IONIS®

Innovation Day 2025:

# Accelerating Growth through Life-Changing Medicines

OCTOBER 7, 2025 | 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, 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.

# Ionis Leadership Here Today

**Brett Monia, Ph.D.**
Chief Executive Officer

**Kyle Jenne**
Chief Global Product Strategy Officer

**Beth Hougen**
Chief Financial Officer

**Wade Walke, Ph.D.**
Senior Vice President, Investor Relations

**Sam Tsimikas, M.D.**
Senior Vice President, Global Cardiovascular Development

**Kenneth Newman, M.D.**
Senior Vice President, Clinical Development

**Holly Kordasiewicz, Ph.D.**
Senior Vice President, Neurology

# Key Thought Leader in the Treatment of Patients with sHTG, FCS and Lipid Disorders


**Robert D. Fishberg, M.D. FACC FNLA**

Associates In Cardiovascular Disease
Diplomat of The American Board Of Clinical Lipidology
Co-chair AMG Lipid Workgroup
Clinical Assistant Professor Of Medicine,
Sidney Kimmel Medical College Of Thomas Jefferson University

# Agenda

| | |
|---|---|
| **Welcome** | Wade Walke, Ph.D. |
| **Accelerating Growth through Life-Changing Medicines** | Brett Monia, Ph.D. |
| **Building a Leading Cardiometabolic Disease Portfolio** | |
| Defining the Unmet Needs and Current Treatment Landscape for Severe Hypertriglyceridemia | Robert D. Fishberg, M.D. FACC FLNA |
| Leading in the Treatment of Triglyceride Driven Diseases<br>Advancing the Next Wave of Innovative Cardiometabolic Disease Medicines | Sam Tsimikas, M.D. |
| Delivering Innovative Cardiometabolic Medicines to People in Need | Kyle Jenne |
| Cardiometabolic Disease Q&A panel | Brett Monia, Ph.D. \| Robert D. Fishberg, M.D. FACC FLNA<br>Sam Tsimikas, M.D. \| Kyle Jenne |
| **BREAK** | |
| **DAWNZERA: Transforming the HAE Treatment Paradigm** | |
| Setting a New Bar for the Prophylactic Treatment of HAE | Kenneth Newman, M.D. |
| Unlocking DAWNZERA's Potential to be the Treatment of Choice for HAE | Kyle Jenne |
| **Advancing our Leading Neurology Portfolio** | |
| Leading the Way in the Treatment of Neurological Diseases<br>Delivering Transformative Neurology Medicines to People in Need | Holly Kordasiewicz, Ph.D.<br>Kyle Jenne |
| **Creating Substantial Value through Accelerating Growth** | Beth Hougen |
| **Final Q&A Panel** | Brett Monia, Ph.D. \| Beth Hougen \| Kyle Jenne \|<br>Kenneth Newman, M.D. \| Holly Kordasiewicz, Ph.D. |
| **Concluding Remarks** | Brett Monia, Ph.D. |

# Accelerating Growth through Life-Changing Medicines

**Brett Monia, Ph.D.**

Chief Executive Officer

# Well Positioned to Deliver Accelerating Growth

**High-value innovative pipeline** fueled by **groundbreaking technology** advances

**Pipeline delivering** positive data enabling **strong trajectory of ongoing** and **near-term launches**[1,2]

**Fully integrated,** commercial-stage biotechnology company

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.

# Transforming Human Health through RNA-Targeted Medicines





**Enabling Better Futures for People with Serious Diseases**

**Prioritize and advance wholly owned pipeline**

**Independently bring medicines to patients with commercial success**

**Expand and diversify drug discovery capabilities**

**Strong Financial Foundation Enables Investing for Growth**

# Strong Track Record of Industry-Leading Success[1-4]

Key achievements over the last two years

**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

**10**
**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 Transformational Medicines in Focused Therapeutic Areas

## Neurology

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

**Rare and prevalent patient populations** in focused disease areas

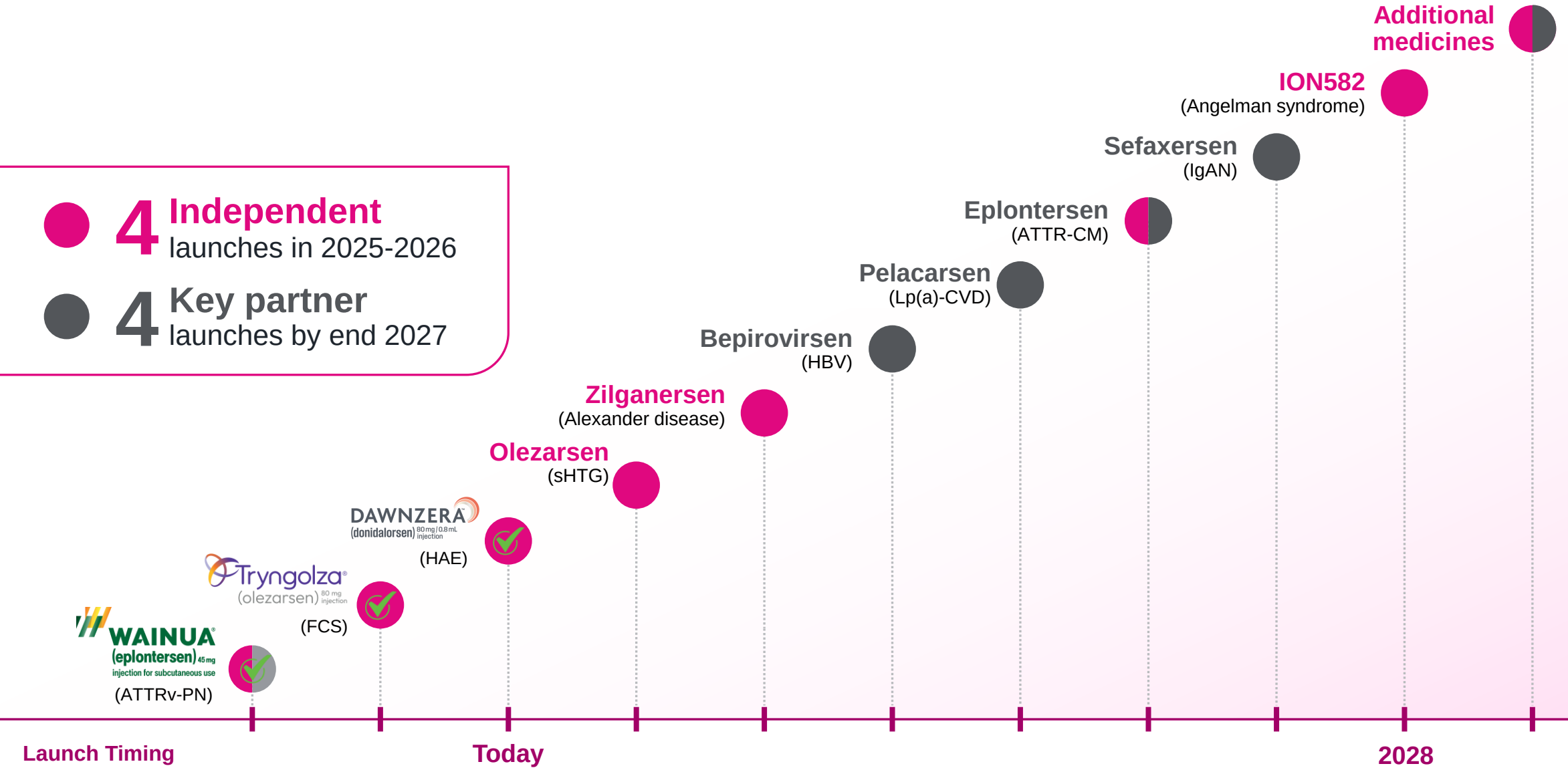
## Cardiometabolic

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

**Potential for Multiple Blockbusters**[1]

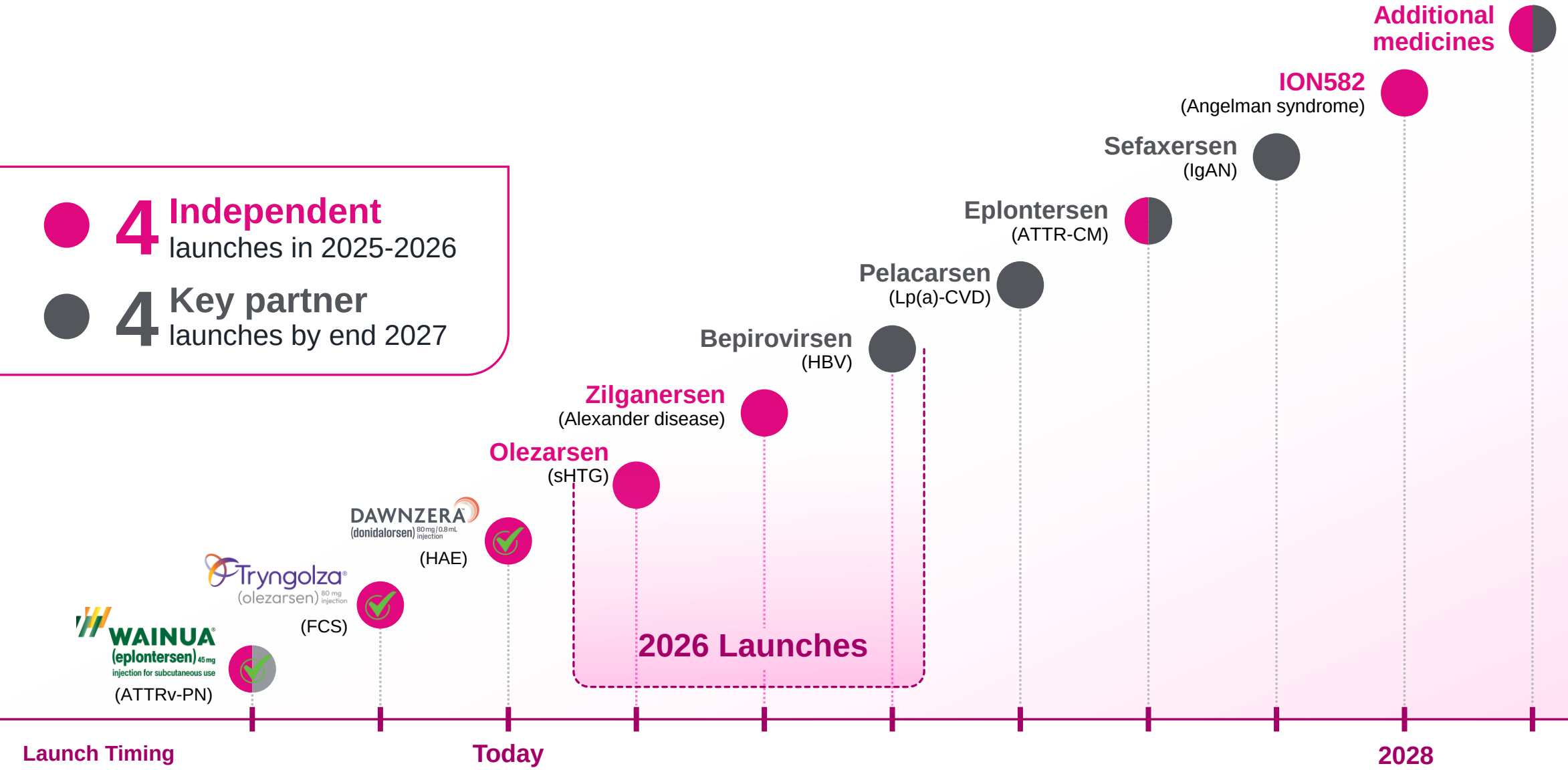
1. Based on current estimates, subject to change.

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



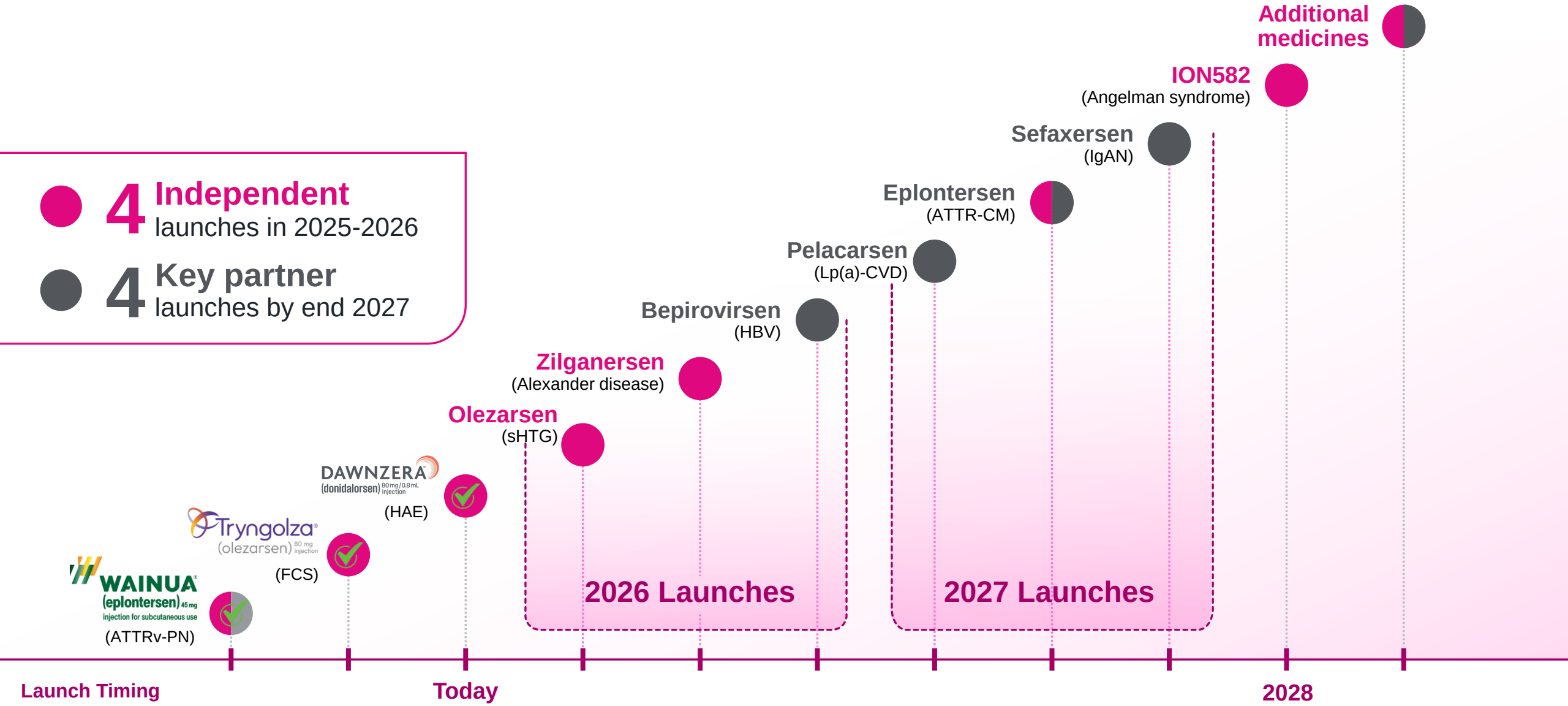

1. Assuming approval. 2. Based on current timing assumptions, subject to change.

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




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

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




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

# TRYNGOLZA®: Strong Start to Our First Independent Launch[1]

## First and Only FDA-Approved Medicine for Adults with FCS

### The Opportunity

Up to **~3,000 people** with FCS in the U.S.[2-6]

### Compelling Product Profile

- **Significant** and **sustained** triglyceride **reductions**
- **Substantial reduction** in **acute pancreatitis** events
- **Once-monthly self-administration**

### Early Launch Excellence

- **Strong** patient **uptake**
- **Favorable** physician **engagement**
- **Positive access** dynamics

**Now Approved in the EU[7]**


Indicated as an adjunct to diet to reduce triglycerides in adults with FCS

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information.2. Dron JS, et al. *BMC Med Genomics* 2020;13(1):23. 3. Hegele RA. *Nat Rev Genet* 2009;10(2):109-21. 4. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 5. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 6. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6. 7. Approved in the EU as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).

# Olezarsen: Poised to Launch in Large Patient Population (sHTG) Next Year[1]

## The Opportunity

**>3 million** people with sHTG in the U.S., including **>1 million people with high-risk sHTG[2]; Blockbuster potential[3]**

## Groundbreaking Clinical Results[4]

- **Highly statistically significant** and clinically meaningful mean **reductions in fasting triglycerides**
- **First** and **only** treatment to **significantly reduce acute pancreatitis** events in people with sHTG

## First Mover Advantage[2]

Positioned to change the **sHTG treatment paradigm** with **launch preparations well underway**

## Next Steps[3]

- Present **detailed data** at **Late-Breaker AHA Session** on November 8th
- **sNDA** submission on track by **YE:2025**[3]
- **Launch** in **2026**[3]


1. Assuming approval. 2. Sanchez et al. Lipids in Health and Disease 2021;20:72; Christian et al., *Am J Cardiol* 2011;107:891-897; Saadatagah S, Pasha AK, Alhalabi L, et al. Coronary Heart Disease Risk Associated with Primary Isolated Hypertriglyceridemia; a Population-Based Study. *J Am Heart Assoc.* 2021;10(11):e019343. 3. Based on current assumptions, subject to change. 4 Topline data from CORE and CORE2 Phase 3 studies.

# DAWNZERA™: Our Second Independent Launch Now Underway[1]

**First** and **Only RNA-Targeted Treatment** to **Prevent HAE Attacks**

## The Opportunity

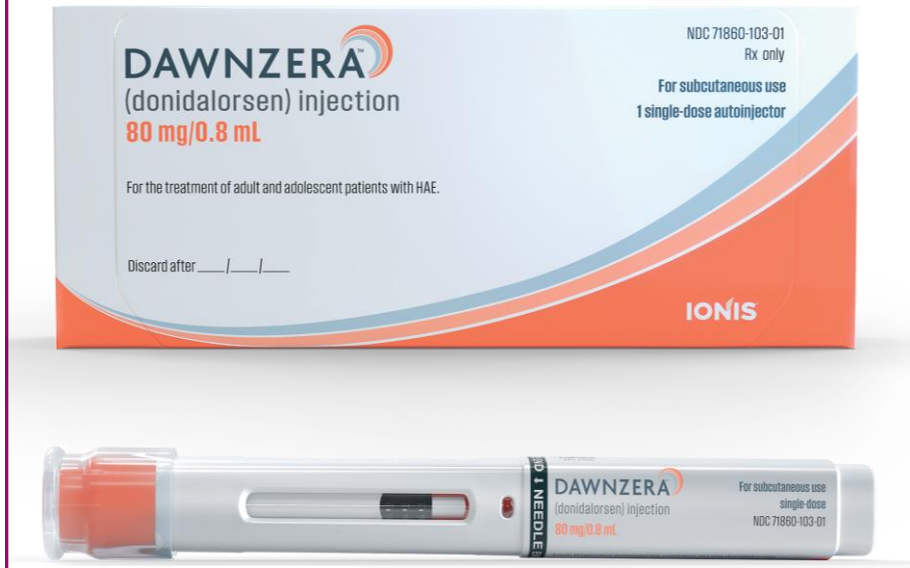
- **~7,000 people** with HAE in the U.S.[2]
- Substantial patient dissatisfaction

## Compelling Product Profile

- **Substantial** and **durable efficacy**, with favorable safety and tolerability
- Roadmap for switching; **strong patient preference**
- **Longest dosing interval option**[3]

## Encouraging Start to Launch

- FDA approved on August 21st
- **Exceptional initial launch execution**
- Focused on enabling **seamless switching**




Indicated for prophylaxis to prevent attacks of HAE in adult and pediatric patients ≥12 years old

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.

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

**The Opportunity**

**~1 in 1-3 million people** with **Alexander disease (AxD)**, a devastating, 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

**First Mover Advantage**

**Positioned** to **transform** the treatment landscape for **AxD**

**Next Steps**[3]

- Present **detailed data** at 2025 CNS Annual Meeting
- **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

## Addressable Population

**>100k people** in major geographies with **Angelman syndrome**, a severe, rare neurodevelopmental disorder[1]

## The Opportunity

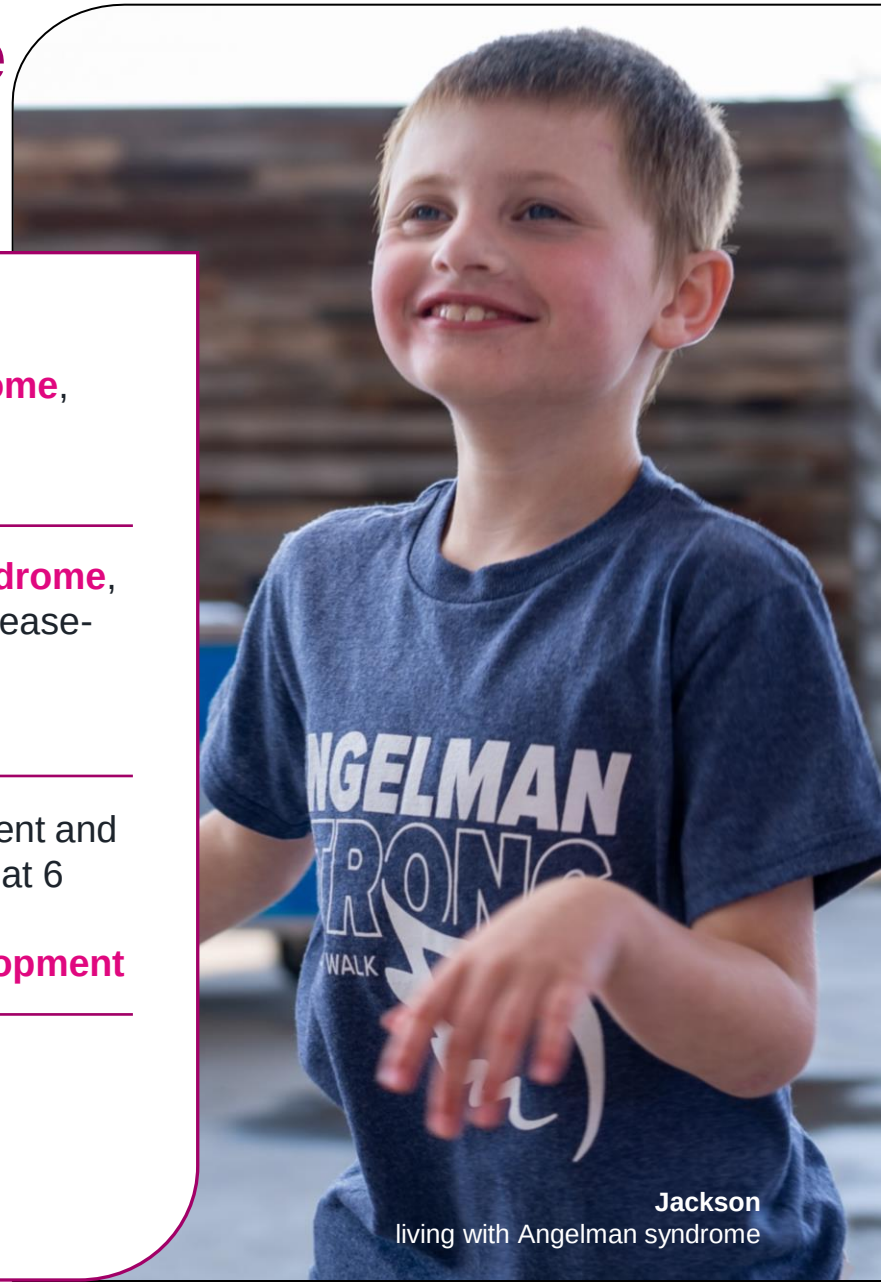
- **Promising investigational medicine** for **Angelman syndrome**, addressing a significant unmet need with no approved disease-modifying treatments
- U.S. Breakthrough therapy designation

## Key Clinical Highlights

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

## Next Steps[3]

**Robust pivotal Phase 3 REVEAL study underway**; full enrollment expected next year and **data in 2027**[3]




**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.

# Focused High-Value Wholly Owned Pipeline to Drive Continued Growth

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

👤 <50K 👤👤 50K – 500K 👤👤👤 >500K

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

# Partnered Medicines Amplify Our Opportunities

## Multiple Phase 3 Readouts Next Year[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]<br><br>**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<br><br>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.

# Transforming Human Health through RNA-Targeted Medicines





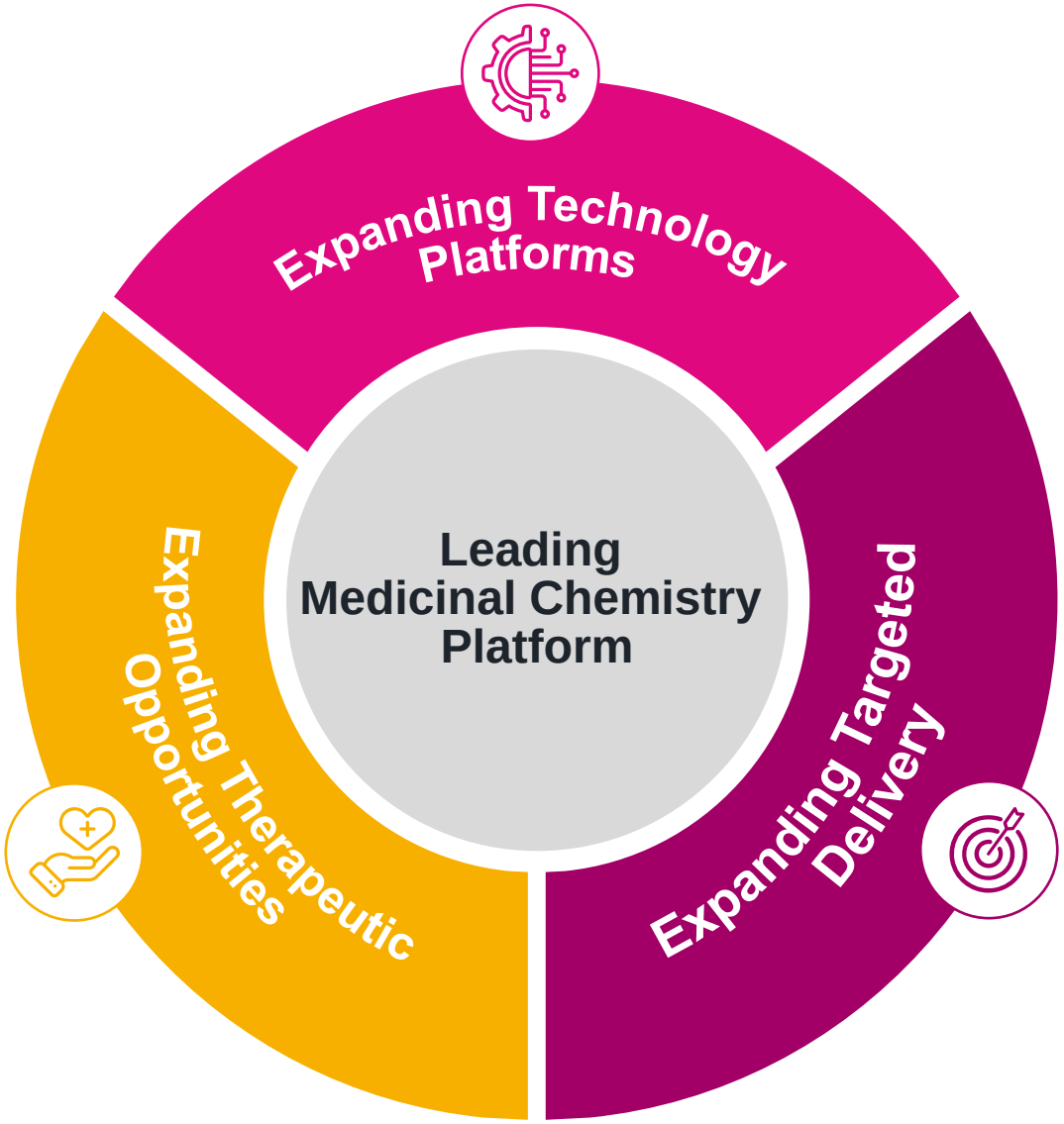
**Enabling Better Futures for People with Serious Diseases**

**Prioritize and advance wholly owned pipeline for commercial success**

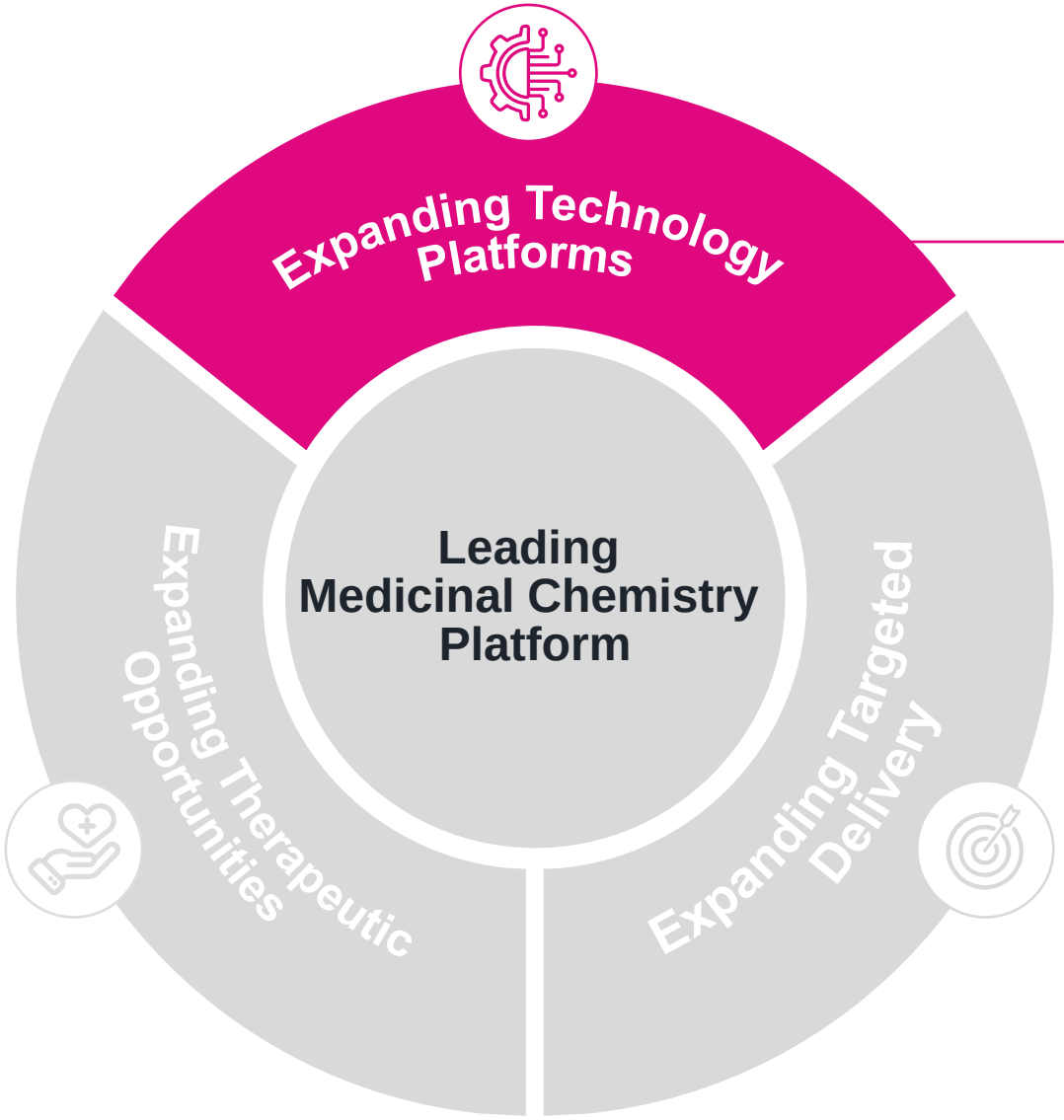
**Independently bring medicines to patients**

**Expand and diversify drug discovery capabilities**

**Strong Financial Foundation Enables Investing for Growth**




# Accelerating Innovation to Strengthen Leadership in RNA-Targeted Medicines




**Broad Range of Technologies** | **Optimizing Potency and Durability** | **Systemic and Local Applications**

## Ionis-Engineered siRNAs

Positive ION775 Phase 1 results support semi-annual dosing

## Ionis-Engineered NMA

Salanersen (SMA) with once-yearly dosing advancing to registrational studies by early 2026[1]

ION337 (Dravet syndrome) first-in-patient study start in H1:2026[1]

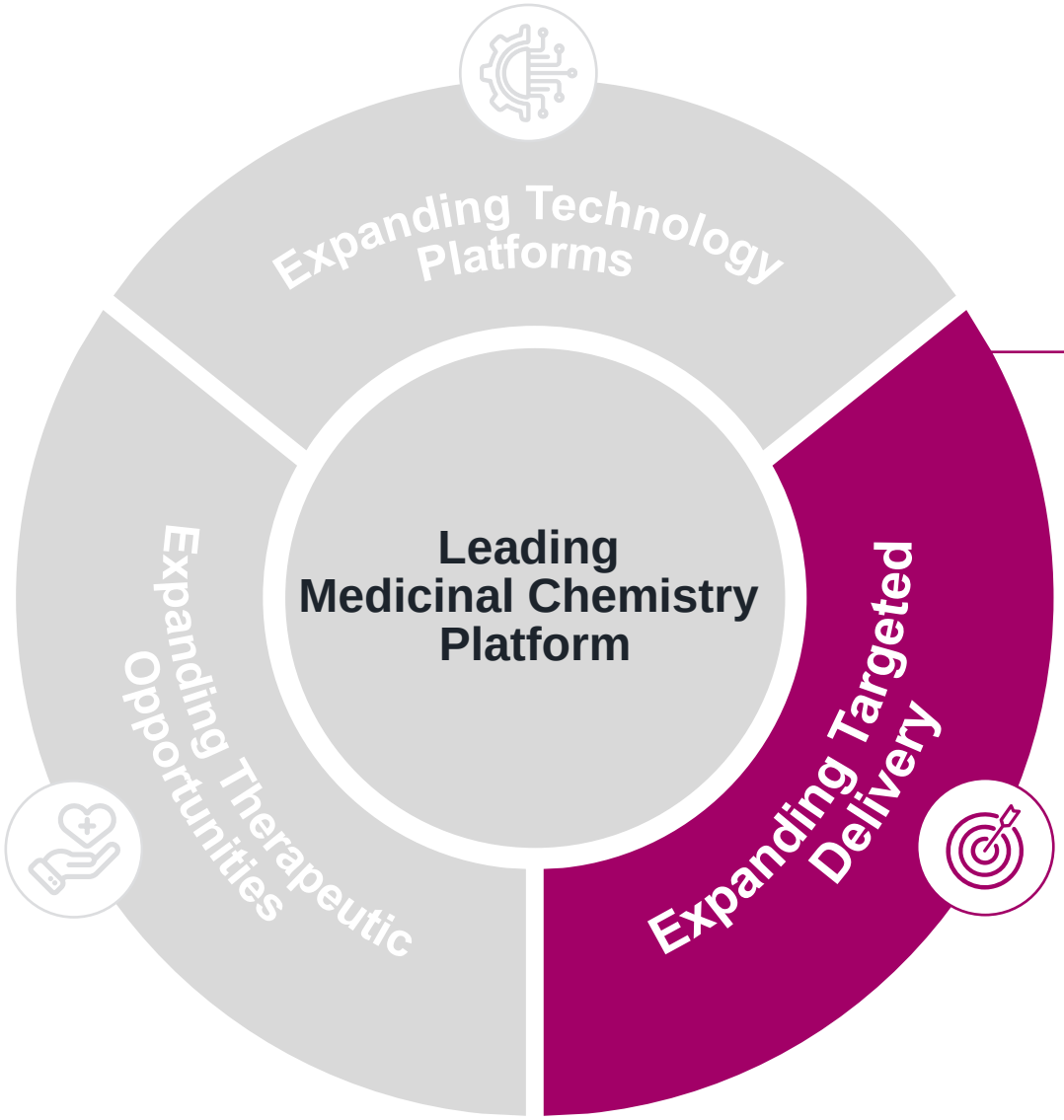
## MsPA Backbone

Multiple programs advancing with the potential to extend duration and improve therapeutic index

## DNA Editing Platform

Highly competitive NHP data; development candidate before YE:2025[1]

1. Based on current assumptions, subject to change.




**Cardiac Muscle** | **Skeletal Muscle** | **Blood Brain Barrier**

## Cardiac and Skeletal Muscle Technology Advancing

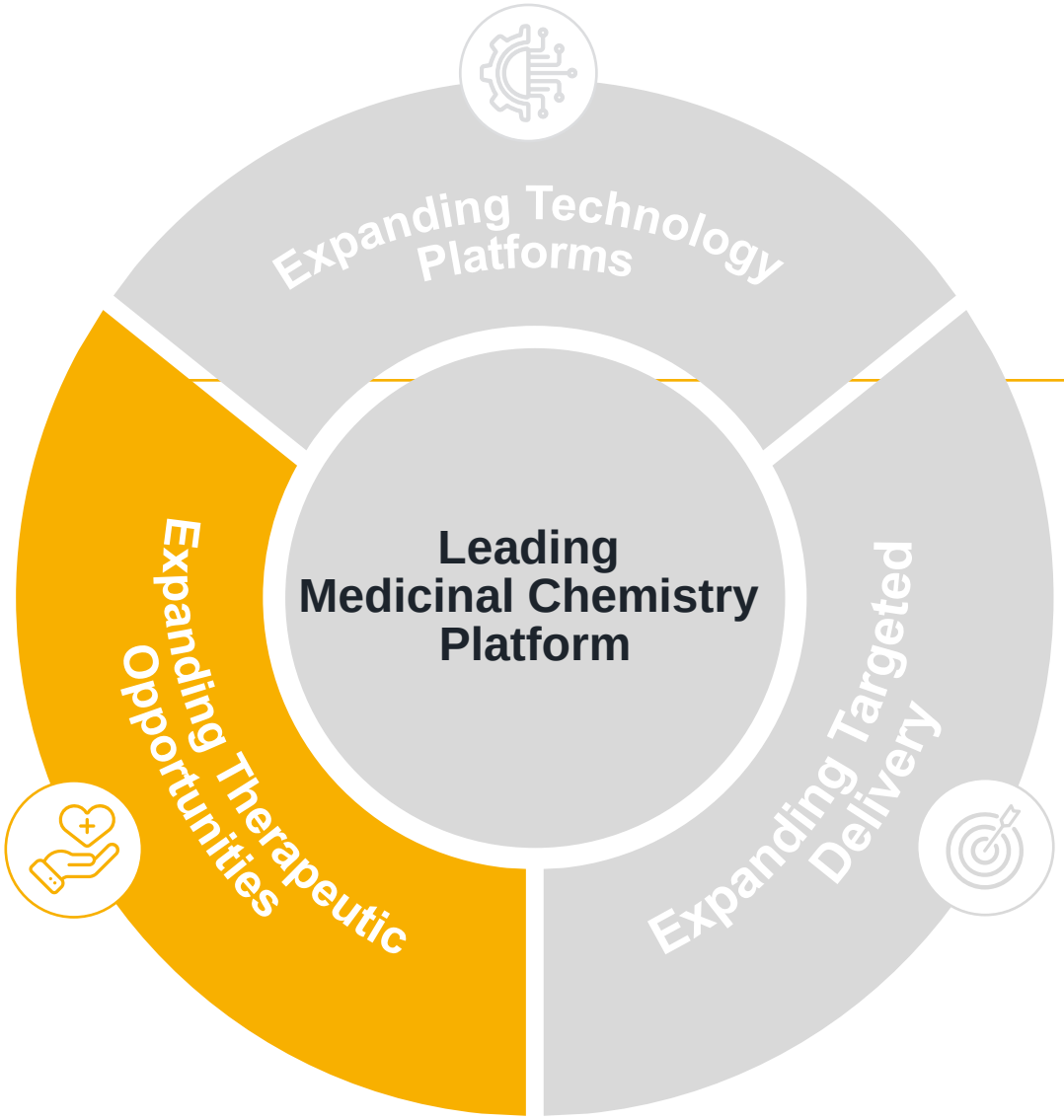
1st medicine targeting cardiac muscle advancing into clinical development before YE:2025[1]

1st candidate targeting skeletal muscle advancing into IND enabling TOX before YE:2025[1]

## Blood Brain Barrier (CNS) Technology Advancing

Best-in-class NHP data; on track to declare 1st candidate before YE:2025[1]

1. Based on current assumptions, subject to change.




**Cardiometabolic | Neurology | Pulmonary**

## Strengthening Cardiometabolic Disease Portfolio

Two candidates targeting cardiac muscle;
1st clinical initiation by YE:2025[1]

## Strengthening Neurology Portfolio

1st neuromuscular candidate advancing into IND enabling TOX before YE:2025[1]

Annual intrathecal dosing for CNS

Blood brain barrier candidates advancing toward clinic

## Pulmonary Delivery

1st candidate utilizing MsPA backbone advancing to IND enabling TOX in 2026[1]

1. Based on current assumptions, subject to change.

# Creating Substantial Value through Accelerating Growth[1]

## Substantial, Sustained Value Creation

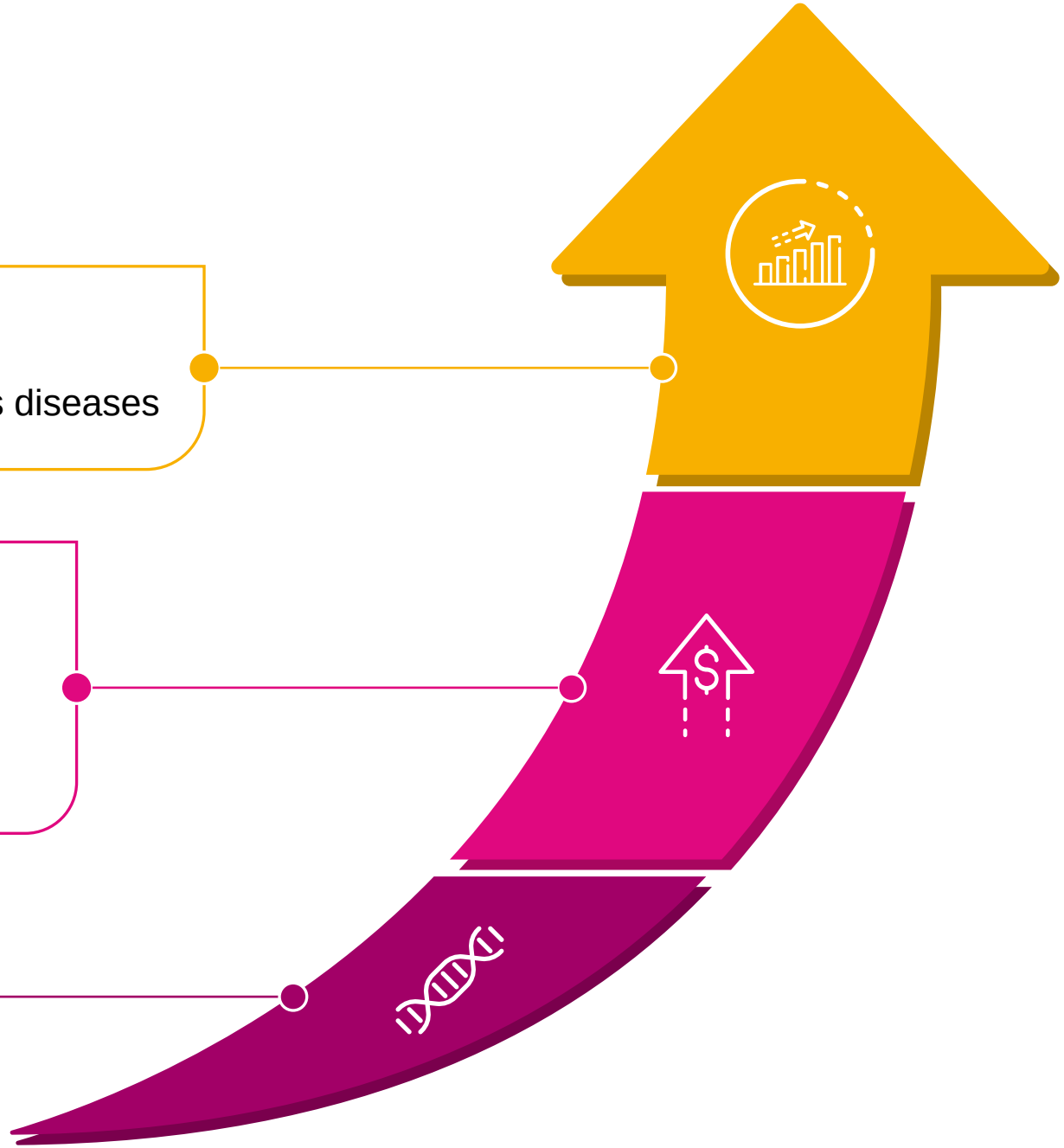
Steady cadence of transformational medicines for serious diseases

## Accelerating Growth

- Substantial and differentiated technology advancements
- High-value focused pipeline advancing
- Ongoing and upcoming launches

## Strong Foundation

- Commitment to innovation
- Proven drug discovery and development engine



1. Based on current assumptions, subject to change.

# Building a Leading Cardiometabolic Disease Portfolio

*Living with FCS* | **RICK**

# Building a Leading Cardiometabolic Disease Portfolio

**Sam Tsimikas, M.D.**
Senior Vice President, Global Cardiovascular Development

# Innovative Cardiometabolic Disease Portfolio Positioned to Deliver Accelerating Value[1,2]

**Targeting major conditions** that cause cardiometabolic diseases, the **leading causes of death globally**

Well-positioned to deliver a **steady cadence** of new **wholly owned** and **partnered medicines to patients in need**

**Leading** in the treatment of **triglyceride driven diseases**

Focused on continuous **innovation to further strengthen our rich cardiometabolic disease pipeline**

1. Timing and expectations based on current assumptions and subject to change. 2. Assuming approval.

Tryngolza® (olezarsen) 80 mg injection

The First and Only FDA Approved Treatment for FCS[1]

Leading in the Treatment of Triglyceride Driven Diseases[2,3]

# TRYNGOLZA:
## Ionis' First Independent Commercial Medicine

**Approved for the treatment of people with FCS, the most severe form of sHTG**

**Potential to expand into the broader sHTG population based on positive data from the Phase 3 CORE and CORE2 studies[2,3]**

IONIS

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information. 2 Timing and expectations based on current assumptions and subject to change. 3. Assuming approval.

# Advancing First and/or Best-in-Class Cardiometabolic Pipeline[1,2]

**2** Wholly Owned Medicines in Clinical Development

**3** Partnered Medicines in Clinical Development

**5** Medicines in Clinical Development

## Wholly Owned Medicines

| | Indication | Preclinical | Ph1 | Ph2 | Ph3 |
|---|---|---|---|---|---|
| **Olezarsen** (ApoC-III) | Severe hypertriglyceridemia | | | | |
| **ION775** (ApoC-III) | Severe hypertriglyceridemia | | | | |
| **ION501** (Undisclosed) | Myocardial disease | | | | |

## Partnered Medicines

| | | | | | |
|---|---|---|---|---|---|
| **Eplontersen** (TTR)[3] | ATTR-CM | | | | |
| **Pelacarsen** (Apo(a)) | Cardiovascular disease | | | | |
| **Tonlamarsen** (Angiotensinogen) | Acute severe hypertension | | | | |
| **ION826** (Undisclosed) | Myocardial disease | | | | |

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.

# Defining the Unmet Needs and Current Treatment Landscape for Managing Severe Hypertriglyceridemia

**Robert D. Fishberg, M.D. FACC FNLA**

Associates in Cardiovascular Disease
Diplomat of The American Board Of Clinical Lipidology
Co-chair AMG Lipid Workgroup
Clinical Assistant Professor Of Medicine,
Sidney Kimmel Medical College Of Thomas Jefferson University

# Disclosures

- Speaker Bureau – Amgen
- Speaking and Advisory Board Honoraria – Regeneron, New Amsterdam, Ionis
- Clinical Research – Novartis, New Amsterdam, Amgen, Family Heart Foundation, Lilly, Arrowhead, Regeneron

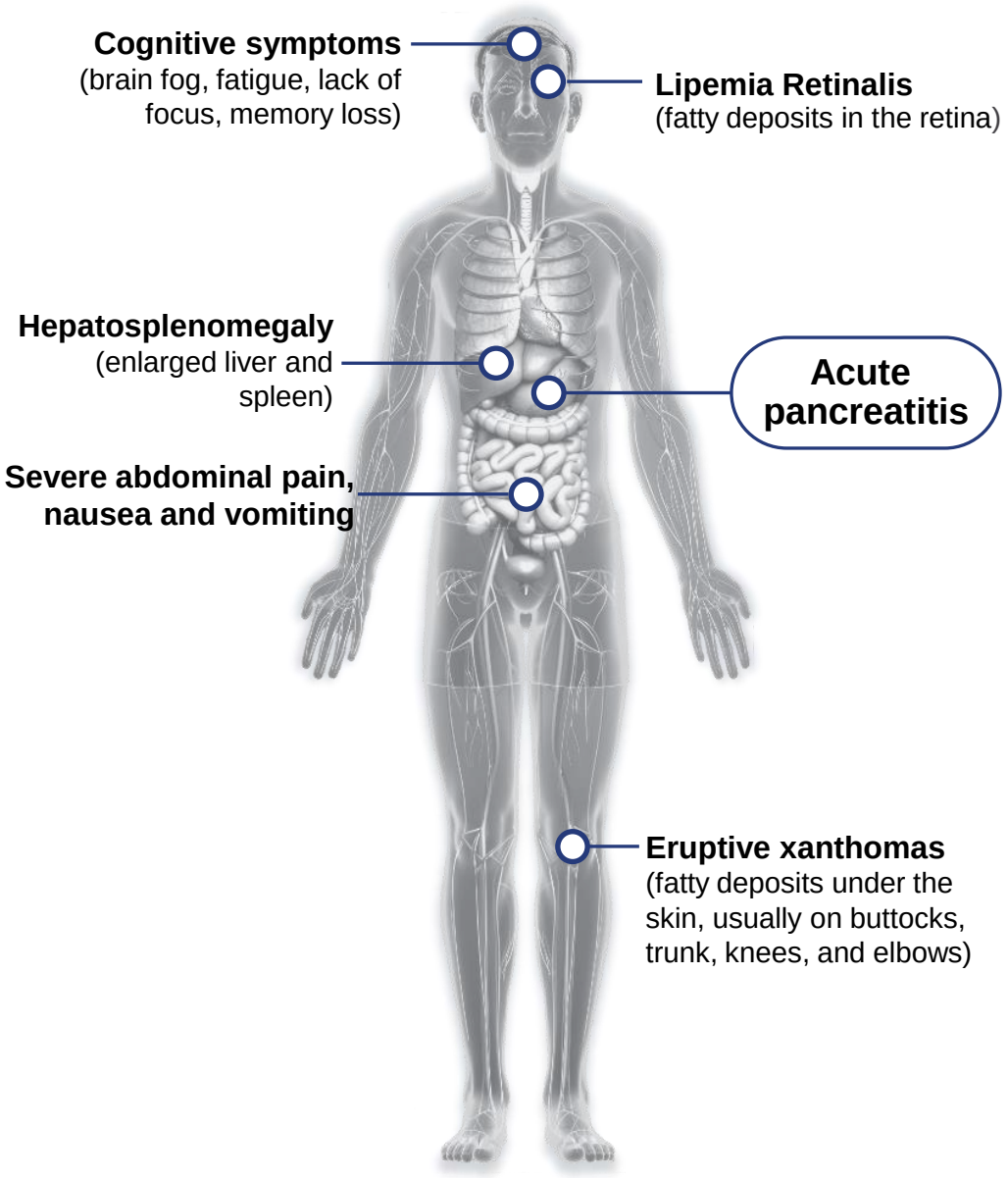
# FCS: Significant Patient Burden and Unmet Need

**Most severe form of sHTG** caused by loss of LPL activity[1,2]

Characterized by **triglyceride levels 10-100x greater than normal, extreme risk of acute, potentially fatal pancreatitis and debilitating chronic symptoms**[1-4]

**High disease burden,** often leading to long-term complications, increased psychological stress and reduced quality of life[5]

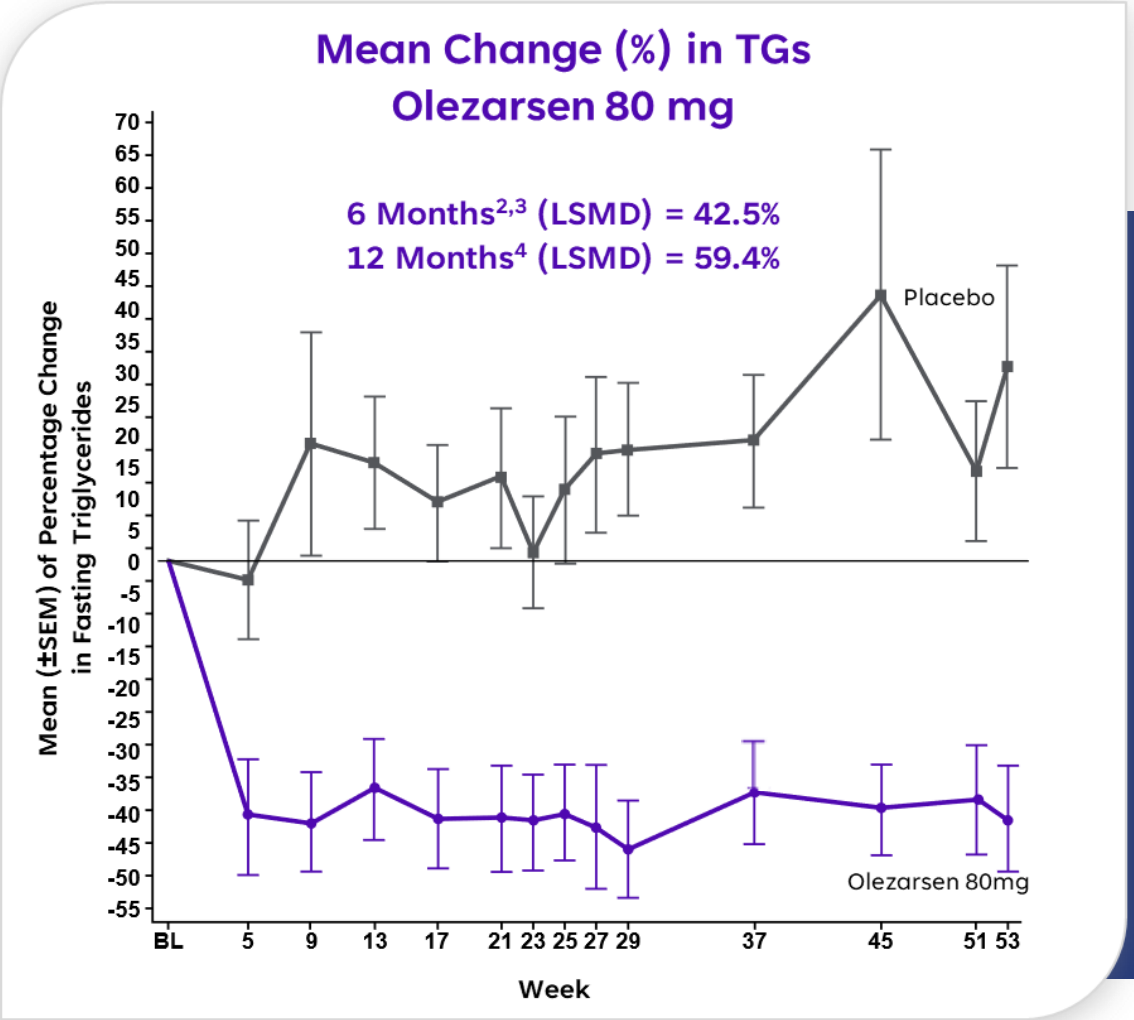
Estimated 1 – 13 people per million with **FCS in the U.S.**[6-10]

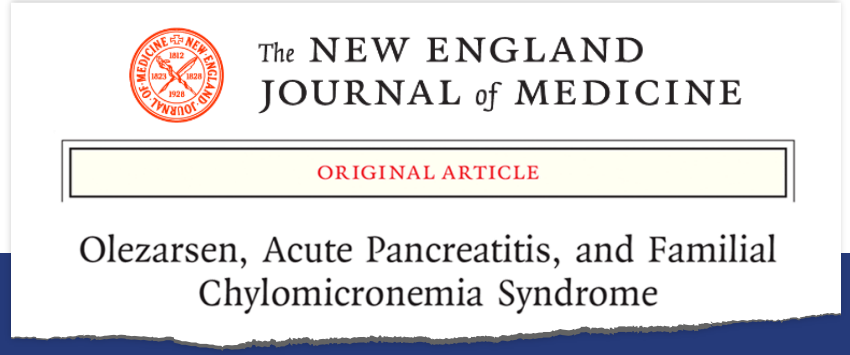



**Clinical Manifestations of FCS**[3,6]

1. Moulin P, et al. *Atherosclerosis* 2018;275:265-72. 2. Brown EE, et al. *J Clin Lipidol* 2020;14(4):398-413. 3. Davidson M, et al. *J Clin Lipidol.* 2018;12(4):898–907. 4. Nawaz H, et al. *Am J Gastroenterol* 2015; 110;1497-1503. 5. Gaudet D, et al. *Lipids Health Dis*. 2020;19(1):120. 6. Brunzell JD, Bierman EL. *Med Clin North Am*. 1982;66(2):455–68. 6. Dron JS, et al. *BMC Med Genomics* 2020;13(1):23. 7. Hegele RA. *Nat Rev Genet* 2009;10(2):109-21. 8. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 9. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 10. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6.

# Pivotal Balance Study Data Supporting TRYNGOLZA in People with FCS[1]

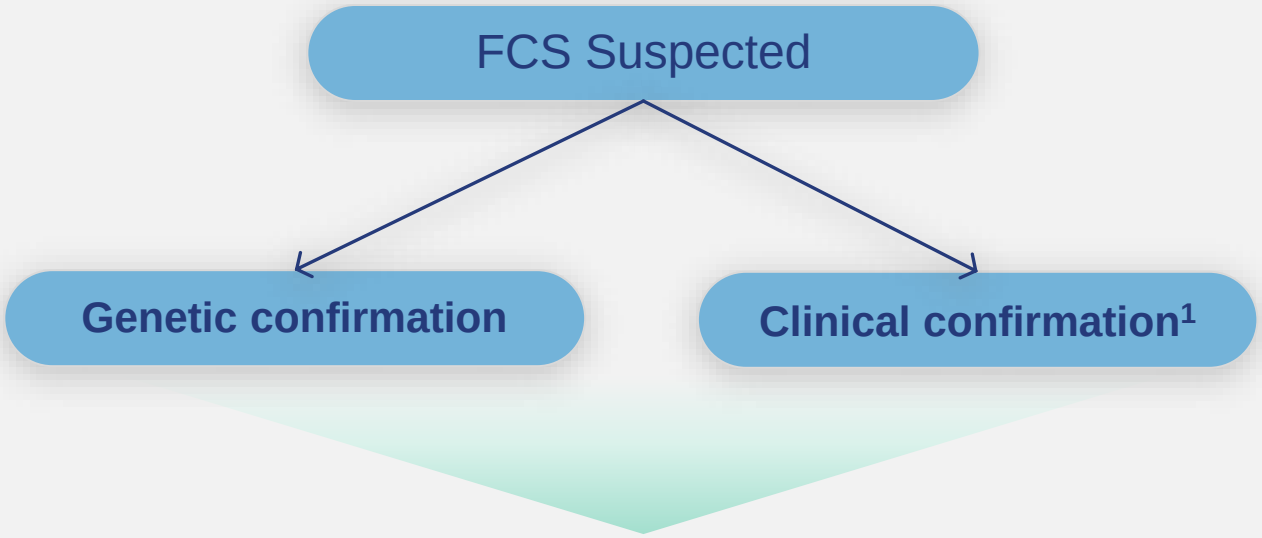


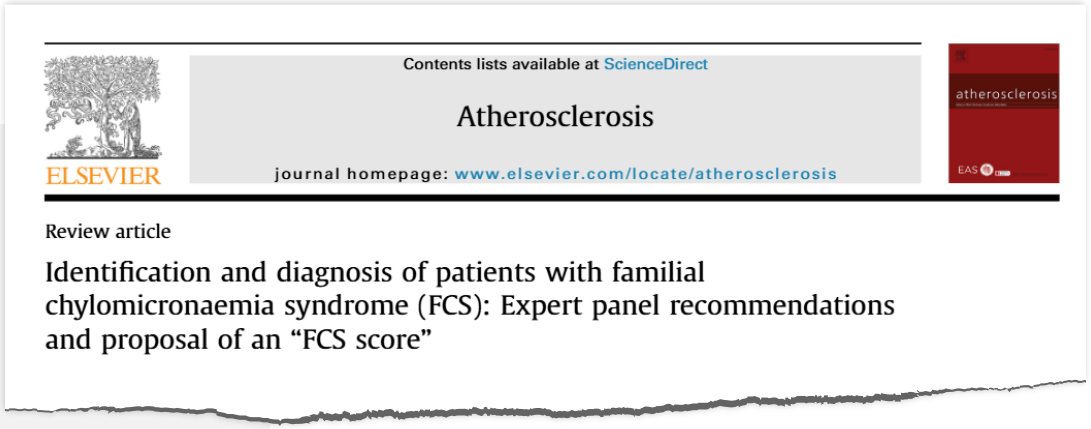




- Significant triglyceride reductions at 6 months compared to placebo in FCS patients
- Triglyceride reductions further improved through 12 months of treatment compared to placebo
- Clinically meaningful reductions in acute pancreatitis and substantially longer time to first event compared to placebo
- 84% reduction in all cause hospitalizations and substantial reduction in days spent in hospital compared to placebo[5]
- Favorable safety and tolerability profile

LSMD, Least squares mean difference. 1. Stroes E, et al. *N Engl J Med.* 2024. 2. Average of weeks 23, 25, and 27. 3. Olezarsen 80 mg at 6 months (p<0.001). 4. Average of weeks 51 and 53. 5. Exploratory endpoint.

# Adults Diagnosed with FCS are Eligible for TRYNGOLZA[1]





Contents lists available at ScienceDirect
Atherosclerosis
journal homepage: www.elsevier.com/locate/atherosclerosis
ELSEVIER
Review article

Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an "FCS score"

1. Fasting TGs >10 mmol/L for 3 consecutive blood analyses (+5)[a]
   - Fasting TGs >20 mmol/L at least once (+1)
2. Previous TGs <2 mmol/L (-5)
3. No secondary factor[b] (except pregnancy[c] and ethinylestradiol) (+2)
4. History of pancreatitis (+1)
5. Unexplained recurrent abdominal pain (+1)
6. No history of familial combined hyperlipidaemia (+1)
7. No response (TG decrease <20%) to hypolipidaemic treatment (+1)
8. Onset of symptoms at age:
   - <40 years (+1)
   - <20 years (+2)
   - <10 years (+3)

FCS score:
≥10: FCS very likely
≤9: FCS unlikely
≤8: FCS very unlikely

1. Moulin P, et al. *Atherosclerosis* 2018;275:265-72.

# TRYNGOLZA® (olezarsen) Case Studies

Atlantic Health System/Atlantic Medical Group

- Large suburban New Jersey-based system
- 300 locations, 6 hospitals
- 1,600 physicians, including 400 advanced practice specialists
- >1M covered lives

## Case Study #1 – Genetically Confirmed FCS

- **TG >1,200 mg/dL, recurrent pancreatitis (20 events), pancreatogenic diabetes**
- Minimal response to gemfibrozil (fibrate), Vascepa (omega-3)
- **Genetics: homozygous LMF1, heterozygous APOA5**
- TRYNGOLZA response: **TG 381 mg/dL**, **no new pancreatitis**

## Case Study #2 – Clinically Confirmed FCS

- **TG >1,400 mg/dL, recurrent pancreatitis, pancreatogenic diabetes**
- Minimal response to fibrate, Vascepa (omega-3)
- **Moulin Score: 13**[1]
- TRYNGOLZA response: **TG 232 mg/dL, with no new pancreatitis**

***"I'm just astonished."***

– patient on TRYNGOLZA response

1. Moulin P, et al. *Atherosclerosis* 2018;275:265-72.

# Severe Hypertriglyceridemia (sHTG) Disease Overview[1-6]

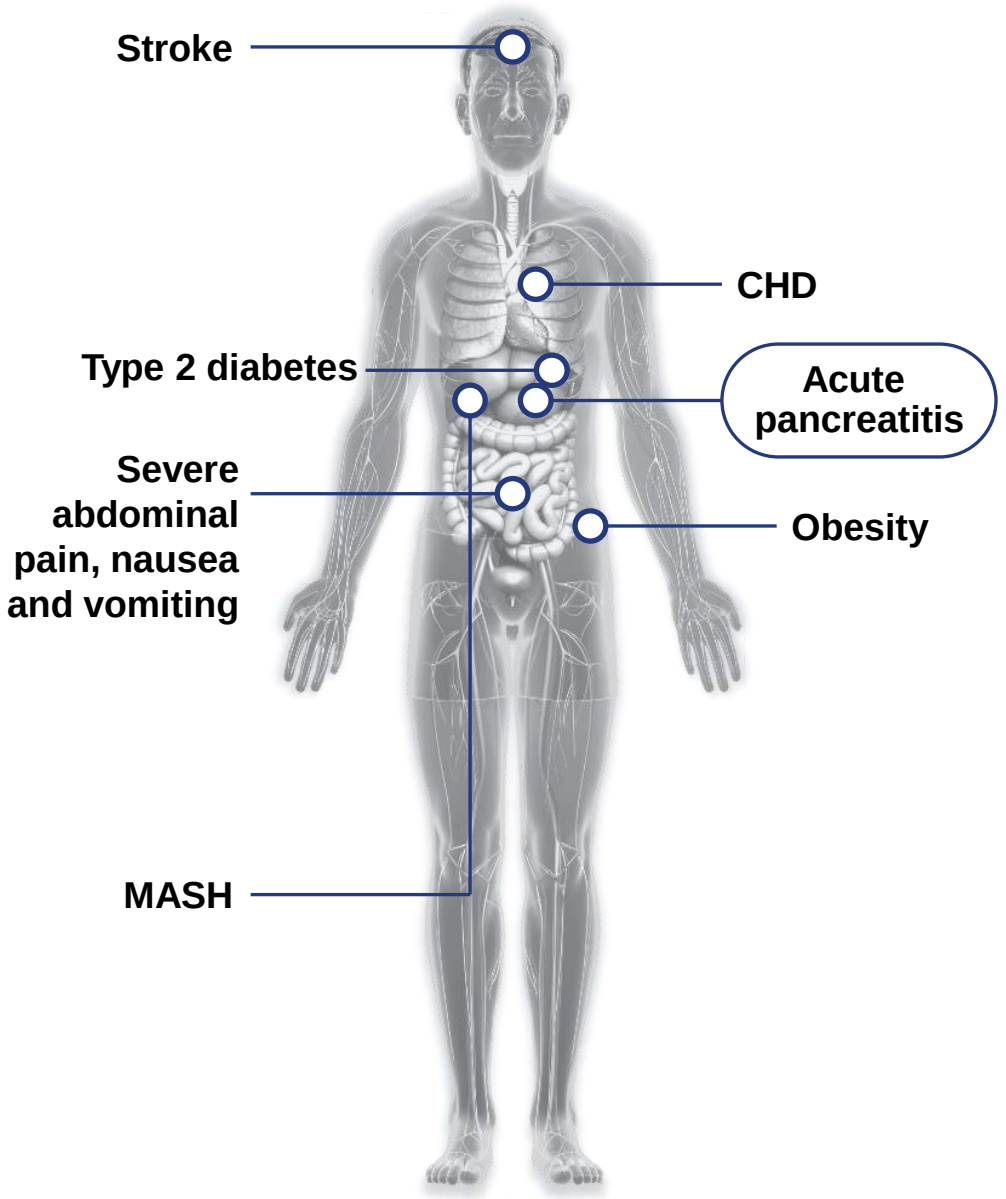
Defined by **fasting triglyceride levels ≥500 mg/dL**[1]

Characterized by **increased risk of acute pancreatitis**, atherosclerotic cardiovascular disease[2]

**Multifactorial**, driven by combination of triglyceride gene variants, lifestyle, obesity, and high-risk comorbidities, including type 2 diabetes, metabolic syndrome, and MASH[2,3]

**Limited benefit from currently available treatments**, including fibrates and omega-3s[4-7]

**Prevalent population, estimated at greater than 3 million people in the U.S.**[8-10]




**Clinical manifestations and comorbidities associated with sHTG**

1. Hegele, et al, *Lancet Diabetes Endocrinol.* 2014 Aug 2(8):655-66 2. Nawaz H, et al. *Am J Gastroenterol*. 2015;110(10):1497-1503. 3. Heterozygous variants in LPL, APOA5, GCKR, APOB, LMF1, GPIHBP1, CREBH1, APOC2, APOE, small-effect variants and/or secondary effects. 4. Patel SB, et al. *Endocr Pract.* 2025;31(2):236-262. 5. Santos-Baez, LS et al. *Front Endocrinol (Lausanne).* 2020;11:616. 6. Skulas-Ray AC, et al. *Circulation*. 2019;140(12):e673-e691. 7. Aldhaleei WA, et al. *Pharmaceuticals* (Basel). 2024;17(2):199. 8. Sanchez et al. *Lipids in Health and Disease* 2021;20:72. 9. Christian et al., *Am J Cardiol* 2011;107:891-897. 10. Saadatagah et al. *J Am Heart Assoc*. 2021;10(11):e019343.
Congenital heart disease, *CHD;* Metabolic dysfunction-associated steatohepatitis, *MASH.*

# Established sHTG Treatment Guidelines[1-6]

Guidelines for clinical practice for the **management of hypertriglyceridemia** consistently **recommend aggressive triglyceride lowering treatment** for all patients with sHTG

ENDOCRINE SOCIETY

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association

ESC European Society of Cardiology

EAS European Atherosclerosis Society

NATIONAL LIPID ASSOCIATION

1. Virani SS, et al. *J Am Coll cardiologist*. 2021;78:960-993. 2. Skulas-Ray AC, et al. *Circulation*. 2019;140(12):e673-e691. 3. Newman CB, et al. *J Clin Endocrinol Metab*. 2020;105(12):dgaa674. 4. Kirkpatrick CF, et al. *J Clin Lipidol*. 2023;17(4):428-451. 5. Ginsberg HN, et al. *Eur Heart J*. 2021;42:4791-4806. 6. Berglund L, et al. *J Clin Endocrinol Metab*. 2012;97:2969-2989.

# Lack of Available Therapies to Reduce Acute Pancreatitis Risk in sHTG[1-4]

## Currently Used Lipid Lowering Therapies

| | |
|---|---|
| **Fibrates** | Approved to reduce triglycerides ≥500 mg/dL. Generally, first-line treatment with modest **(~20%-30%)** triglyceride reductions in sHTG. **No benefit demonstrated in acute pancreatitis.** |
| **Omega-3 fatty acids** | Approved to reduce triglycerides ≥500 mg/dL. Generally, used in combination with other agents with modest **(~20%)** triglyceride reductions in sHTG. **No benefit demonstrated in acute pancreatitis.** |
| **Statins** | **Not indicated to reduce triglycerides in sHTG.** Modest **(~20%)** triglyceride reductions seen in people with hypercholesterolemia and sHTG. **No benefit demonstrated in acute pancreatitis** |
| **Niacin** | Approved to reduce triglycerides ≥500 mg/dL but not recommended for use due to significant adverse events. Modest **(~20%)** triglyceride reductions in sHTG. **No benefit demonstrated in acute pancreatitis.** |
| **GLP-1** | **Not indicated for triglyceride reduction in sHTG.** Minimal triglyceride reductions seen in people with Type 2 diabetes and sHTG. **Guidelines suggest avoiding use in people with a history of acute pancreatitis.**[5] |

1. Patel SB, et al. *Endocr Pract.* 2025;31(2):236-262. 2. Santos-Baez, LS et al. *Front Endocrinol (Lausanne).* 2020;11:616.3. Skulas-Ray AC, et al. *Circulation*. 2019;140(12):e673-e691. 4. Aldhaleei WA, et al. *Pharmaceuticals* (Basel). 2024;17(2):199. 5. Aldhaleei WA, et al. *Pharmaceuticals (Basel)*. 2024;17(2):199.

# Leading in the Treatment of Triglyceride Driven Diseases

**Sam Tsimikas, M.D.**
Senior Vice President, Global Cardiovascular Development

# Olezarsen: Positioned to Change the sHTG Treatment Paradigm[1]


## Groundbreaking Clinical Results:

Highly statistically significant and clinically meaningful mean reductions in fasting triglycerides

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

Favorable safety and tolerability

**Present detailed data at AHA in November[1]**

**File sNDA by YE:2025[1]**

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

# ApoC-III is a Key Regulator of Plasma Triglycerides[1,2]

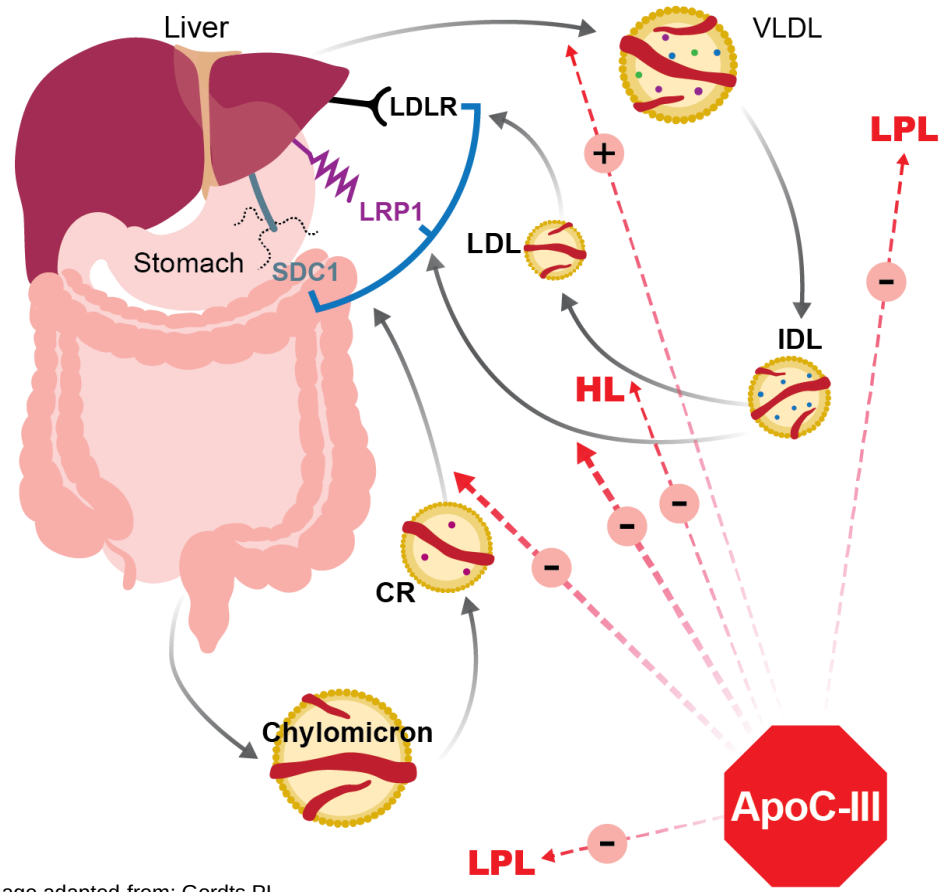



Image adapted from: Gordts PL, et al. *J Clin Invest.* 2016;126:2855

## Apolipoprotein C-III (apoC-III)

Key regulator of triglyceride clearance

High apoC-III concentrations reduce triglyceride metabolism by limiting lipoprotein lipase (LPL) activity and triglyceride-rich lipoprotein (TRL) clearance

## Olezarsen: Designed to reduce the production of ApoC-III

Olezarsen is designed to reduce triglyceride levels by reducing the production of apoC-III

By reducing apoC-III, olezarsen increases LPL activity and TRL clearance, resulting in significant reductions in triglyceride levels in people with sHTG

Olezarsen demonstrated clinically meaningful reductions in triglycerides and acute pancreatitis events in the Phase 3 Balance study in people with FCS and in the Phase 3 CORE and CORE2 studies in people with sHTG



1. Gordts PL et al. *J Clin Invest* 2016;126:2855–66. 2. Kohan AB. *Curr Opin Endocrinol Diabetes Obes*. 2015;22:119-125.

# Olezarsen Phase 3 Program Designed to Support Potential in sHTG[1]

## Severe Hypertriglyceridemia (sHTG)

CORE a hypertriglyceridemia study

CORE2 a hypertriglyceridemia study

Pivotal studies in people w/ sHTG (fasting TG ≥500 mg/dL)

Registrational studies

1,063 participants

**Largest Pivotal Program Ever Conducted in sHTG**

## Moderate Hypertriglyceridemia (HTG)

Essence TIMI 73b

Phase 3 study in people with moderate HTG and elevated CVD risk (fasting TG ≥150 mg/dL)[2]

Results support safety database

1,478 participants

IONIS

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. Conducted in people with TG ≥150-500 mg/dL with or at risk for ASCVD and included exploratory group of people with baseline TG ≥500 mg/dL.

# Groundbreaking Topline Results from the CORE and CORE2 Studies of Olezarsen

**Sam Tsimikas, M.D.**
Senior Vice President, Global Cardiovascular Development

# Olezarsen CORE and CORE2 Phase 3 Studies[1]

## DESIGN

**Two randomized, double-blind, placebo-controlled studies** of olezarsen Q4W in **1,063 participants** with fasting triglycerides ≥500 mg/dL

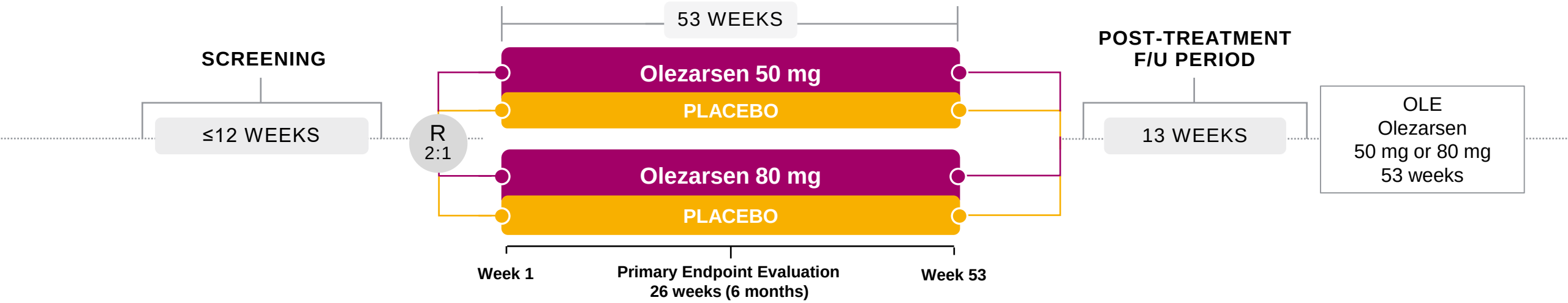
- Stratified by baseline triglyceride levels >880 mg/dL and pancreatitis history[2]
- 99% of participants were on standard lipid-lowering therapy

## ENDPOINTS[1]

**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 endpoints:** fasting triglycerides at 12 months, apoC-III and lipid measures at 6 and 12 months




1. CORE: clinicaltrials.gov/NCT05079919; CORE2: clinicaltrials.gov/NCT05552326. 2. Within 10 years prior to screening.

# Baseline Characteristics

| Published in *American Heart Journal*[1] | CORE (n=617) | CORE2 (n=446) |
|---|---|---|
| Age, Median years | 54 | 55 |
| Diabetes Mellitus | 59% | 68% |
| AP History, prior 10 years | 22% | 13% |
| Fasting Triglycerides, Median (Mean[2]) mg/dL | 836 (1,182) | 749 (1,023) |
| • Fasting Triglycerides ≥880 mg/dL | 47% | 37% |
| Total Cholesterol, Median mg/dL | 231 | 217 |
| • LDL Cholesterol | 59 | 62 |
| • HDL Cholesterol | 25 | 27 |
| Lipid Lowering Therapies | 99% | 100% |
| • Statin | 73% | 78% |
| • Fibrate | 67% | 61% |
| • Omega-3 fatty acid | 34% | 31% |
| • Ezetimibe | 23% | 22% |
| • PCSK9 inhibitor | 3% | 2% |
| • Niacin | 1% | 3% |
| • ≥2 Therapies | 67% | 64% |

1. Marston, et al. *Am Heart J.* 2025;286:125–135. 2. Based on topline results.

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

| Primary Endpoint | Placebo | Olezarsen 50 mg | Olezarsen 80 mg |
|---|---|---|---|
| **CORE** | | | |
| % Reduction from baseline[2] | 0.5% | 63% | 73% |
| % Placebo-adjusted reduction[1] | | 63% | 72% |
| P-value[3] | | p<0.0001 | p<0.0001 |
| **CORE2** | | | |
| % Reduction from baseline[2] | 14% | 63% | 68% |
| % Placebo-adjusted reduction[1] | | 49% | 55% |
| P-value[3] | | p<0.0001 | p<0.0001 |

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

1. Least-squares mean difference of percent reduction in fasting triglycerides. 2. Least-squares mean. 3. P-values are based on comparison between each olezarsen group and placebo group in percent reduction in fasting triglycerides.

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

**85%**

*(p=0.0002)*

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

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

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

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

# Favorable Safety and Tolerability Observed in the CORE and CORE2 Studies

| | CORE | | | CORE2 | | |
|---|---|---|---|---|---|---|
| | Placebo | Olezarsen 50 mg | Olezarsen 80 mg | Placebo | Olezarsen 50 mg | Olezarsen 80 mg |
| Any AEs | 79% | 77% | 81% | 73% | 75% | 69% |
| Serious AEs | 15% | 11% | 13% | 16% | 8% | 10% |
| AEs Leading to Discontinuation | 2% | 3% | 5% | 1% | 6% | 5% |

Adverse events (AEs) were generally balanced, and serious adverse events (SAEs) occurred less frequently with olezarsen

Injection site reactions, which were mostly mild, were the most common AE and occurred more frequently with olezarsen

# Next Steps to Bring Olezarsen to People with sHTG

1

**CORE and CORE2 Detailed Data Presentation at AHA**

**November 2025[1]**

2

**U.S. sNDA Filing by YE:2025[1]**

**Additional Global Filings 2026[2]**

3

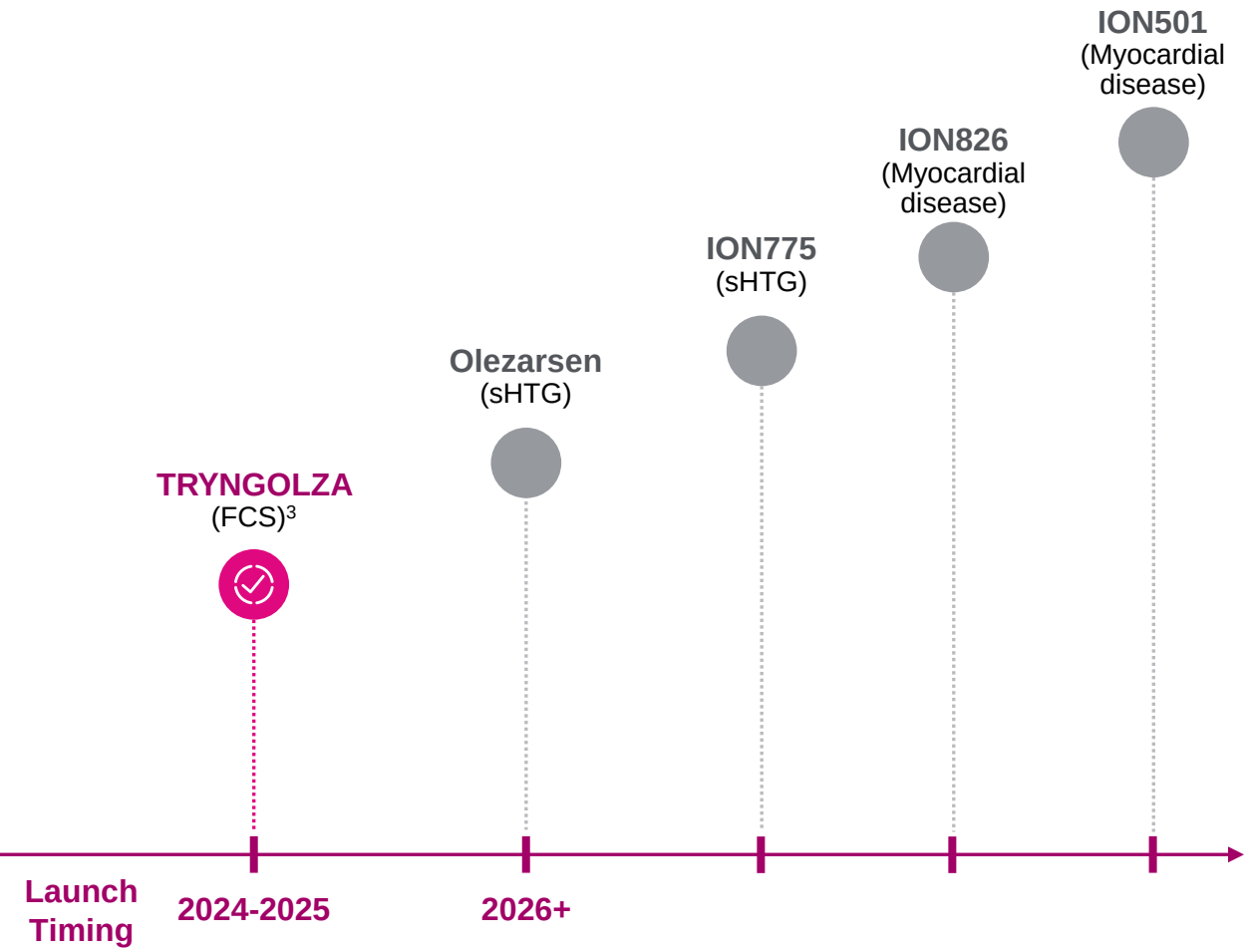
**U.S. Launch H2:2026[1]**

1. Timing expectations are based on current assumptions and are subject to change. 2. Granted Sobi exclusive olezarsen commercial rights outside the U.S., Canada and China. Granted Theratechnologies exclusive rights to commercialize olezarsen in Canada.

# Advancing the Next Wave of Innovative Cardiometabolic Disease Medicines

**Sam Tsimikas, M.D.**
Senior Vice President, Global Cardiovascular Development

# Positioned to Deliver a Steady Cadence of Wholly Owned Cardiometabolic Disease Medicines to the Market[1,2]




**Multiple** advancing **wholly owned medicines** addressing **rare** and **prevalent cardiometabolic conditions**

**Extending** our **leadership** in **sHTG**

- **TRYNGOLZA: first** and **only FDA** approved treatment for FCS[3]
- **Olezarsen: first** and **only treatment** to **significantly reduce acute pancreatitis** events in sHTG
- **ION775:** optimized siRNA designed to enable **enhanced durability** for **semiannual dosing**

Leveraging new **cardiac muscle delivery technology to treat myocardial disease: ION826, ION501**

1. Timing expectations are based on current assumptions and are subject to change. 2. Assuming approval. 3. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information.

# ION775: ApoC-III siRNA with Potential for Enhanced Clinical Profile[1,2]

Ionis' **most advanced liver-targeted siRNA** with potential to extend Ionis' leadership in the **treatment of severely elevated triglycerides**

Designed using Ionis' siRNA optimization capabilities to maximize **durability** to enable **semiannual dosing**

**ION775 Phase 1 single-ascending dose study** in healthy volunteers with moderate triglyceride elevations **underway**

1. Timing expectations are based on current assumptions and are subject to change. 2. Based on interim results from a Phase 1 study in healthy volunteers with moderate triglyceride elevations.

# ION775: ApoC-III siRNA for the Treatment of sHTG

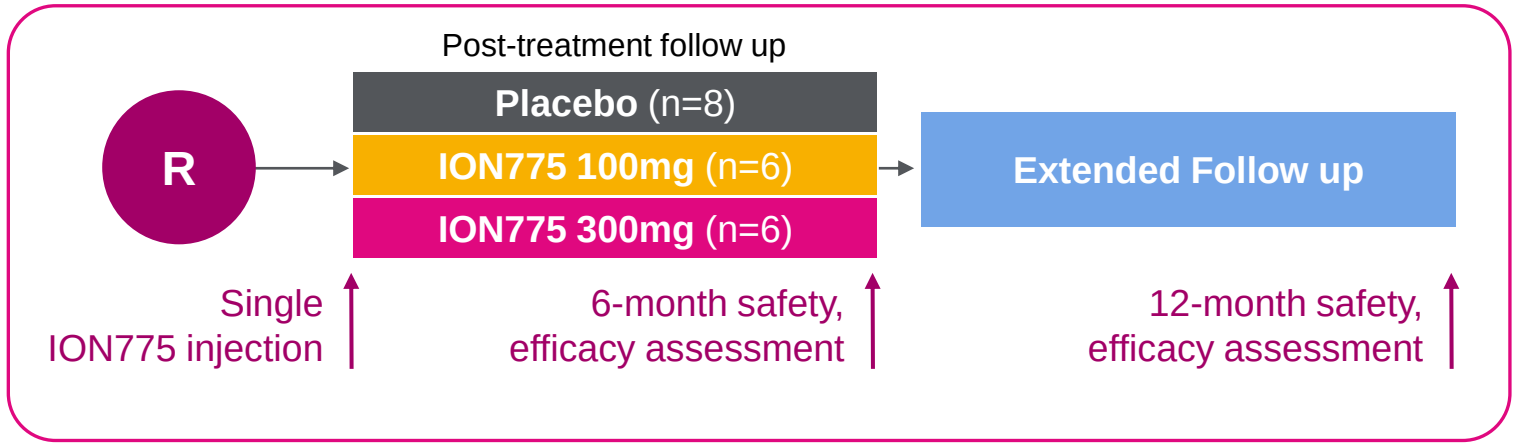
## Phase 1 study in healthy volunteers with moderate triglyceride elevations

Phase 1, randomized, double-blind, placebo-controlled, single-ascending dose study in healthy volunteers with fasting triglycerides ≥150 mg/dL and ≤500 mg/dL

Designed to assess safety, tolerability and effects on apoC-III, fasting triglycerides and other key lipid parameters of single doses of ION775

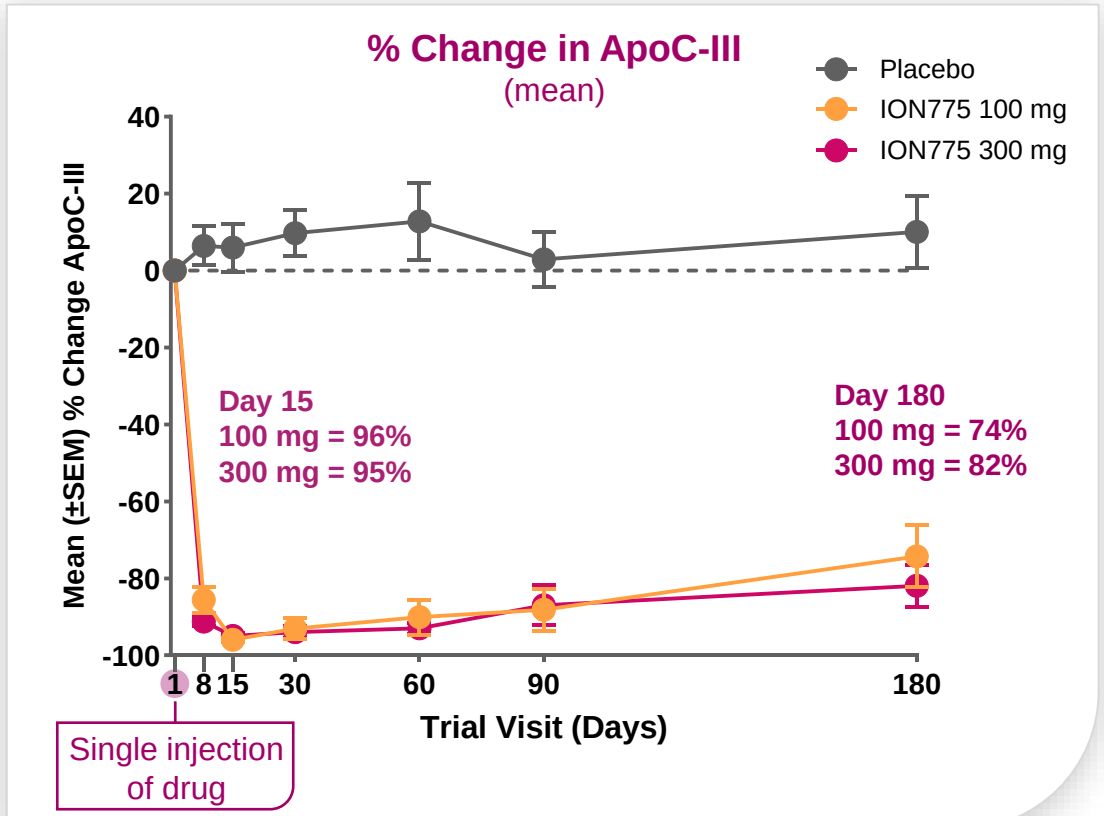
Participants in the 100 mg and 300 mg dose groups had baseline fasting triglycerides of 227 mg/dL and 211 mg/dL, respectively

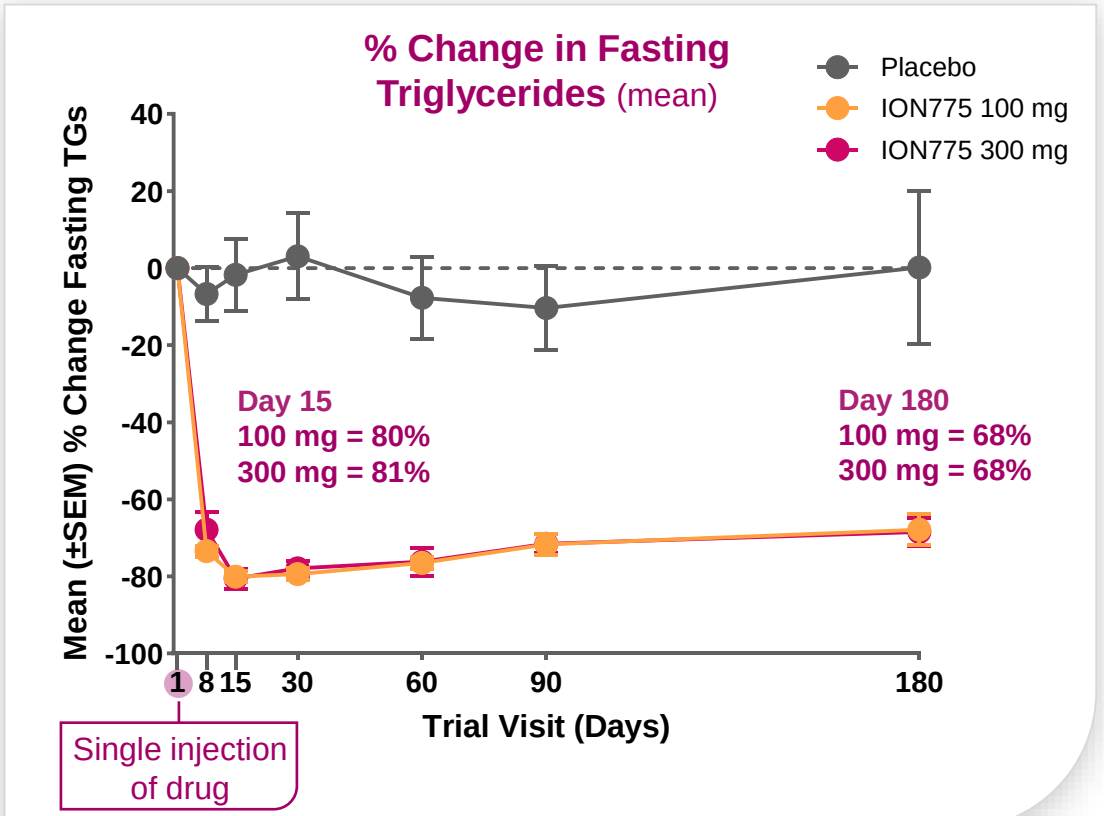
Interim results reported for 100 mg and 300 mg doses assessed at 6 months



# Rapid, Substantial and Durable Reductions in ApoC-III and Triglycerides with Single Doses of ION775

Interim Phase 1 results with ION775 100 mg and 300 mg assessed through 6 months




Robust reductions in apoC-III and fasting triglycerides support **potential for semiannual dosing with ION775**[1]

1. Based on interim results from a Phase 1 study in healthy volunteers with moderate triglyceride elevations.

# **ION775:** Ionis' **Most Advanced Liver-Targeted siRNA** with Potential to Extend Ionis' Leadership in the **Treatment of Severely Elevated Triglycerides**[1,2]

**Positive interim Phase 1 results** in healthy volunteers with elevated triglycerides **support potential** for **semiannual dosing** with **ION775**

**Substantial, durable** and **sustained reductions** in **apoC-III** and **triglycerides** at 6 months

**Favorable safety and tolerability**

On track to initiate **Phase 2 study** in patients with **moderate** and **severe triglyceride elevations next year**

1. Timing expectations are based on current assumptions and are subject to change. 2. Based on interim results from a Phase 1 study in healthy volunteers with moderate triglyceride elevations.

# Key Cardiometabolic Program Events: Late 2025 and 2026[1]

## Early and Mid-Stage Clinical Events

### 2025

**ION775**
Phase 1 interim data
(Healthy Volunteers + TG >150 mg/dL)

### 2026

**ION775**
Phase 2 study start
(sHTG)

**ION501**
Complete IND TOX
(myocardial disease)

## Phase 3 Clinical Events

### 2025

**Olezarsen**
Detailed data
(sHTG)

**TRYNGOLZA**
EU approval
(FCS)

### 2026

**Pelacarsen**
Lp(a) HORIZON data
(Lp(a)-CVD)

**Eplontersen**
CARDIO-TTRansform data
(ATTR-CM)

## Regulatory Events

### 2025

**Olezarsen**
U.S. Submission
(sHTG)

### 2026

**Olezarsen**
U.S. Approval
(sHTG)

**Olezarsen**
EU Submission
(sHTG)

**Eplontersen**[2]
U.S. & EU Submission
(ATTR-CM)

**Pelacarsen**[2]
U.S. Submission
(Lp(a)-CVD)

## Product Launches

### 2025

**TRYNGOLZA**
EU
(FCS)

### 2026

**Olezarsen**[3]
U.S.
(sHTG)

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. Pending Phase 3 data readout. 3. Pending regulatory approval.

# Innovative Cardiometabolic Disease Portfolio Positioned to Deliver Accelerating Value[1,2]

- **Targeting major conditions** that cause cardiometabolic diseases, the **leading causes of death globally**
- Defining a new **treatment paradigm** for **FCS** with **TRYNGOLZA** and potential to **expand into sHTG** with **groundbreaking** new **CORE and CORE2 study results**
- Well-positioned to deliver a **steady cadence** of new **wholly owned** and **partnered medicines to patients in need**
- Focused on continuous **innovation to further strengthen our rich portfolio of cardiometabolic disease medicines**

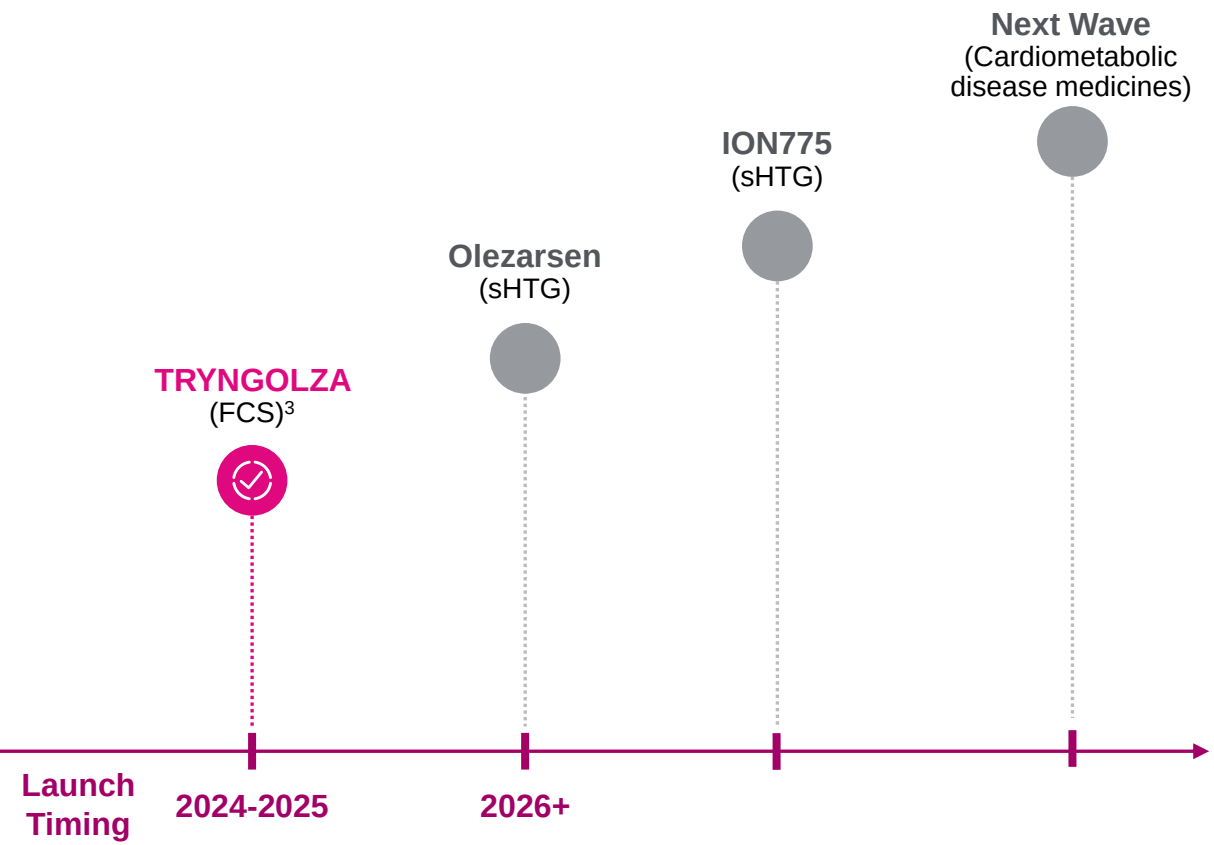
1. Timing and expectations based on current assumptions and subject to change. 2. Assuming approval.

# Delivering Innovative Cardiometabolic Medicines to People in Need

**Kyle Jenne**

Chief Global Product Strategy Officer

# Building a Leading Cardiometabolic Commercial Portfolio[1,2]




## TRYNGOLZA (olezarsen)[3]

- First wholly owned launch underway in FCS

## Olezarsen in sHTG

- Preparing today for success in broader sHTG launch
- Blockbuster potential (>$1B)

## Next Wave of Cardiometabolic Medicines

- Flexible and scalable commercial organization
- ION826 (myocardial disease), ION501 (myocardial disease)

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

# Familial Chylomicronemia Syndrome (FCS): Severe, Rare, Potentially Fatal Disease


**Familial Chylomicronemia Syndrome**
Genetic Form of sHTG with High Patient Burden

**People**
with FCS in the U.S.[1-5]

**Majority**
of U.S. FCS population undiagnosed[1-5]

**~24 years**
Median age of diagnosis[6]

Characterized by **triglyceride levels 10-100x higher** than normal[7,8]

FCS diagnosis made by **genetics or clinical confirmation**[9]

Results in extreme risk of **acute, recurrent and potentially fatal pancreatitis**, **debilitating chronic symptoms** (i.e. abdominal pain, fatigue, brain fog, etc.)[10,11]

**High disease burden**, frequent **hospitalizations**, **psychological stress** and reduced **quality of life**[12]

**TRYNGOLZA (olezarsen)**

**First and only** FDA-approved treatment for FCS[13]

Significant and sustained **triglyceride reductions**, substantial **reduction in acute pancreatitis events** and **favorable safety and tolerability**[14]

1. Dron JS, et al. *BMC Med Genomics* 2020;13(1):23. 2. Hegele RA. *Nat Rev Genet* 2009;10(2):109-21. 3. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 4. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 5. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6. 6. Gaudet D, et al. *N Engl J Med*. 2014;371:2200-2206. 7. Moulin P, et al. *Atherosclerosis* 2018;275:265-72. 8. Brown EE, et al. *J Clin Lipidol* 2020;14(4):398-413. 9. Hegele RA, et al. *J Clin Lipidology* 2024. 10. Davidson M, et al. *J Clin Lipidol.* 2018;12(4):898–907. 11. Nawaz H, et al. *Am J Gastroenterol* 2015; 110;1497-1503. 12. Gaudet D, et al. *Lipids Health Dis*. 2020;19(1):120. 13. TRYNGOLZA (olezarsen) is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see Full Prescribing Information. 14. Stroes E, et al. *N Engl J Med*. 2024.

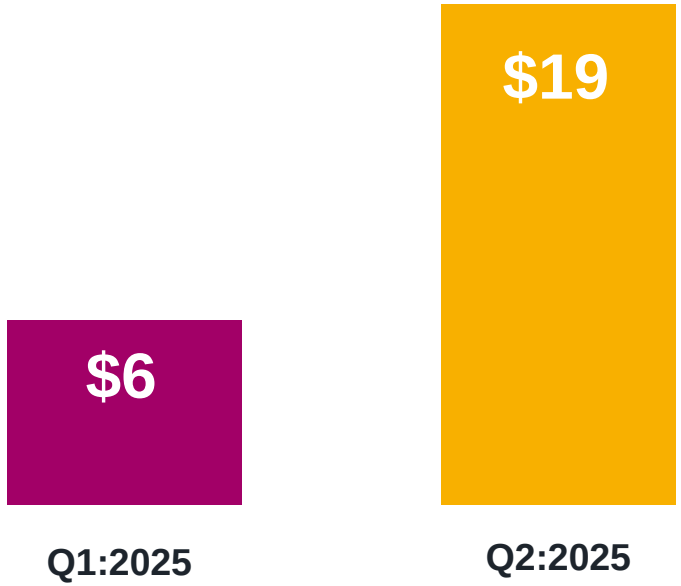
# TRYNGOLZA: First and Only FDA-Approved Treatment for FCS[1,2]


**Robust efficacy and safety**

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

**Convenience of once-monthly self-administration with an autoinjector**

**TRYNGOLZA**
**Product Sales, net**
(millions)




**$75-80 million**
**FY2025 net revenue guidance[3]**

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see Full Prescribing Information. 2. For the quarter ended June 30, 2025. 3. As provided in Q2:2025 earnings press release.

# Strong Commercial Execution and Product Profile Driving Robust Uptake[1-3]

## Strong Patient Uptake

Effective patient identification efforts

Breadth and depth of unique physicians prescribing TRYNGOLZA continues to grow with many having prescribed to two or more patients

Highly favorable feedback

## Robust Physician Engagement

Targeting over 3,000 physicians

Leveraging omnichannel capabilities to reach >30K HCPs

50% cardiologists, 30% endocrinologists, 20% lipidologists and internal medicine

TRYNGOLZA awareness gaining traction

## Positive Access Dynamics

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

Clinically diagnosed and genetically confirmed patients gaining access

>90% of patients had $0 out-of-pocket costs in commercial setting

1. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults as an adjunct to diet; see Full Prescribing Information. 2. For the quarter ended June 30, 2025. 3 On-label patients with FCS.

# IONIS EVERY STEP Designed to Meet the Unique Needs of the FCS Community

Tryngolza® (olezarsen) 80 mg injection

IONIS EVERY STEP™ SUPPORT SERVICES

- Dedicated personal support from Patient Education Managers
- Disease education, injection training and connection to additional resources
- Authorization and reauthorization assistance, delivery coordination and refill reminders to support adherence
- Financial support programs[2]

**Nearly all patients have opted into IONIS EVERY STEP[1]**

1. As of June 30, 2025. 2. For commercially covered patients only. Medicare, Medicaid, TRICARE, Department of Defense, or Veterans Administration, or any other state or federal government-funded patients are not eligible.

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

## Patient Finding is Critical

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

## Targeted HCP Education is Essential

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

**Further extending reach** with omnichannel and targeted marketing

## Establishing Broad, Durable Access is Key

Important that formal **policies** support both **clinical** and **genetic testing pathways**

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

# Positioned for sHTG Market Success

**Kyle Jenne**
Chief Global Product Strategy Officer

# **Severe Hypertriglyceridemia:** Prevalent Condition with Significant Unmet Medical Need

## Substantial Unmet Need

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

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

## Market Poised for New Treatment

**HCPs and patients dissatisfied** with current sHTG treatments

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

## Significant Market Opportunity[1-3]

**>3 million people with sHTG and triglycerides ≥500 mg/dL in the U.S.**

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

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

# Acute Pancreatitis: Potentially Fatal Outcome of sHTG

**The risk of potentially fatal triglyceride-induced acute pancreatitis is serious and requires urgent action**[1]

**~5-fold**
**Higher risk**
of acute pancreatitis with sHTG vs. normal triglyceride levels[2]

**Up to 8%**
**Mortality**
associated with sHTG-driven acute pancreatitis[1]

**~$100,000**
**Annual costs**
for healthcare resulting from sHTG-pancreatitis with hospitalization[3,4]



1. Nawaz H, et al. *Am J Gastroenterol.* 2015;110(10):1497-1503. 2. Kessler A, et al. *J Clin Lipidol.* e67May-June, 2025. 3. Kessler A, et al. *J Clin Lipidol.* e119May-June, 2025. 4. In reimbursed costs.

# Olezarsen is Well Positioned to Address the Unmet Needs Associated with sHTG and Acute Pancreatitis

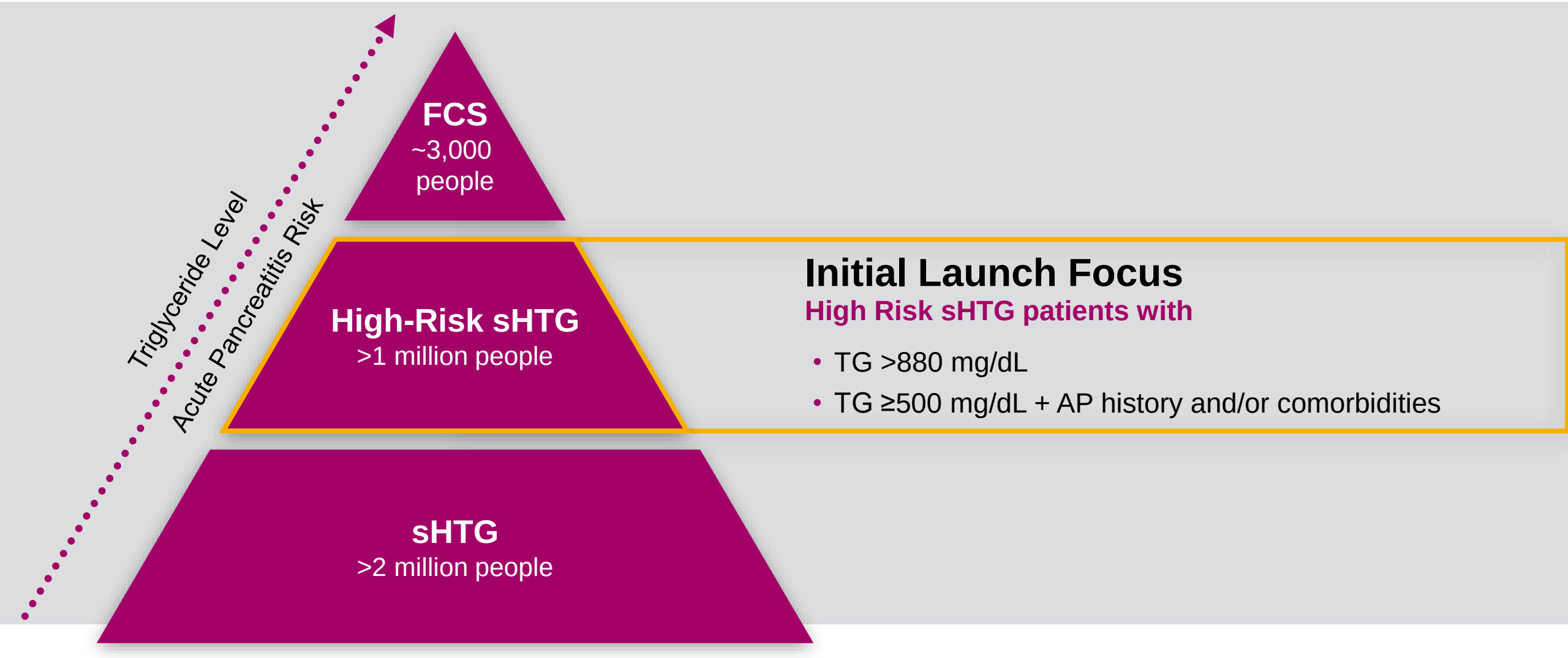
"*A treatment that meaningfully lowers triglycerides **and** reduces acute pancreatitis risk – something we've never seen before – would be a **game-changer**.*"

– sHTG KOL

1. **Highly statistically significant** and **clinically meaningful** reductions in fasting **triglycerides**[1]
2. **First and only** treatment to **significantly reduce acute pancreatitis** events in **people with sHTG**[1]
3. **Favorable safety** and **tolerability**[1]
4. **Simplicity** of **monthly self-administration** with an **autoinjector**

1. As reported in the topline results from the Phase 3 CORE and CORE2 studies of olezarsen in people with sHTG.

# Initial U.S. Launch to Focus on High-Risk sHTG[1,2]




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

# HCPs are Dissatisfied with Current Standard-of-Care Triglyceride-Lowering Therapies[1]

**~70%** Of HCPs rapidly initiate **aggressive triglyceride-lowering treatment** in people with **high-risk sHTG**

**>80%** Of HCPs unable to get patients' **triglycerides** below the threshold for **acute pancreatitis risk** (<500 mg/dL) with standard **lipid-lowering therapies**

**~70%** Of HCPs believe **triglycerides** are **difficult to manage** with standard **lipid-lowering therapies**

"*Of the medical crises we manage, acute pancreatitis is the one that keeps me up at night.*"

*– leading cardiologist*

*"Acute pancreatitis is more frightening than a heart attack – less predictable and far harder to manage."*

*– leading endocrinologist*

*"I regularly see my patients' pancreas destroyed after one pancreatitis attack."*

*– leading lipidologist*

1. U.S. HCP Segmentation Research

# Realizing the Blockbuster Potential of Olezarsen in sHTG[1,2]

## Targeting Key HCPs

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

**Actively treating high-risk sHTG** patients with standard of care

## Expanding Disease Awareness[3]

Leveraging ongoing TRYNGOLZA launch to **include sHTG education with key HCPs**

**Engaging >30K HCPs** in disease state education

## Building a Right-Sized Field Team

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

**Flexibility to scale** as the market evolves

## Attractive Payer and Access Dynamics[4]

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

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

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

# Olezarsen:
## Potential Blockbuster Medicine Positioned to Change the sHTG Treatment Paradigm[1,2]

Groundbreaking **CORE and CORE2 study** results

- Highly **statistically significant** and **clinically meaningful** mean **reductions in fasting triglycerides**
- First and only treatment to **significantly reduce acute pancreatitis events** in people with sHTG
- Favorable **safety** and **tolerability**

HCPs, patients and payers **poised for new advance in the treatment of sHTG**

**First mover advantage;** commercial organization designed **for sHTG launch success**

Preparing today to bring a steady cadence of **new cardiometabolic medicines** to **patients in need** well into the future

IONIS

1. Timing and expectations based on current assumptions and subject to change. 2. Assuming approval.

# Q&A

**Brett Monia, Ph.D.**
Chief Executive Officer

**Robert D. Fishberg, M.D.**
Key Thought Leader in the Treatment of Patients with sHTG, FCS and Lipid Disorders

**Sam Tsimikas, M.D.**
Senior Vice President, Global Cardiovascular Development

**Kyle Jenne**
Chief Global Product Strategy Officer

IONIS

Innovation Day 2025:

# Accelerating Growth through Life-Changing Medicines

## Break

OCTOBER 7, 2025 | Nasdaq: IONS






# DAWNZERA™

Transforming the HAE
Treatment Paradigm

*Living with HAE* | **Lauren**

# Setting a New Bar for the Prophylactic Treatment of HAE

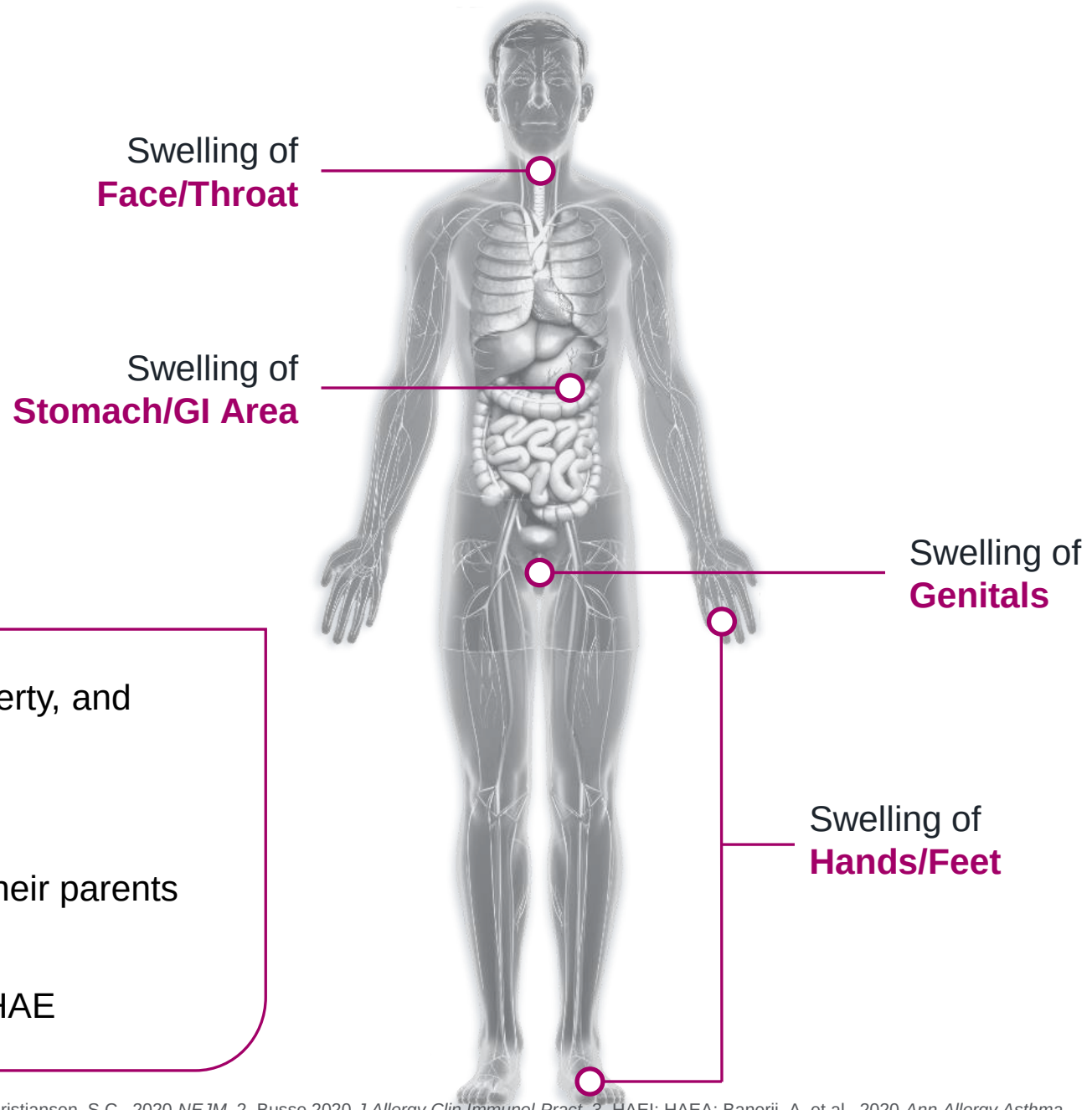
**Kenneth Newman, M.D.**

Senior Vice President, Clinical Development

# Hereditary Angioedema (HAE)[1-7]

A **rare**, chronic and **potentially life-threatening genetic condition**

Patients experience **recurrent attacks of severe swelling** in various parts of the body




**Symptoms usually appear early in life**, most often by puberty, and may increase in severity with age

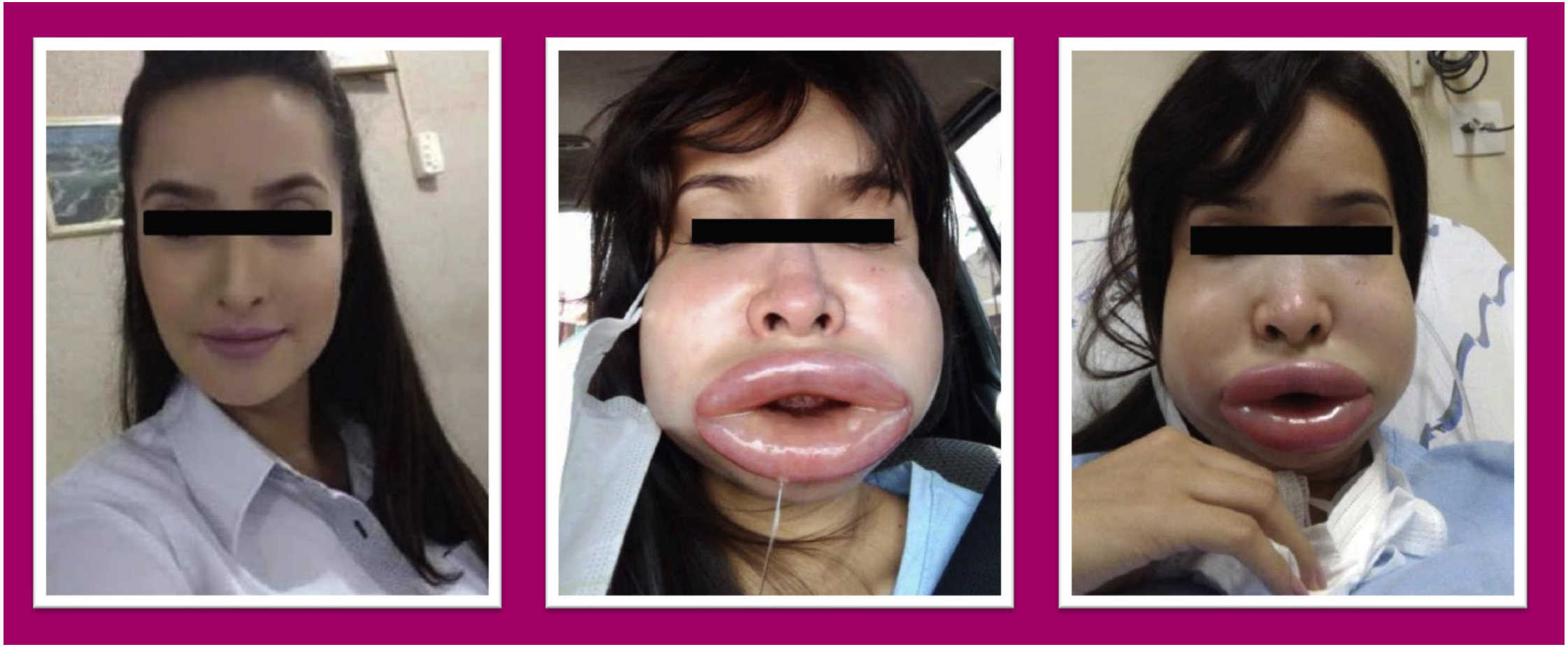
On average, it takes **five years to diagnosis**

**Children have a 50% chance of inheriting HAE** if one of their parents has the condition

**25%** of people diagnosed **do not** have a **family history** of HAE

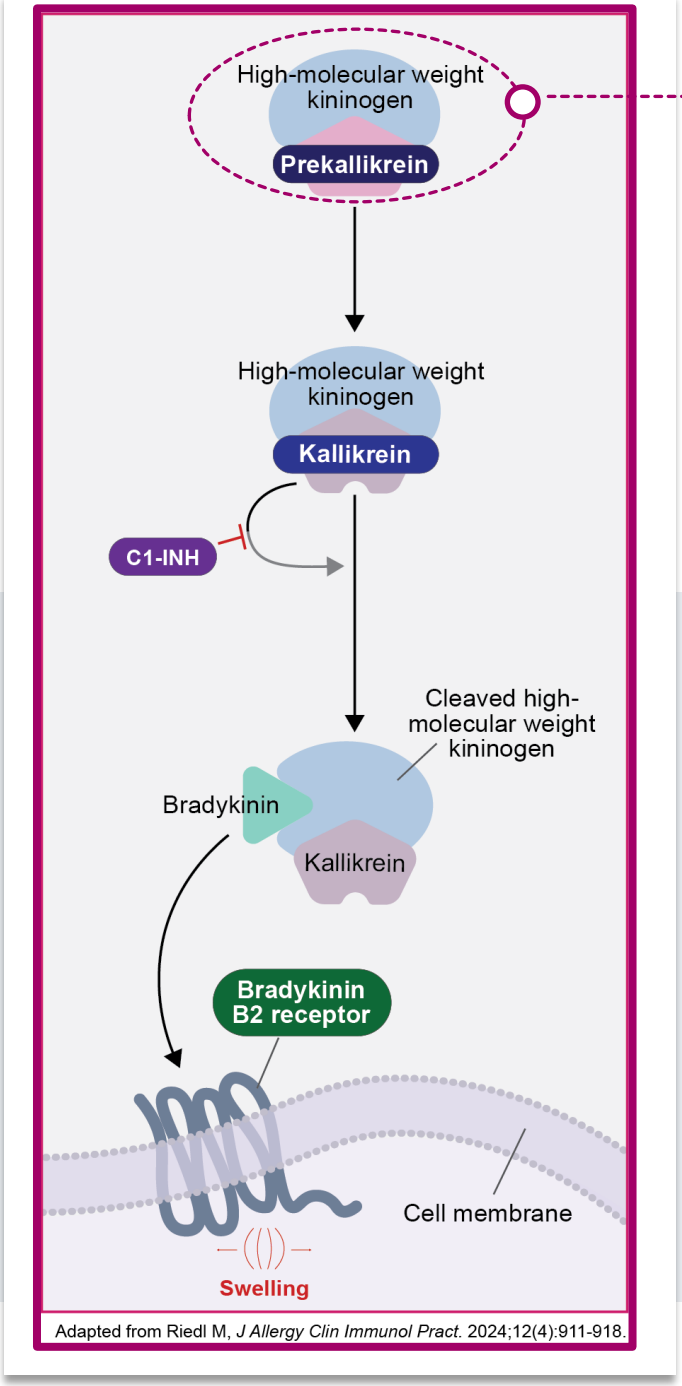
1. Busse, P.J. and Christiansen, S.C., 2020 *NEJM.* 2. Busse 2020 *J Allergy Clin Immunol Pract*. 3. HAEI; HAEA; Banerji, A. et al., 2020 *Ann Allergy Asthma Immunol.* 4. Banerji, A. et. al. 2015 *Allergy & Asthma*. 5. Bernstein J. Am J Manag Care. 2018;24:s292-s298. 6. Riedl et al. 2023 *J ALLERGY CLIN 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* 16:100812. 7. Banerji, A. et al., 2020 *Ann Allergy Asthma Immunol.*

# HAE Attacks are Unpredictable, Debilitating and Can be Fatal[1]



1. Images from Arruda LK,et al. *J Aller Clin Immun* 2021. https://doi.org/10.1016/j.jaci.2021.05.023.

# DAWNZERA's Novel Target: PKK at the Start of the Kallikrein-Kinin Pathway




Adapted from Riedl M, *J Allergy Clin Immunol Pract.* 2024;12(4):911-918.

**Novel HAE Target: PKK**

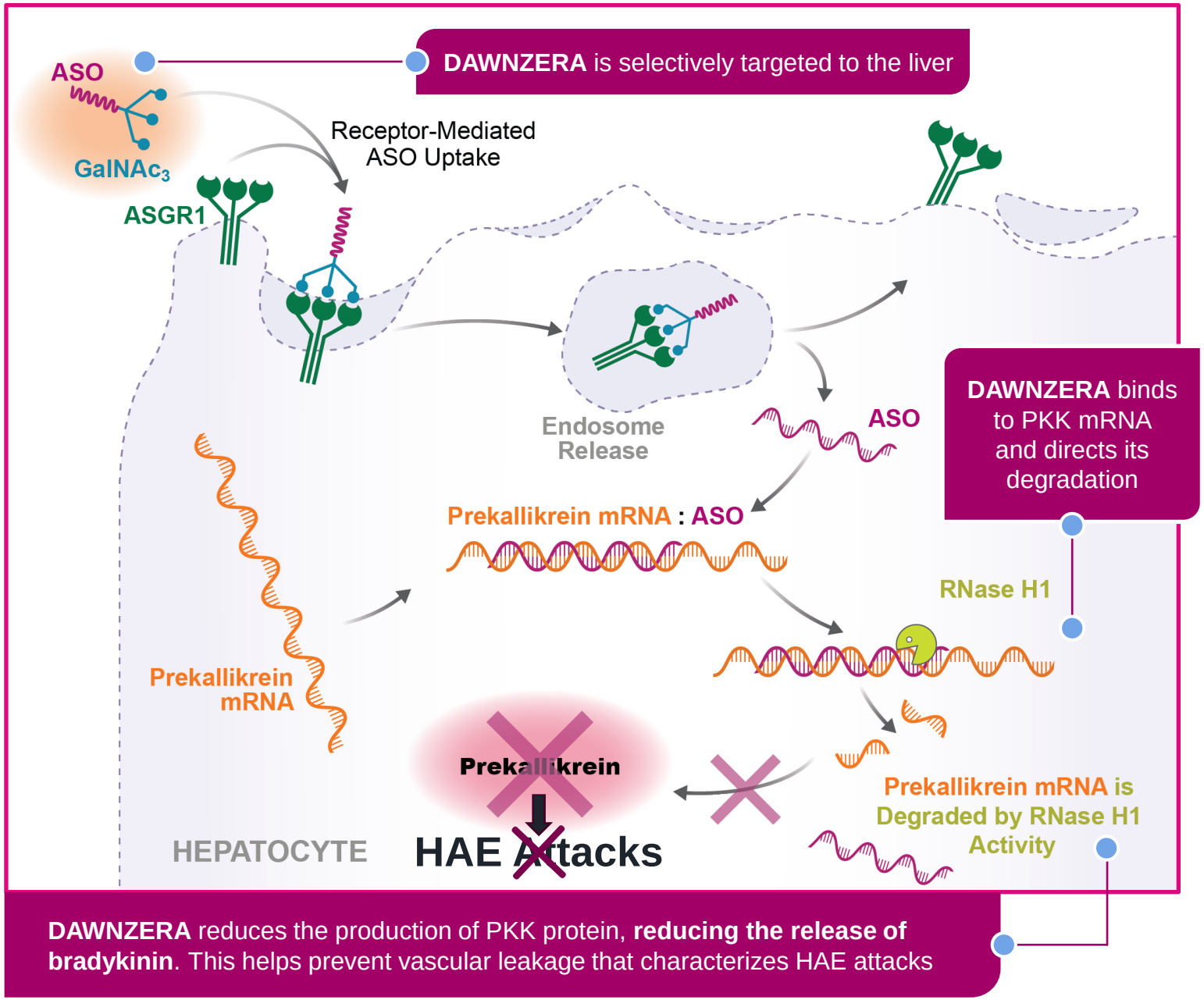
**Low levels or inadequate C1 esterase inhibitor (C1-INH) activity** causes aberrant activation of the kallikrein-kinin pathway[1]

- Plasma prekallikrein **(PKK)** is produced in the liver and is the **precursor of kallikrein**
- **Uncontrolled kallikrein** activation leads to **elevated bradykinin** levels and **HAE symptoms**

1. Lumry (2103) Am. J. Manag. *Care*. 19:S103-S110.

# DAWNZERA: First and Only RNA-Targeted Medicine for HAE[1-4]

**DAWNZERA** binds to prekallikrein (PKK) mRNA to **limit** plasma protein **production** at the **source** — in the liver, **where it's made**




**DAWNZERA** reduces the production of PKK protein, **reducing the release of bradykinin**. This helps prevent vascular leakage that characterizes HAE attacks

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 MA, Bordone L, Revenko A, et al. Clinical progress in hepatic targeting for novel prophylactic therapies in hereditary angioedema. *J Allergy Clin Immunol Pract.* 2024;12(4):911-918. doi:10.1016/j.jaip.2023.12.025. 3. Riedl MA, Tachdjian R, Lumry WR, et al. Efficacy and safety of donidalorsen for hereditary angioedema. *N Engl J Med.*2024;391(1):21-31. doi:10.1056/NEJMoa2402478. 4. Smith TD, Riedl MA. The future of therapeutic options for hereditary angioedema. *Ann Allergy Asthma Immunol.* 2024;133(4):380-390. doi:10.1016/j.anai.2024.04.029.

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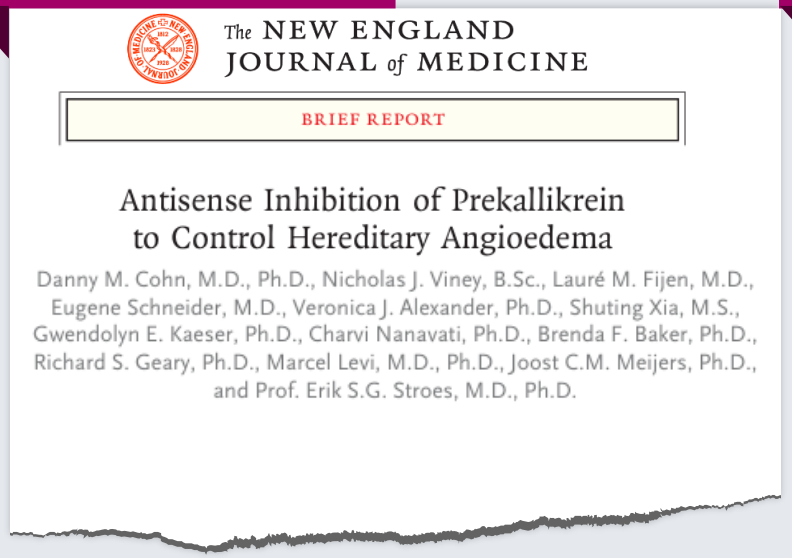
# Data from DAWNZERA Highlighted in Multiple *NEJM* Publications

## Phase 1 Data



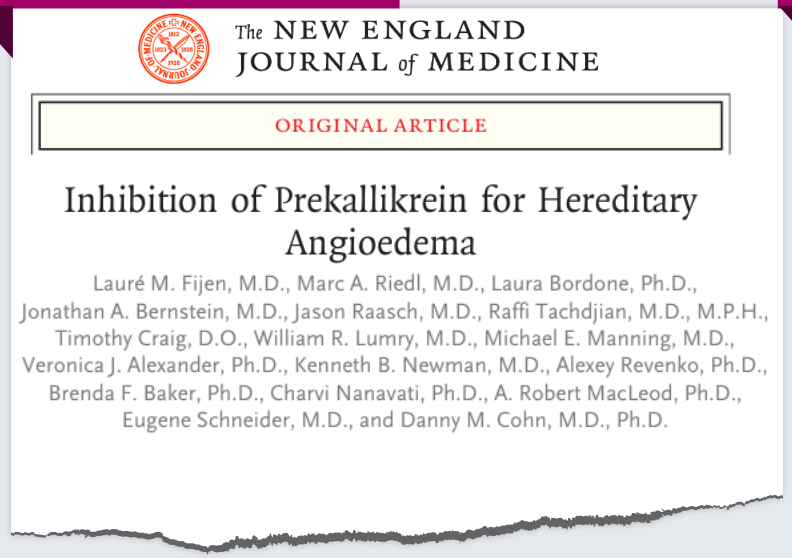
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Antisense Inhibition of Prekallikrein to Control Hereditary Angioedema

Danny M. Cohn, M.D., Ph.D., Nicholas J. Viney, B.Sc., Lauré M. Fijen, M.D., Eugene Schneider, M.D., Veronica J. Alexander, Ph.D., Shuting Xia, M.S., Gwendolyn E. Kaeser, Ph.D., Charvi Nanavati, Ph.D., Brenda F. Baker, Ph.D., Richard S. Geary, Ph.D., Marcel Levi, M.D., Ph.D., Joost C.M. Meijers, Ph.D., and Prof. Erik S.G. Stroes, M.D., Ph.D.

## Phase 2 Data



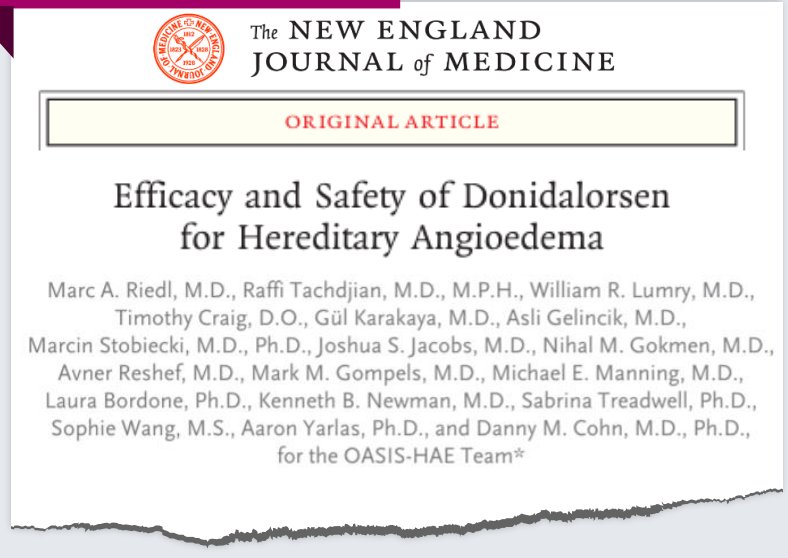
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Inhibition of Prekallikrein for Hereditary Angioedema

Lauré M. Fijen, M.D., Marc A. Riedl, M.D., Laura Bordone, Ph.D., Jonathan A. Bernstein, M.D., Jason Raasch, M.D., Raffi Tachdjian, M.D., M.P.H., Timothy Craig, D.O., William R. Lumry, M.D., Michael E. Manning, M.D., Veronica J. Alexander, Ph.D., Kenneth B. Newman, M.D., Alexey Revenko, Ph.D., Brenda F. Baker, Ph.D., Charvi Nanavati, Ph.D., A. Robert MacLeod, Ph.D., Eugene Schneider, M.D., and Danny M. Cohn, M.D., Ph.D.

## Phase 3 Data



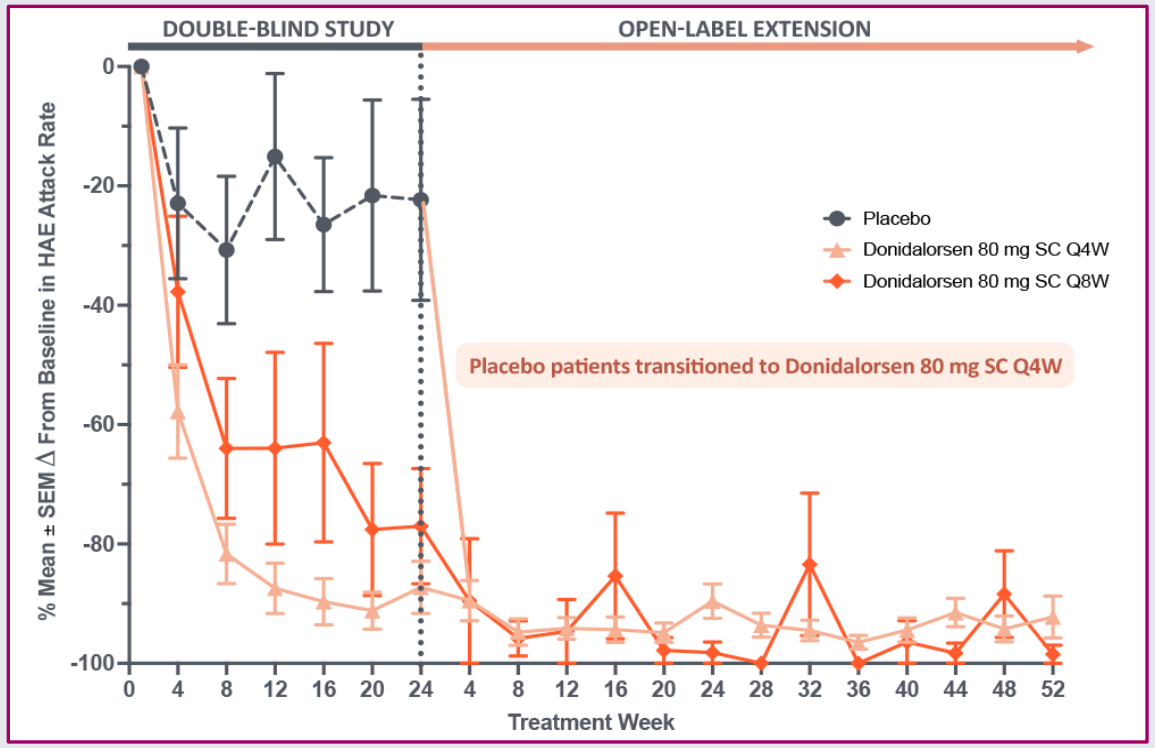
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Donidalorsen for Hereditary Angioedema

Marc A. Riedl, M.D., Raffi Tachdjian, M.D., M.P.H., William R. Lumry, M.D., Timothy Craig, D.O., Gül Karakaya, M.D., Asli Gelincik, M.D., Marcin Stobiecki, M.D., Ph.D., Joshua S. Jacobs, M.D., Nihal M. Gokmen, M.D., Avner Reshef, M.D., Mark M. Gompels, M.D., Michael E. Manning, M.D., Laura Bordone, Ph.D., Kenneth B. Newman, M.D., Sabrina Treadwell, Ph.D., Sophie Wang, M.S., Aaron Yarlas, Ph.D., and Danny M. Cohn, M.D., Ph.D., for the OASIS-HAE Team*

# 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]

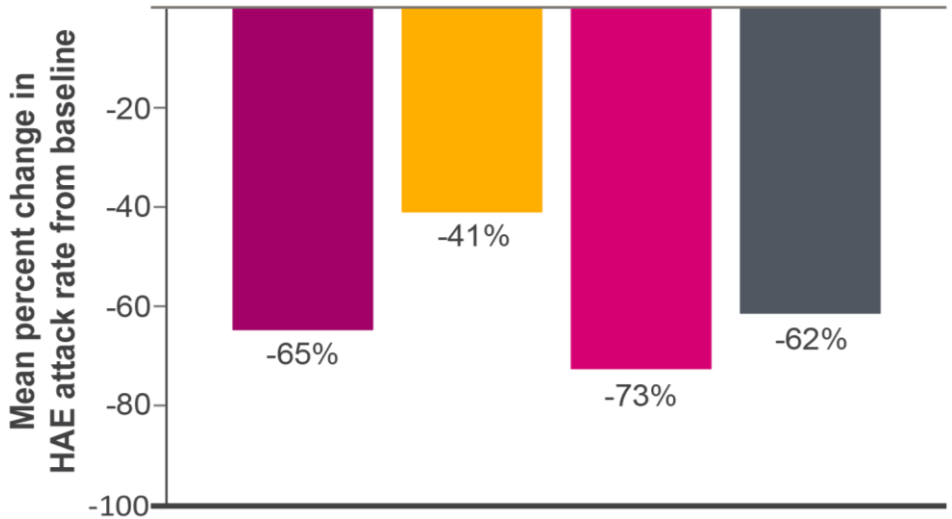
## High levels of disease control[4,5]

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.

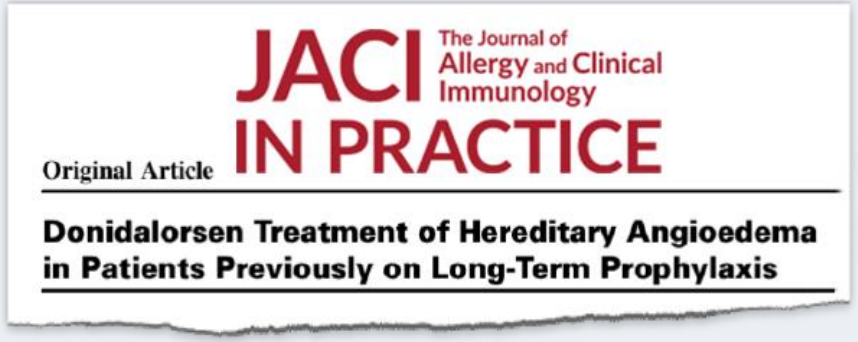
# DAWNZERA Substantially Reduced HAE Attack Rates After Switching from Prior Prophylactic Treatment[1,2]

OASIS-Plus Switch Cohort Results

## % Reduction in HAE Attack Rate After Switching to DAWNZERA



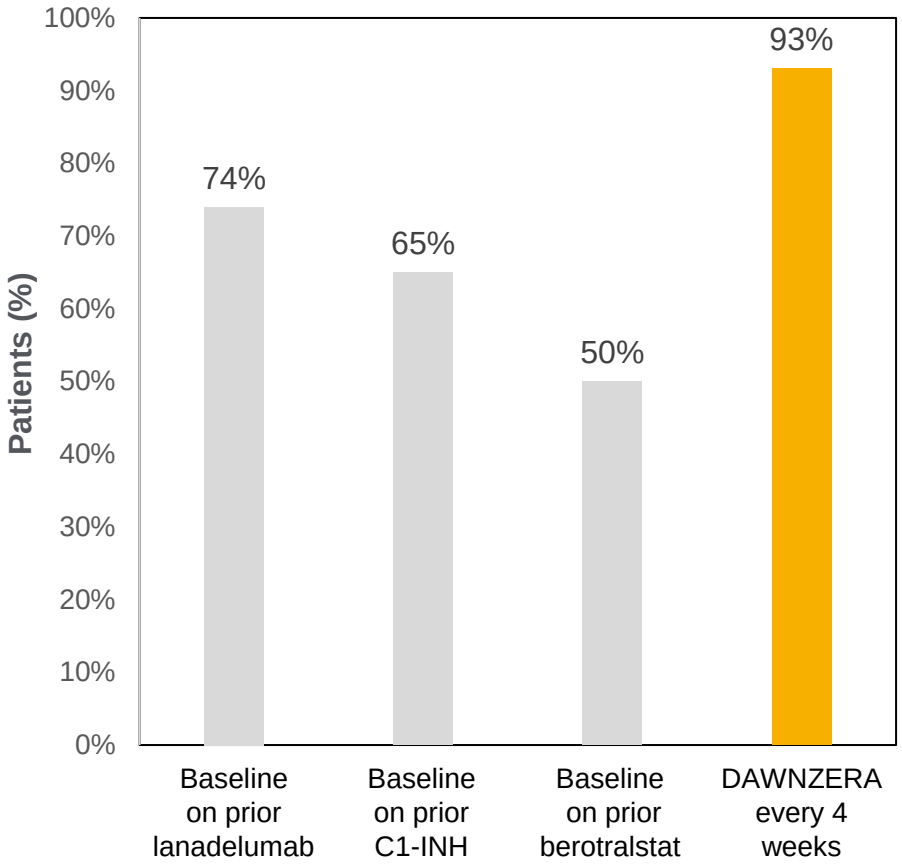

| Prior LTP: | Lanadelumab | C1INH | Berotralstat | Total |
|---|---|---|---|---|
| n = | 31 | 22 | 11 | 64 |
| Baseline, mean ± SD = | 0.69 ± 1.09 | 0.61 ± 0.96 | 1.80 ± 1.92 | 0.85 ± 1.28 |
| Week 16 (donidalorsen Q4W), mean ± SD = | 0.24 ± 0.33 | 0.36 ± 0.69 | 0.48 ± 0.53 | 0.33 ± 0.51 |




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.

# Additional Positive Results from the Open-Label Switch Cohort[1,2]

## Mean Proportion of Patients Well-Controlled on AECT[3]




**84%**

of

**Switch Patients**

Surveyed

**Preferred**

**DAWNZERA**

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. 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.

# Favorable Long-Term Safety and Tolerability[1]

**The safety of DAWNZERA reflects an average exposure duration of 14 months in 171 patients aged ≥12 y/o across 3 clinical trials**

The majority of AEs were **mild** to **moderate**[3]

All injection-site reactions were **mild** and **nonserious**, and the majority resolved **without receiving any treatment**[3]

## Adverse Reactions (≥ 5% with DAWNZERA and more common than placebo) in OASIS-HAE at Week 24

| Adverse reaction, n (%) | DAWNZERA Q4W (n=45) | DAWNZERA Q8W (n=23) | Placebo (n=22) |
|---|---|---|---|
| Injection-site reactions | 11(24) | 1(4) | 1(5) |
| Upper respiratory tract infection | 4(9) | 2(9) | 1(5) |
| Urinary tract infection | 4(9) | 2(9) | 0 |
| Abdominal discomfort | 3(7) | 0 | 0 |

**AEs were mild or moderate at 1 year in OASISplus OLE**[2]



1. DAWNZERA is approved in the U.S. for hereditary angioedema in adults and pediatric patients 12 years of age and older; see Full Prescribing Information.2. Tachdijan R, Reidl MA, Bordone L, et al. Long-term safety of donidalorsen for the treatment of hereditary angioedema. 3. *N Engl J Med* 2024;391:21-31 DOI: 10.1056/NEJMoa2402478 VOL. 391 NO. 1.

# Multiple Poster Presentations at Upcoming American College of Allergy, Asthma & Immunology Annual Scientific Meeting


American College of Allergy, Asthma & Immunology

November 6-10, 2025

## Including……

**1-Year Results** from **Phase 3 OASISplus** Open-Label Extension Study of **DAWNZERA**

**1-Year Results** from **Switch Cohort** from **Phase 3 OASISplus** Open-Label Extension Study of **DAWNZERA**

**4-Year Analysis** from **Phase 2** Open-Label Extension Study of **DAWNZERA**

# Setting a New Bar for Prophylactic HAE Treatment[1-3]

## First and Only RNA-Targeted Medicine for HAE

### EFFICACY

Substantial and sustained **attack rate reduction**

**Long-term** disease control

Roadmap for switching; **strong patient preference**

### TOLERABILITY

**Favorable** safety and tolerability

**Low volume** autoinjector

Contains **no citric acid**, which is associated with injection-site pain

### CONVENIENCE

**Longest** dosing interval

**No** loading dose

Self-administered in just **10 seconds**

Can be stored at room temperature for up to **6 weeks**

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. Clinical results include: Phase 3 placebo-controlled OASIS-HAE study, Phase 3 OASISplus which includes open-label extension cohort and switch cohort. 3. Market data on file.

# Unlocking DAWNZERA's Potential to be the Treatment of Choice for HAE

**Kyle Jenne**

Chief Global Product Strategy Officer

# DAWNZERA Launch Off to Encouraging Start[1]

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

## Launch Underway

FDA approval on August 21st

First patient self-administered DAWNZERA within 10 days of approval

Exceptional initial commercial execution

## Positive Physician Engagement

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

Repeat prescribers

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

## Encouraging Early Launch Signals

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

Patient starts across the U.S.

Strong initial payer engagement

1. DAWNZERA is approved in the U.S. for hereditary angioedema in adults and pediatric patients 12 years of age and older; see Full Prescribing Information.

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

- **~7,000** people with HAE in the U.S.[3]
- **~75%** of people with HAE in the U.S. are on LTPs
- **~1,000** allergists/ immunologists treat **90%** of HAE patients
- **~20%** of people with HAE have historically switched treatments annually
- **>90%** of people with HAE are interested in trying a new prophylactic therapy[4]

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

1. DAWNZERA is approved in the U.S. for hereditary angioedema in adults and pediatric patients 12 years of age and older; see Full Prescribing Information. 2. Market data on file. 3. Riedl et al. 2023 *J ALLERGY CLIN IMMUNOL PRACT* VOLUME 11, NUMBER 8; Sylvestre et al 2021 *J ALLERGY CLIN IMMUNOL PRACT* VOLUME 9, NUMBER 12; Nieto et al 2023 World Allergy Organization Journal. 4. Ionis-sponsored Harris Poll results. 5. Based on current estimates.

# Remaining Unmet Need: Efficacy, Tolerability, Convenience[1]

People with HAE **still experience breakthrough attacks** with current medications

Continued **need** for a prophylactic treatment offering **improved tolerability** that is **easy to use**

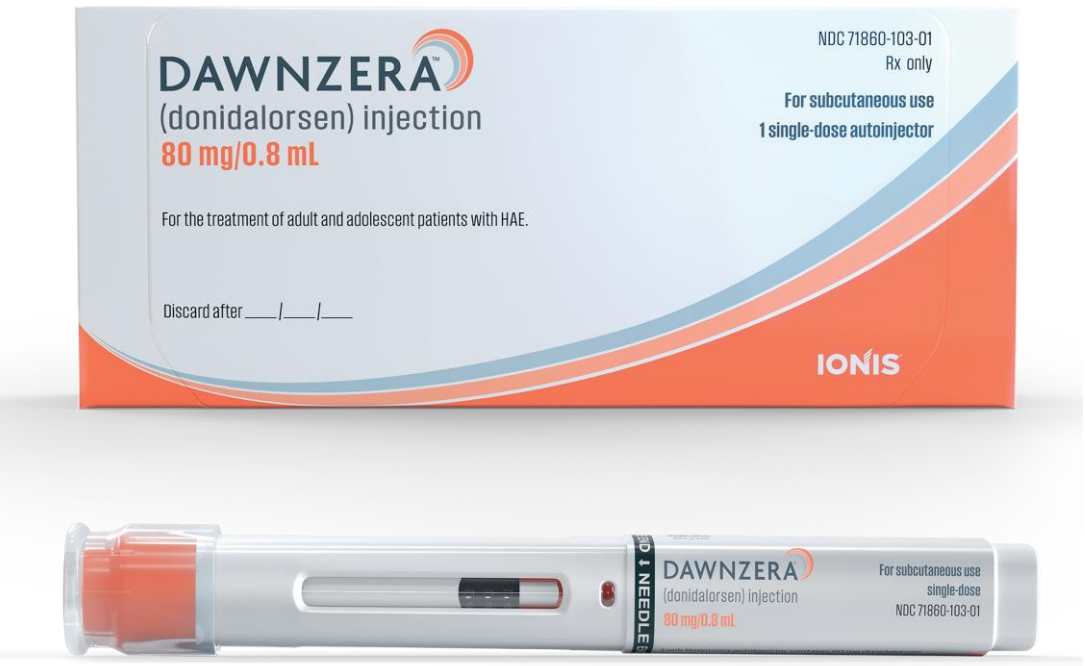
**Frequent dosing increases treatment burden**

Nearly all prophylactic treatments require daily, weekly or bi-weekly dosing that can negatively impact patient compliance

**People with HAE are looking for long-term disease control to regain their freedom and improve their quality of life**

1. Market data on file.

# DAWNZERA's Compelling and Comprehensive Profile[1-3]




Indicated for prophylaxis to prevent attacks of HAE in adult and pediatric patients ≥12 years old

## EFFICACY

Substantial and sustained attack rate reduction with long-term durability

Strong disease control

## TOLERABILITY

Patient-friendly self-administered autoinjector

- Low 0.8mL volume
- Contains no citric acid, which is associated with injection-site pain

## CONVENIENCE

Longest dosing interval option: every four- or eight-weeks

No loading dose

Takes just 10 seconds to self-administer

Can be stored at room temperature for up to six weeks

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. Clinical results include: Phase 3 placebo-controlled OASIS-HAE study, Phase 3 OASISplus which includes open-label extension cohort and switch cohort. 3. Market data on file.

# Targeted Patient Segments for DAWNZERA[1,2]

**Patients Switching from Other LTPs** + **Patients Previously Treated with Only On-Demand Therapy** + **Newly Diagnosed Patients**

## Majority are Switch Patients

**Efficacy**: those experiencing breakthrough attacks on current treatment

**Tolerability**: those experiencing side effects on current treatment

**Convenience**: those seeking less frequent dosing and/or those who struggle with maintaining compliance on current treatments


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.

# 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.

# DAWNZERA Launch Strategy Designed for Success[1]

## Patient & HCP Focus

**Unmet need education**

Empowering people with HAE to demand more from their long-term prophylactic

## Commercial Execution

**Experienced U.S. commercial team**

Extensive HAE and/or Allergy/Immunology experienced team deployed since late Spring

## Comprehensive Support Program

**Patients and HCP services to enable seamless switch**

Patient assistance, authorization support, financial support for eligible patients

## Coverage & Reimbursement

**Market access team engaging with payers**

To ensure access for people who may benefit from DAWNZERA

## Omnichannel Engagement

**Targeted HCP and patient engagement**

Innovative marketing capabilities to extend commercial team reach

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.

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

IONIS EVERY STEP™ SUPPORT SERVICES

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

1. DAWNZERA is approved in the U.S. for hereditary angioedema in adults and pediatric patients 12 years of age and older; see Full Prescribing Information. 2. For commercially-covered patients only. Medicare, Medicaid, TRICARE, Department of Defense, or Veterans Administration, or any other state or federal government-funded patients are not eligible.

# DAWNZERA: Transforming the Treatment Paradigm

## Launch Off to Encouraging Start

**Exceptional Initial Commercial Execution**

**Positive Physician and Patient Feedback**

**Strong Initial Payer Engagement**

1. DAWNZERA is approved in the U.S. for hereditary angioedema in adults and pediatric patients 12 years of age and older; see Full Prescribing Information. 2. Clinical results include: Phase 3 placebo-controlled OASIS-HAE study, Phase 3 OASISplus which includes open-label extension cohort and switch cohort. 3. Market data on file.

# Leading the Way in the Treatment of Neurological Diseases

**Holly Kordasiewicz, Ph.D.**

Senior Vice President, Neurology

# Advancing our Leading Neurology Portfolio

*Living with Angelman Syndrome* | **Jackson**

# 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 **next year** 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 Neurology Pipeline

**6** Wholly Owned Medicines in Clinical Development

**5** Partnered Medicines in Clinical Development

**11** Medicines in Clinical Development

## Wholly Owned Medicines

| | Indication | Preclinical | Ph1 | Ph2 | Ph3 |
|---|---|---|---|---|---|
| **Zilganersen** (GFAP) | Alexander disease | | | | |
| **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 | | | | |
| **Additional medicines** in lead optimization and preclinical development | | | | | |

## 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 | | | | |

# Executing on Established Strategy to Expand Wholly Owned Neurology Portfolio

Advancing potentially transformative medicines, utilizing robust prioritization process with an industry-leading team

## Right Targets

Focus on **disease-modifying** targets for patients with significant need

Select targets **central to disease** with high **transformative** potential

## Right Development Path

Select targets with tools that enable **efficient drug development**

Streamlined development paths with opportunities for **rapid proof of concept**

## Right Commercial Fit

**Innovative** commercial **organization** to **reach** patients and leverage **synergies across multiple medicines**

# Continuing to Strategically Build Wholly Owned Neurology Pipeline

## Rare Pediatric Neurology

**Zilganersen**
Alexander disease

**ION582**
Angelman syndrome

**ION356**
Pelizaeus-Merzbacher disease

**ION440**
MECP2 Duplication syndrome

**ION337**
Dravet syndrome

## Dementia

**ION717**
Prion disease

**3 Medicines**
in lead optimization and preclinical development

## Motor Disease

**ION464**
Multiple System Atrophy (MSA)

**2 Medicines**
in lead optimization and preclinical development

## Neuromuscular Disease

**4 Medicines**
in lead optimization and preclinical development

# Rare Pediatric Neurology

## Significant Need for Transformative Therapies

1 in 6 children are affected by a neurological disorder[1]

## Our Technology is Uniquely Suited to Address Neurological Diseases

Many diseases in children are caused by a mutation or change in a single gene

Young developing brains have a tremendous capacity for growth and repair

Opportunities for efficient, rapid clinical development

## Areas of Focus within Rare Pediatric Neurology

- **Leukodystrophies**
- **Neurodevelopmental Disorders**
- **Epilepsies**
- **Intellectual Disability**

1. St. Jude; Neurological Disorders: A New Direction, Spring 2021

# Zilganersen for the Treatment of Alexander Disease

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

**Grayson and family**
living with Alexander disease

## Alexander Disease (AxD)[2-5]

Fatal and Progressive Ultra-Rare Childhood Neurological Disorder

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

Caused by mutations in *GFAP*

~65% of cases occur in childhood

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

## Zilganersen

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

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

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

1. Topline pivotal results reported on September 22, 2025. 2. Yoshida T, Sasaki M, Yoshida M, et al. Nationwide survey of Alexander disease in Japan and proposed new guidelines for diagnosis. *J Neurol*. 2011;258(11):1998-2008; 3. Heim et al., Am J Med Genet 1997; 71:475-478 and Cohen et al., Ann Hum Genet 2020; 84:11–28. Messing, Albee. Alexander Disease: A Guide for Patients and Families. Colloquium Series on Neuroglia in Biology and Medicine: From Physiology to Disease. Vol. 3. No. 1. *Morgan & Claypool Life Sciences*, 2017; 4. Prust M, et al. GFAP mutations, age at onset, and clinical subtypes in Alexander disease. *Neurology*. 2011;77(13):1287-1294. 5. Srivastava et al., 1993. 6. Assuming approval. 7. Based on current timing estimates, subject to change.

# Innovative Study Design to Assess Zilganersen in People with AxD

**DESIGN**

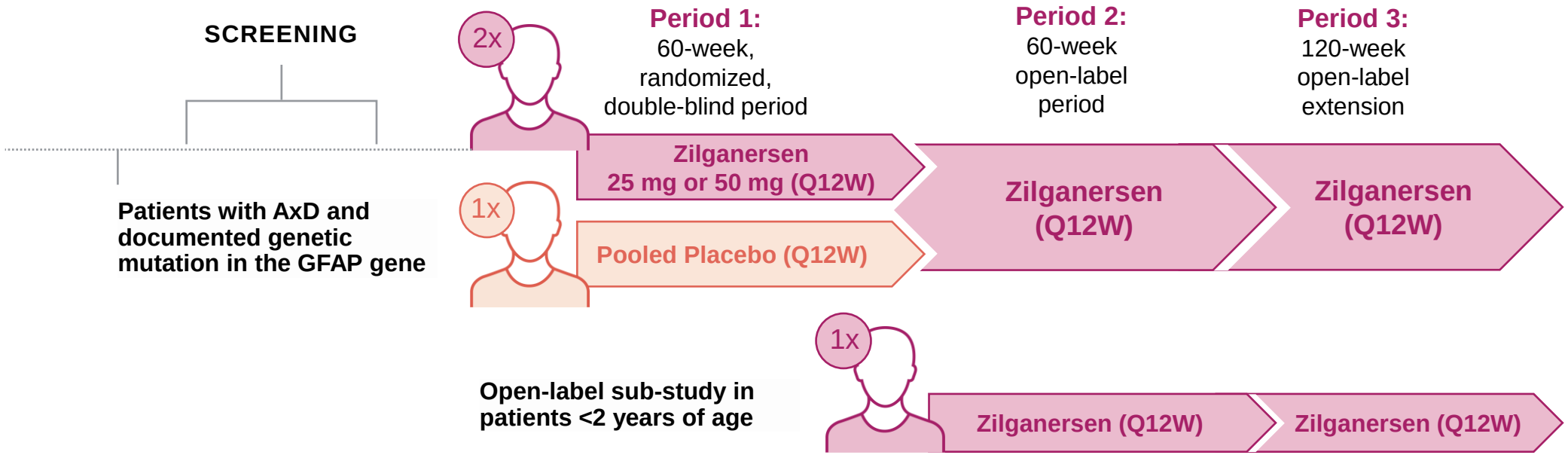
**A global, randomized, double-blind, controlled study in 54 patients** with AxD

**Primary analysis set:** ambulatory patients ≥5 years old at baseline and adults with motor symptoms for <5 years

An open-label sub-study in patients <2 years of age

**PRIMARY ENDPOINT**

**Percentage change in gait speed** as assessed by the **10-Meter Walk Test** (10MWT) at Week 61 in patients **(primary analysis set)**



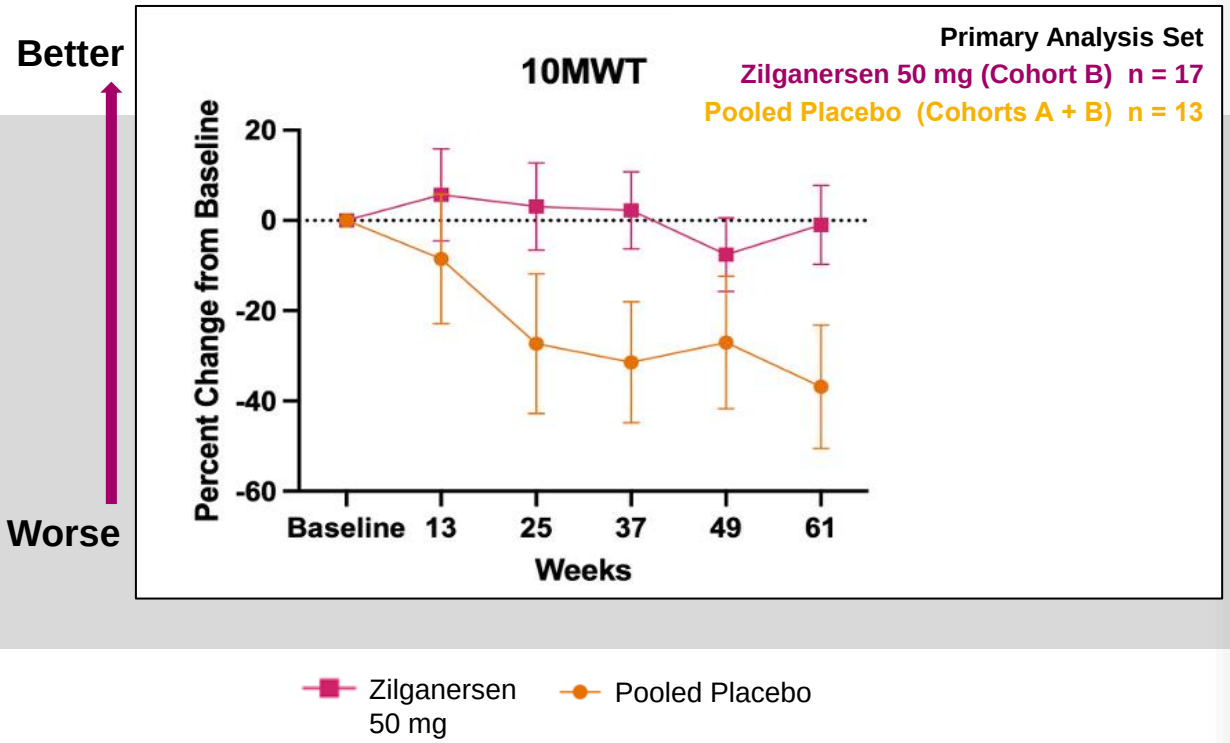
# Zilganersen: Patient Disposition and Analysis Sets

| | 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<br>Male (%)<br>Female (%) | <br>3 (37.5)<br>5 (62.5) | <br>7 (29.2)<br>17 (70.8) | <br>7 (41.2)<br>10 (58.8) | <br>4 (80.0)<br>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: Statistically Significant Difference in Pivotal Study Primary Endpoint[1]




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

**Key secondary endpoints consistently favored zilganersen**

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

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

# 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. Topline pivotal results reported on September 22, 2025. 2. The death was in the 25mg dosing group (not in the primary analysis set) and deemed not related to study drug.

# Angelman Syndrome: Severe Neurodevelopmental Disorder with a Clear Unmet Medical Need

**Jasmine**
living with Angelman syndrome

## Angelman Syndrome
Severe, Rare Neurodevelopmental Disorder[1-4]

**Profound developmental impairment** resulting in need for lifelong, fulltime supervision

Caused by loss of function of the ***UBE3A* gene**

Symptom onset and diagnosis **~2 years old**

**Not progressive**, associated with normal life expectancy

Prevalence: Estimated 1 in 21,000 people with Angelman syndrome worldwide

- >**100,000** people in major geographies

## Clear Unmet Medical Need[5,6]

**No approved disease-modifying treatments**

Current treatments only help to manage some symptoms

1. Yakoreva et al. *A Eur.* J. Hum. Genet. (2019). 2. Luk. Eur. J. Méd. Genet. (2016). 3. Mertz et al. Am. J. Méd. Genet. Part A (2013). 4. Wheeler et al. J *Neurodev Disord*. (2023). 5. Clayton-Smith. *J Med* Genet (2003). 6. Besten, et al. Am. *J. Méd*. Genet. Part A (2021).

# ION582: A Promising New Investigational Medicine for Angelman Syndrome

**Jackson**
living with Angelman syndrome

## ION582

**Promising Investigational Medicine for Angelman Syndrome**, addressing a significant unmet need with no approved disease-modifying treatments

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

## Positive Results Seen in the HALOS Study[1]

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

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

**Infant cohort recently added, with first patient dosed**

**Long-term data continues to support development**

## Robust Pivotal Phase 3 REVEAL Study Now Underway[2]

Full enrollment expected next year[3]

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

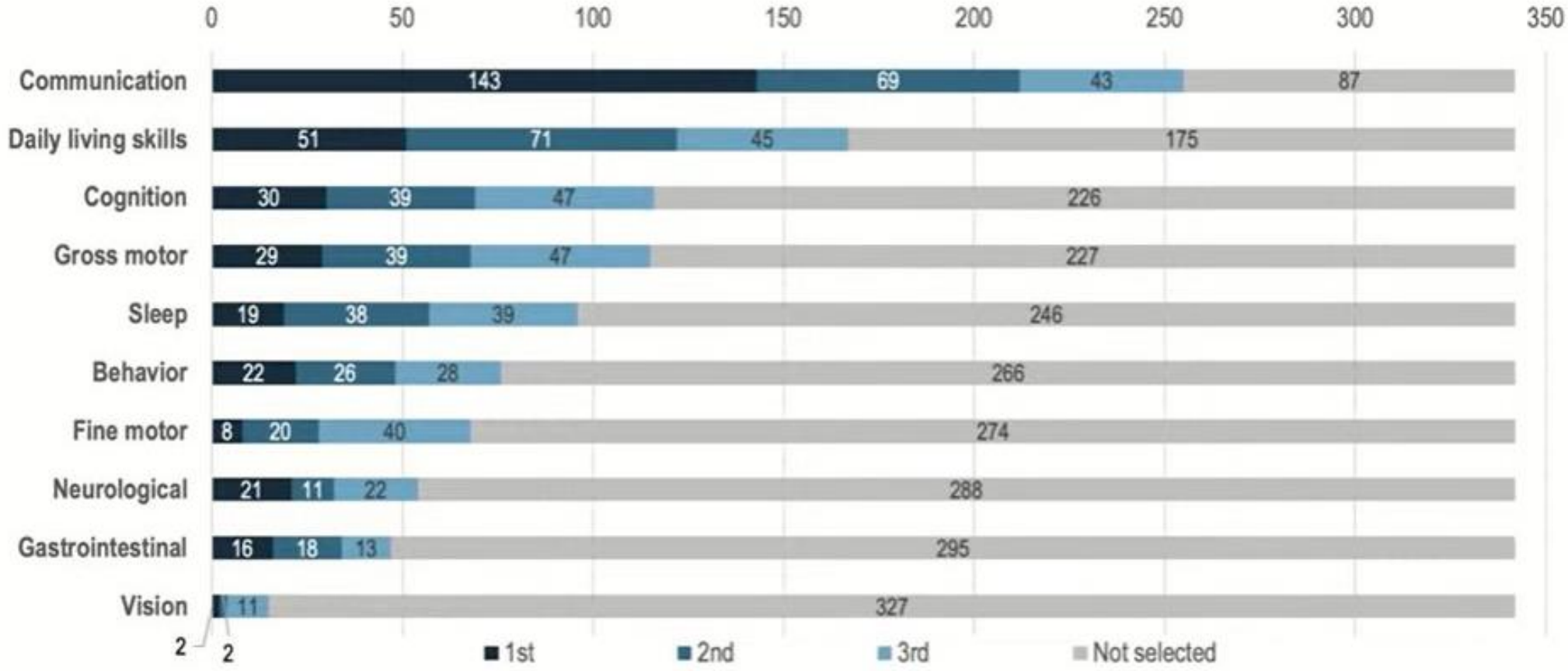
IONIS

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

# Most Impactful Symptom for Families of People Living with Angelman Syndrome: Communication

ASF/FAST survey from Angelman syndrome EL-PFDD meeting in April 2025[1]

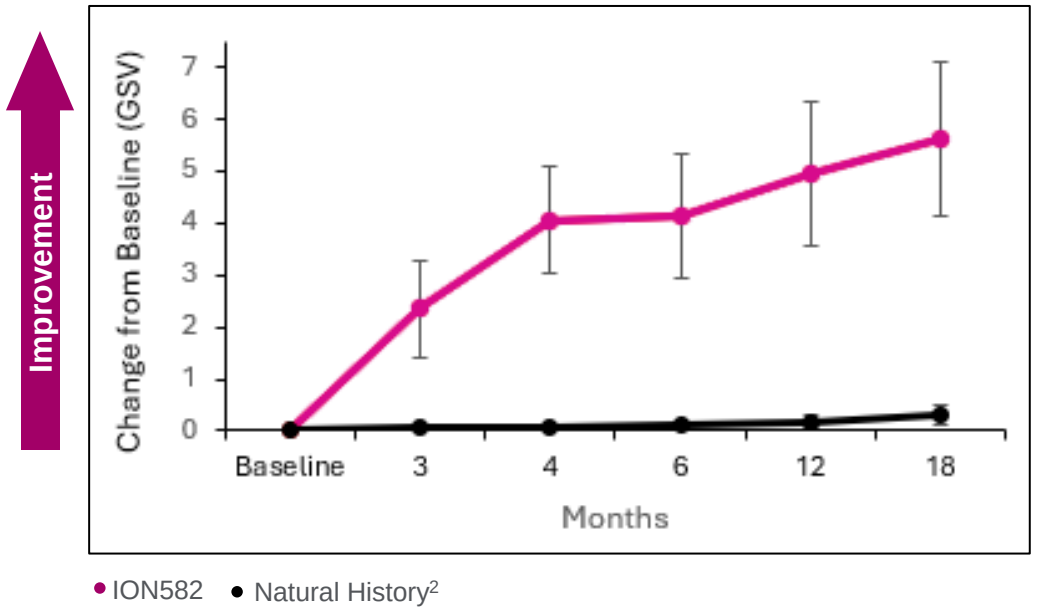
**Top 3 'symptom domains' having most impact on individuals with Angelman syndrome**




1. ASF and FAST Hope in Action Survey results from the April 7, 2025, Externally-led PFDD meeting. Survey included n=342 caregiver respondents, reporting on people living with Angelman Syndrome who were 53% male, 64% deletion, 16% mutation and 13% UPD/ID, with a mean age 11.3 years (1-51). Meeting recording available: https://angelmanadvocates.org/el-pfdd-meeting. Voice of the Patient report pending.

# 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]

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

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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

# ION337: Potential Best-in-Class Medicine for Dravet Syndrome Utilizing Ionis' NMA Technology

**Karly**
living with Dravet syndrome

## Dravet syndrome (DS)

A serious, rare genetic epilepsy with no approved disease-modifying treatment[1]

For >85% of patients, DS is caused by loss of function in the ***SCN1A* gene,** and a subsequent decrease in Nav1.1 function[2]

**15-20%** of **children** and **adolescents** with DS die before adulthood[3]

Prevalence: **>35,000** people in major geographies[1], ~1:16,000 (incidence)[4]

## ION337

Is designed to ***upregulate SCN1A***

Utilizes **Ionis' NMA chemistry** to improve potency of ASOs that modulate splicing

First in-Patient (FIP) **study** of ION337 to **start in H1:2026**[3]

Plan to evaluate **extended dosing interval** in FIP study

1. Gao et al. *J Clin Med*, 2023 2. Hollenack 2019 (US); Schubert-Bast 2022 (Germany); Bjurulf 2022 (Sweden). Includes: U.S., EU and UK. 2. Carvill et al. *Neurology*, 2014 3.Cooper et al. Epilepsy Research, 2016 4. Symonds 2021 (Scotland); Brunklaus 2012 (UK); Bjurulf 2022 (Sweden); Ishii 2017 (Japan). 3. Based on current timing estimates, subject to change.

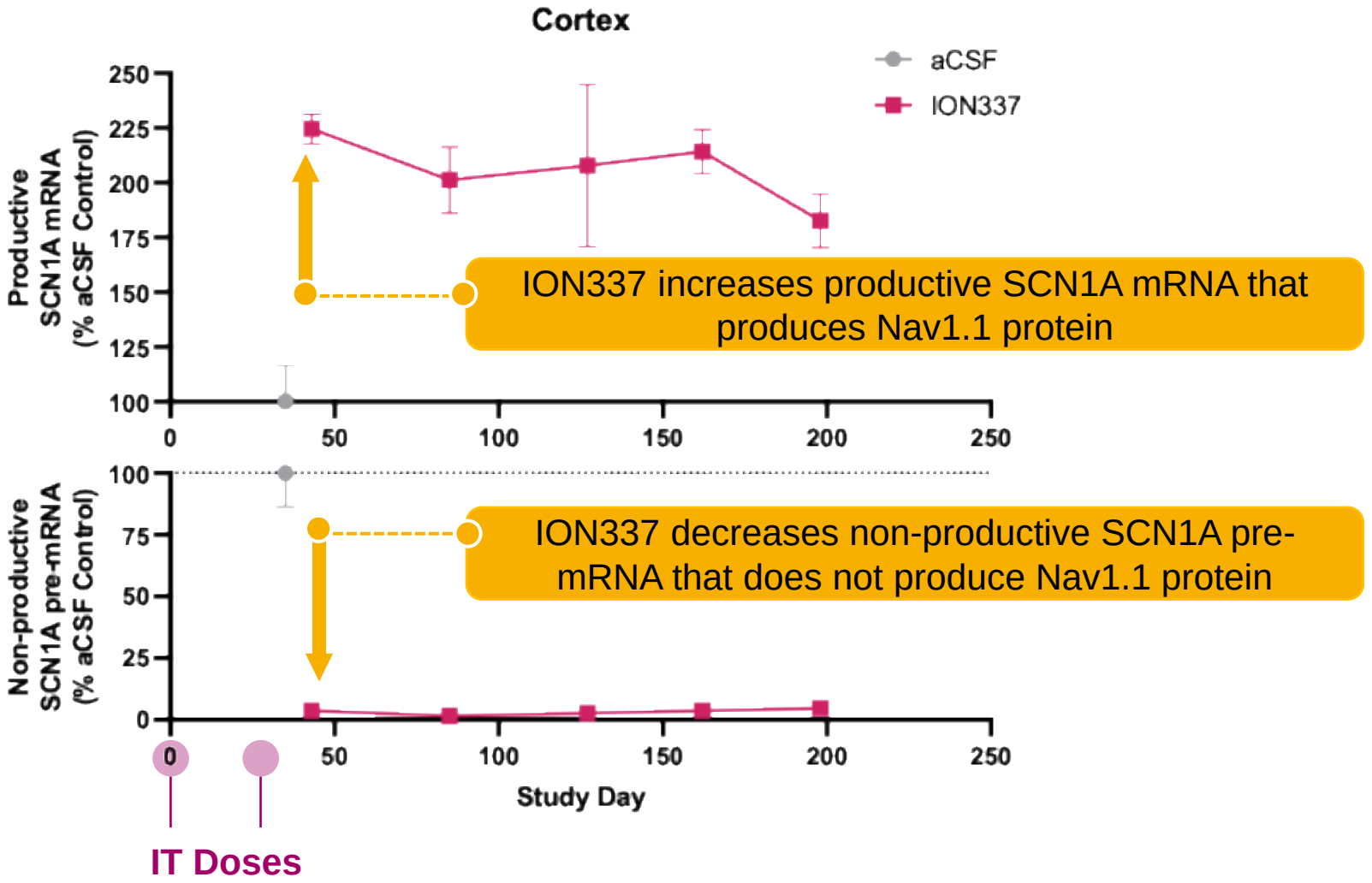
# ION337 Achieves Potent and Durable Splice Modulation of SCN1A in Non-Human Primates[1]

## ION337

A potent splice modulator utilizing **Ionis' proprietary NMA technology**

ION337 in non-human primates (NHP) achieves **maximal and sustained modulation of SCN1A** for up to 24 weeks[2]

Preclinical profile of **ION337** - potency, durability and safety - supports **sustained maximal splice modulation** in patients with **infrequent dosing**

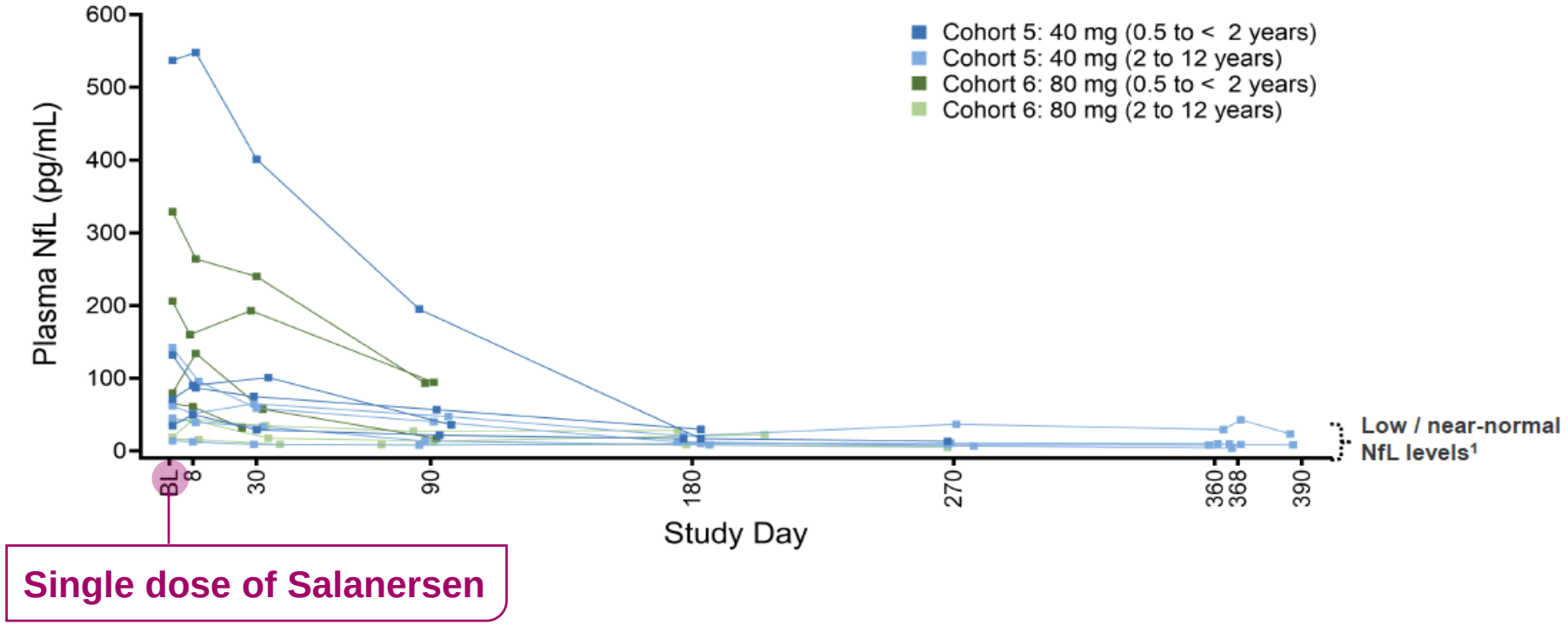



1. ASO delivered IT to juvenile cynomolgus NHP on study days 1 and 28, n=3 ION337 treated animals per timepoint. Exon inclusion/exclusion SCN1A qPCR data normalized to n=6 aCSF treated NHP necropsied on day 35. Data presented is from the frontal cortex.2. Time from second dose.

# Proof Point — Ionis NMA Chemistry in SMA Trial Improved Potency and Supported Extended Dosing

Salanersen interim Phase 1 biomarker data supports extended dosing with Ionis' proprietary NMA chemistry

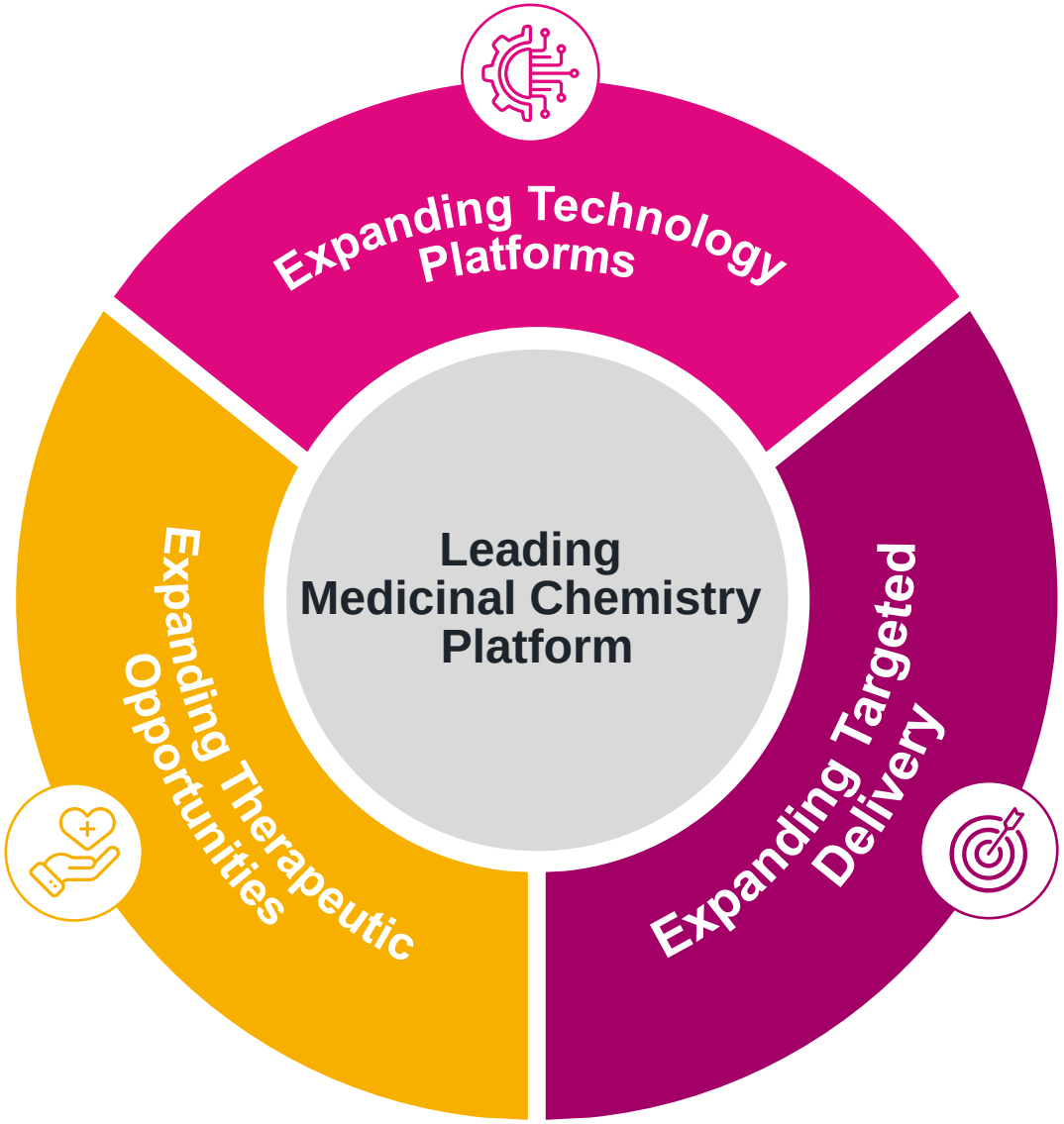
**Salanersen** using Ionis' NMA splice modulating **antisense oligonucleotide (ASO)** targeting SMN2, to increase full length SMN protein




**Plasma neurofilament light chain (NfL) was reduced by 70% in SMA patients at Day 180**

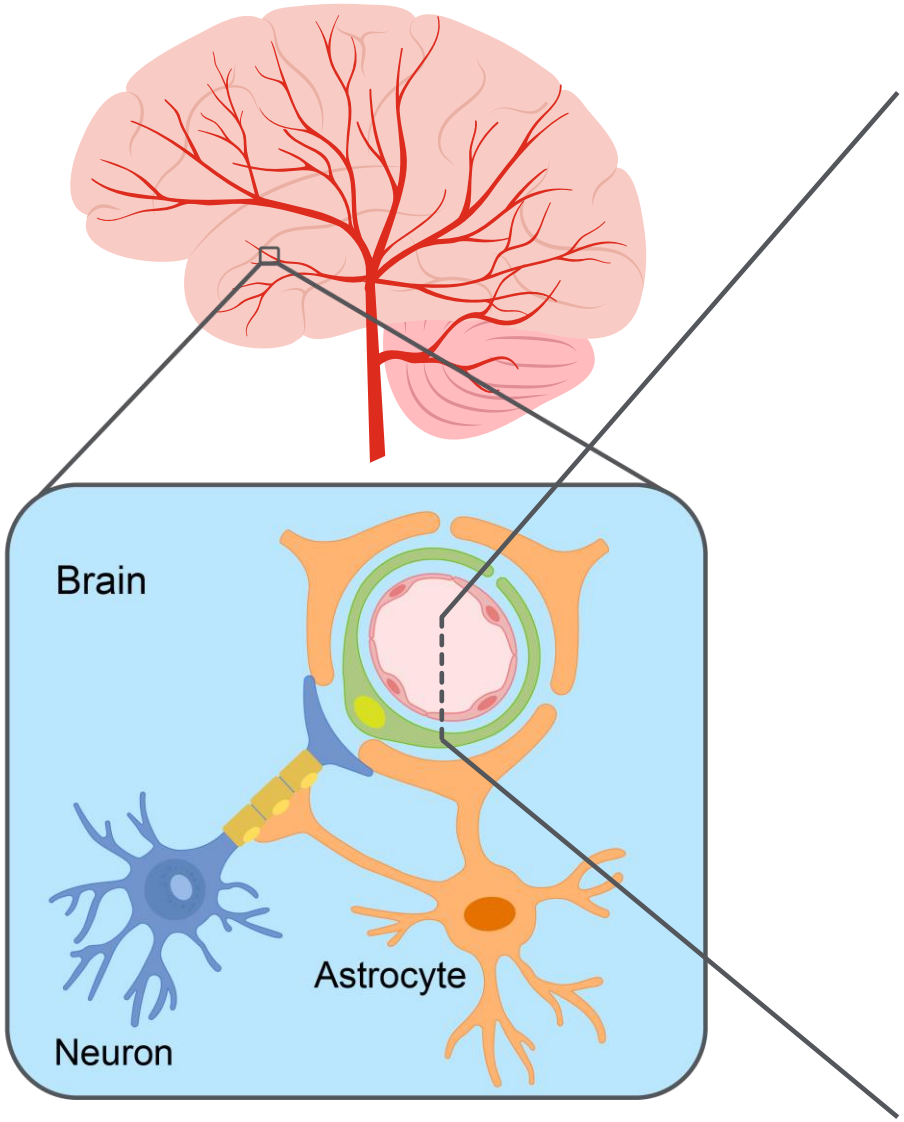
**Reductions were sustained at 1 year following treatment with Salanersen[1,2]**

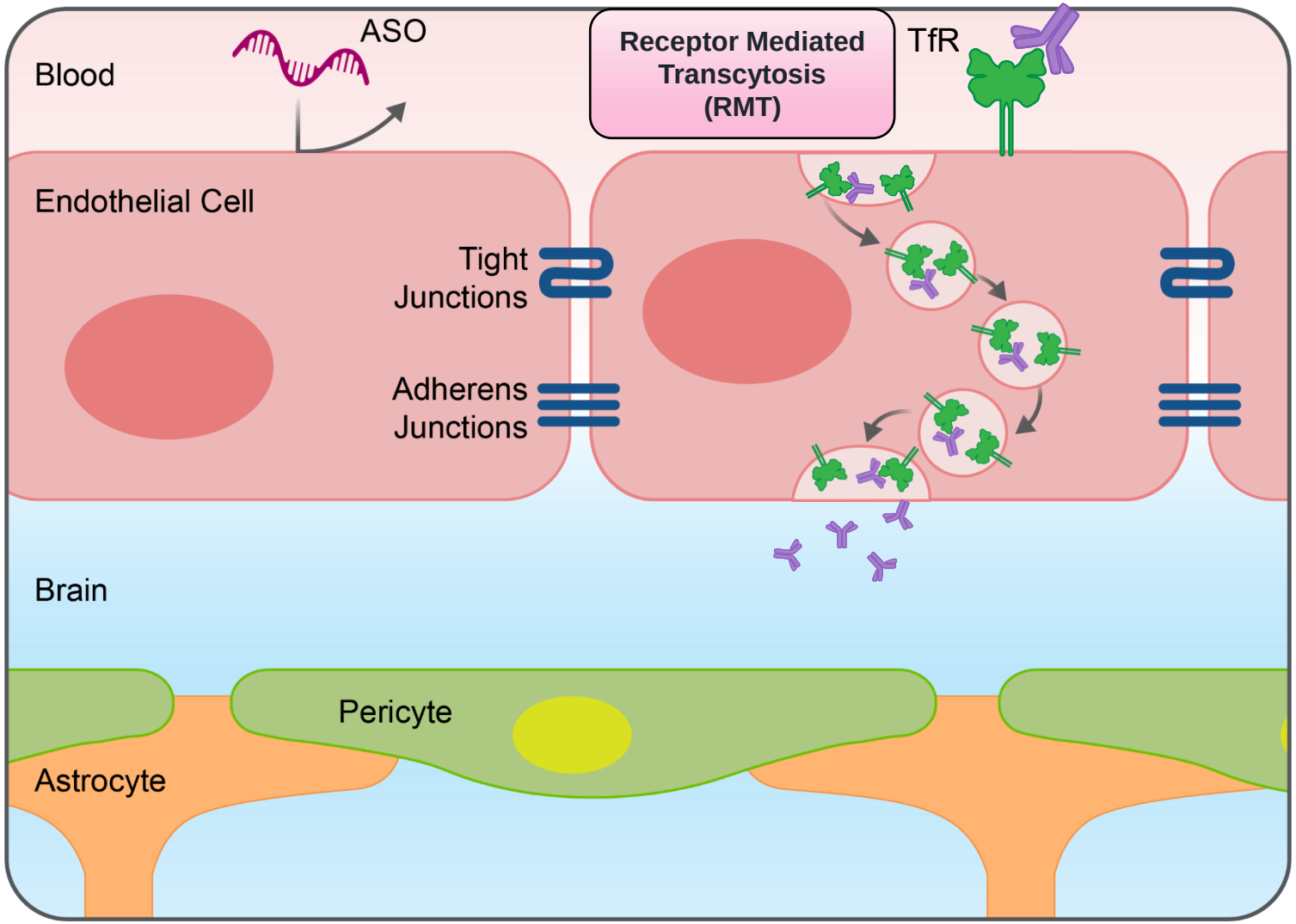
1. In SMA patients with elevated baseline concentrations; Elevated baseline defined as exceeding 95th percentile for serum in neurologically healthy children of similar ages. Patients enrolled were previously on gene therapy with poor response 2. Kotulska-Jóźwiak et al. Cure SMA 2025.




# Accelerating Innovation to Strengthen Leadership in RNA-Targeted Medicines

# Next Cutting-Edge Innovation:
# Systemic Delivery Across the Blood Brain Barrier



# Systemic CNS Delivery: Potential to Transform Our Leading Neurology Portfolio

## Key Initiatives

- **Delivering** oligonucleotides across the **blood brain barrier (BBB)** would enable **multiple new opportunities** in neurology
- Harnessing **VHH** 'nanobody' as first delivery system to cross the **BBB**[1]
- Advancing Bicycle delivered Ionis RNA therapeutic to deliver therapeutics across the BBB with SubQ dosing

## Ionis Advantages

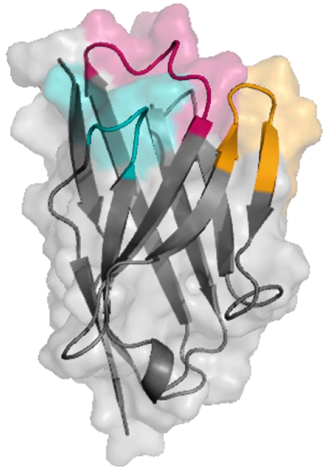
- Combines **Ionis expertise** in RNA-therapeutics for the CNS with **VHH-technology**
- Early data with Ionis siRNA and VHH delivery in NHP is **best-in-class**
- Advancing small peptide technology for convenient **SubQ delivery**

1. Licensed technology from Vect-Horus.

# Targeted Delivery with VHH Conjugated to Industry-Leading ASO and siRNA Therapeutics

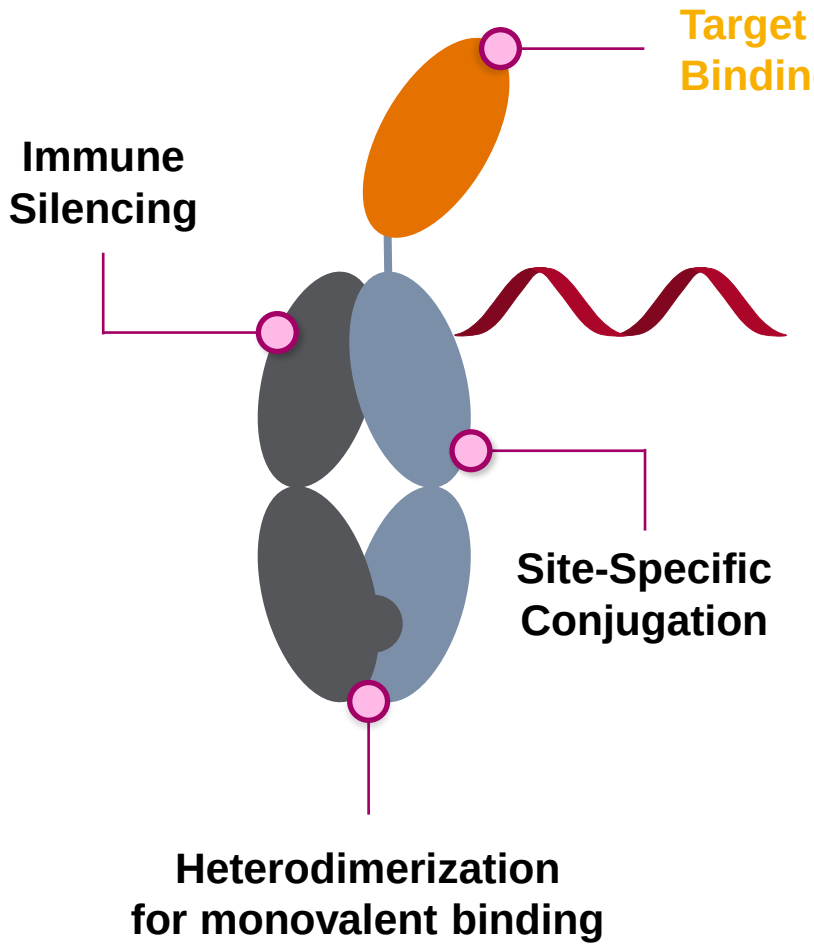
Monovalent VHH-Fc fusions with site specific bioconjugation to ASO and siRNA therapeutics

## Vect-Horus VHH

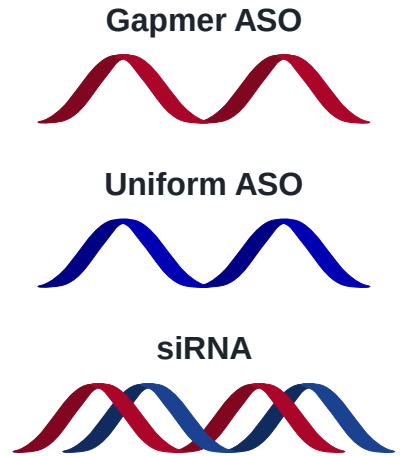


Over **100** unique variants

**Human-Cyno-Mouse** Reactivity




## Ionis Oligonucleotides

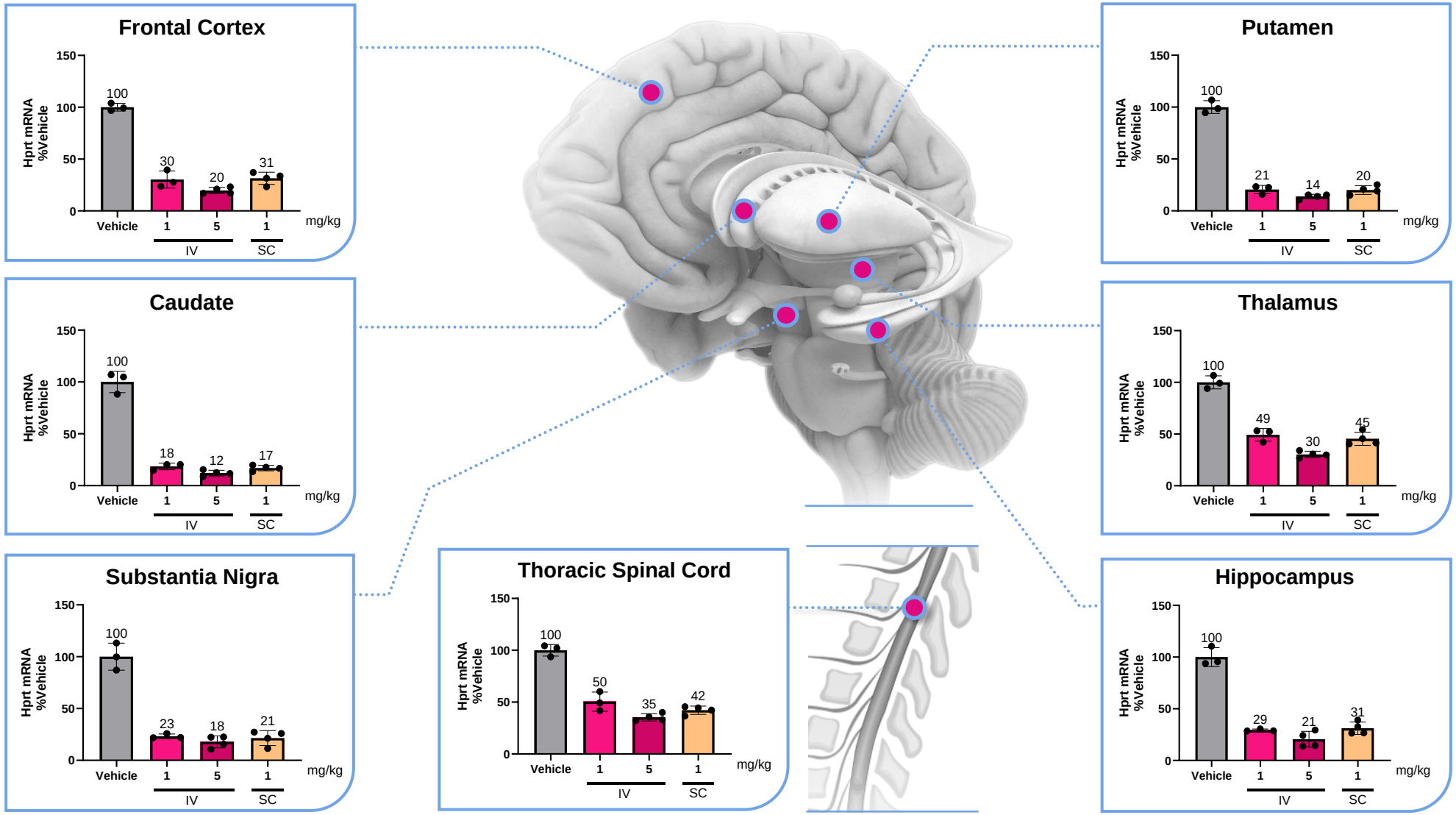



**Industry-leading** chemistries

**Multiple** therapeutic indications

**Extensive** clinical validation

# Successful Systemic Delivery via IV and SubQ Delivery to Non-Human Primate Brain with VHH Delivered siRNA[1]




**Strong Target Reduction in Deeper Brain Regions**

1. NHP treated with vehicle or VHH conjugated Hprt siRNA delivered intravenously (IV) at 1 or 5 mg/kg or subcutaneously (SC) at 1mg/kg. mRNA quantified by qPCR and normalized to vehicle treated NHP.

# Key Neurology Program Events: Late 2025 and 2026[1]

## Early and Mid-Stage Clinical Events

**ION356**
(PLP1)
Complete Phase 1/2 enrollment (PMD)

**ION337**
(SCN1A)
First-in-patient study start (Dravet syndrome)

**Wholly Owned Neuromuscular Program**
Advancing in IND-enabling toxicology (undisclosed)

## Mid-Stage Data

**ION464**
(SNCA)
Phase 1/2 data (Multiple System Atrophy)

**IONIS-MAPT$_{Rx}$**
(TAU)
Phase 2 data (Alzheimer's disease)

**ION717**
(PRNP)
Phase 1/2 data (Prion)

**Tominersen**
(HTT)
Phase 2 data (Huntington's disease)

## Phase 3 Clinical Events

**ION582**
(UBE3A-ATS)
Enrollment completion (Angelman syndrome)

**Ulefnersen**
FUSION data (FUS-ALS)

**Salanersen**
(SMN)
Study start (SMA)

## Regulatory Events and Product Launches

**Zilganersen**
(GFAP)
U.S. submission & approval (Alexander disease)

**Higher Dose Nusinersen**
(SMN)
U.S. & EU approval (SMA)

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.

# Leading the Way in the Treatment of Neurological Diseases

- Strong track record in delivering **first-in-class** medicines
- **Advancing high-value pipeline** of wholly owned and partnered medicines
- Focused on continuous **innovation** and **advancing proven technology**
- Well-positioned to deliver a **steady cadence of medicines to people with serious diseases**

# Poised to Deliver Transformative Neurology Medicines to People in Need

**Kyle Jenne**
Chief Global Product Strategy Officer

# Executing on Established Strategy to Expand Wholly Owned Neurology Portfolio

## Right Targets

Focus on **disease-modifying** targets for patients with significant need

Select targets **central to disease** with high **transformative** potential

## Right Development Path

Select targets with tools that enable **efficient drug development**

Streamlined development paths with opportunities for **rapid proof of concept**

## Right Commercial Fit

**Innovative** commercial **organization** to **reach** patients and leverage **synergies across multiple medicines**

# Building a Successful Neurology Commercial Portfolio[1,2]

**Commercial Synergies**

- Focus on centers of excellence
- Leverage patient services across medicines

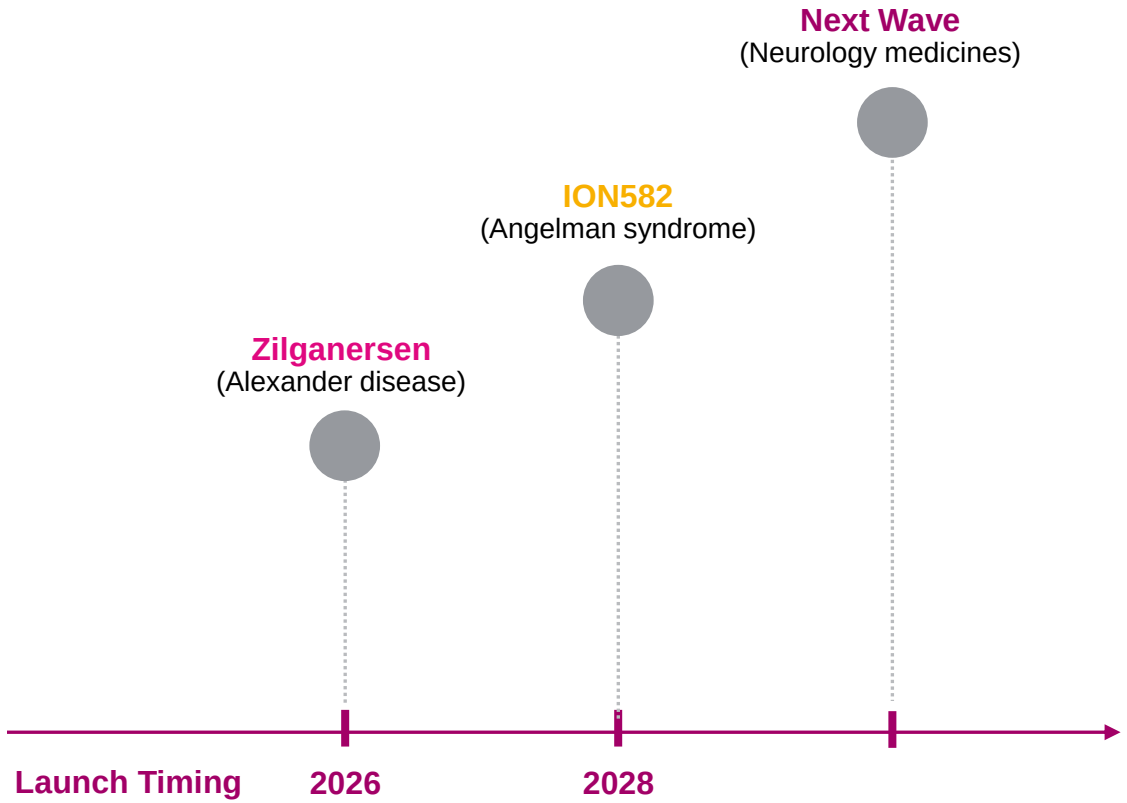
**Disease Education**

- Focus on patient identification, genetic testing and guidelines
- Emphasis on field medical support

**Expanding Reach**

- Deploy broad range of tools to reach HCPs and patient community

**Each neurology launch unlocks additional synergies, accelerating growth opportunities**




1. Assuming approvals. 2. Timing expectations based on current assumptions and subject to change.

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

## Substantial Unmet Need

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

**No approved disease-modifying treatments**

## Well-Established Patient Community

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

## Strategy to Reach Patients

**Evaluation** and **diagnosis**

**Treatment management**

**Fulfillment** and **adherence**

IONIS

1. Assuming approval. 2. Timing expectations based on current assumptions and subject to change.

# Innovative Commercial Organization with Proven Ability to Bring Medicines to People with Serious Diseases

**Top-Tier Team**

**Demonstrated Strong Initial Launch Execution**

**Scalable Capabilities for Future Launches**

# Creating Substantial Value through Accelerating Growth

**Beth Hougen**

Chief Financial Officer

# Creating Substantial Value through Accelerating Growth[1]

## Substantial, Sustained Value Creation

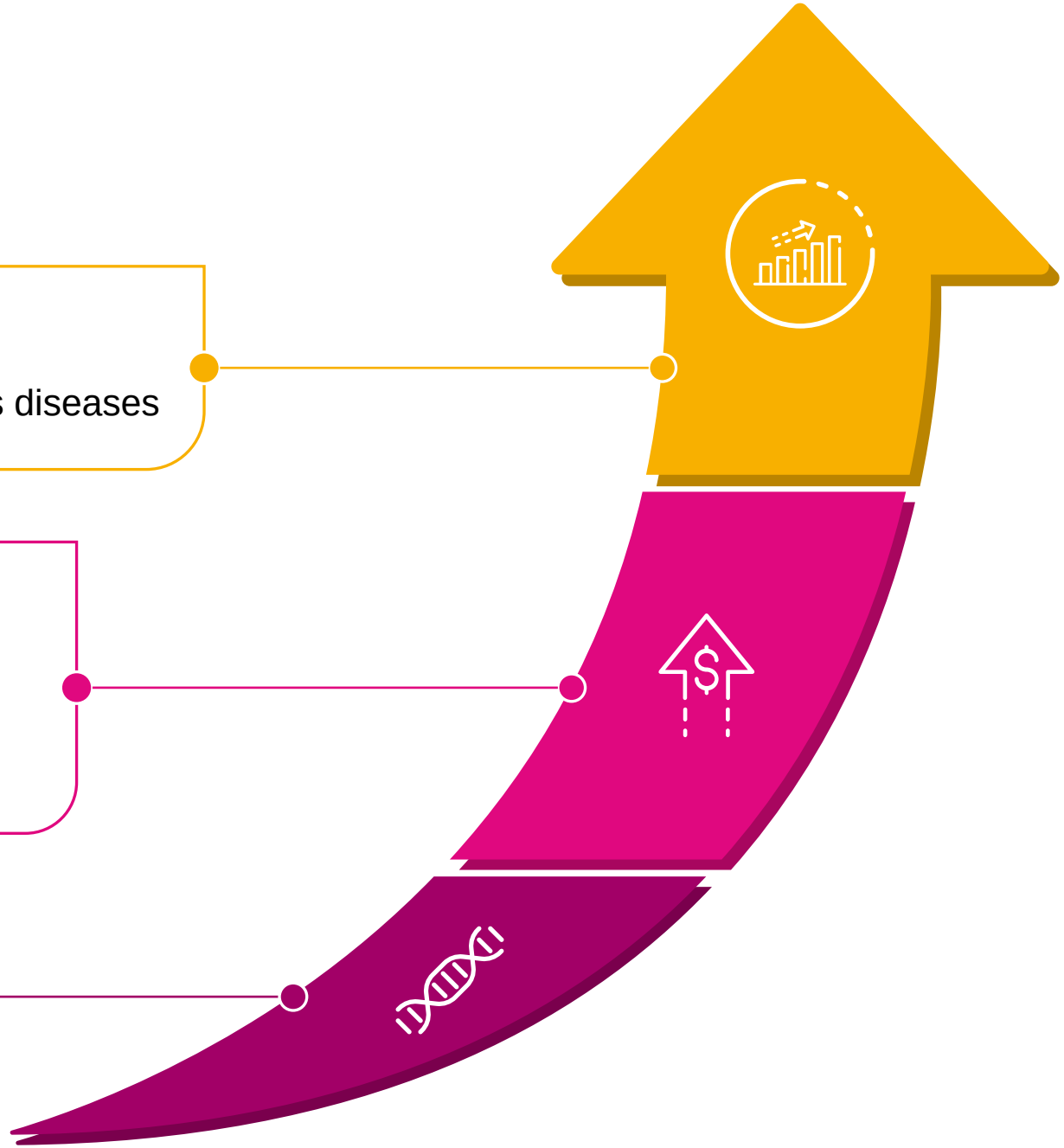
Steady cadence of transformational medicines for serious diseases

## Accelerating Growth

- Ongoing and upcoming launches
- High-value focused pipeline advancing
- Substantial and differentiated technology advancements

## Strong Foundation

- Commitment to innovation
- Proven drug discovery and development engine



1. Based on current assumptions, subject to change.

# Well Positioned to Execute on Value-Generating Priorities[1]

**Substantial Cash Resources**

**~$2.0B**
in cash (FY25 guidance)

**Efficient Capital Structure**

**Low-Cost, Well-Structured Debt**
supports long-term plans

**Disciplined Expense Management**

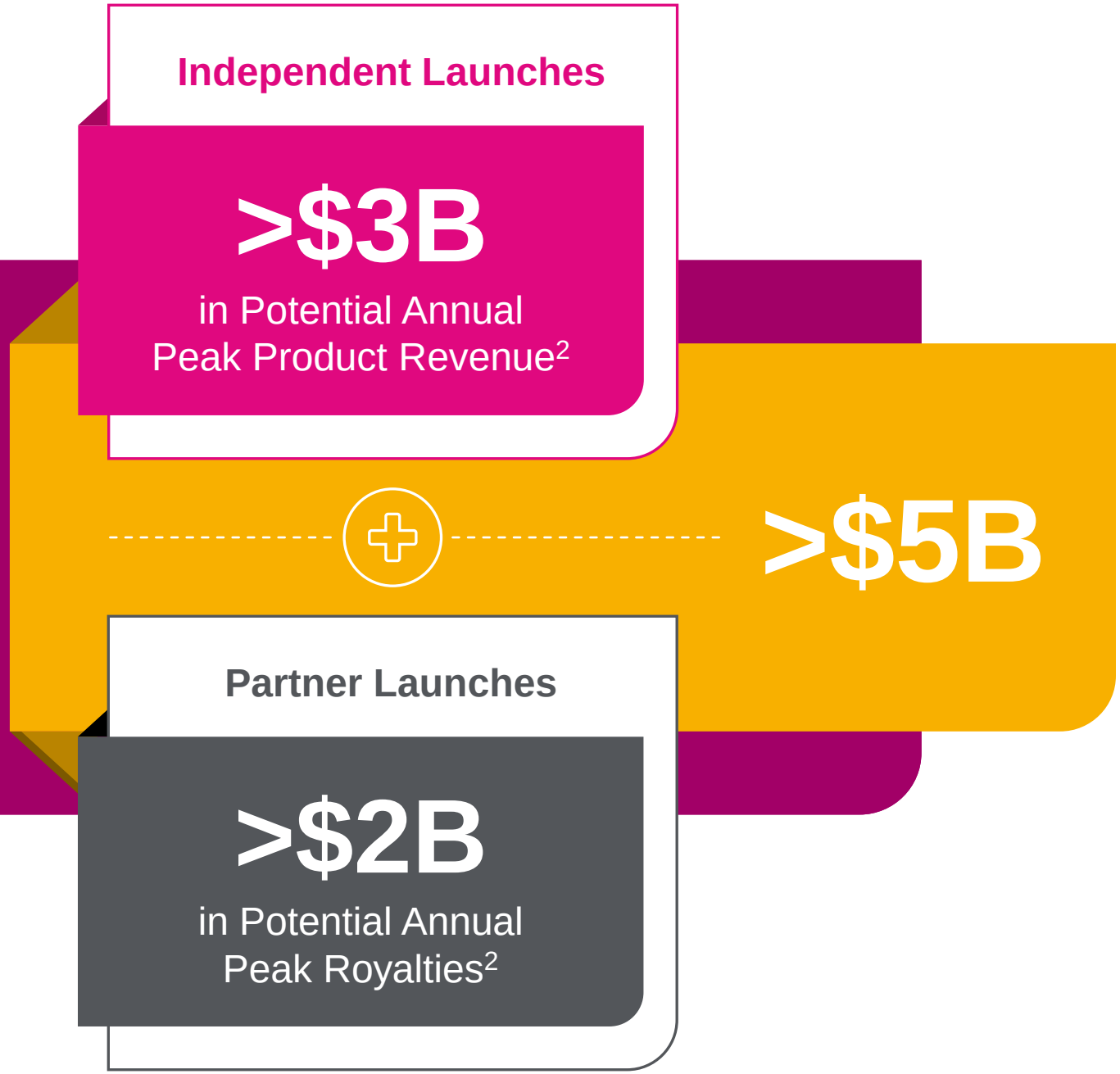
**R&D Expenses**
remaining stable

**SG&A Expenses**
investment in-line with launches

**Investing for Growth is Ionis' Top Capital Allocation Priority**

1. Based on current assumptions, subject to change.

# Recent Launches and Late-Stage Medicines Provide Substantial Revenue Growth Opportunity[1]

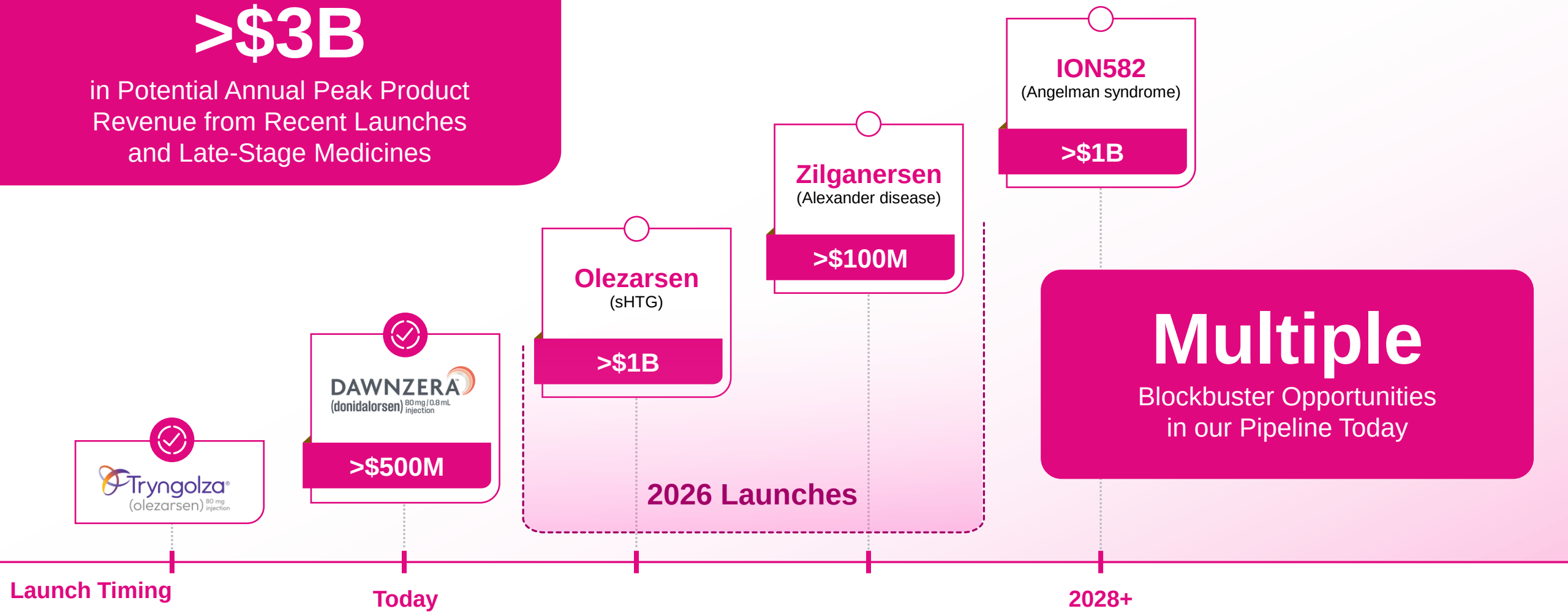



1. Assuming approval. Estimated timing of potential U.S. approval based on current assumptions and subject to change. 2. Peak sales estimates based on current estimates and subject to change. Partnered royalties based on public disclosure made by the respective partner and Ionis' contractual royalty rates for each medicine.

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

**>$3B**

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

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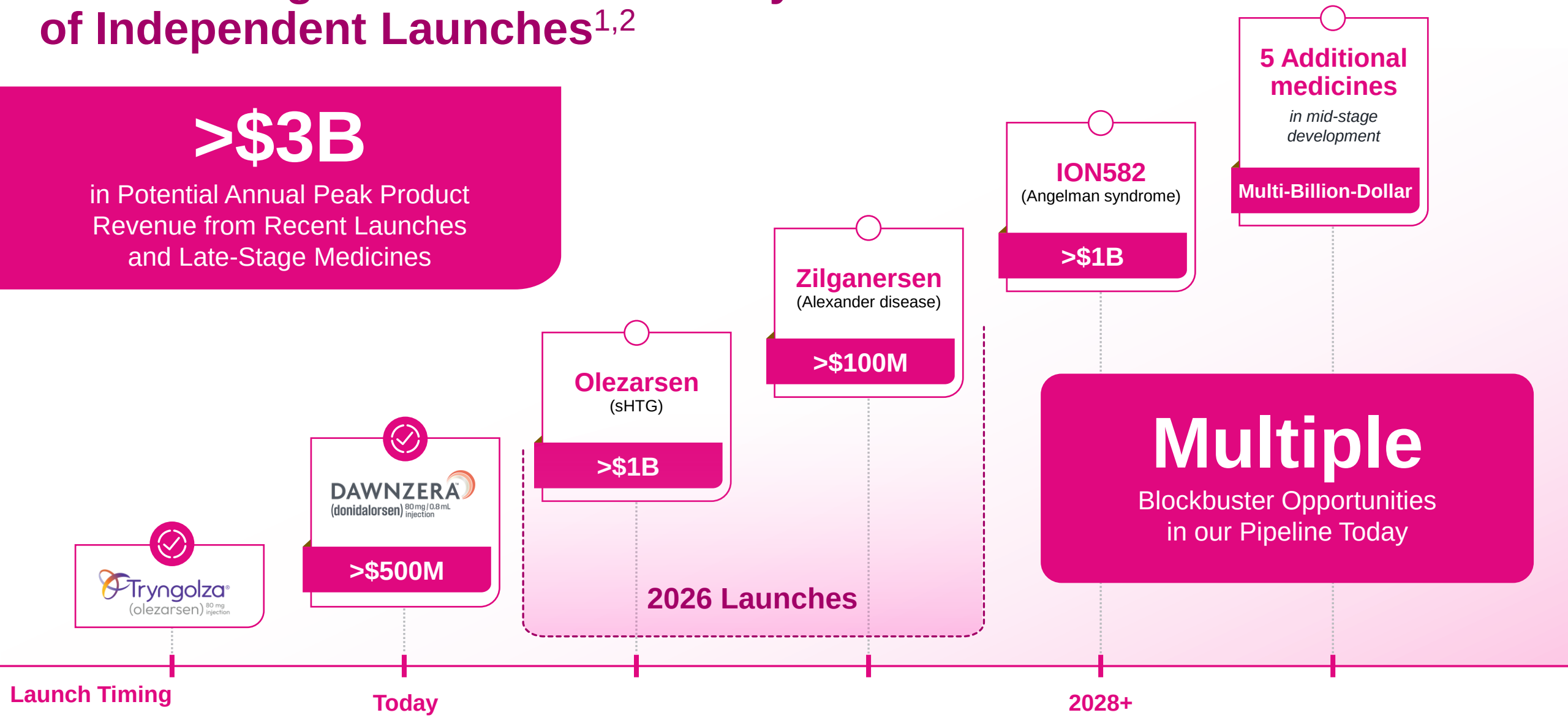



1. Assuming approval. 2. Based on current estimates, subject to change.

# Significant Upside Potential from Late-Stage Partnered Programs

**>$6B**

in Remaining Partner Payments

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

**Royalties**

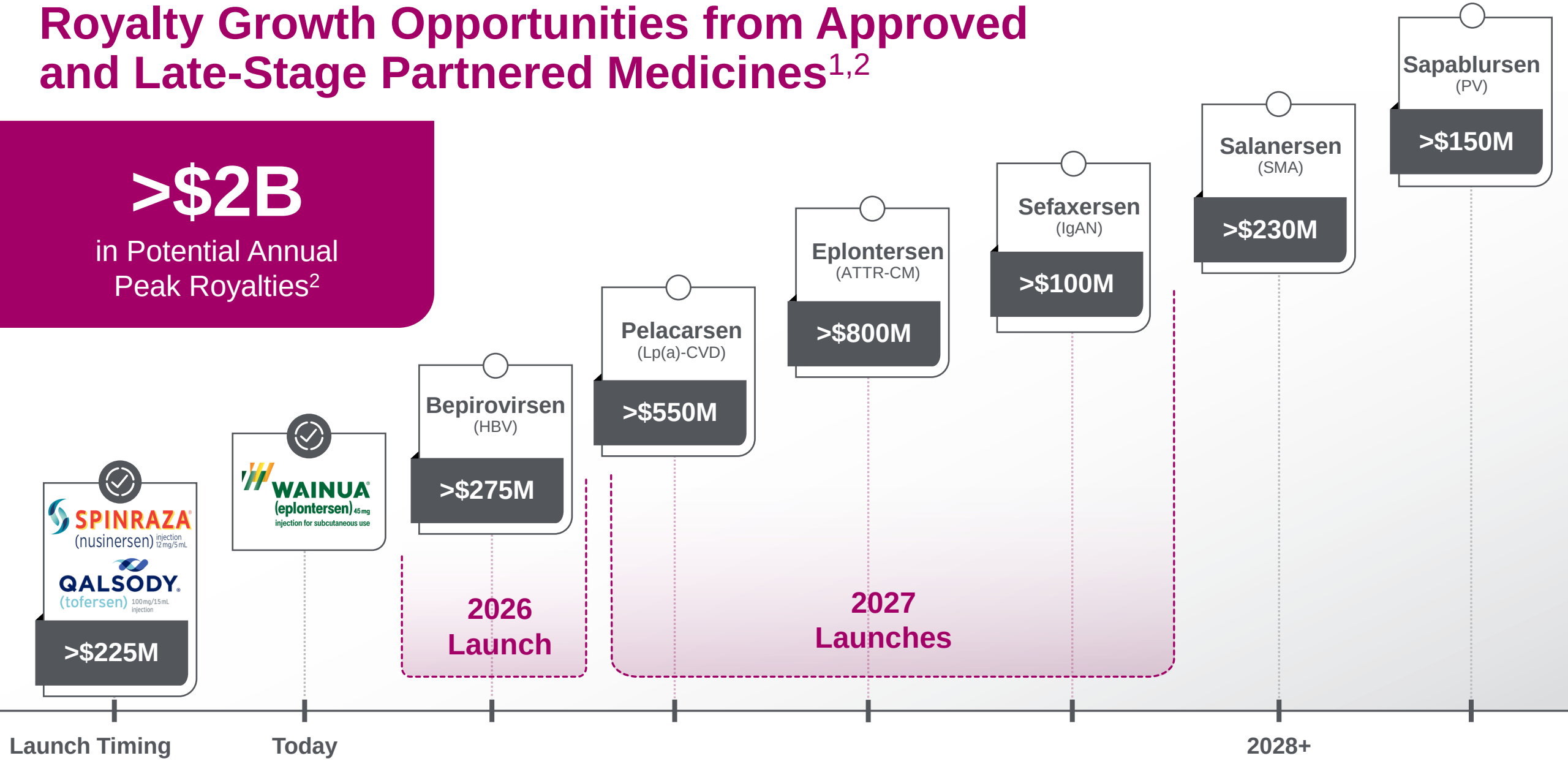
**Nearly All Partner Revenue Drops to the Bottom Line as Profit**

| | Total Remaining Payments | Royalties |
|---|---|---|
| **Bepirovirsen**<br>HBV | **~$200M** | Tiered, up to low teens |
| **Pelacarsen**[2,3]<br>Lp(a)-CVD | **$1.3B** | Tiered, mid-teens to low 20% |
| **WAINUA**<br>ATTRv-PN<br>ATTR-CM | **$3.3B** | US: mid-20%<br>OUS: Tiered up to high teens |
| **Sefaxersen**<br>IgAN | **>$390M** | Tiered, high-teens to 20% |
| **Salanersen**<br>SMA | **>$550M** | Tiered, mid-teens to mid-20% |
| **Sapablursen**<br>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.

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

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

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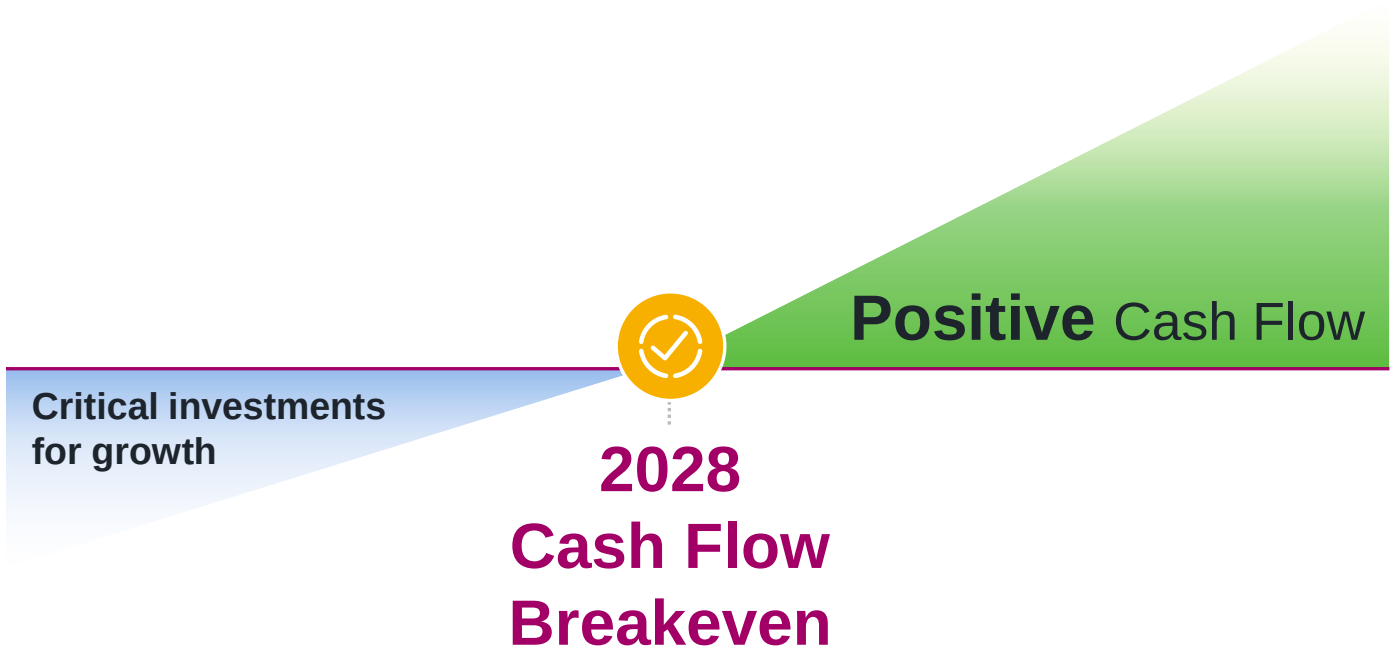
# Clear Path to Sustained Positive Cash Flow[1]




## Key Drivers

- Growing revenue from **new product launches**
- **Growing royalty revenue** from multiple marketed medicines and additional medicines poised to reach patients in the short- and mid-term
- **Strong foundation** with substantial recurring R&D revenue from multiple sources
- Commitment to **disciplined expense management**

1. Based on current assumptions, subject to change.

# Creating Substantial Value through Accelerating Growth

## Strong Financial Foundation

**~$2.0B** of **cash** and short-term investments[1]

**Efficient capital structure**

**Disciplined expense management**

## Accelerating Growth

Ongoing and upcoming **independent launches** to power **growth**[2,3]

**Significant upside** potential from **partner launches**

## Substantial, Sustained Value Creation

**Steady cadence** of **transformational medicines** for serious diseases

**Strong revenue growth**[2,3]

**Clear path to sustained positive cash flow**[2,3]

**2028 cash flow breakeven**[2]



1. FY2025 guidance. 2. Based on current estimates, subject to change. 3. Assuming approval.

# Q&A

**Brett Monia, Ph.D.**
Chief Executive Officer

**Beth Hougen**
Chief Financial Officer

**Kyle Jenne**
Chief Global Product Strategy Officer

**Kenneth Newman, M.D.**
SVP, Clinical Development

**Holly Kordasiewicz, Ph.D.**
SVP, Neurology

# Accelerating Growth through Life-Changing Medicines

**Brett Monia, Ph.D.**

Chief Executive Officer

# Well-Positioned to Build on Strong Momentum

Key Upcoming Catalysts[1]

**2**
**NDA Submissions in Next Few Months**

**2**
**Independent Launches Next Year[2]**

**5**
**Phase 3 Data Readouts in 2026**

**Multiple**
**Phase 2 Data Readouts in 2026**

**≥2**
**Phase 3 Study Starts in 2026**

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

# Accelerating Growth through Life-Changing Medicines

**Building a Leading Cardiometabolic Disease Portfolio**

**Leading the Way in the Treatment of Neurological Diseases**

**Accelerating Revenue Growth[1,2]**

**2028 Cash Flow Breakeven[1]**

**Clear Path to Sustained Positive Cash Flow[1]**

## Sustained Value Creation

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

# Transforming Human Health through RNA-Targeted Medicines











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Innovation Day 2025:

# Accelerating Growth through Life-Changing Medicines

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