Transforming the Treatment of sHTG

Results from the Olezarsen CORE and CORE2 Studies

November 8, 2025

Agenda

Topic	Speaker
Transforming Human Health through Life-Changing Medicines	**Brett Monia, Ph.D.** *CEO*
Addressing sHTG through ApoC-III Inhibition	**Sam Tsimikas, M.D.** *SVP, Global CV Development*
Groundbreaking Results from the CORE and CORE2 Studies	**Sam Tsimikas, M.D.** *SVP, Global CV Development*
Delivering Olezarsen to People with sHTG: Positioned for Commercial Success	**Kyle Jenne,** *Chief Global Product Strategy Officer*
Bringing a Steady Cadence of Transformational Medicines to People with Serious Diseases	**Brett Monia, Ph.D.** *CEO*
Q&A	**Brett Monia, Ph.D.** *CEO* **Richard Geary, Ph.D.** *Chief Development Officer* **Sam Tsimikas, M.D.** *SVP, Global CV Development* **Kyle Jenne,** *Chief Global Product Strategy Officer*

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Forward-Looking Statements

This presentation includes forward-looking statements regarding our business, financial guidance and the therapeutic and commercial potential of our commercial medicines, additional medicines in development and technologies and our expectations regarding development and regulatory milestones. Any statement describing Ionis' goals, expectations, financial or other projections, 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.

Transforming Human Health through Life-Changing Medicines

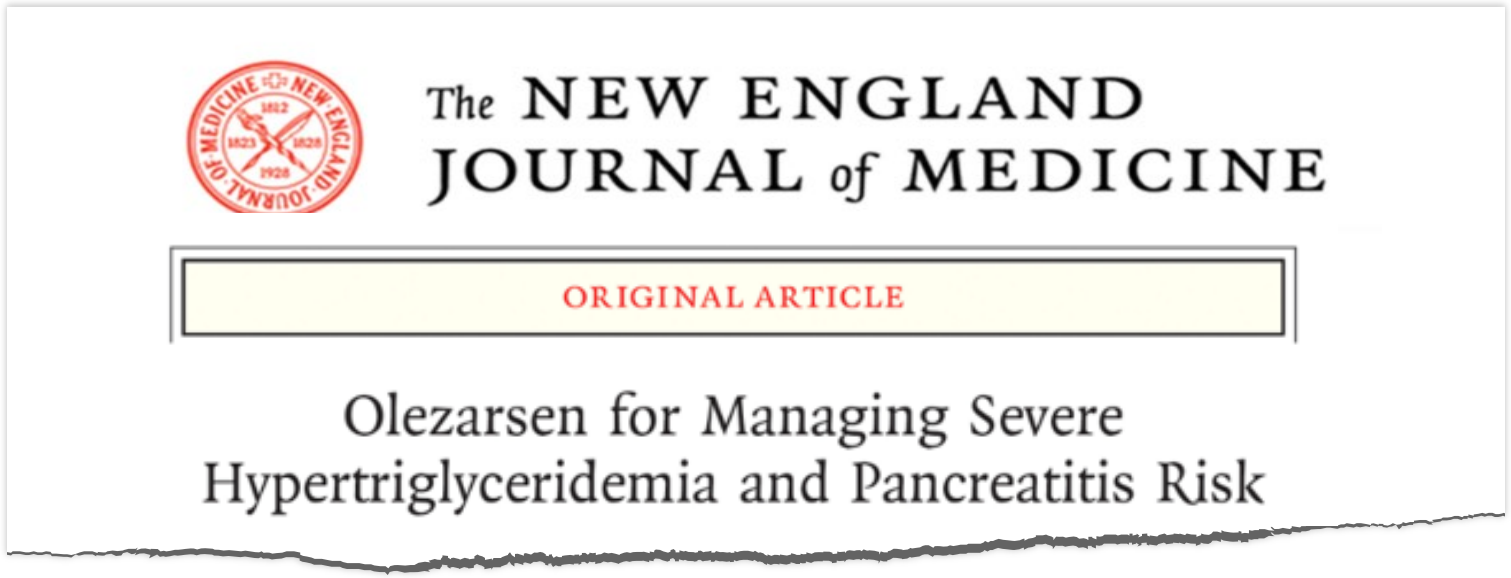
Brett Monia, Ph.D.
Chief Executive Officer

Positive Detailed Olezarsen Results

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

CORE
a hypertriglyceridemia study

CORE2
a hypertriglyceridemia study



Delivering a Steady Cadence of Transformational Medicines

Commercializing Multiple Medicines through Partners[1]

WAINUA (eplontersen) 45 mg injection for subcutaneous use

SPINRAZA (nusinersen) injection 12 mg/5 mL

QALSODY (tofersen) 100 mg/15 mL injection

First Independent Launch

Tryngolza (olezarsen) 80 mg injection

First and only FDA-approved treatment for adults with **FCS**, adjunct to diet[2]

Second Independent Launch

DAWNZERA (donidalorsen) 80 MG INJECTION

First and only RNA-targeted medicine to prevent **HAE** attacks in patients 12 years and older[3]

Two Additional Independent Launches (2026[4,5])

Olezarsen

Potential to be the new standard of care for people with **sHTG**

Zilganersen

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

Multi-Billion-Dollar Revenue Potential[5]

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: 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** investigational treatment to **significantly reduce acute pancreatitis** events in people with sHTG

First Mover Advantage[2]

Positioned to be the **new standard of care** for people with **sHTG**; **launch preparations well underway**

Next Steps[3]

- **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 Data from CORE and CORE2 Phase 3 studies.

Addressing sHTG through ApoC-III Inhibition

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

Severe Hypertriglyceridemia (sHTG)[1-6]

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

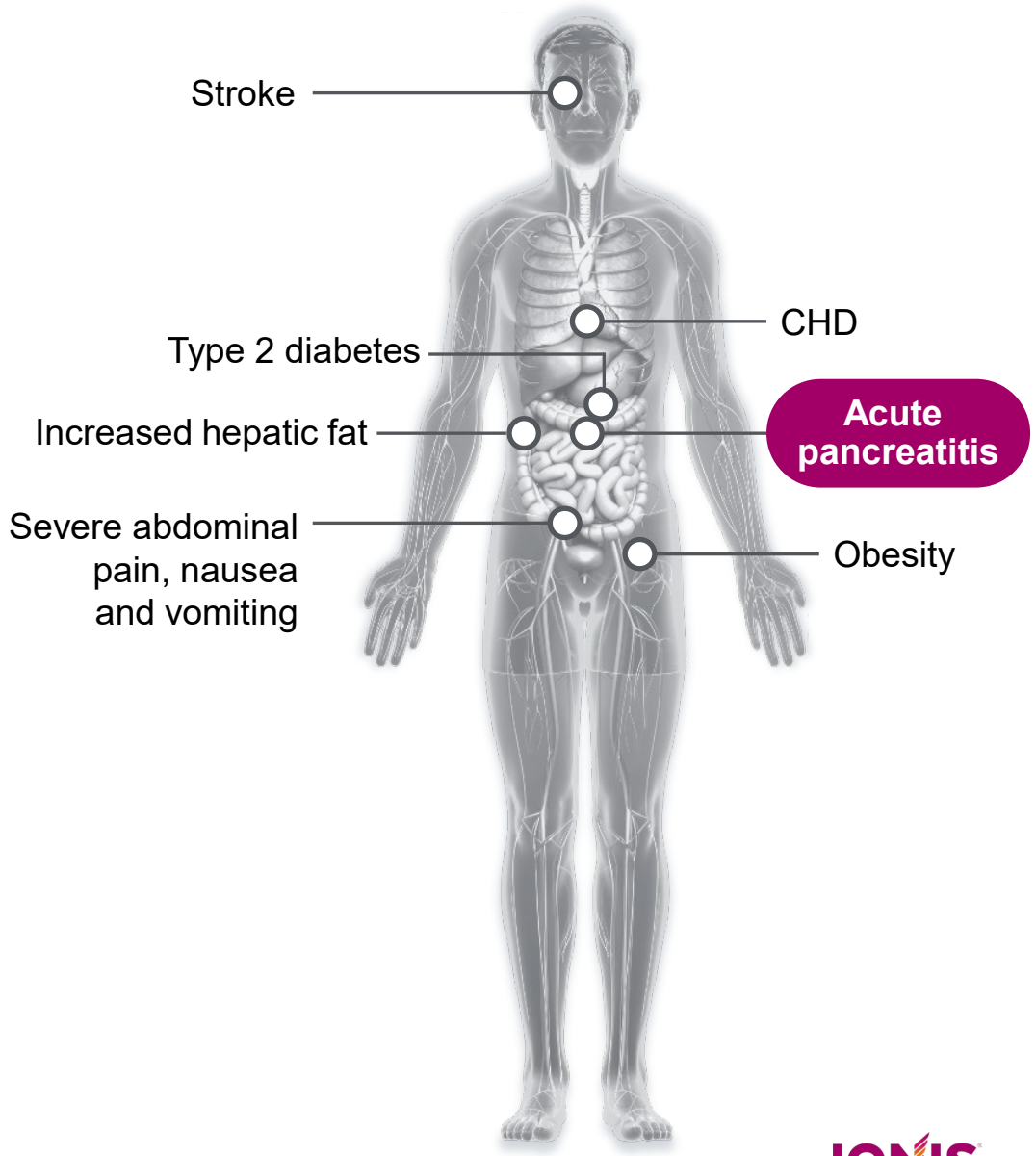
Characterized by **increased risk of acute pancreatitis**, atherosclerotic cardiovascular disease[2]

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

Limited benefit from currently available 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.*

Established sHTG Treatment Guidelines

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

nla 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.

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

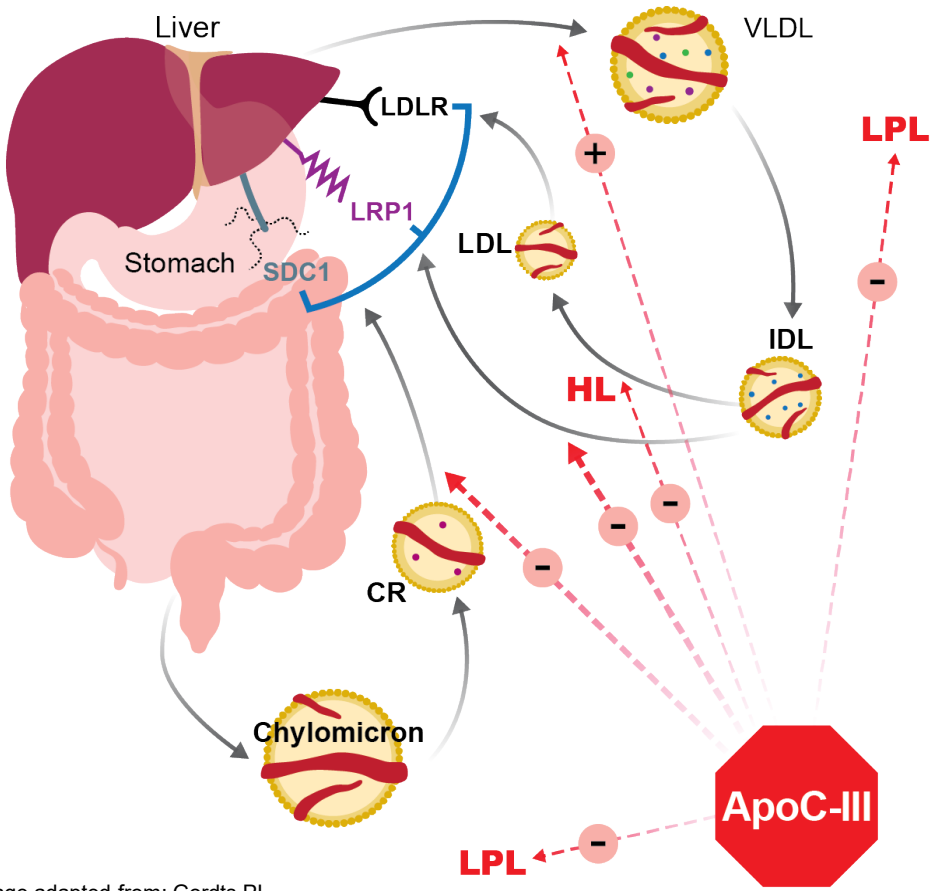


Image adapted from: Gordts PL, et al. *J Clin Invest.* 2016;126:2855

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

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

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.

Groundbreaking Results from the CORE and CORE2 Studies

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

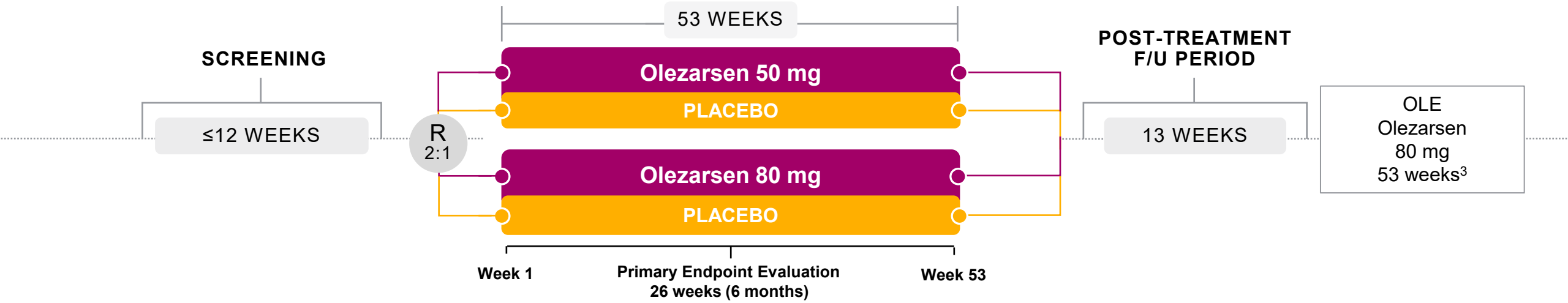
- Stratified by triglyceride levels ≥880 mg/dL at qualification visit and pancreatitis history[2]
- 99% of participants were on standard lipid-lowering therapy

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. 3. Small number of patients on 50 mg in OLE.

Baseline Characteristics

	CORE (n=617)	CORE2 (n=444)[1]
Age, Median years	54	54
Diabetes Mellitus	60%	69%
AP History	23%	13%
Fasting Triglycerides, Median (Mean) mg/dL • Fasting Triglycerides ≥880 mg/dL	832 (1,182) 47%	748 (1,025) 37%
Total Cholesterol, Median mg/dL • LDL Cholesterol • HDL Cholesterol	231 59 25	216 61 27
Lipid Lowering Therapies[2] • ≥2 Therapies	99% 67%	99% 63%

1. Two patients in the placebo arm of CORE2 did not receive IP and were not included in the primary analysis. 2. Baseline lipid lowering therapy includes any use of statins, omega-3 fatty acids, fibrates, PCSK9, or other lipid-modifying medications taken before the first dose of study drug and continued after the first dose of study drug.

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

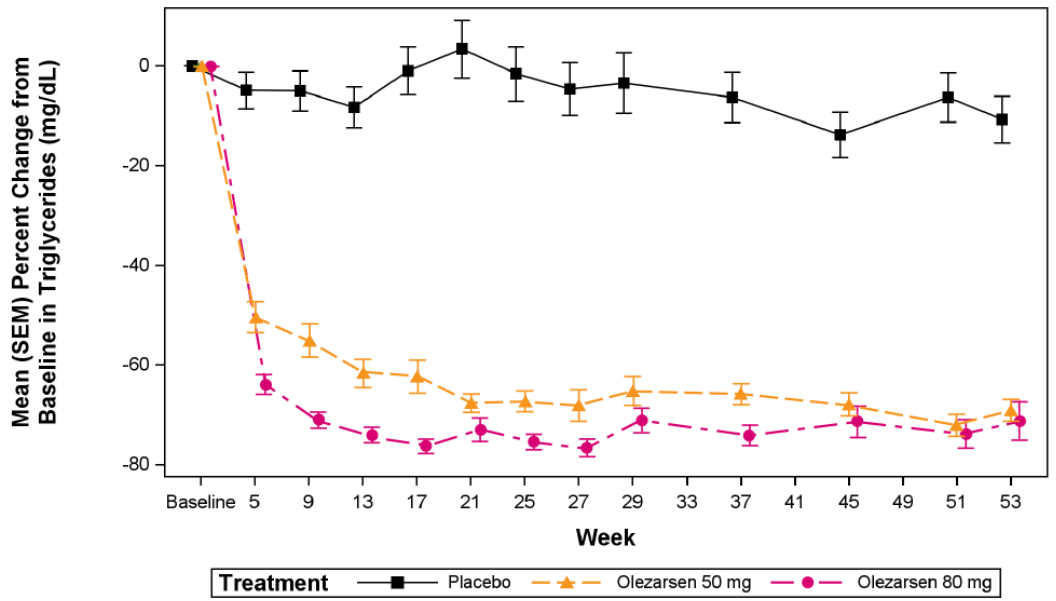
Primary Endpoint	Placebo	Olezarsen 50 mg	Olezarsen 80 mg
CORE			
% Reduction from baseline[2]	0.5%	63%	73%
% Placebo-adjusted reduction[1]		63%	72%
P-value[3]		p<0.001	p<0.001
CORE2			
% Reduction from baseline[2]	14%	63%	68%
% Placebo-adjusted reduction[1]		49%	55%
P-value[3]		p<0.001	p<0.001

Up to a **72%** placebo-adjusted mean reduction in fasting triglycerides on top of standard of care[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.

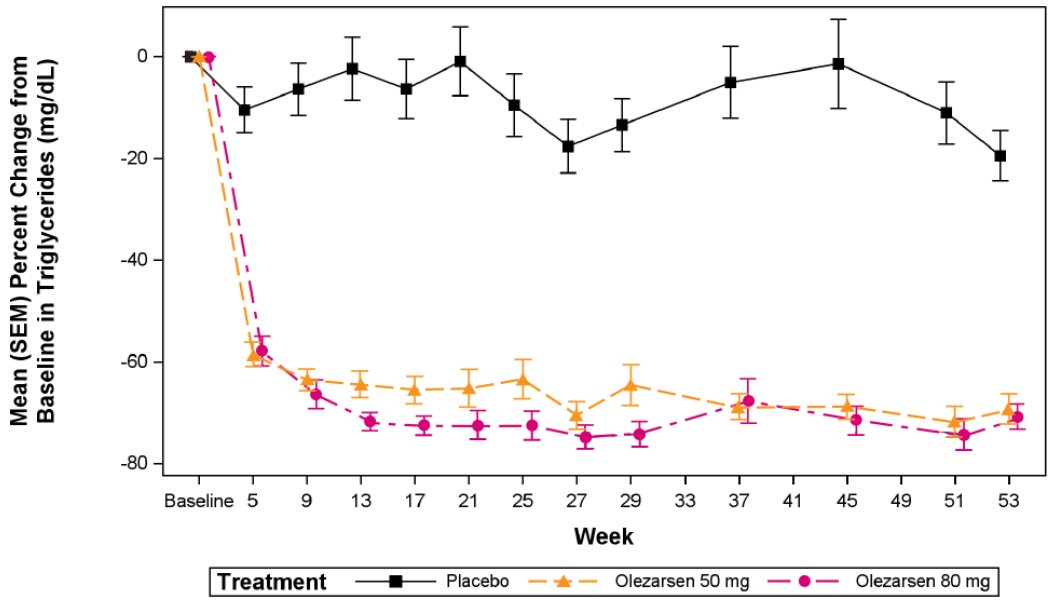
Rapid and Significant Triglyceride Reduction Sustained over 12 Months

CORE



Number of Patients														
Placebo	208	198	201	200	200	199	188	188	194	195	187	170	182
Olezarsen 50 mg	205	198	192	193	197	190	189	171	191	186	182	170	180
Olezarsen 80 mg	204	199	196	195	196	188	182	178	189	190	182	173	179

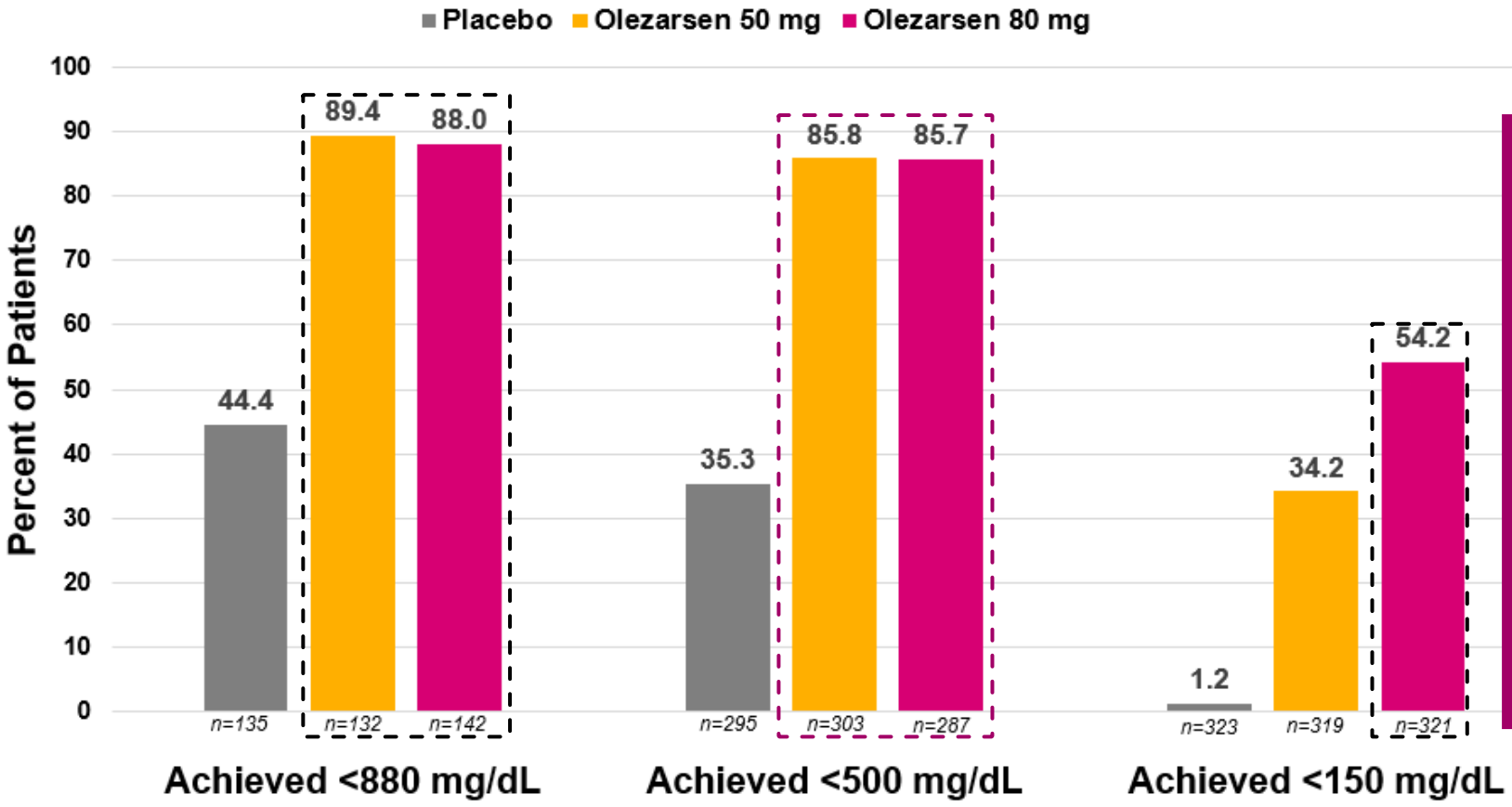
CORE2



Number of Patients														
Placebo	148	143	142	141	140	139	132	131	140	136	132	123	131
Olezarsen 50 mg	149	143	143	140	141	140	137	135	138	136	133	118	127
Olezarsen 80 mg	147	142	141	137	137	135	130	128	129	132	132	120	129

Vast Majority of Patients Achieved Triglyceride Levels Below Risk Threshold for Acute Pancreatitis[1]

At 12 months with olezarsen treatment in CORE and CORE2 pooled data



86%

of olezarsen-treated patients achieved triglycerides of <500 mg/dL

P<0.001 for each dose at each threshold vs placebo

1. 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.

Olezarsen: First and Only Investigational Treatment to Significantly Reduce Acute Pancreatitis Events in People with sHTG

Analysis Cohort	Placebo (n=356)	Olezarsen (n=705)	Treatment Effect	
	Pancreatitis Subjects / Events	Pancreatitis Subjects / Events	Mean RR (95% CI)	P-Value
Overall treatment population[3]	17 / 22	5 / 7	0.15 (0.05, 0.40)	**<0.001**
TG ≥880 mg/dL + prior pancreatitis	14 / 19	4 / 6	0.17 (0.06, 0.47)	**<0.001**

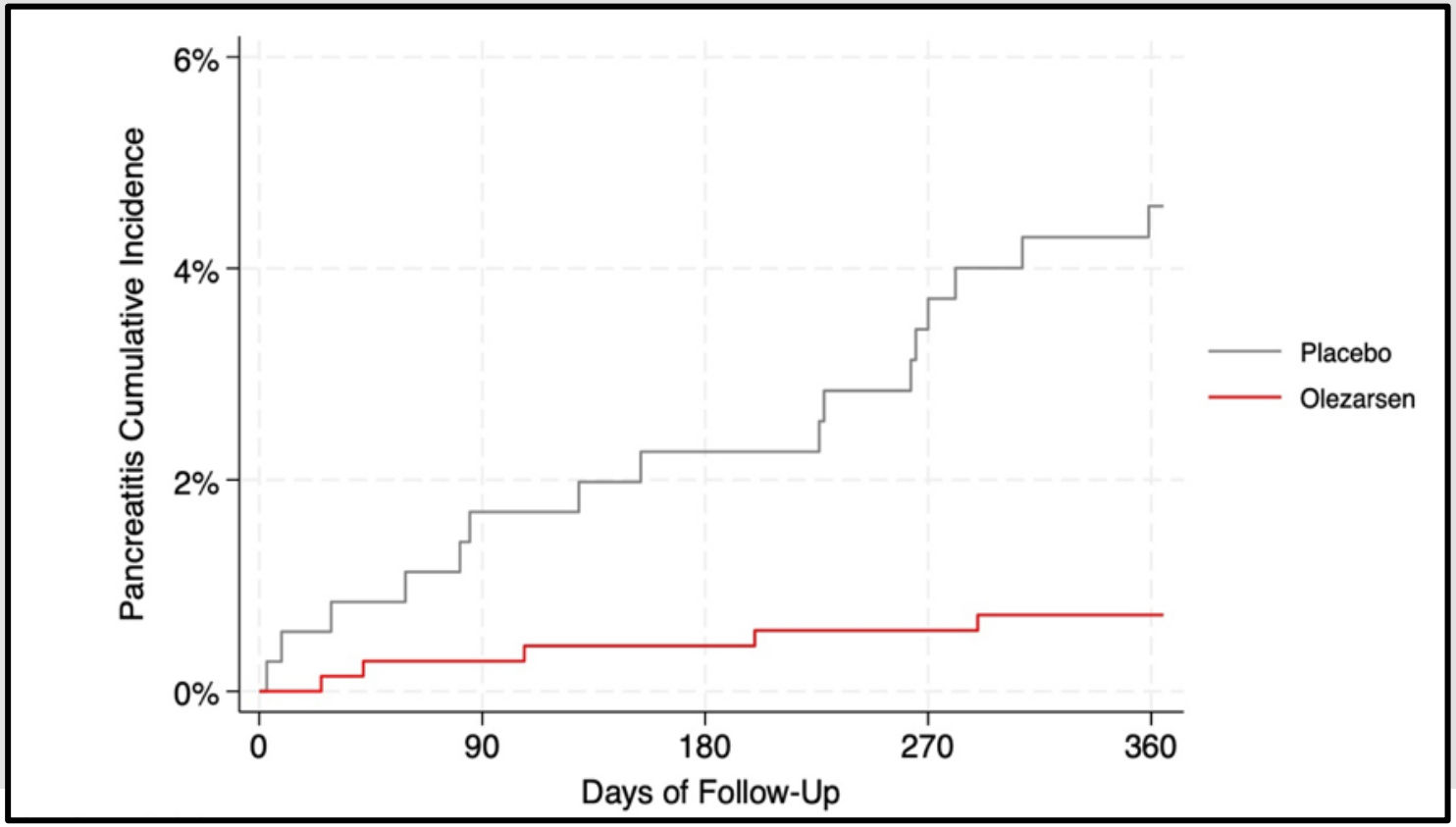
85%

Reduction in acute pancreatitis events compared to placebo[1]

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

Low Number Needed to Treat Highlights Strong Clinical Impact and Urgency to Treat

Number of Patients Needed to Treat (NNT) over One Year to Prevent One Acute Pancreatitis Event with Olezarsen:



NNT=20

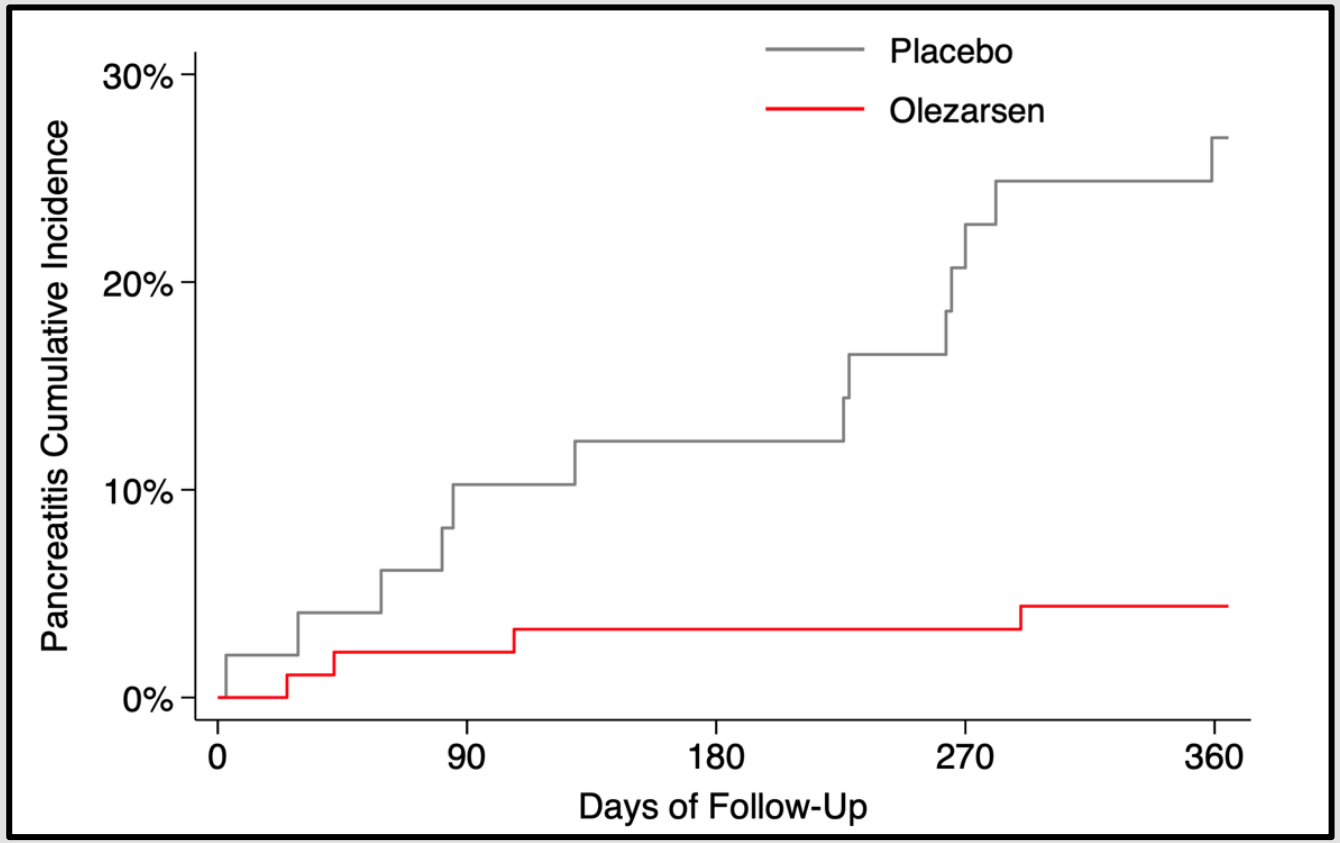
patients

in the overall treatment population[1]

1. Using the mean rates from the binomial regression model, the number of patients needed to treat over one year to prevent one episode of acute pancreatitis was 25 in the overall treatment population (pooled analysis across both doses and studies).

Even Fewer Patients Needed To Treat in Highest-Risk Group[1]

Number of Patients Needed to Treat (NNT) over One Year to Prevent One Acute Pancreatitis Event with Olezarsen:



NNT=4

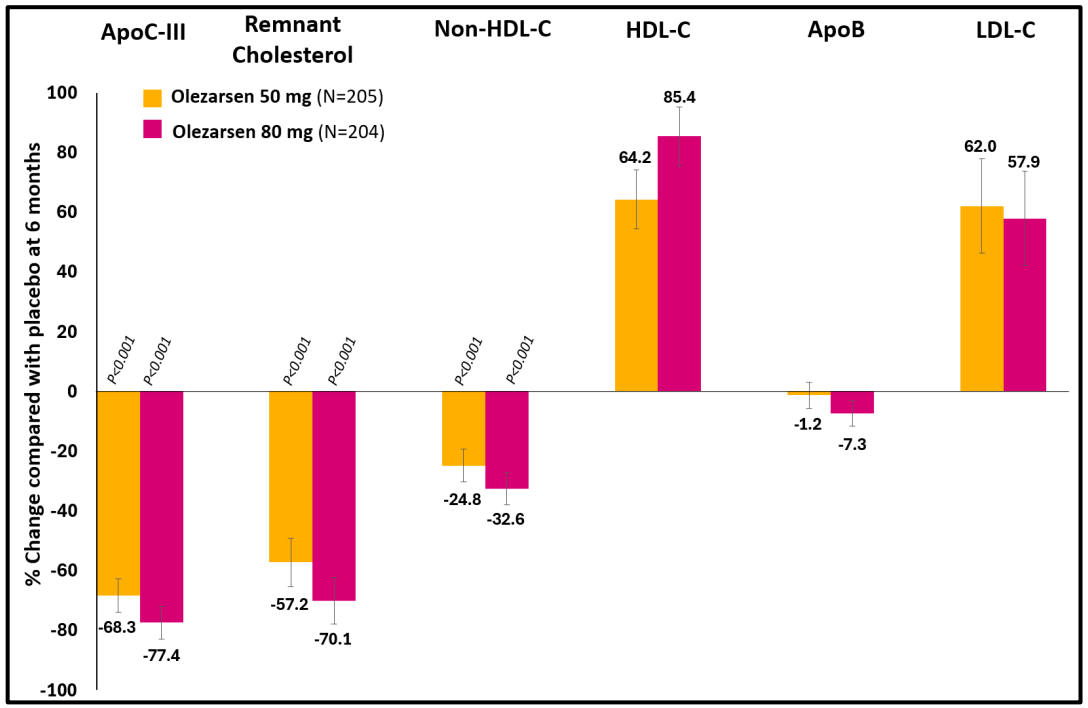
patients

for those with baseline TGs ≥880 mg/dL and history of AP

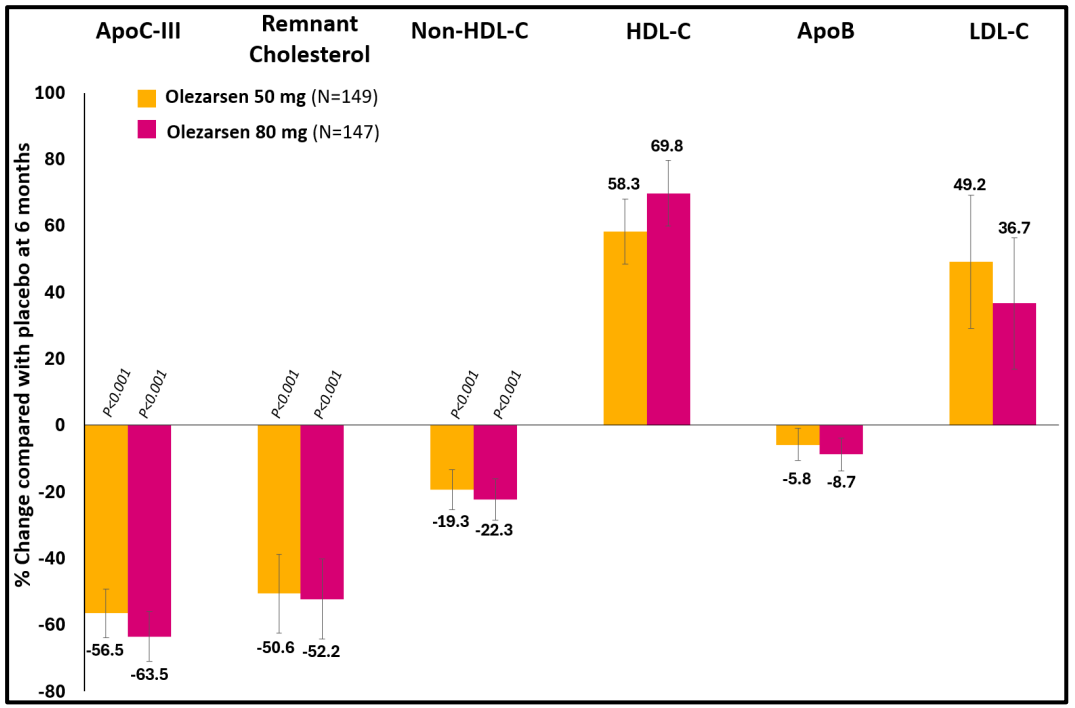
1. Using the mean rates from the binomial regression model, the number of patients needed to treat over one year to prevent one episode of acute pancreatitis was 4 in the high-risk subgroup with TG ≥880 and prior pancreatitis (pooled analysis across both doses and studies), n=141.

Positive Effect on Additional Secondary and Exploratory Endpoints: Lipid Parameters

CORE



CORE2



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

Serious adverse events (SAEs) occurred less frequently with olezarsen

Adverse events (AEs) were generally balanced

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

Key Safety Parameters
Pooled analysis across CORE and CORE2

	Placebo (n=356)	Olezarsen 50 mg (n=354)	Olezarsen 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.

Other Parameters Generally Consistent with Previous Study Results[1]

	Placebo (n=356)	Olezarsen 50 mg (n=354)	Olezarsen 80 mg (n=351)
Hepatic parameters[2]			
ALT or AST ≥3x ULN	2%	3% *P=0.60*	7% *P=0.003*
ALT or AST ≥5x ULN	1%	1% *P=0.99*	1% *P=0.47*
Total bilirubin ≥2x ULN	<1%	<1% *P=0.99*	1% *P=0.56*
Absolute change in HFF[3]	0.14%	2.28% *P=0.052*	4.18% *P<0.001*
Platelet count			
<100K/uL	3%	2% *P=0.26*	7% *P=0.03*
<75K/uL	2%	1% *P=0.18*	2% *P=0.76*
HbA1c, placebo-adjusted change		0.25% *P=0.006*	0.24% *P=0.009*

Pooled analysis across CORE and CORE2

1. The events shown occurred during treatment or within 28 days after treatment. 2. There were no cases meeting Hy's Law criteria. 3. HFF = hepatic fat fraction, measured at baseline and 12 months as part of MRI substudy (n=252).

Olezarsen:

Positioned to be the New Standard of Care for Severe Hypertriglyceridemia[1]

Groundbreaking clinical results:

- **Highly statistically significant** and **clinically meaningful mean reductions** in **fasting triglycerides** of **up to 72% on top of standard of care**
  - 86% of olezarsen-treated patients achieved triglyceride levels below 500 mg/dL
  - Up to 54% of olezarsen-treated patients achieved normal triglyceride levels
- **First and only** investigational treatment to **significantly reduce acute pancreatitis** events in people with sHTG
  - 85% reduction in acute pancreatitis events compared to placebo
- **Favorable safety** and **tolerability**

Submit sNDA by YE 2025 for both 80 mg and 50 mg doses[1]

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

Delivering Olezarsen to People with sHTG: Positioned for Commercial Success

Kyle Jenne

Chief Global Product Strategy Officer

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 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 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.

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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.

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

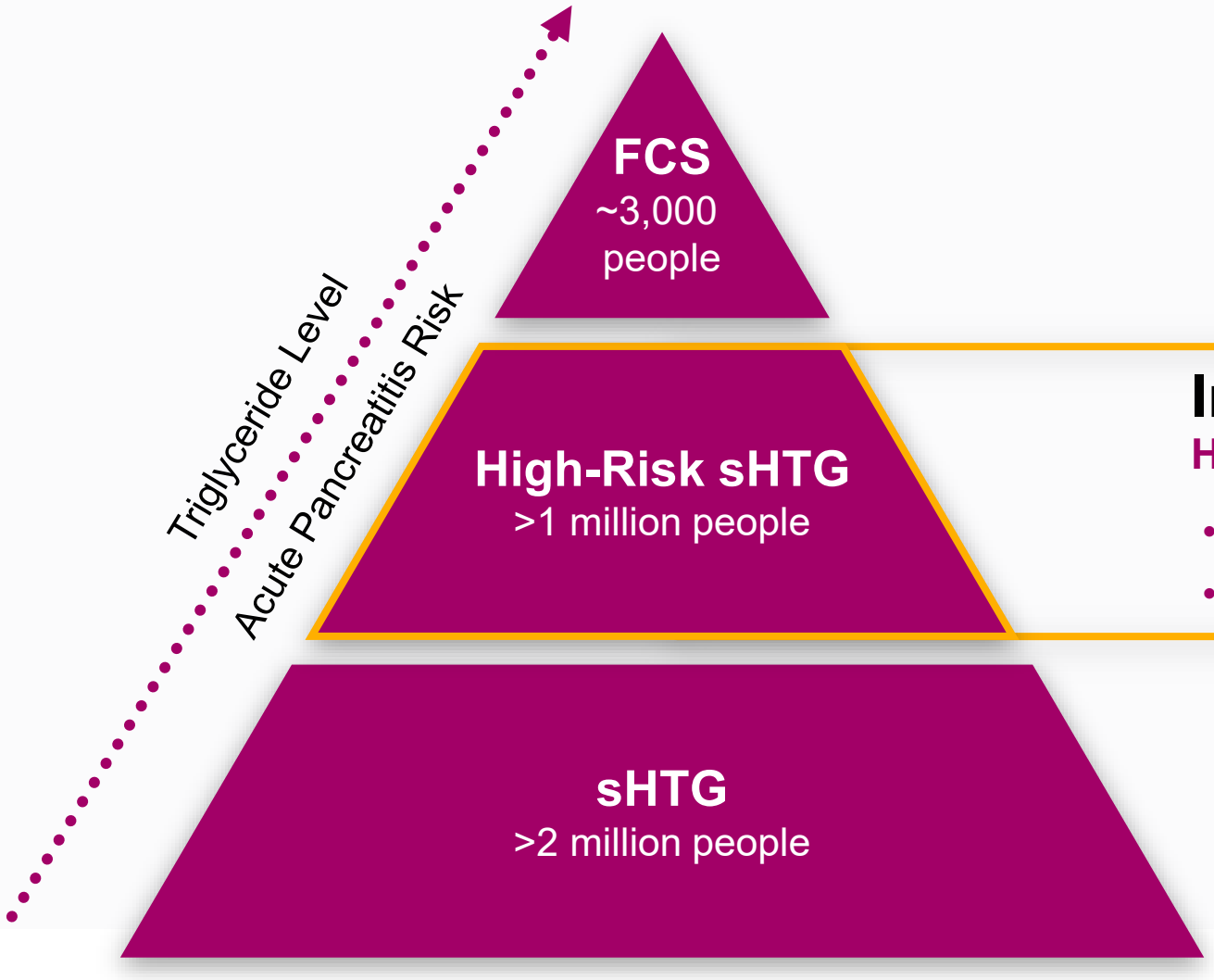
"*A treatment that meaningfully lowers triglycerides **and** reduces acute pancreatitis risk – something we've never seen before – would be a **game-changer**.*"

– sHTG KOL

1. **Highly statistically significant** and **clinically meaningful** reductions in fasting **triglycerides**[1]
2. **First** and **only** investigational 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. Data from CORE and CORE2 Phase 3 studies.

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



Initial Launch Focus

High Risk sHTG patients with

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

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.

Realizing the Blockbuster Potential of Olezarsen in sHTG[1-4]

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 be the New Standard of Care in sHTG Treatment[1-3]

up to **72%** **reduction**

in fasting triglycerides

- Highly statistically significant -
- Clinically meaningful -

85%

reduction in
acute pancreatitis events

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

Commercial organization designed for

sHTG Launch Success

1st

Mover Advantage

1. Timing and peak sales expectations based on current assumptions and subject to change. 2. Assuming approval. 3. Data from CORE and CORE2 Phase 3 studies.

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

Independent Launches in <1 year[2]

Tryngolza™ (olezarsen) 80 mg injection | DAWNZERA™ (donidalorsen) 80 MG INJECTION

2

Independent Launches Planned Next Year[3]

Olezarsen (sHTG) | Zilganersen (AxD)

4

Key Partner Launches by end of 2027[4]

Bepirovirsen (HBV) | Pelacarsen (Lp(a)-CVD) | Eplontersen (ATTR-CM) | Sefaxersen (IgAN)

Accelerating Value Creation

1. Timing expectations based on current assumptions and subject to change. 2. 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. 3. Assuming approval. 4. Assuming positive data and approval.

Q&A

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