



Expanding the Olezarsen Opportunity: Positive CORE and CORE2 Topline Results

September 2, 2025



Agenda

Topic	Speaker
Transforming Innovative Science into Life-Changing Medicines	Brett Monia, Ph.D. <i>CEO</i>
Development Program Designed to Support Olezarsen for the Treatment of sHTG	Sam Tsimikas, M.D. <i>SVP, Global CV Development</i>
Groundbreaking Topline Results from the Landmark CORE & CORE2 Studies	Sam Tsimikas, M.D. <i>SVP, Global CV Development</i>
Delivering Olezarsen to People with sHTG	Kyle Jenne, <i>Chief Global Product Strategy Officer</i>
Bringing a Steady Cadence of Transformational Medicines to People with Serious Diseases	Brett Monia, Ph.D. <i>CEO</i>
Q&A	

Forward-Looking Statements

This presentation includes forward-looking statements regarding the therapeutic and commercial potential of our commercial medicines, olezarsen, 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.

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Transforming Innovative Science into Life-Changing Medicines

Brett Monia, Ph.D.
Chief Executive Officer

Positive Topline Olezarsen Results

The first and only treatment to significantly reduce acute pancreatitis events in people with sHTG



C@RE

a hypertriglyceridemia study

C@RE₂

a hypertriglyceridemia study

Delivering a Steady Cadence of Transformational Medicines

Commercializing Multiple Medicines through Partners¹

 **WAINUA**[™]
(eplontersen)

 **SPINRAZA**[®]
(nusinersen) injection
12 mg/5 mL

 **QALSODY**[®]
(tofersen) injection
100 mg/15 mL

First Independent Launch

 **Tryngolza**[™]
(olezarsen) 80 mg injection

First and only FDA-approved treatment for adults with **FCS**, adjunct to diet²

Second Independent Launch

DAWNZERA[™]
(donidalorsen) 80 MG INJECTION

First and only RNA-targeted medicine to prevent **HAE** attacks in patients 12 years and older³

Two Additional Independent Launches (2026^{4,5})

Olezarsen

Potential to change the treatment paradigm for people with **sHTG**

Zilganersen

Potential first disease-modifying treatment for people with **Alexander disease**

Multi-Billion-Dollar Revenue Potential⁵

1. Co-developing and commercializing WAINUA for ATTRv-PN and ATTR-CM in U.S. with AstraZeneca. 2. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see [Full Prescribing Information](#). 3. 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](#). 4. Timing and expectations based on current assumptions and subject to change. 5. Assuming approval.

Olezarsen:

Potential Blockbuster
Medicine Positioned to
Change the sHTG
Treatment Paradigm¹

Groundbreaking Clinical 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

Present full data at a medical congress later this year¹

File sNDA by YE 2025¹

Launch preparations well underway¹

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



Development Program Designed to Support Olezarsen for the Treatment of sHTG

Sam Tsimikas, M.D.

Senior Vice President, Global Cardiovascular Development

Olezarsen Phase 3 Development Program Designed to Support Potential in sHTG¹

Severe Hypertriglyceridemia (sHTG)



- Pivotal studies in people w/ sHTG (fasting TG \geq 500 mg/dL)
- Registrational studies
- 1,063 participants

Largest Pivotal Program Ever Conducted in sHTG

Moderate Hypertriglyceridemia (HTG)



- Ph3 study in people with moderate HTG and elevated CVD risk (fasting TG \geq 150 mg/dL)²
- Results support safety database
- 1,478 participants

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

Positive Results from Olezarsen Phase 3 Essence Study Highlighted at ESC 2025 and Published in *NEJM*^{1,2}

ESC Congress 2025 Madrid

TOGETHER WITH
World Congress of Cardiology

29 August to 1 September



#ESCCongress
#WCCardio



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting APOC3 with Olezarsen
in Moderate Hypertriglyceridemia

Positive Phase 3 Essence Study Results

- Enrolled 1,478 participants with moderate HTG (fasting TG ≥ 150 mg/dL) and elevated CVD risk³
- Statistically significant placebo-adjusted fasting TG reductions of 58% (50 mg) and 61% (80 mg) at 6 months⁴
- Nearly 90% of olezarsen-treated participants had normal TG levels (fasting TG < 150 mg/dL) at 6 months⁵
- Met all key secondary endpoints, including a significant reduction in apoB, and a nearly 70% mean reduction in remnant cholesterol⁶
- Favorable safety and tolerability

1. Essence-TIMI 73b, Olezarsen in patients with hypertriglyceridemia at high cardiovascular risk, presented at [ESC Congress 2025](#). 2. Bergmark, B, et al. *N Engl J Med*. 2025. 3. 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. 4. Primary endpoint; achieved statistically significant placebo-adjusted 61% and 58% reductions in fasting TG levels, on top of standard of care, at 6 months with the 80 mg and 50 mg monthly doses, respectively ($p < 0.0001$). 5. evaluated in patients with available TG values in the primary efficacy cohort. 6. Key secondary endpoints included percent changes in triglyceride levels at 12 months, proportion of patients who achieve fasting TG < 150 mg/dL and percent changes in other lipid parameters, including apoC-III, remnant cholesterol, non-HDL-C and apoB, compared to placebo over the treatment period.

Favorable Safety and Tolerability Results Observed in Essence Study Support Olezarsen Potential in sHTG

- AEs, SAEs and SAEs leading to discontinuation were balanced across treatment arms
- Injection site reactions were the most common adverse event that occurred more frequently with olezarsen, which were generally mild

	Placebo (n=369)	Olezarsen 50 mg (n=276)	Olezarsen 80 mg (n=832)
Any AEs	72%	73%	77%
Leading to discontinuation	5%	4%	7%
Serious AEs	11%	9%	14%
Leading to discontinuation	1%	1%	2%
Injection Site Reaction	2%	15%	16%
Mild	2%	13%	15%
Moderate	<1%	3%	3%
Severe	0	0	0



Groundbreaking Topline Results from the Landmark CORE & CORE2 Studies

Sam Tsimikas, M.D.

Senior Vice President, Global Cardiovascular Development

Severe Hypertriglyceridemia: Prevalent condition with significant unmet medical need

Severely Elevated Triglycerides

Fasting triglycerides ≥ 500 mg/dL

Multifactorial, driven by combination of genetics, diabetes, obesity, metabolic syndrome, lifestyle, etc.

Increased risk of acute pancreatitis, which can be life-threatening

Substantial Unmet Need

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

Prevalent Population^{1,2,3}

>3 million people with sHTG in the U.S., including >1 million people with high-risk sHTG

High-risk sHTG includes people with TGs >880mg/dL and ≥ 500 mg/dL with a history of acute pancreatitis

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.

Olezarsen CORE and CORE2 Phase 3 Studies¹



DESIGN

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

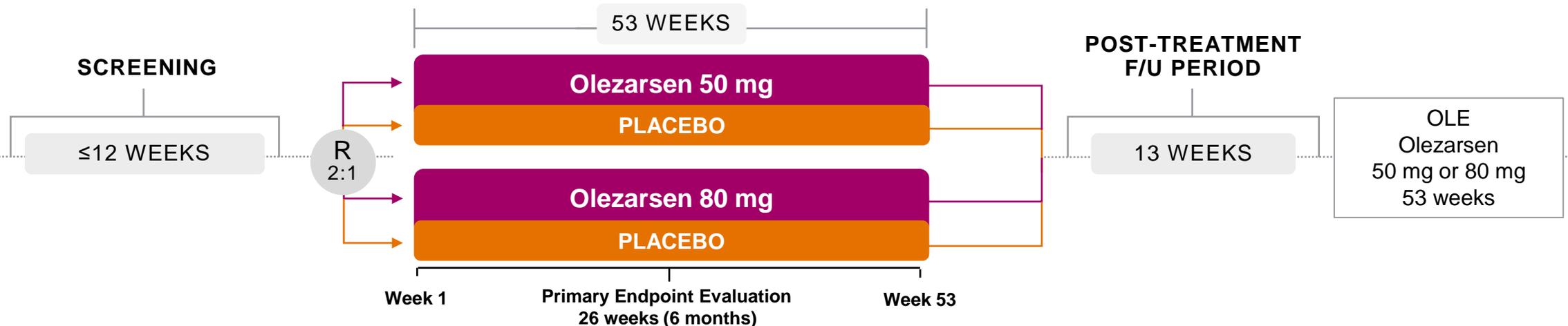
- Stratified by baseline triglyceride levels > 880 mg/dL and pancreatitis history²
- 99% of participants were on standard lipid-lowering therapy

ENDPOINTS¹

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 & lipid measures at 6 & 12 months



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

Baseline Characteristics



Published in <i>American Heart Journal</i> 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 Months¹



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 triglycerides¹

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^{1,2,3}

85%

(p=0.0002)

Reduction in acute pancreatitis events compared to placebo^{1,2,3}

Secondary endpoint, pooled olezarsen (50mg and 80mg) 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%

- AEs were generally balanced, and SAEs occurred less frequently with olezarsen
- Injection site reactions, which were mostly mild, were the most common AE and occurred more frequently with olezarsen

Olezarsen CORE and CORE2 Studies:

Groundbreaking Results
from Landmark Studies in
People with sHTG

Highly statistically significant and clinically meaningful placebo-adjusted mean reductions of up to 72% in fasting triglycerides¹

Highly statistically significant 85% reduction in acute pancreatitis events²

Favorable safety and tolerability

Full data from CORE and CORE2 to be presented at medical congress later this year³

1. P-values are based on comparison between each olezarsen group and placebo group in percent reduction in fasting triglycerides.

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

3. Timing expectations are based on current assumptions and are subject to change.



Delivering Olezarsen to People with sHTG

Kyle Jenne
Chief Global Product Strategy Officer

Acute Pancreatitis is the Most Severe Risk Associated with sHTG



The risk of potentially life-threatening triglyceride-induced acute pancreatitis is serious and requires urgent action¹

**~5-fold
Higher risk**

of acute pancreatitis with sHTG vs. normal triglyceride levels²

**Up to 8%
Mortality**

associated with sHTG-driven acute pancreatitis^{1,3}

**~17 days
In hospital**

average in-hospital stay per acute pancreatitis event¹



“I regularly see my sHTG patients suffer their first acute pancreatitis attack. After that, their pancreas is absolutely destroyed.”

– leading lipidologist

“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



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**

2

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

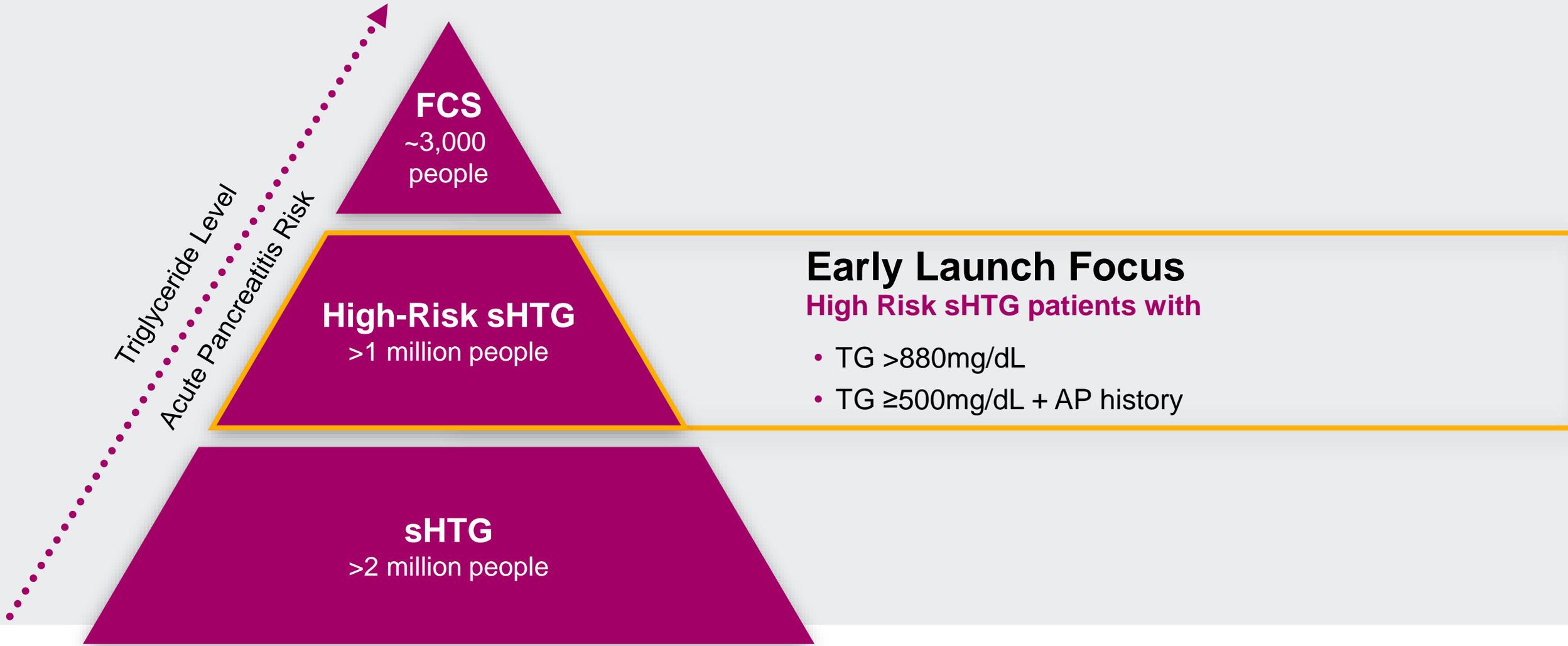
3

Favorable **safety** and **tolerability**

4

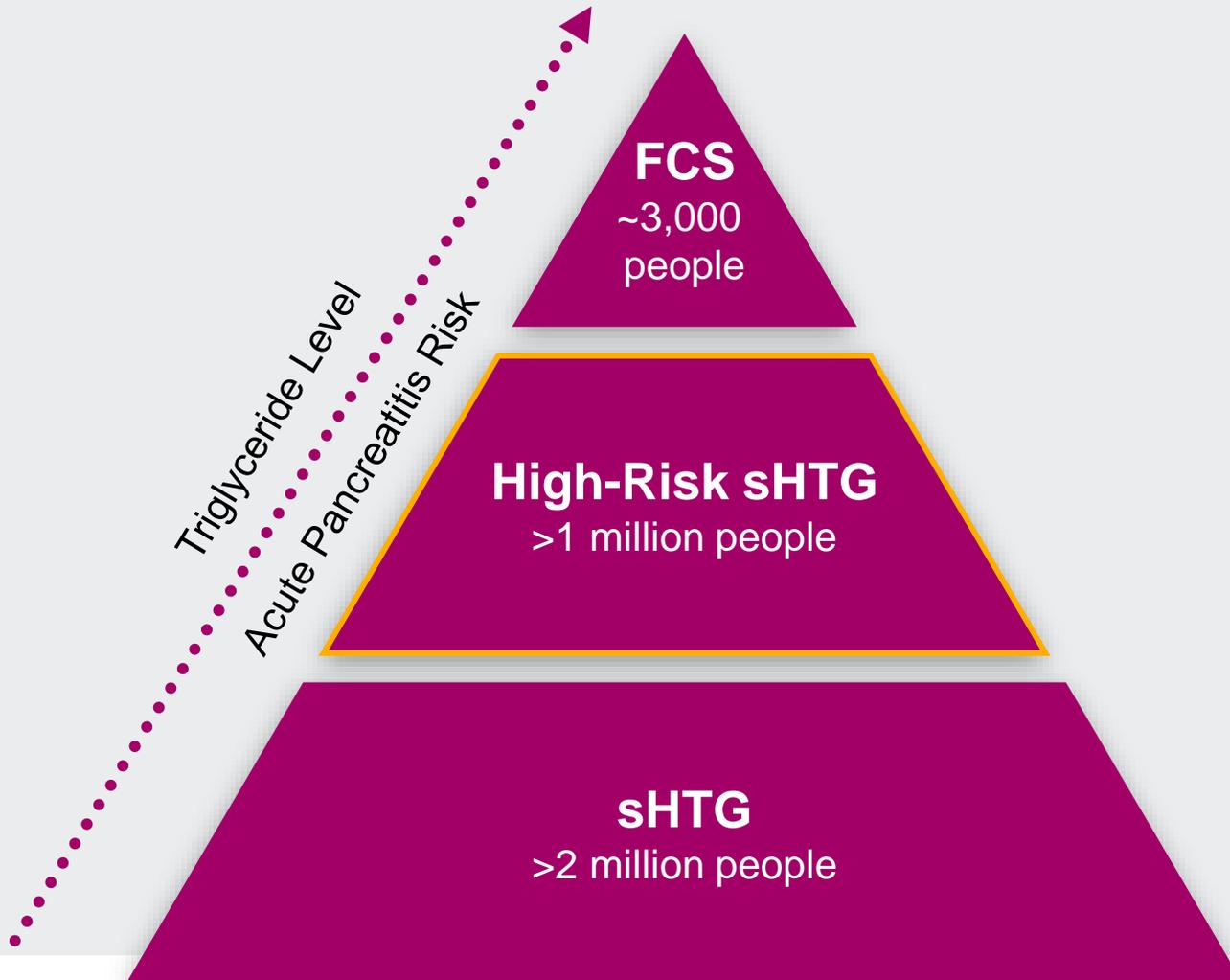
Potential to offer the **simplicity** of **monthly self-administration** with an **autoinjector**

Initial U.S. Launch to Focus on High-Risk sHTG to Achieve Blockbuster Potential^{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.

Initial U.S. Launch to Focus on High-Risk sHTG to Achieve Blockbuster Potential^{1,2}



Early Launch Focus

Patient population:

High Risk sHTG patients with

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

Physician Targets:

cardiologists, endocrinologists, lipidologists

Field engagement and education:

ongoing through TRYNGOLZA launch

Commercial organization: cardiometabolic account specialists to focus on target high-risk treaters at launch. Flexibility to scale organization as market evolves.

Omnichannel marketing resources: to amplify and extend field team programming

Next Steps to Bring Olezarsen to People with sHTG

1



**CORE & CORE2
Full Data Presentation**

H2 2025¹

2



**U.S. sNDA Filing
by YE 2025¹**



**Additional
Global filings 2026²**

3



**U.S. Launch
H2 2026¹**

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.



Bringing a Steady Cadence of Transformational Medicines to People with Serious Diseases

Brett Monia, Ph.D.
Chief Executive Officer

Delivering a Steady Cadence of Transformational Medicines^{1,2}

2

**Independent
Launches in <1 year³**

 **Tryngolza™**
(olezarsen) 80 mg injection

 **DAWNZERA™**
(donidalorsen) 80 MG INJECTION

2

**Independent Launches
Planned Next Year^{2,4}**

Olezarsen (sHTG) | Zilganersen (AxD)

Multi-Billion Dollar
Opportunity^{1,2}

Transforming Innovative Science into Life-Changing Medicines

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. Assuming approval. 3. TRYNGOLZA is approved in the U.S. for Familial Chylomicronemia Syndrome in adults; see [Full Prescribing Information](#). 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](#). 4. Olezarsen, severe hypertriglyceridemia (sHTG); zilganersen, Alexander disease (AxD).



Q&A

