalorsen** — EU approval (HAE)
- **Olezarsen** — U.S. approval (sHTG)
- **Zilganersen** — U.S. submission & approval (AxD)
- **Higher Dose Nusinersen[2]** — U.S. approval (SMA)
- **Bepirovirsen** — Submission & approval (CHB)
- **Pelacarsen** — U.S. submission (Lp(a)-CVD)
- **Eplontersen** — U.S. submission (ATTR-CM)

Product Launches

- **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. Refilled with the FDA

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