



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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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



The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olezarsen for Managing Severe
Hypertriglyceridemia and Pancreatitis Risk

Delivering a Steady Cadence of Transformational Medicines

Commercializing Multiple Medicines through Partners¹

WAINUA
(eplontersen)^{45mg}
injection for subcutaneous use

SPINRAZA
(nusinersen)^{injection}
12mg/5mL

QALSODY
(tofersen)^{100mg/15mL}
injection

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 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 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: Poised to Launch in Large Patient Population (sHTG) Next Year¹



The Opportunity

>3 million people with sHTG in the U.S., including >1 million people with high-risk sHTG²; Blockbuster potential³



Groundbreaking Clinical Results⁴

- 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 Advantage²

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



Next Steps³

- sNDA submission on track by YE:2025³
- Launch in 2026³



Brandi
living with sHTG

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/dL¹

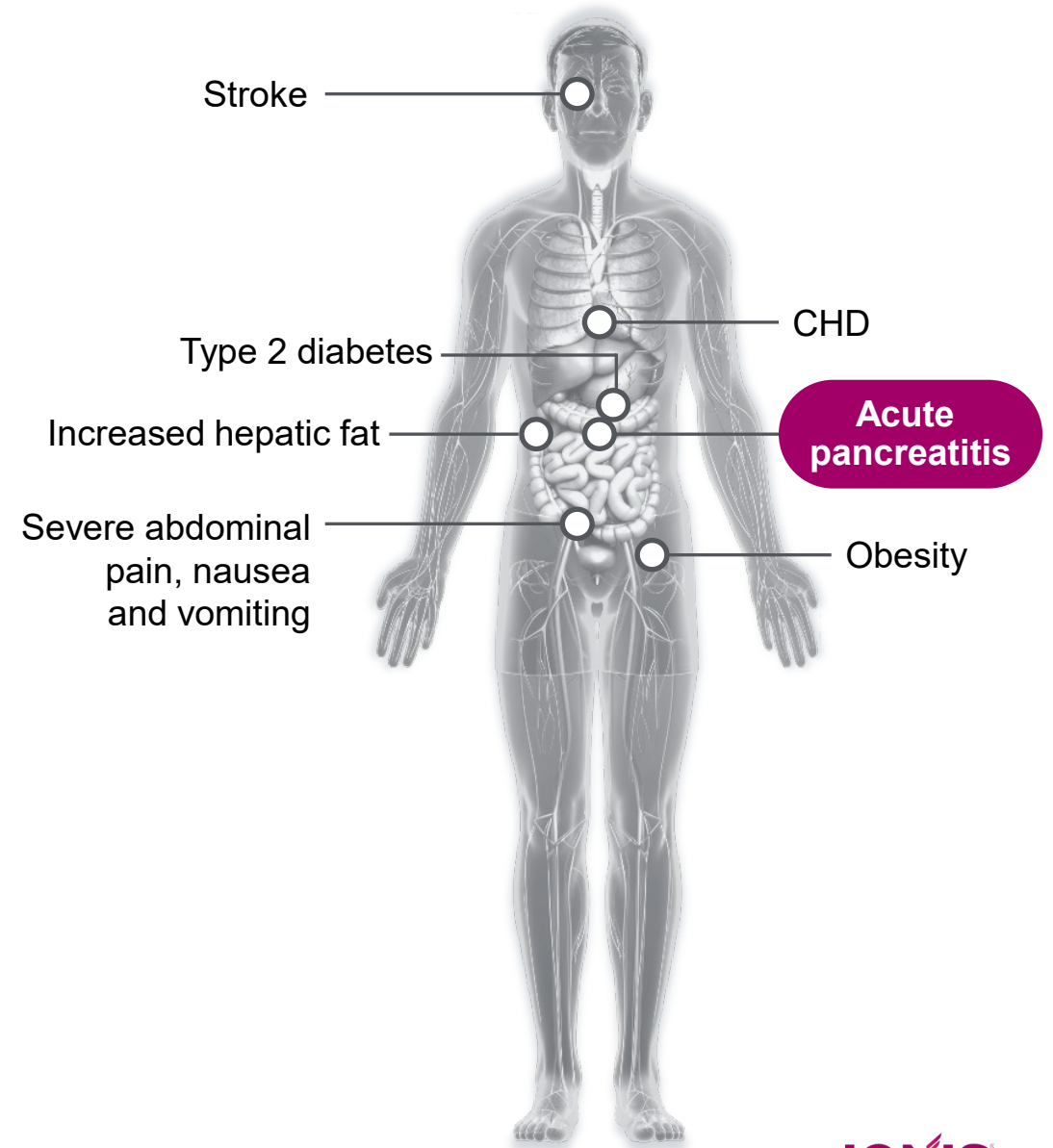
Characterized by increased risk of acute pancreatitis, atherosclerotic cardiovascular disease²

Driven by combination of triglyceride gene variants, lifestyle, obesity, and high-risk comorbidities^{2,3}

Limited benefit from currently available treatments⁴⁻⁷

>3 million people in the U.S. with sHTG⁸⁻¹⁰

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

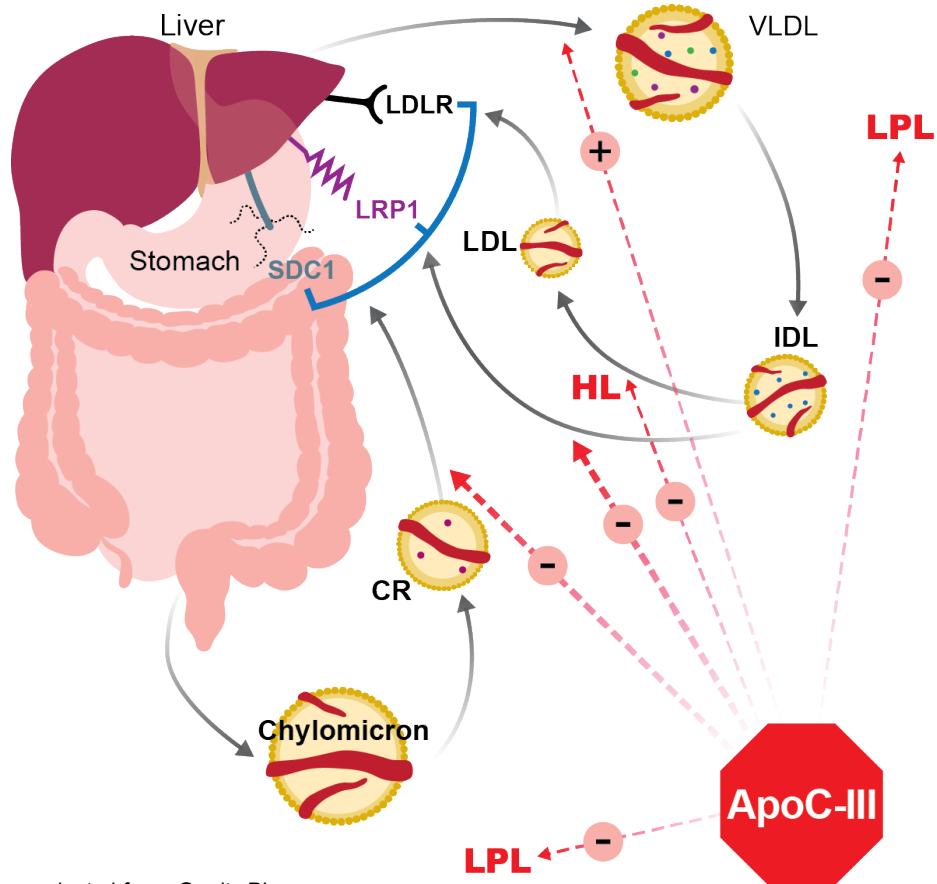
Guidelines for clinical practice for the management of hypertriglyceridemia consistently recommend aggressive triglyceride lowering treatment for all patients with sHTG



American Heart Association®



ApoC-III is a Key Regulator of Plasma Triglycerides^{1,2}



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

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

Olezarsen Phase 3 Program Designed to Support Potential in sHTG

Severe Hypertriglyceridemia (sHTG)



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

Registration studies

1,063 participants

Largest Pivotal Program Ever Conducted in sHTG

Moderate Hypertriglyceridemia (HTG)



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 Studies¹



DESIGN

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

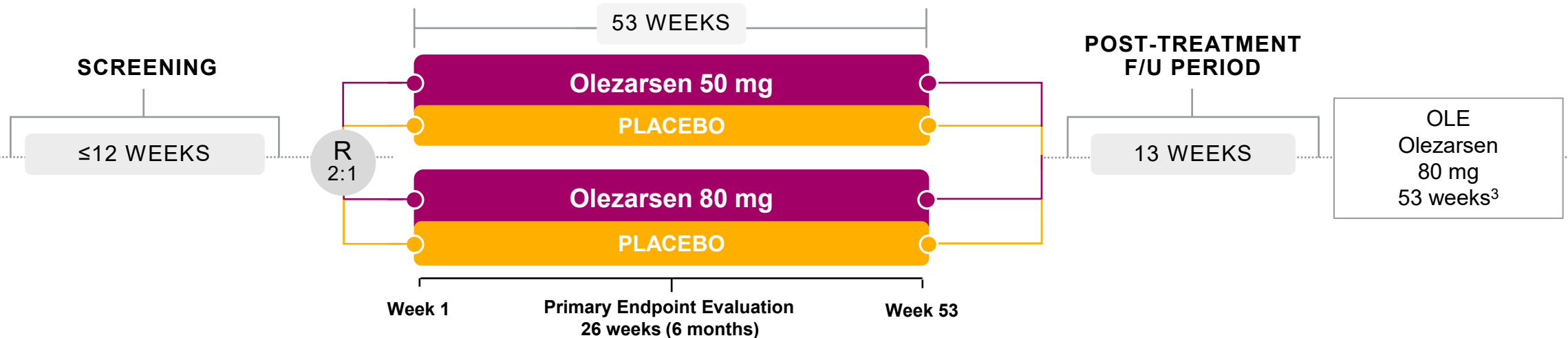
- Stratified by triglyceride levels ≥ 880 mg/dL at qualification visit and pancreatitis history²
- 99% of participants were on standard lipid-lowering therapy

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 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 | 832 (1,182) | 748 (1,025) |
| • Fasting Triglycerides ≥880 mg/dL | 47% | 37% |
| Total Cholesterol, Median mg/dL | 231 | 216 |
| • LDL Cholesterol | 59 | 61 |
| • HDL Cholesterol | 25 | 27 |
| Lipid Lowering Therapies ² | 99% | 99% |
| • ≥2 Therapies | 67% | 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 |

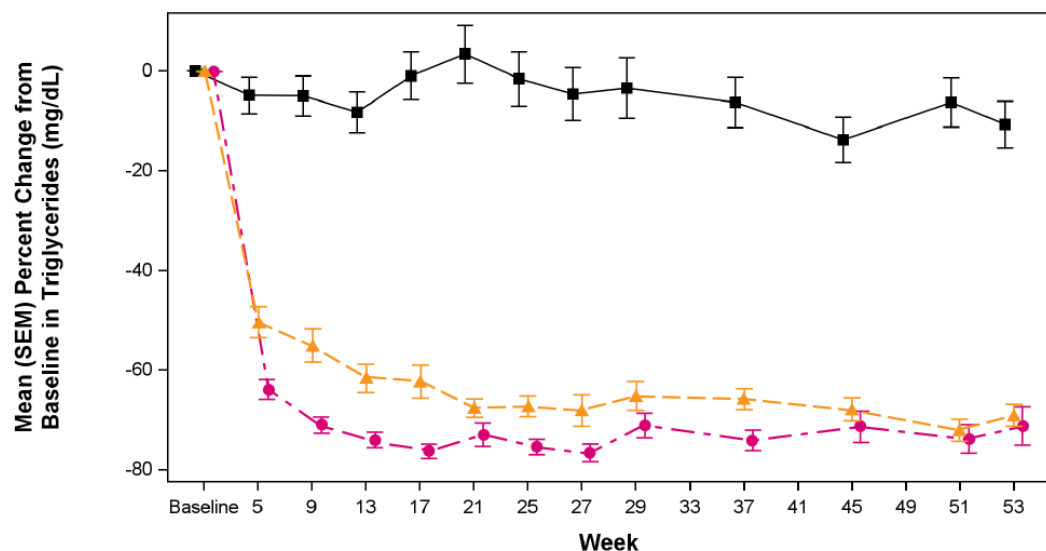
Up to a **72%**
placebo-adjusted
mean reduction in
fasting triglycerides on
top of standard of care¹

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

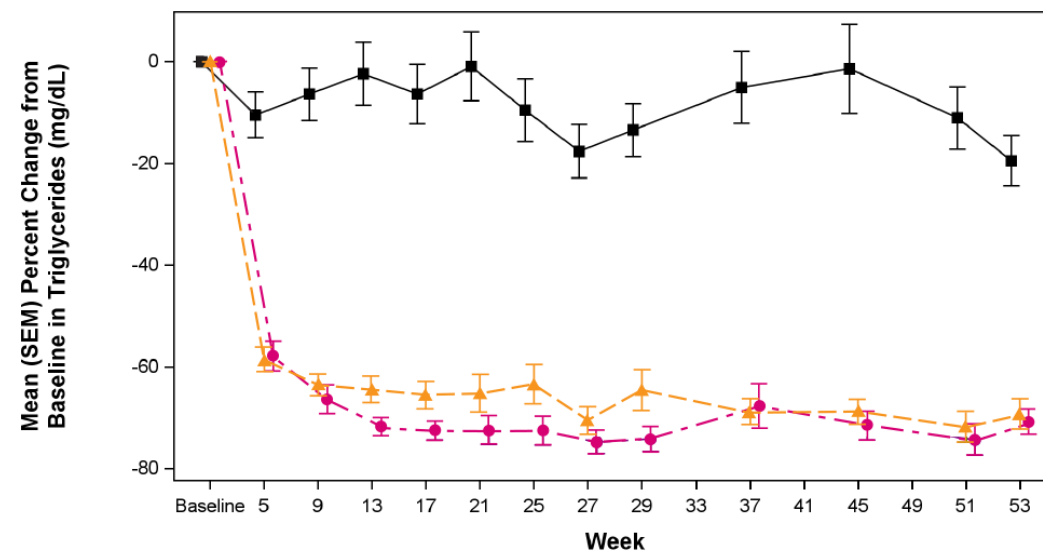


Treatment —■— Placebo —▲— Olezarsen 50 mg —●— Olezarsen 80 mg

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



Treatment —■— Placebo —▲— Olezarsen 50 mg —●— Olezarsen 80 mg

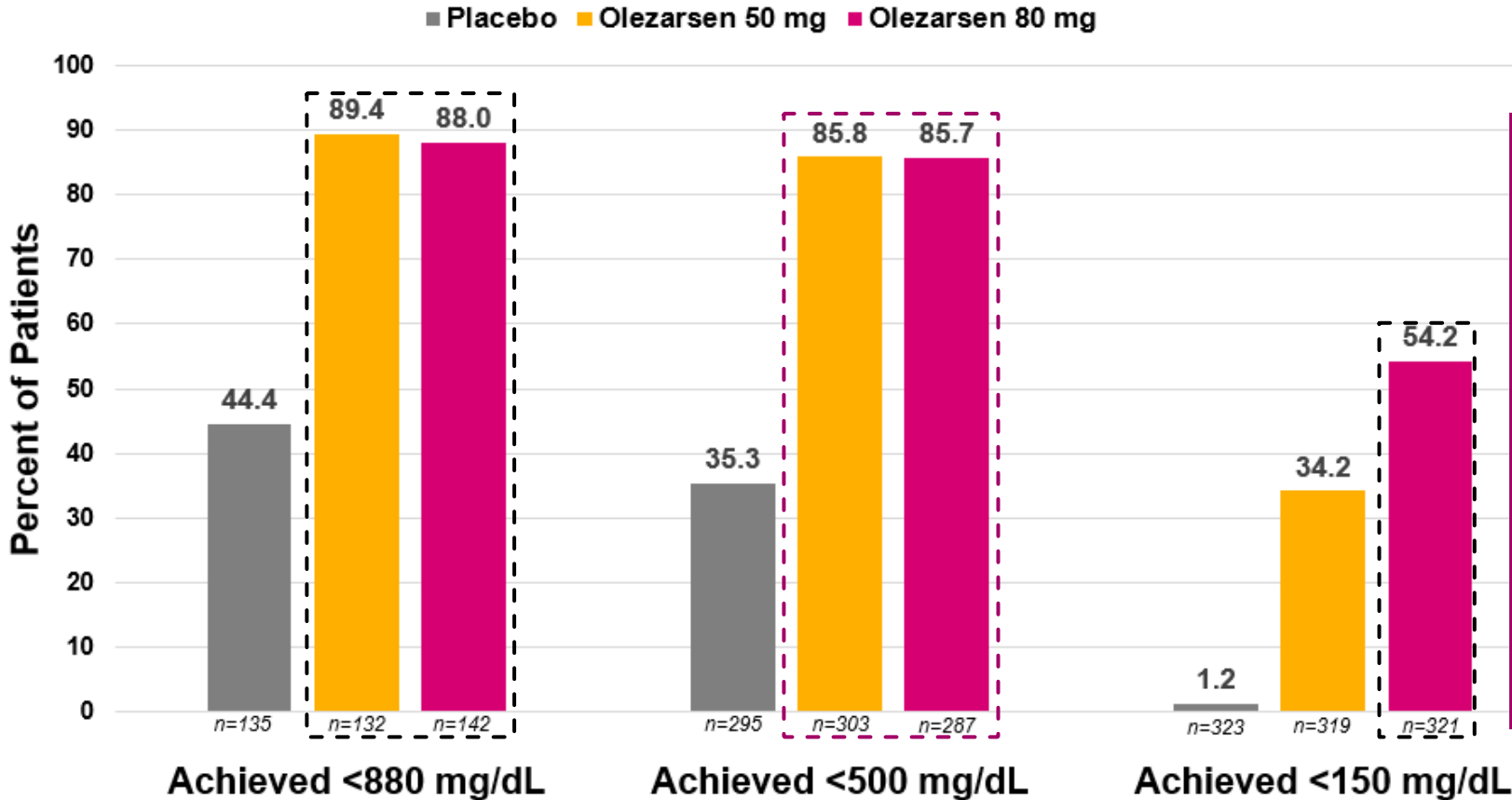
Number of Patients

| | | | | | | | | | | | | | |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 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 Pancreatitis¹



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%

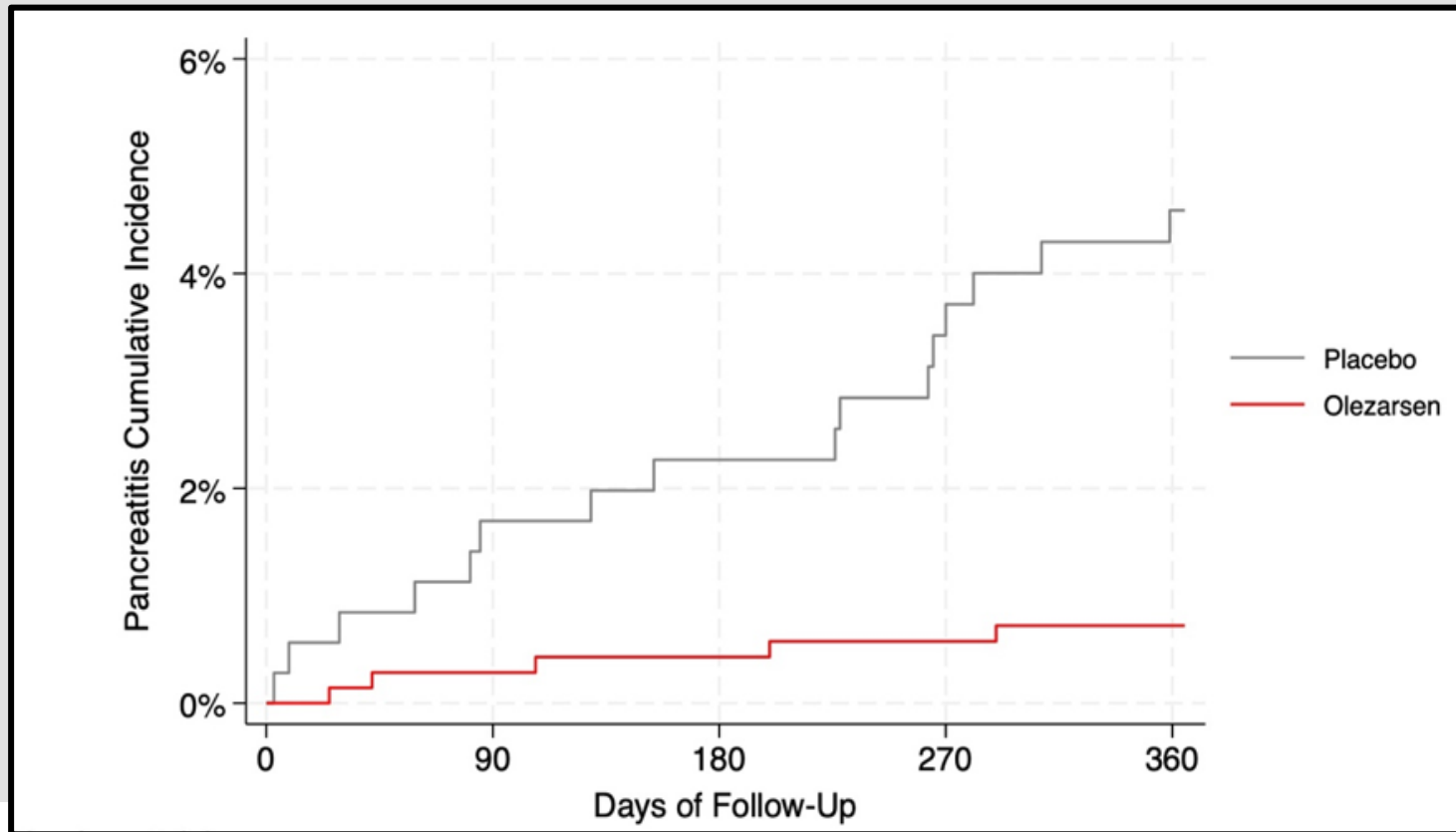
Reduction in acute pancreatitis events compared to placebo¹

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:



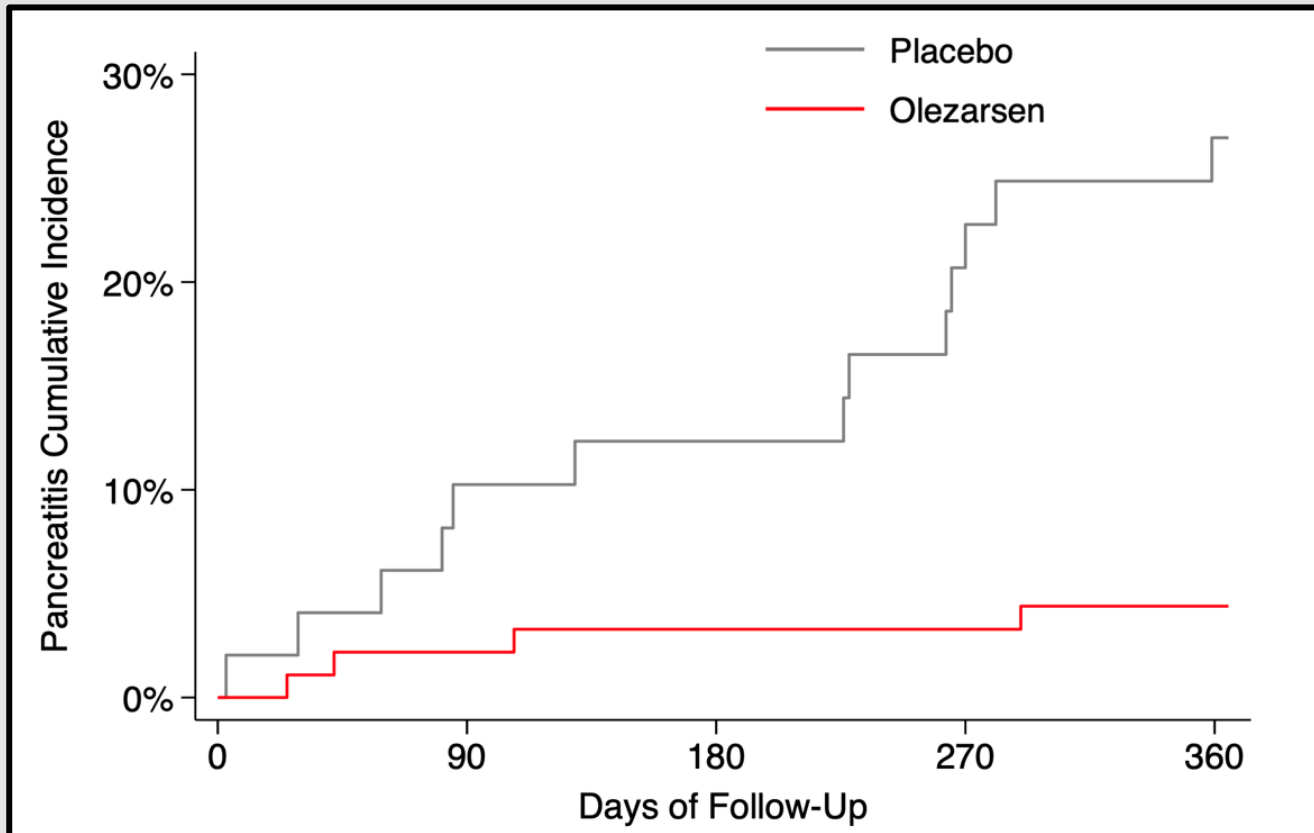
NNT=20
patients
in the overall
treatment
population¹

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 Group¹



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



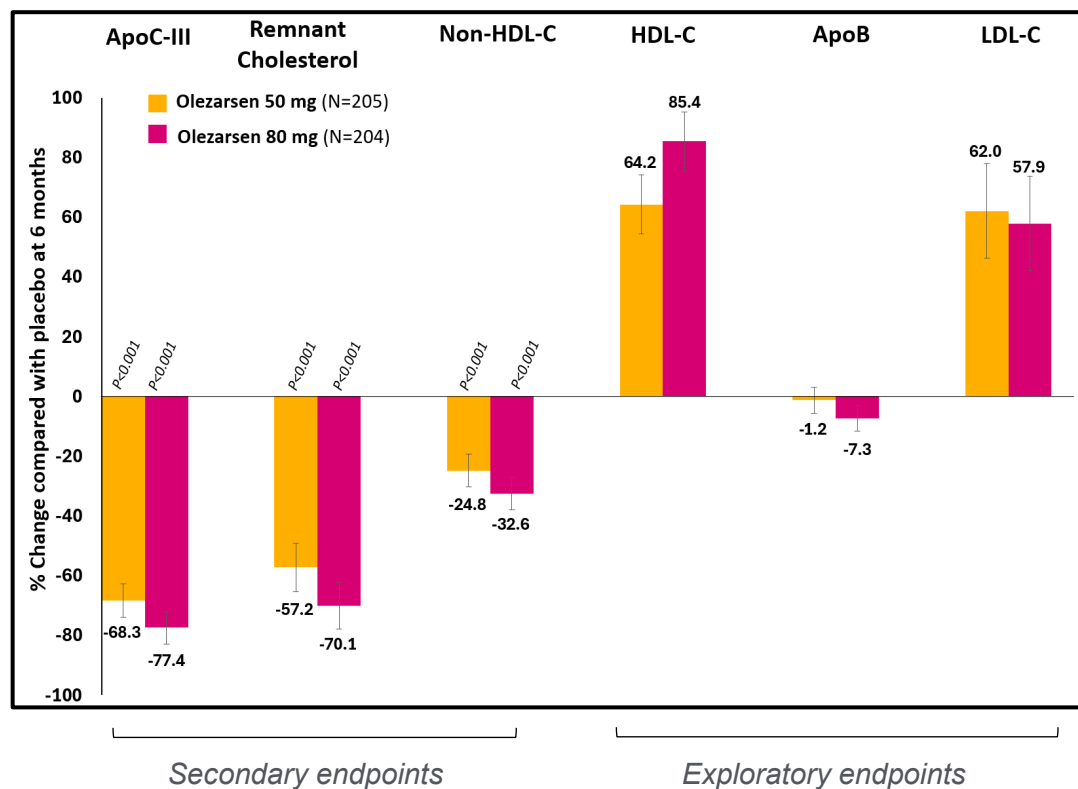
NNT=4
patients
for those with baseline
TGs ≥ 880 mg/dL
and history of AP

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.

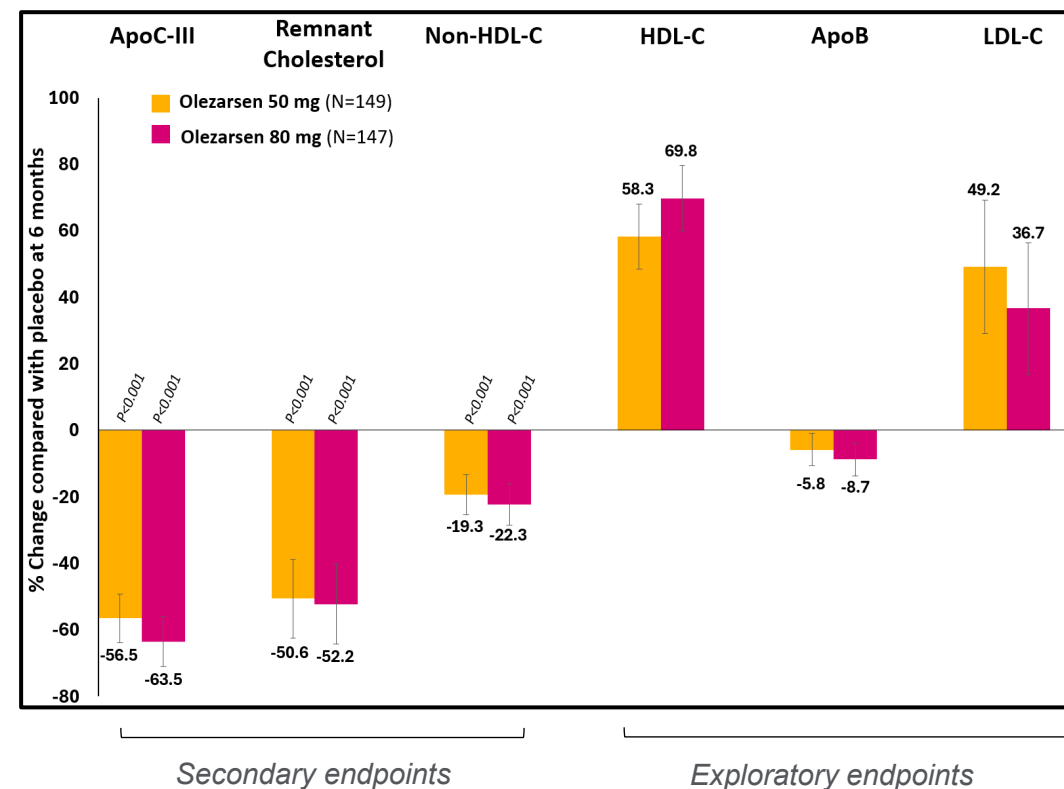
Positive Effect on Additional Secondary and Exploratory Endpoints: Lipid Parameters



CORE



CORE2



Favorable Safety and Tolerability Observed in the CORE and CORE2 Studies¹



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% <i>P=0.86</i> | 76% <i>P=0.64</i> |
| Leading to drug discontinuation | 2% | 3% <i>P=0.25</i> | 4% <i>P=0.09</i> |
| Serious | 14% | 9% <i>P=0.04</i> | 11% <i>P=0.24</i> |
| Leading to drug discontinuation | 0.3% | 1% <i>P=0.22</i> | 0.6% <i>P=0.57</i> |
| Any injection site reaction | 1% | 10% <i>P<0.001</i> | 17% <i>P<0.001</i> |
| 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 Results¹



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

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:

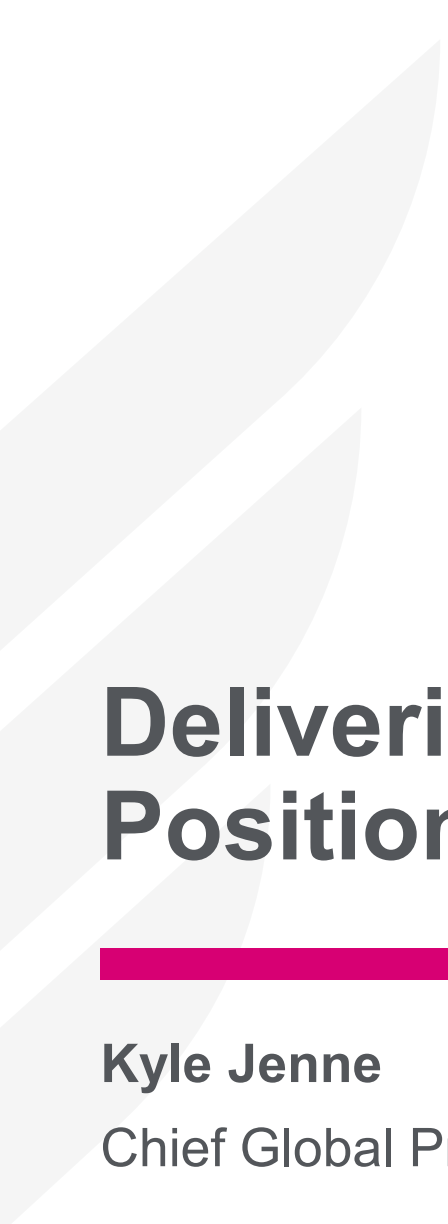
Positioned to be the
New Standard of Care
for Severe
Hypertriglyceridemia¹

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 doses¹

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 Opportunity¹⁻³

>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.

Acute Pancreatitis: Potentially Fatal Outcome of sHTG



The risk of potentially fatal 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
pancreatitis¹

~\$100,000
Annual costs

for healthcare resulting
from sHTG-pancreatitis
with hospitalization^{3,4}

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

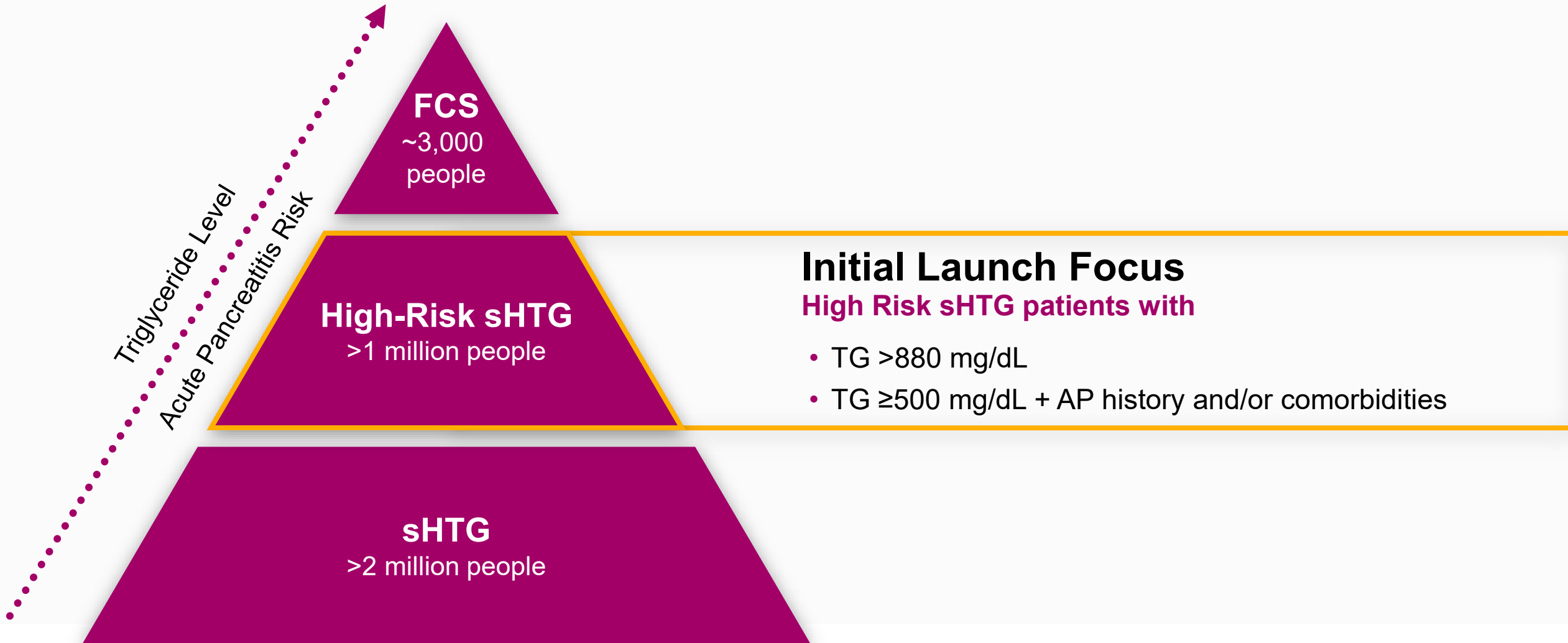
3

Favorable safety and **tolerability**¹

4

Simplicity of **monthly self-administration** with an **autoinjector**

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.

Realizing the Blockbuster Potential of Olezarsen in sHTG¹⁻⁴



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 Awareness³

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 Dynamics⁴

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

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

Olezarsen: Potential Blockbuster Medicine Positioned to be the New Standard of Care in sHTG Treatment¹⁻³

up to **72%** reduction

in fasting triglycerides

- Highly statistically significant -
- Clinically meaningful -

85%

**reduction in
acute pancreatitis events**

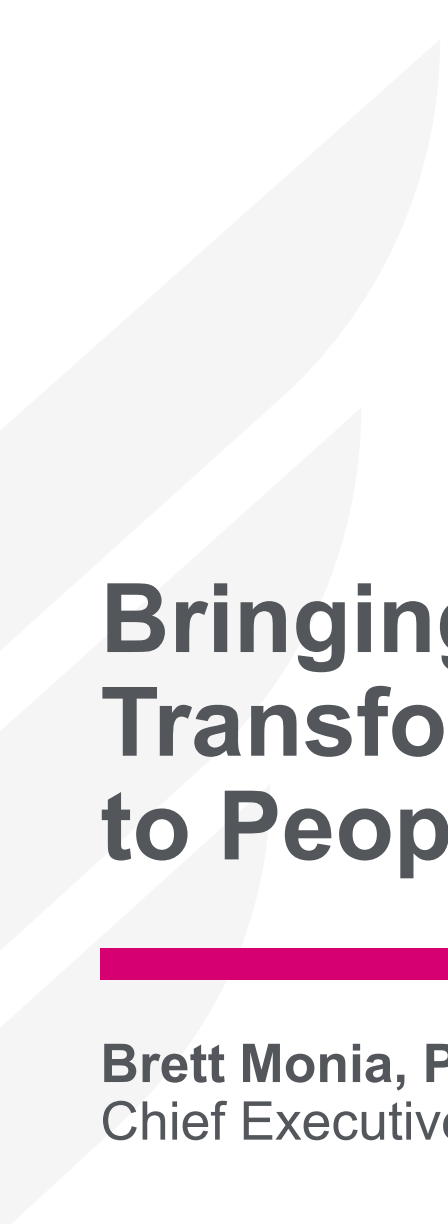
First and only investigational treatment to **significantly reduce acute pancreatitis events** in people with sHTG

Commercial organization designed for

**sHTG Launch
Success**

1st

Mover Advantage



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 Medicines¹

2

Independent Launches in <1 year²

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

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

2

Independent Launches Planned Next Year³

Olezarsen (sHTG) | Zilganersen (AxD)

4

Key Partner Launches by end of 2027⁴

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

Transforming Human Health through RNA-Targeted Medicines

