sHTG FDA Approval

TRYNGOLZA®:
Indicated as an adjunct to diet to reduce triglycerides (TG) and the risk of acute pancreatitis in adults with severe hypertriglyceridemia
(sHTG: TG greater than or equal to 500 mg/dL)

June 2026

Nasdaq: IONS

Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of TRYNGOLZA and our other commercial medicines, additional medicines in development and technologies and our expectations regarding development and regulatory milestones. Any statement describing Ionis' goals, expectations, financial or other projections or guidance, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties including but not limited to those related to our commercial products and the medicines in our pipeline, and particularly those inherent in the process of discovering, developing and commercializing medicines that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such medicines. Ionis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Ionis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Ionis. Except as required by law, we undertake no obligation to update any forward-looking statements for any reason. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Ionis' programs are described in additional detail in Ionis' annual report on our Form 10-K for the year ended December 31, 2025, and our most recent Form 10-Q quarterly filing, which are on file with the SEC. Copies of these and other documents are available at www.ionis.com.

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

On Today's Call

Brett Monia, Ph.D.
Chief Executive Officer

Sam Tsimikas, MD
SVP, Global Cardiovascular Development

Kyle Jenne
Chief Global Product Strategy Officer

Agenda

Topic	Speaker
TRYNGOLZA (olezarsen): The first-ever medicine approved to prevent acute pancreatitis in sHTG	**Brett Monia, Ph.D.,** Chief Executive Officer
TRYNGOLZA (olezarsen): Groundbreaking Clinical Results Support a Broad Indication	**Sam Tsimikas, M.D.,** SVP, Global Cardiovascular Development
TRYNGOLZA (olezarsen): Transforming Treatment in Severe Hypertriglyceridemia	**Kyle Jenne,** EVP, Chief Global Product Strategy Officer
Breakthrough Therapies Driving Accelerating Growth	**Brett Monia, Ph.D.,** Chief Executive Officer
Q&A	

TRYNGOLZA® (olezarsen): First-ever Medicine Approved to Prevent Acute Pancreatitis in sHTG

Brett Monia, Ph.D.
Chief Executive Officer

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NOW APPROVED

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TRYNGOLZA is now approved in the U.S.; see Full Prescribing Information.

TRYNGOLZA:
Poised to Become Ionis' First Multi-Billion Dollar Medicine

- Landmark approval as the **first-ever medicine to prevent acute pancreatitis** in sHTG

- **Highly statistically significant** and **clinically meaningful** reductions in fasting **triglycerides**[1]
- **First and only** treatment to **significantly reduce acute pancreatitis** events in **people with sHTG**[1]

- **Simplicity** of monthly **self-administration** with a patient-friendly **autoinjector**
- 50 and 80mg doses **provide dosing flexibility**

- **First mover** advantage
- Reaffirming **2026 TRYNGOLZA net product sales $100-110M**
- Product to be in the channel in the **coming days**

Annual Peak Product Revenue Opportunity[2]

>$3B

1. Marston NA, Bergmark BA, Alexander VJ, et al. Olezarsen for managing severe hypertriglyceridemia and pancreatitis risk. *N Engl J Med.* 2026;394(5):429-441. doi:10.1056/NEJMoa2512761. 2. Peak sales expectations based on current assumptions and subject to change.

TRYNGOLZA® (olezarsen): Groundbreaking Clinical Results Support a Broad Indication

Sam Tsimikas, M.D.
SVP, Global Cardiovascular Development

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sHTG: A Serious, Underserved Disease[1-6]

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

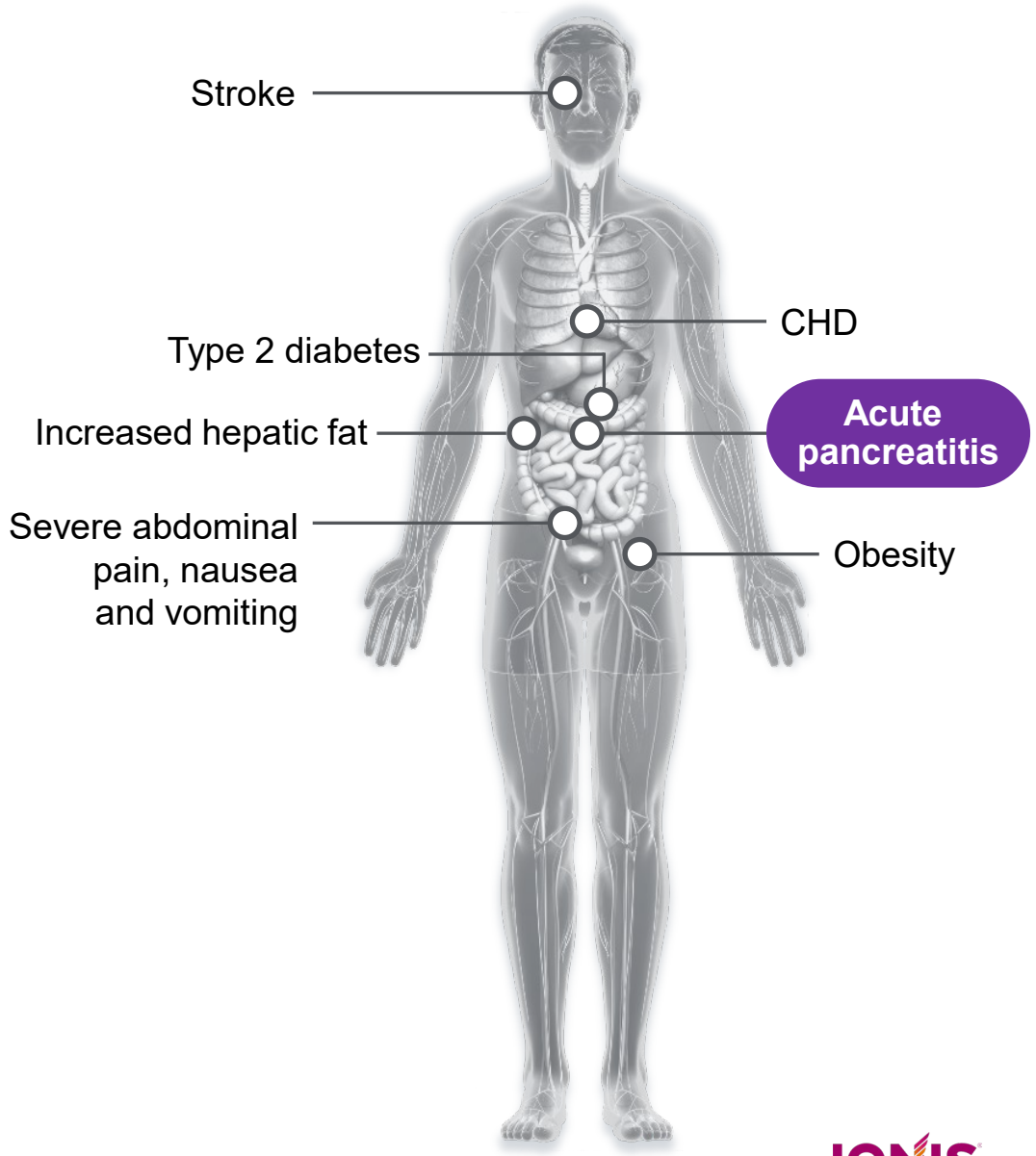
Characterized by **increased risk of acute pancreatitis**, atherosclerotic cardiovascular disease[2]

Driven by combination of **triglyceride gene variants**, **lifestyle**, **obesity**, and **high-risk comorbidities**[2,3]

Limited benefit from legacy treatments[4-7]

>3 million people in the U.S. with sHTG[8-10]

sHTG Clinical Manifestations and Comorbidities



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.*

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

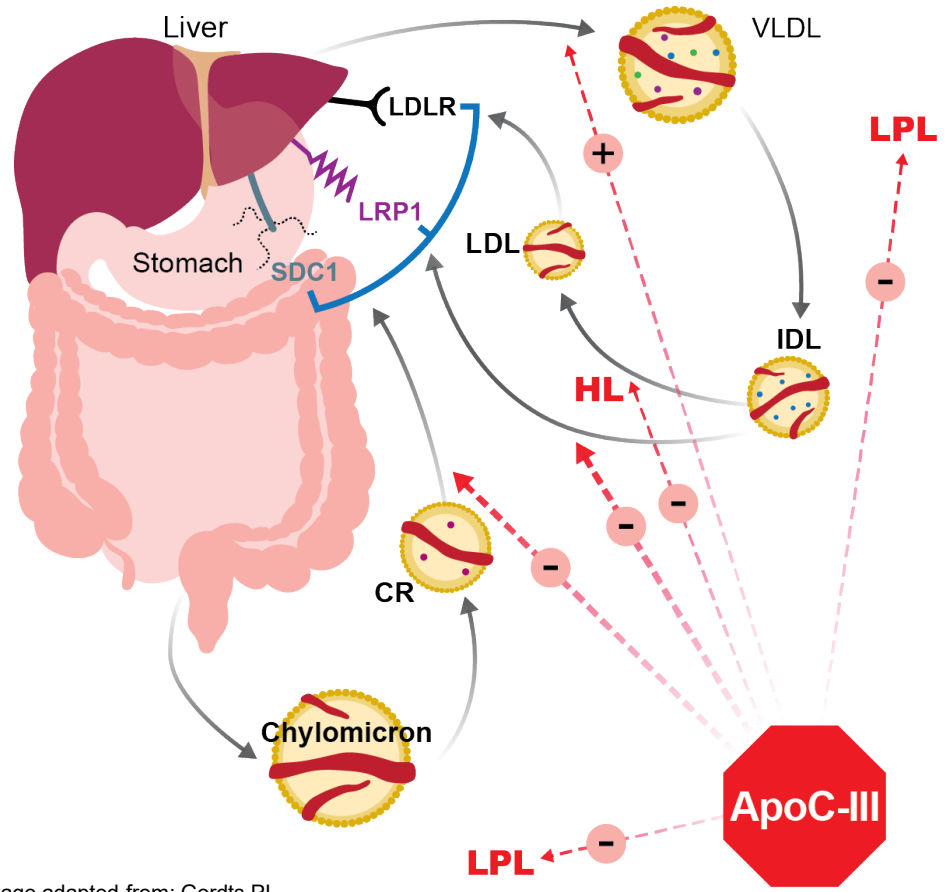


Image adapted from: Gordts PL, et al. *J Clin Invest.* 2016;126:2855

Apolipoprotein C-III (apoC-III)

Key regulator of triglyceride clearance

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

TRYNGOLZA: Designed to reduce the production of ApoC-III

TRYNGOLZA is an ASO-GalNAc3 conjugate that binds to apoC-III mRNA leading to mRNA degradation and resulting in a reduction of serum apoC-III protein

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

TRYNGOLZA 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.

TRYNGOLZA Groundbreaking Phase 3 Program Supported sHTG Approval

Severe Hypertriglyceridemia (sHTG)

CORE a hypertriglyceridemia study

CORE2 a hypertriglyceridemia study

Pivotal studies in people with 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)[1]

Results support safety database

1,478 participants

1. 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.

Vast Majority of Patients Treated with TRYNGOLZA Achieved Triglyceride Levels Below Risk Threshold for Acute Pancreatitis[1,2]

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

Up to a **72%**

placebo-adjusted mean reduction in fasting triglycerides[1,2]

(p<0.0001)

86%

achieved TG levels **below 500 mg/dL**[1,2]

Up to 54%

achieved **normal TG levels** (≤150 mg/dL)[1,2]

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

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TRYNGOLZA: The First & Only Treatment to Significantly Reduce Acute Pancreatitis Events in People with sHTG[1,3]

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

Up to a **91%**

Reduction in acute pancreatitis events compared to placebo at 12 months[3]

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

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

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

1. *The New England Journal of Medicine*, "Olezarsen for Managing Severe Hypertriglyceridemia and Pancreatitis Risk." Marston, et al. 2. Using the mean rates from the binomial regression model, the number of patients needed to treat over one year to prevent one episode of acute pancreatitis was 25 in the overall treatment population (pooled analysis across both doses and studies). 3. From USPI. Data based on the 50 mg dose at 12 months. TRYNGOLZA is now approved in the U.S.; see Full Prescribing Information.

Favorable Safety and Tolerability Observed in the CORE and CORE2 Studies[1]

Serious adverse events (SAEs) occurred less frequently with TRYNGOLZA

Adverse events (AEs) were generally balanced

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

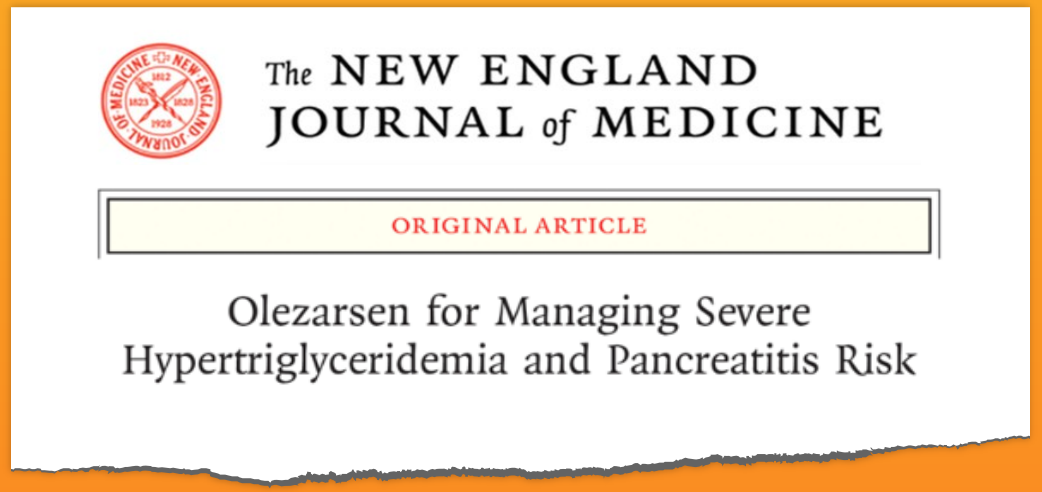
Key Safety Parameters

Pooled analysis across CORE and CORE2

	Placebo (n=356)	TRYNGOLZA 50 mg (n=354)	TRYNGOLZA 80 mg (n=351)
Treatment-emergent adverse events:			
Any	75%	75% *P=0.86*	76% *P=0.64*
Leading to drug discontinuation	2%	3% *P=0.25*	4% *P=0.09*
Serious	14%	9% *P=0.04*	11% *P=0.24*
Leading to drug discontinuation	0.3%	1% *P=0.22*	0.6% *P=0.57*
Any injection site reaction	1%	10% *P<0.001*	17% *P<0.001*
Mild	1%	10%	15%
Moderate	0	1%	3%
Severe	0	0	0

1. The events shown occurred during treatment or within 28 days after treatment.

Pivotal TRYNGOLZA Data Published in Leading Journals



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Accelerating Value through Commercial Execution

Kyle Jenne

EVP, Chief Global Product Strategy Officer

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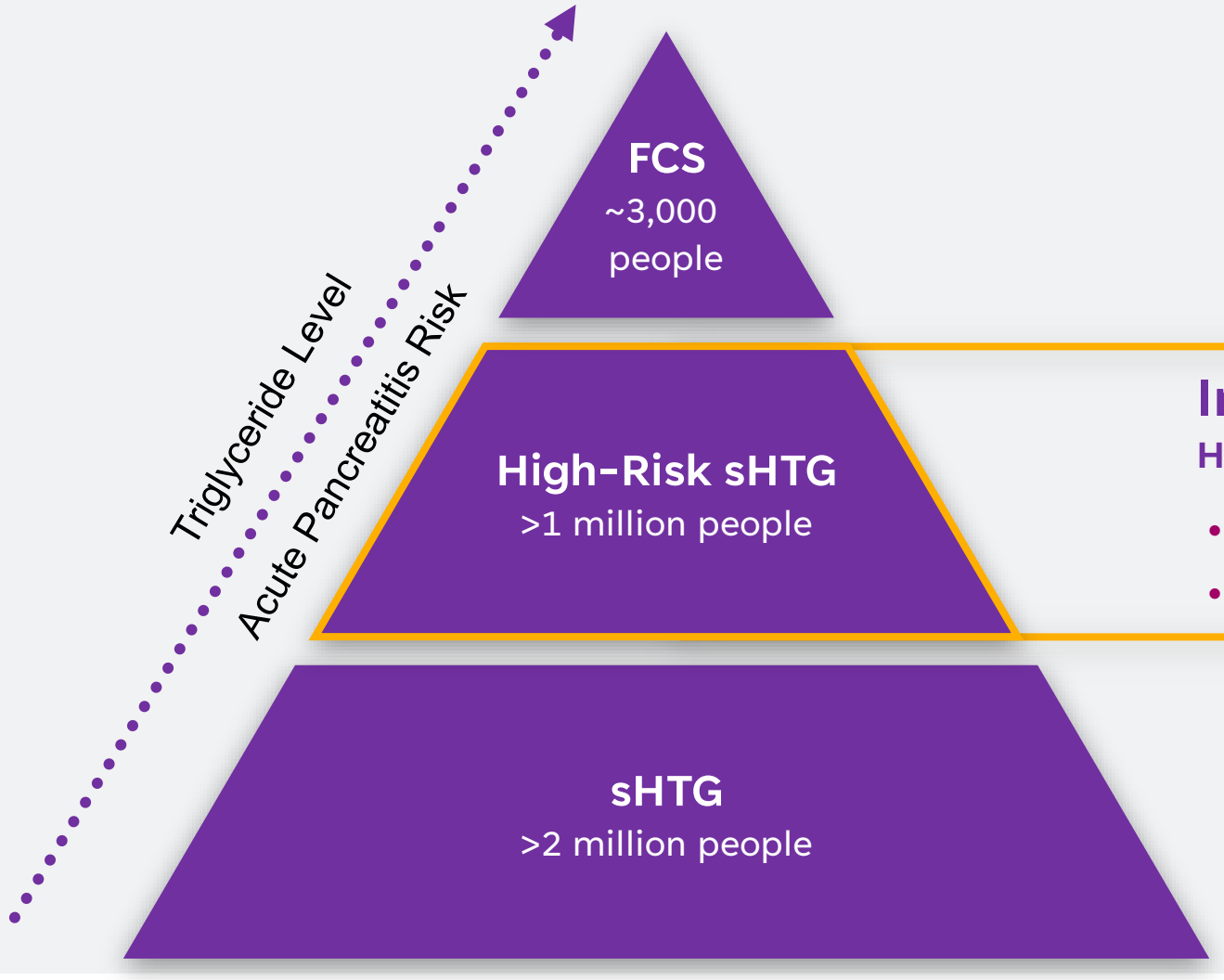
Initial U.S. Launch to Focus on People Living with High-Risk sHTG[1]



Initial Launch Focus

High Risk sHTG patients with

- TG >880 mg/dL
- TG ≥500 mg/dL + AP history and/or comorbidities

1. 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.

Severe Hypertriglyceridemia: A 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 other treatments, including **fibrates** and **omega-3s**

Market Poised for New Treatment

HCPs and patients dissatisfied with other sHTG treatments

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

Significant Market Opportunity[1-3]

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

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

Realizing the Blockbuster Potential of TRYNGOLZA in sHTG[1]

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

Up-Sized Field Team

Cardiometabolic field team in place to effectively target HCPs at launch

Flexibility to scale as the market evolves

Attractive Payer and Access Dynamics[2]

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

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

1. Peak sales estimates based on current assumptions and subject to change. 2. U.S. Payer Research.

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

IONIS EVERY STEP™ SUPPORT SERVICES

- Convenient patient enrollment into Ionis Every Step
- Disease, product, access and injection education
- Specialty pharmacy support
- Access support for HCPs
- Affordability and Patient Assistance programs

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Breakthrough Therapies Driving Accelerating Growth

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2026 Key Value-Driving Events[1]

Clinical Events

Phase 3

Bepirovirsen
B-Well data
(CHB)

Eplontersen
CARDIO-TTRansform data
(ATTR-CM)

Sefaxersen
IMAGINATION data
(IgAN)

ION582
Enrollment completion
(Angelman syndrome)

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

Ulefnersen
FUSION data
(FUS-ALS)

Sapablursen
Phase 3 initiation
(PV)

Salanersen
Phase 3 initiation
(SMA)

Phase 2

Diranersen
CELIA data
(Alzheimer's disease)

Tominersen
GENERATION HD2 data
(Huntington's disease)

Tonlamarsen
Phase 2 data
(Uncontrolled hypertension)

Regulatory Actions

DAWNZERA
EU approval
(HAE)

TRYNGOLZA
U.S. approval
EU submission
(sHTG)

Zilganersen
U.S. submission
U.S. approval
(AxD)

High Dose Nusinersen
U.S. approval
EU approval
(SMA)

Bepirovirsen
Submission
Approval
(CHB)

Pelacarsen
U.S. submission
(Lp(a)-CVD)

Eplontersen
U.S. submission
(ATTR-CM)

Product Launches

DAWNZERA
EU
(HAE)

TRYNGOLZA
U.S.
(sHTG)

Zilganersen
U.S.
(Alexander disease)

Bepirovirsen
U.S. & Japan
(CHB)

1. Timing expectations are based on current assumptions and are subject to change, timing of partnered program catalysts based on partners' most recent publicly available disclosures. Green checkmark indicates event was achieved.

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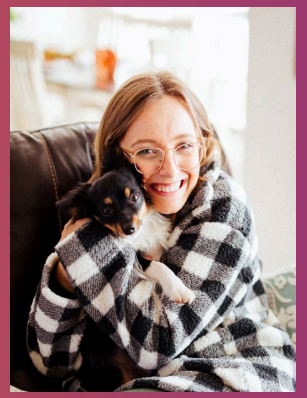








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