Olezarsen: Balance Study Results

April 8, 2024

Nasdaq: IONS

Forward-Looking Statements

This presentation includes forward-looking statements regarding the therapeutic and commercial potential of olezarsen, Ionis' technologies, and Ionis' other products in development. 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, 2023, which is on file with the SEC. Copies of these and other documents are available at www.ionispharma.com.

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

Agenda

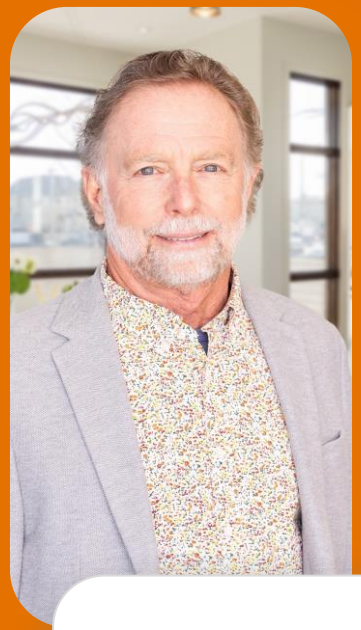
Topic	Speaker
Delivering Next-level Value to Patients & All Stakeholders	**Brett Monia, Ph.D.** *CEO*
Olezarsen: Addressing Two Distinct Diseases of High Unmet Need	**Sam Tsimikas, M.D.** *SVP, Global CV Development*
Phase 3 Balance Study Results	**Erik Stroes, M.D.** *Department of Vascular Medicine at Amsterdam University Medical Center*
Delivering Olezarsen to FCS Patients in Need	**Jonathan Birchall** *Chief Commercial Officer*
Concluding Remarks	**Brett Monia, Ph.D.** *CEO*
Q&A	

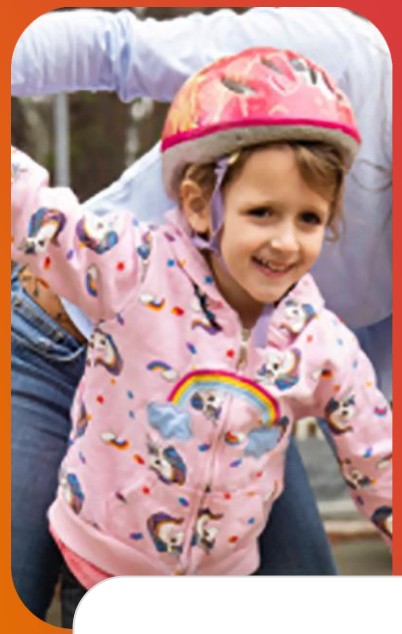
Delivering Next-level Value to Patients & All Stakeholders

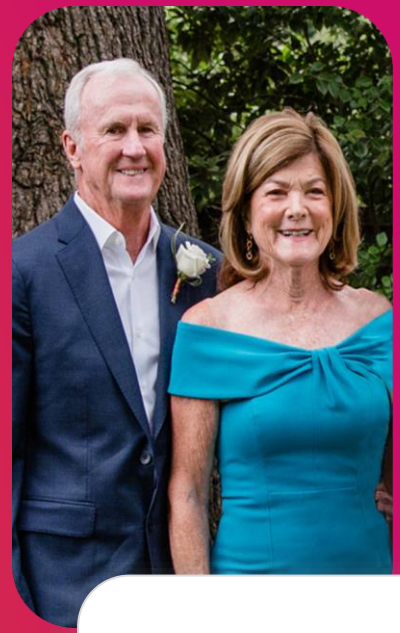
Brett Monia, Ph.D.
Chief Executive Officer

Next-Level Value for Patients & All Stakeholders

Scientific and Clinical Innovation **Financial Responsibility**








Prioritizing and Expanding the Ionis Wholly Owned Pipeline

Delivering Ionis Medicines Directly to Patients

Technology Leadership

Realizing the Promise of our Innovative Medicines[1]

First Ionis-Branded Medicine[2]

WAINUA (eplontersen) 45 mg injection for subcutaneous use

Launched in ATTRv-Polyneuropathy January 2024

Ongoing fully enrolled Phase 3 study for ATTR Cardiomyopathy[3]

Co-developing and commercializing in the U.S. with AstraZeneca

First Ionis Independent Launches[1,4]

Olezarsen

Launch in FCS expected by YE:2024[4]

Pivotal sHTG program on track

Blockbuster opportunity[5]

Donidalorsen

Launch in HAE expected in 2025[4]

Efficient commercial organization

Establishing global access

Next Wave of Wholly Owned Medicines

Leading Neurology Pipeline

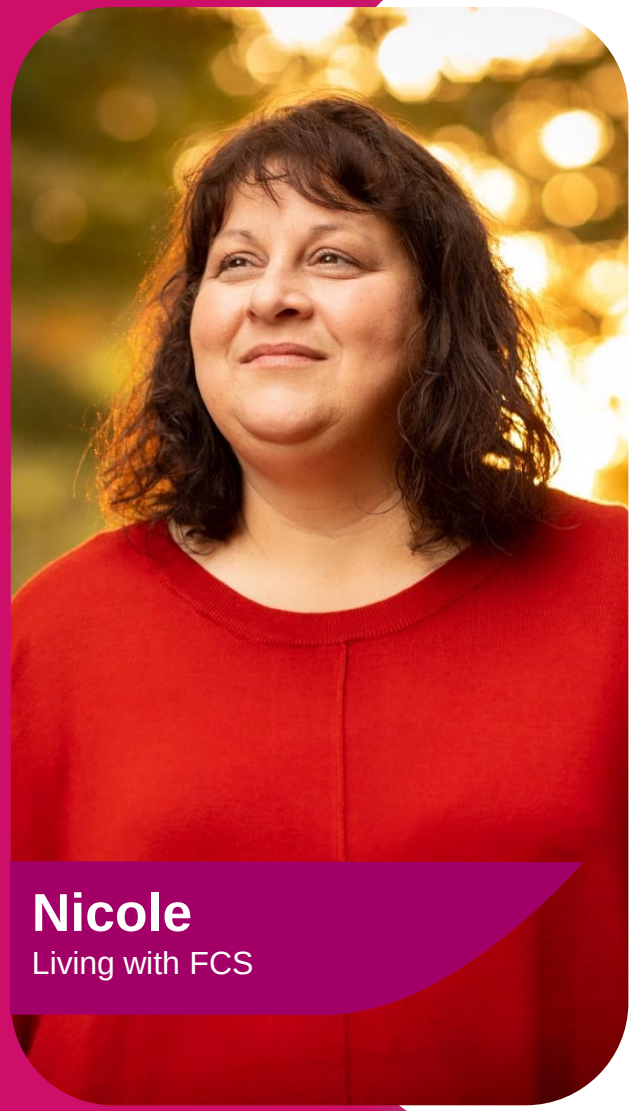
Proven track record of delivering first-in-class disease modifying medicines

6 wholly owned medicines in clinical development by YE:2024

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. WAINUA: www.wainua.com 3. Data planned for ATTR-CM as early as 2025. 4. Assuming approval. 5. In aggregate.

Olezarsen:

Potential to become the **Standard-of-Care** Treatment for Patients with **Severely Elevated Triglycerides**[1,2]



Substantial unmet need

Positive Balance study results[3]**:**

- Robust reductions in apoC-III, TGs & favorable safety and tolerability
- Markedly lower rate of acute pancreatitis vs. placebo

Regulatory filings for **FCS** in progress and potential FDA approval in **2024**[4]

1st independent launch[4]

Exciting rare disease opportunity

1. Based on data generated to date. 2. Timing based on current estimates and subject to change. 3. Due to statistical hierarchy, reductions in apoC-III and acute pancreatitis are considered exploratory. 4. Assumes priority review and approval.

Olezarsen: Addressing Two Distinct Diseases of High Unmet Need

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

Olezarsen: Addressing Two Distinct Populations of Patients with Urgent Unmet Need[1-3]

Familial Chylomicronemia Syndrome

- **Rare disease opportunity** ~1-13 people per million in the U.S.[4-6]
- **No approved treatments** in the U.S.
- **Significant risk** for acute, potentially fatal pancreatitis
- **Potential first indication** launch for olezarsen

Severe Hypertriglyceridemia

- **Large addressable** market, >3 million patients in the U.S.[7-10]
- **Limited benefit** from current standard of care
- **Treatment guidelines** recommend preventative treatment
- **Clear** regulatory path

1. Timing expectations and peak sales estimates based on current assumptions and subject to change. 2. Assuming approval. 3.Applies to total addressable market. 4. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 5. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6. 6. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 7. Sanchez et al. *Lipids in Health and Disease* 2021;20:72. 8. Berberich et al. *Lipids in Health and Disease* 2021;20:98. 9. Fan et al., *J Clin Lipidology* 2019; 13:100-108. 10. Christian et al., *Am J Cardiol* 2011;107:891-897.

Olezarsen is Delivering Robust Data Supporting its Potential as a Breakthrough Treatment for FCS and sHTG[1]

Familial Chylomicronemia Syndrome (FCS)

Balance
a familial chylomicronemia syndrome study

- Balance study in FCS patients demonstrated substantial reductions in apoC-III, TGs, marked AP reductions and favorable safety and tolerability[2]
- Data presented at ACC, published in *NEJM*[3]
- EAP in FCS now open, OLE progressing well
- U.S. Breakthrough Therapy and Orphan drug designations
- U.S. and EU filings on track this year
- Prepared to launch by YE: 2024[4]

Bridge
TIMI 73a

- Phase 2b study in patients with TG ≥200 mg/dL (HTG) and TG ≥500 mg/dL (sHTG)
- Supportive exposure study
- Statistically significant reductions in apoC-III, TGs, meaningful reductions in apoB, non-HDL-C, markers of CV risk, favorable safety and tolerability
- Data presented in late-breaker presentation at ACC, published in *NEJM*[5]

1. Timing expectations are based on current assumptions and are subject to change. 2. Due to statistical hierarchy, reductions in apoC-III and acute pancreatitis are considered exploratory. 3. Stroes E, et al. *N Engl J Med*. 2024.
4. Assuming priority review and approval. 5. Bergmark, B, et al. *N Engl J Med*. 2024.

Olezarsen is Delivering Robust Data Supporting its Potential as a Breakthrough Treatment for FCS and sHTG[1]

Familial Chylomicronemia Syndrome (FCS)

The NEW ENGLAND JOURNAL of MEDICINE

- Balance study in FCS patients demonstrated

ORIGINAL ARTICLE

Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome

Erik S.G. Stroes, M.D., Ph.D., Veronica J. Alexander, Ph.D., Ewa Karwatowska-Prokopczuk, M.D., Ph.D., Robert A. Hegele, M.D., Marcello Arca, M.D., Christie M. Ballantyne, M.D., Handrean Soran, M.D., Thomas A. Prohaska, M.D., Ph.D., Shuting Xia, M.S., Henry N. Ginsberg, M.D., Joseph L. Witztum, M.D., and Sotirios Tsimikas, M.D., for the Balance Investigators*

- Phase 2b study in patients with TG ≥200

ORIGINAL ARTICLE

Olezarsen for Hypertriglyceridemia in Patients at High Cardiovascular Risk

Brian A. Bergmark, M.D.*, Nicholas A. Marston, M.D.*, M.P.H., Thomas A. Prohaska, M.D., Ph.D., Veronica J. Alexander, Ph.D., André Zimerman, M.D., Ph.D., Filipe A. Moura, M.D., Ph.D., Sabina A. Murphy, M.P.H., Erica L. Goodrich, M.S., Shuanglu Zhang, M.P.H., Daniel Gaudet, M.D., Ph.D., Ewa Karwatowska-Prokopczuk, M.D., Ph.D., Sotirios Tsimikas, M.D., Robert P. Giugliano, M.D., and Marc S. Sabatine, M.D., M.P.H., for the Bridge–TIMI 73a Investigators

*Drs. Bergmark and Marston contributed equally to this article.

1. Timing expectations are based on current assumptions and are subject to change. 2. Due to statistical hierarchy, reductions in apoC-III and acute pancreatitis are considered exploratory. 3. Stroes E, et al. *N Engl J Med*. 2024.
4. Assuming priority review and approval. 5. Bergmark, B, et al. *N Engl J Med*. 2024.

Olezarsen is Delivering Robust Data Supporting its Potential as a Breakthrough Treatment for FCS and sHTG[1]

Severe Hypertriglyceridemia (sHTG)

CORE
a hypertriglyceridemia study

- Pivotal study in patients w/ TG ≥500 mg/dL (sHTG)
- Registrational study
- ~540 patients
- Enrolling

CORE2
a hypertriglyceridemia study

- Pivotal study in patients w/ TG ≥500 mg/dL (sHTG)
- Confirmatory registrational study
- ~390 patients
- Enrolling

Essence
TIMI-73b

- Supportive Ph3 study in patients w/ TG ≥200-500 mg/dL (HTG)
- Supports exposure database
- >1,400 patients
- Enrollment complete

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

FCS: Significant Patient Burden and Unmet Need

Rare, Underrecognized, Genetically Driven[1-8]

- Estimated 1 – 13 people per million with FCS in the U.S.
- Underrecognized, diagnosis often missed or delayed
- Identified by genetic mutations resulting in loss of lipoprotein lipase (LPL) activity with defined clinical criteria
- Characterized by inability to clear plasma triglycerides
  - Results in TGs 10-100x above normal levels

Significant Patient Burden[9]

- Extreme risk for acute, potentially fatal, pancreatitis
- Chronic, debilitating multi-organ symptoms
- Significant impact on ability to work, socialize and care for families

Clear Unmet Medical Need[1]

- No approved treatments in the U.S.
- Current triglyceride-lowering therapies ineffective in FCS patients
- Severely restrictive diet, limited compliance
  - <15-20g fat/day (~1 Tbsp olive oil)
  - No alcohol

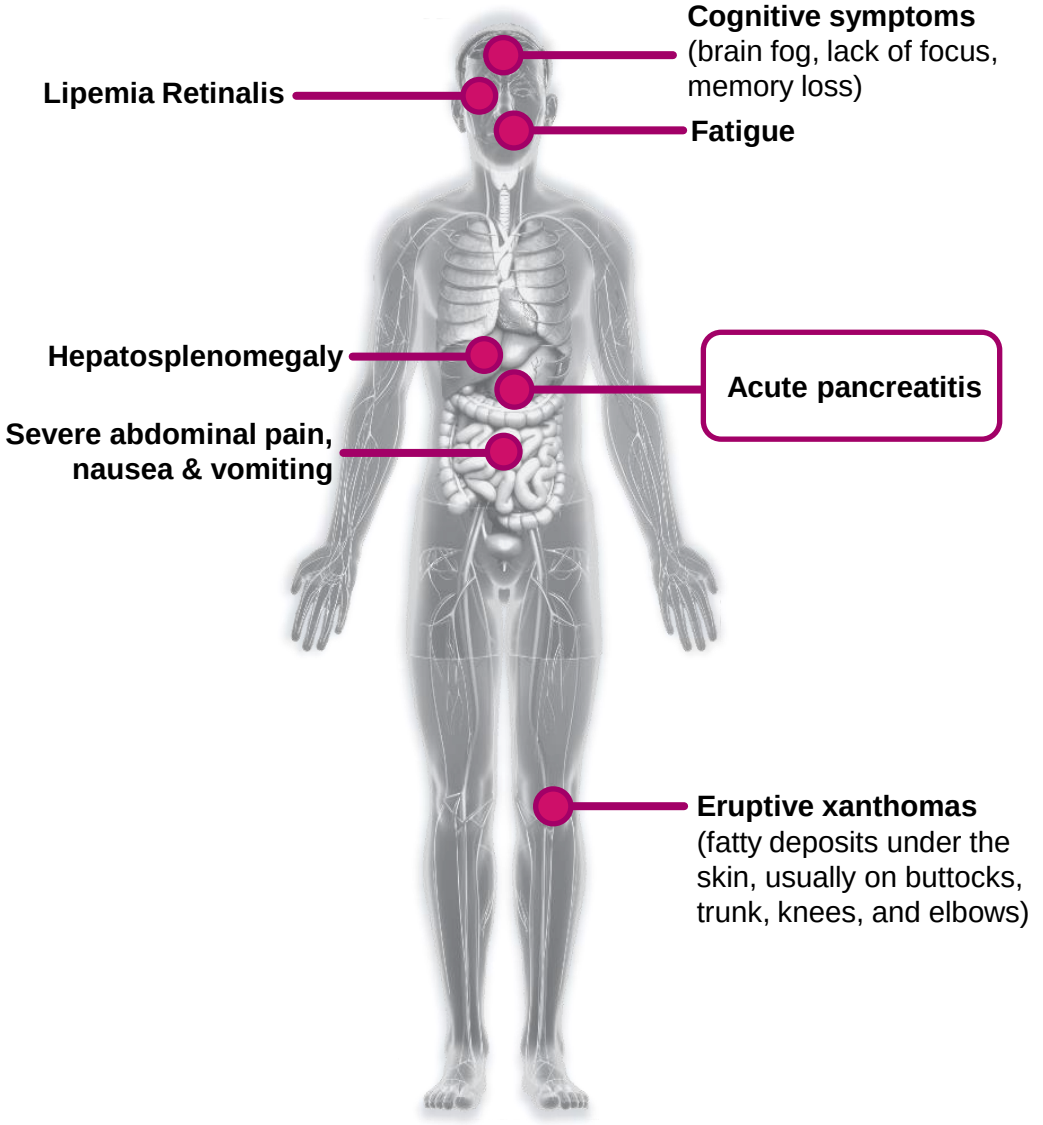
1. Moulin P, et al. *Atherosclerosis* 2018;275:265-72. 2. Brown EE, et al. *J Clin Lipidol* 2020;14(4):398-413. 3. Stroes E, et al. *Atheroscler Suppl* 2017:23:1-7. 4. Dron JS, et al. *BMC Med Genomics* 2020;13(1):23. 5. Hegele RA. *Nat Rev Genet* 2009;10(2):109-21. 6. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 7. Tripathi M, et al. *Endocr Pract* 2021;27(1):71-6. 8. Warden BA, et al. *J Clin Lipidol* 2020;14(2):201-6. 9. Gaudet D, et al. *N Engl J Med*. 2014;371:2200-2206.

Acute Pancreatitis: Severe, Potentially Fatal Complication of FCS

FCS-Driven Acute Pancreatitis

- FCS often diagnosed in early adulthood following acute pancreatitis; attacks can begin in childhood or infancy[1]
- Often results in hospitalization and intensive care, and surgery for pain control, infections, etc.[2]
- Associated with persistent organ failure, pancreatic necrosis, endocrine insufficiency, higher mortality[2]

Clinical Manifestations of FCS[3,4]

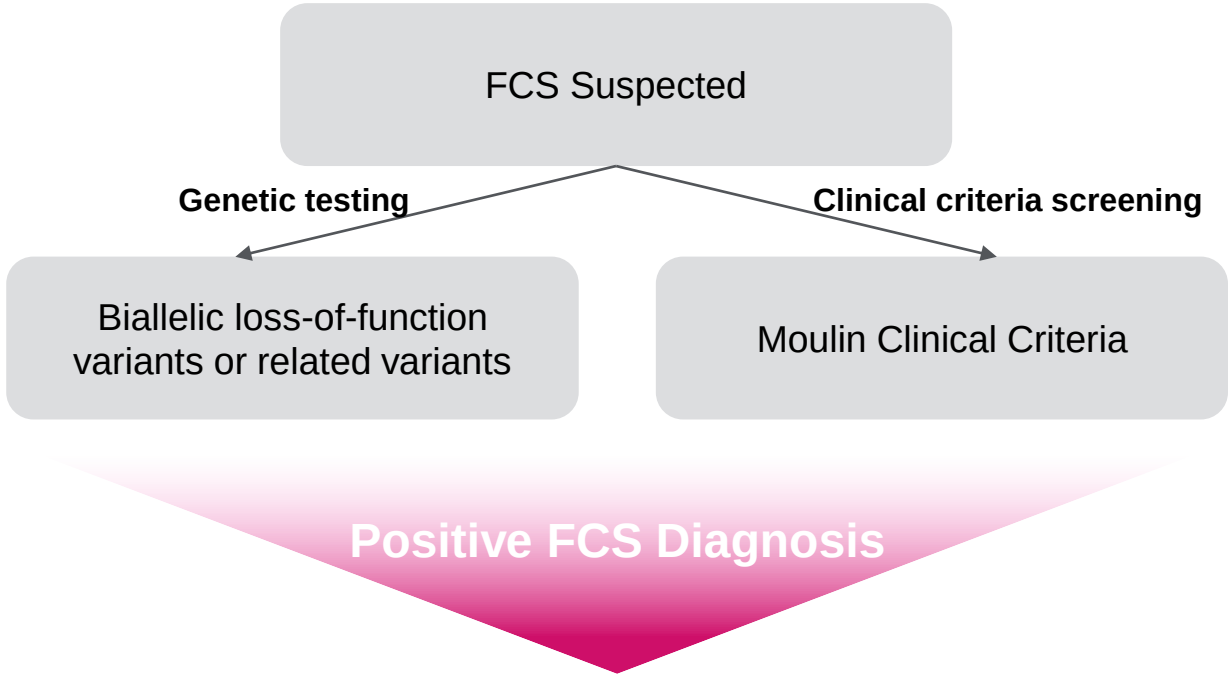


1. Gaudet D, et al. *N Engl J Med*. 2014;371:2200-2206. 2. Gaudet D, et al. *J Clin Lipidol*. 2016;10:3:680-681. 3. Brunzell JD, Bierman EL. *Med Clin North Am*. 1982;66(2):455–68. 4. Davidson M, et al. *J Clin Lipidol.* 2018;12(4):898–907

FCS Diagnosis is Based on Genetic Identification or Established Clinical Criteria[1,2]

- FCS diagnosis is based on identification of genetic variants associated with a loss of LPL activity or meeting established Moulin clinical criteria
- Moulin criteria for FCS diagnosis:
  - Persistent, current and historic TGs >880mg/dL
  - No secondary contributing factors
  - History of AP and unexplained abdominal pain
  - No sHTG family history
  - Refractory to standard lipid lowering therapy
  - Young age of onset

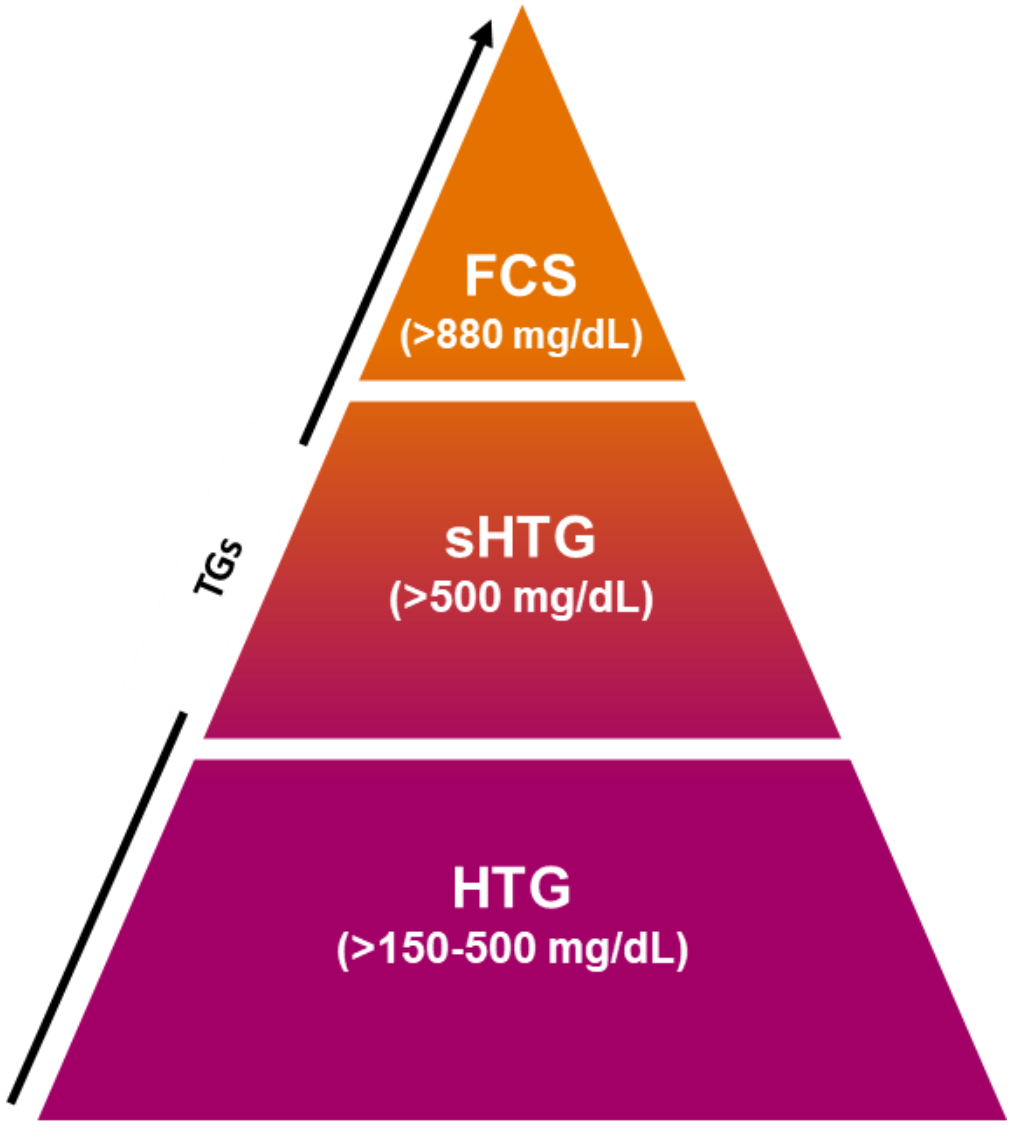
Genetic identification and/or clinical criteria distinguishes FCS from conditions with overlapping symptoms, such as sHTG



~1-13 individuals per million in the U.S.

1. Moulin P, et al. *Atherosclerosis* 2018;275:265-72. 2. Stroes E, et al. *Atheroscler Suppl* 2017:23:1-7.

FCS, sHTG and HTG Patients Have Distinct Clinical Profiles[1]



FCS (TG >880 mg/dL)

- Monogenic[2]
- Loss of LPL activity
- Markedly reduced TRL clearance
- Resistance to triglyceride-lowering therapies

sHTG (TG >500 mg/dL)

- Polygenic[3]
- Functional but potentially reduced LPL activity
- Functional but reduced TRL clearance

HTG (TG >150-500 mg/dL)

- Cardiovascular or metabolic risk factors, including obesity, diabetes, metabolic syndrome, high LDL-C, etc.

1. Hegele, et al, *Lancet Diabetes Endocrinol.* 2014 Aug;2(8):655-66 2. Homozygous or compound heterozygous variants in LPL, APOC2, APOA5, LMF1, GPIHBP1, and GPD1. 3. Heterozygous variants in LPL, APOA5, GCKR, APOB, LMF1, GPIHBP1, CREBH1, APOC2, APOE, small-effect variants and/or secondary effects.

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

Plasma triglycerides are broken down through two mechanisms:

1. Systemic lipoprotein lipase (LPL) activity
2. Triglyceride-rich lipoprotein (TRL) clearance

High levels of apoC-III reduce activity of both mechanisms, which results in elevated levels of plasma triglycerides

By reducing apoC-III production, olezarsen is designed to increase both LPL activity and TRL clearance

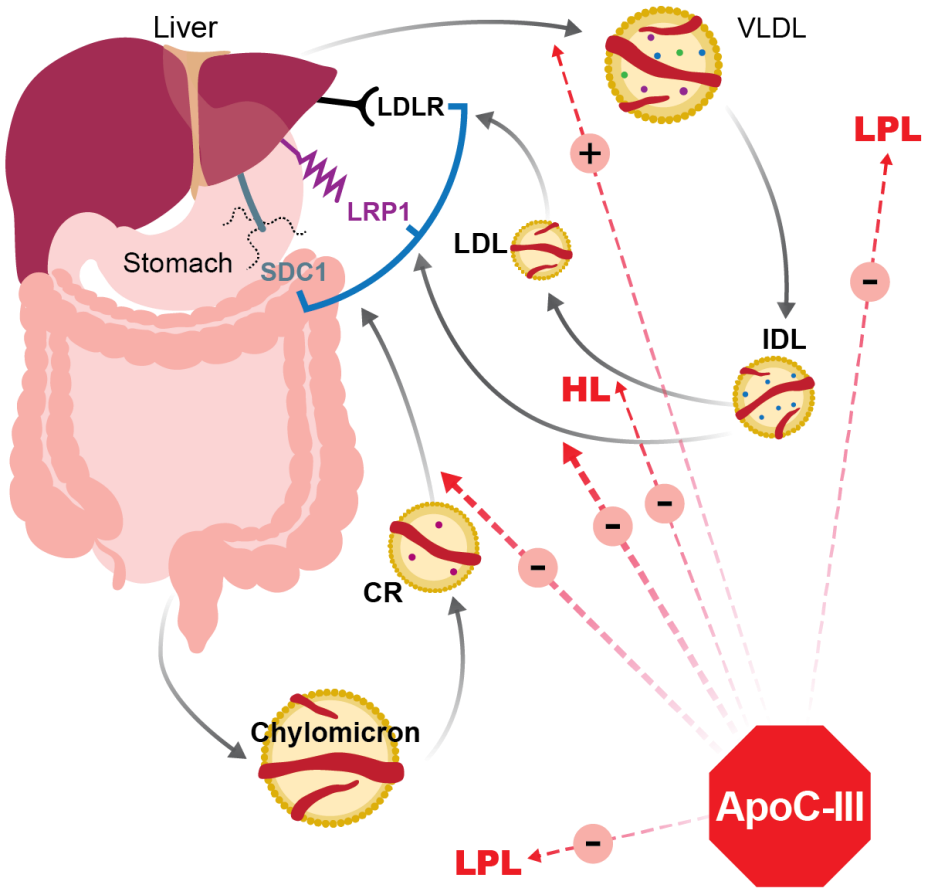


Image adapted from: Gordts PL, et al. *J Clin Invest.* 2016;126:2855

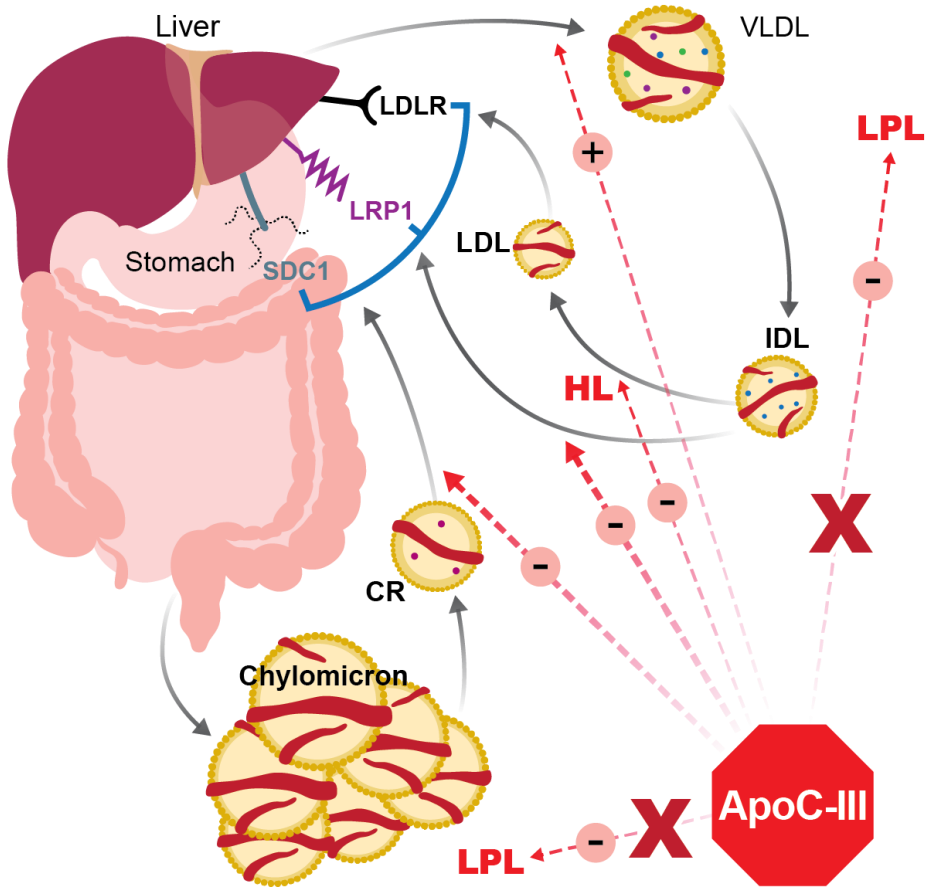
1. Gordts PL et al. *J Clin Invest* 2016;126:2855–66. 2. Kohan AB. *Curr Opin Endocrinol Diabetes Obes*. 2015;22:119-125.

In FCS, Loss of LPL Activity Results in Increased Resistance to Triglyceride-Lowering Treatments[1,2]

Loss of LPL activity results in dependence on less efficient, TRL-clearance mechanism:

- ✗ Systemic lipoprotein lipase (LPL) activity
- ✓ Triglyceride-rich lipoprotein clearance

Patients with LPL activity are expected to show greater magnitude of effect with triglyceride-lowering treatment



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

Bridge Study: Significant Reductions in ApoC-III and Triglycerides in HTG and sHTG Patients Treated with Olezarsen

Bridge TIMI 73a

Olezarsen 80mg:

- 93% of patients with HTG achieved normal levels at 6 months (<150mg/dL)
- ApoC-III: 73% (6 months) and 71% (12 months) reduction vs. placebo[1]
- Triglycerides: 53% (6 months) and 55% (12 months) reduction vs. placebo[1]
- Favorable safety and tolerability

Olezarsen 80mg, sHTG subgroup:

- ApoC-III: 86% (6 months) and 91% (12 months) reduction from baseline[2]
- Triglycerides: 83% (6 months) and 86% (12 months) reduction from baseline[2]
- Favorable safety and tolerability

Looking ahead: CORE & CORE2

- Data in CORE and CORE2 studies in patients with sHTG expected to be similar to sHTG patient data from Bridge based on normal LPL activity

1. Placebo-adjusted, p<0.001. 2. Not placebo-adjusted; placebo changes in apoC-III of -14% and -31% and in triglycerides of -35% and -48% observed at 6 and 12 months, respectively.

Olezarsen Data from Studies to Date Support Potential for Positive Study Outcomes in Patients with FCS and sHTG

- Patients with FCS, sHTG and HTG have distinct clinical profiles. FCS is characterized by a loss of LPL activity and resistance to triglyceride-lowering treatments.
- Olezarsen demonstrated robust apoC-III and triglyceride reductions in patients with sHTG and HTG in the Bridge study.
- The substantial triglyceride reductions in patients with sHTG in Bridge are anticipated to be similar to results from sHTG patients in the CORE and CORE2 studies.
- Olezarsen has demonstrated a favorable safety and tolerability profile in all studies to date.

Olezarsen treatment has the potential to make a profound difference in the lives of patients with FCS and sHTG

Phase 3 Balance Study Results

Erik Stroes, M.D.
Department of Vascular Medicine, Amsterdam University Medical Center

Disclosures

Erik Stroes reports advisory board/lecturing fees paid to his institution by Amgen, AstraZeneca, Ionis Pharmaceuticals, Merck, Novartis, and Novo Nordisk;

and investigator-initiated study grants from Ionis Pharmaceuticals, Novartis, and Novo Nordisk.

Olezarsen is an investigational drug in late-stage development

Funding: Ionis Pharmaceuticals

Preventing Acute Pancreatitis is the Key Goal in Treating Patients with FCS

- **Potentially deadly acute pancreatitis is the most severe complication of FCS**
- **FCS patients have minimal to no response to conventional TG-lowering therapies[1]**

85% of FCS Patients

Have experienced an AP event in their lifetime[2]

360-fold Increased risk

of AP attacks vs. normal triglyceride levels[3]

~2 times higher mortality

With severe HTG vs. normal triglyceride levels[4]

1. Stroes E, et al. *Atheroscler Suppl* 2017:23:1-7. 2. Davidson M, et al. *J Clin Lipidol.* 2018;12L898-907. 3. Gaudet D, et al. *Atheroscler Suppl.* 2010;11(1):55-60. 4. Nawaz H, et al. *Am J Gastroenterol*. 2015;110:1497-1503.

Phase 3 Balance Study in Patients with FCS

Balance
a familial chylomicronemia syndrome study

DESIGN

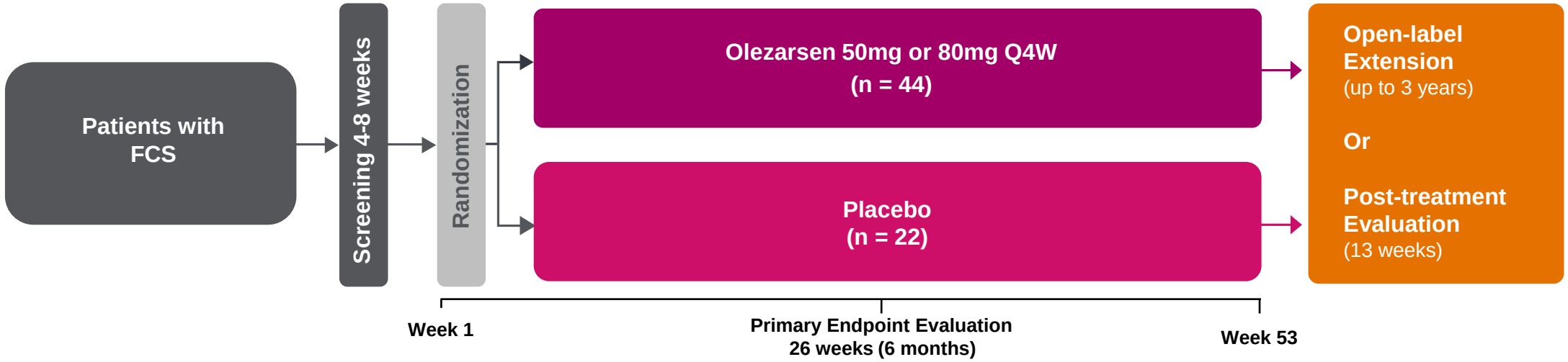
Randomized, double-blind, placebo-controlled study of monthly subcutaneous olezarsen in 66 patients with FCS, fasting TG ≥ 880 mg/dL (10 mmol/L)

- Genetically identified FCS
- ≥65% of patients with history of pancreatitis[1]
- Majority of patients on stable lipid-lowering therapy

ENDPOINTS

Primary outcome measure: Percent change in fasting triglycerides (TG) from baseline to month 6 with olezarsen 80mg and 50mg monthly

Key secondary endpoints: Change from baseline: fasting TG (12 months), reduction in pancreatitis events



1. Within 10 years prior to screening.

Patient Disposition

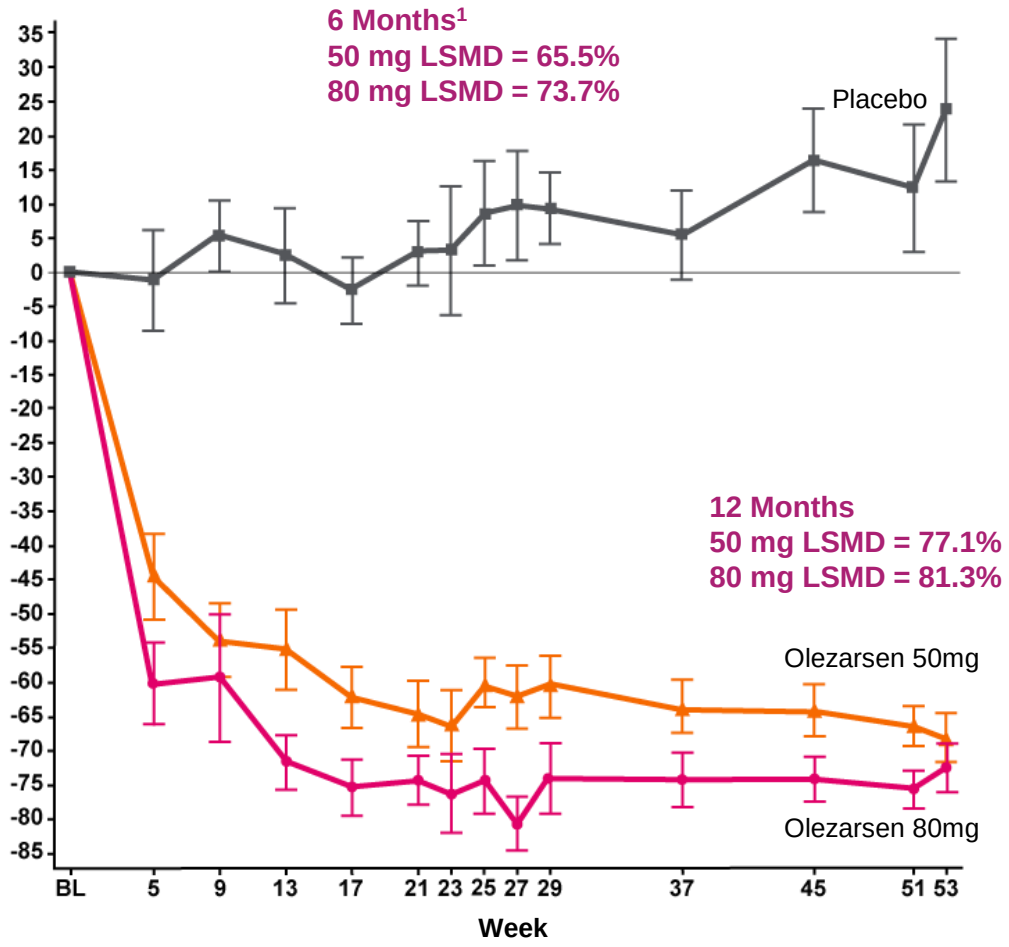
	Placebo	Olezarsen 50 mg	Olezarsen 80 mg
N	23	21	22
Completed Treatment	22 (95.7%)	19 (90.5%)	19 (86.4%)
Discontinued Study Treatment	1 (4.3%)	2 (9.5%)	3 (13.6%)

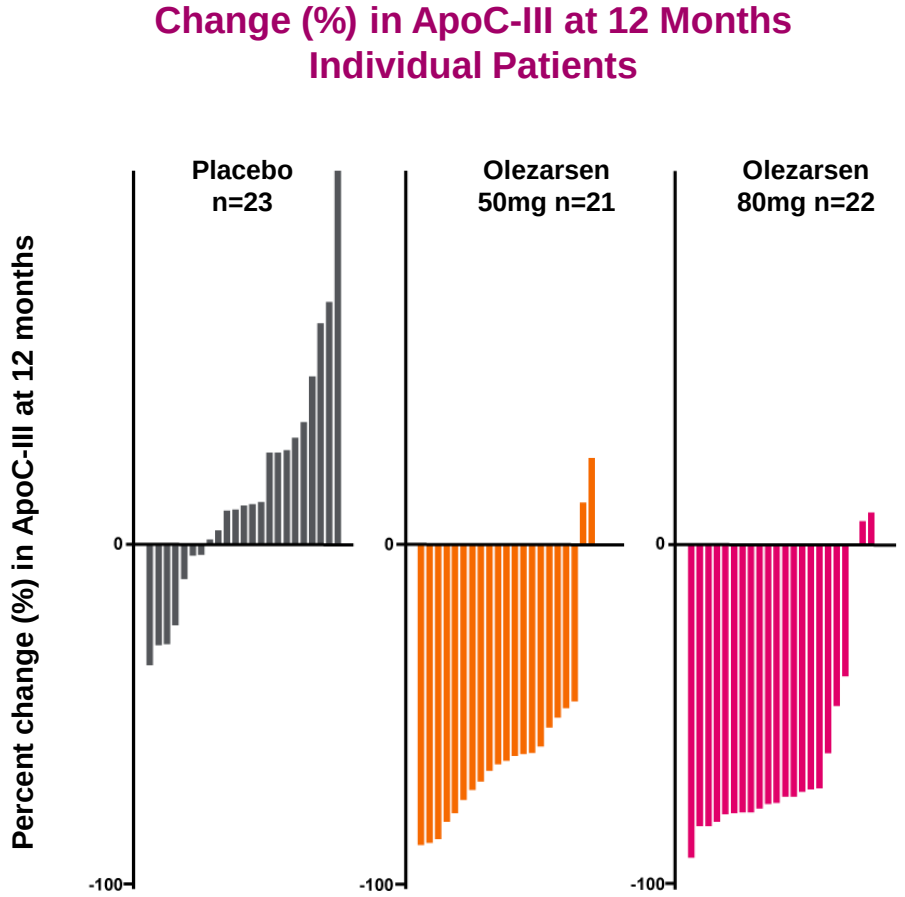
All 60 patients who completed the placebo-controlled portion of Balance entered the open-label extension study

Baseline Characteristics

Baseline Characteristics	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
Age, Mean years (SD)	44.0 (14.7)	43.2 (12.1)	47.7 (13.3)
BMI (kg/m^2), Mean (SD)	24.2 (4.1)	22.4 (3.5)	25.1 (6.0)
Triglycerides, mg/dL, mean (SD)	2596 (1256)	2684 (1235)	2613 (1499)
AP History, prior 10 years, n (%)	15 (65%)	15 (71%)	17 (77%)
ApoC-III, mg/dL, mean (SD)	27.7 (11.7)	27.7 (10.5)	27.5 (11.6)
≥1 concomitant lipid-lowering medication, n (%)	13 (57%)	9 (43%)	15 (68%)
Concomitant medications, n (%)			
• Statin	7 (30%)	4 (19%)	5 (23%)
• Omega-3 fatty acid	7 (30%)	6 (29%)	12 (55%)
• Fibrate	11 (48%)	8 (38%)	11 (50%)
• Other	3 (13%)	0	3 (14%)

Olezarsen Treatment Resulted in Robust and Sustained Reductions in Serum ApoC-III Levels through 12 Months

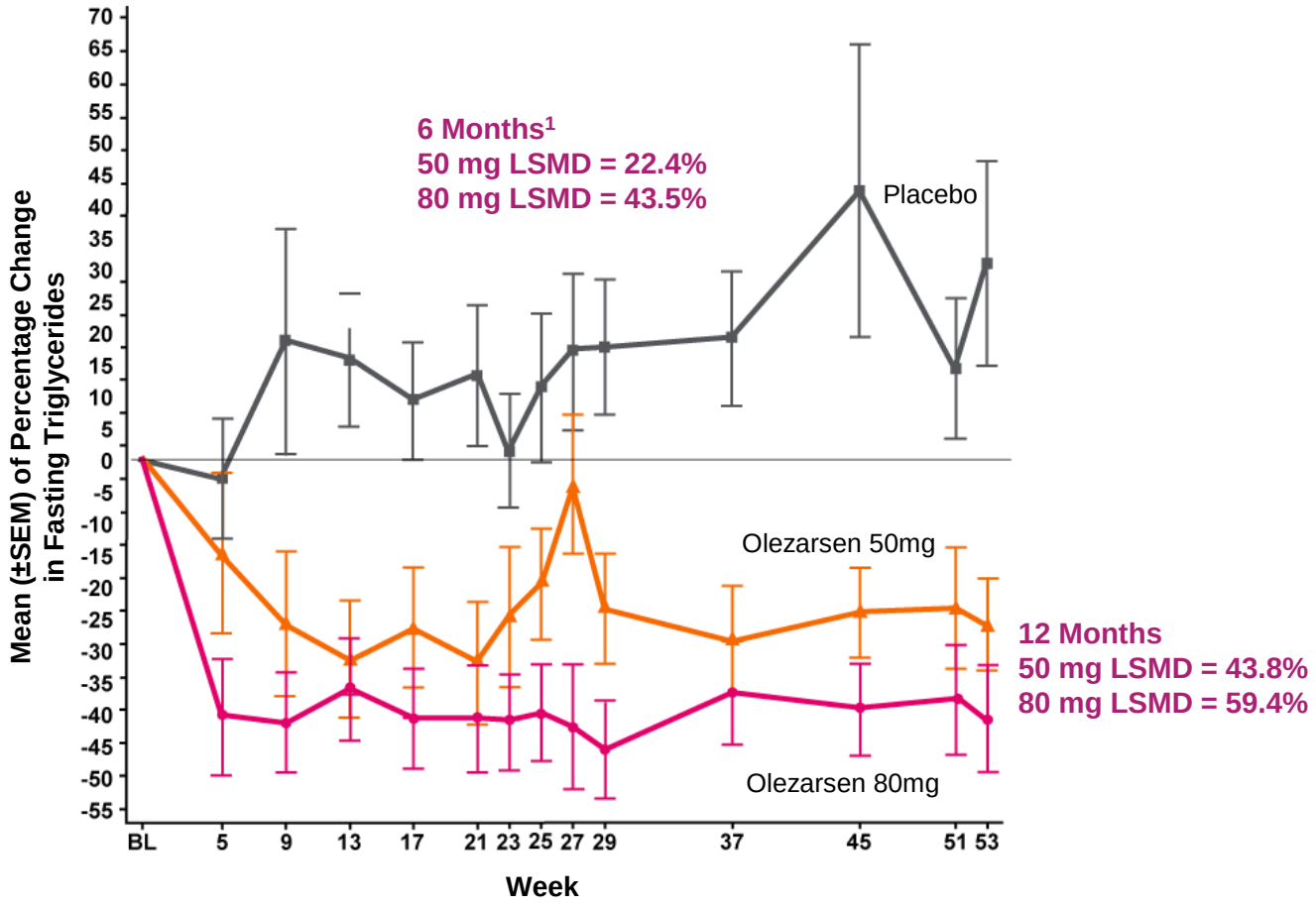


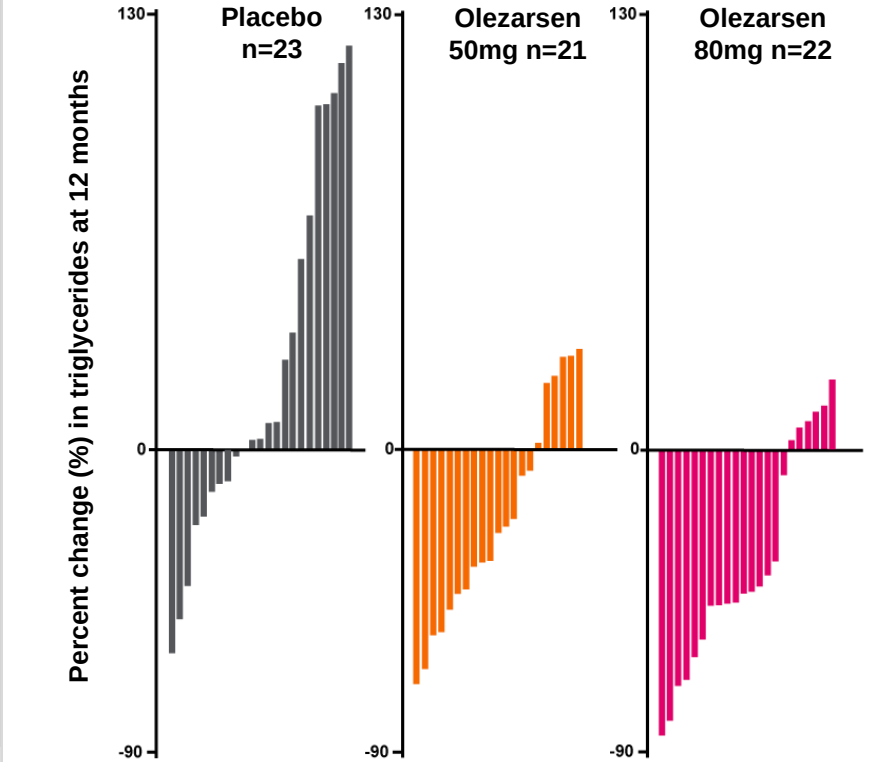


LSMD, Least squares mean difference. 1. Average of weeks 23, 25, and 27. 2. Average of weeks 51 and 53.

Olezarsen Treatment Resulted in Robust and Significant Reduction in Triglycerides at 6 Months[1,2]

Triglycerides further reduced through 12 months of treatment





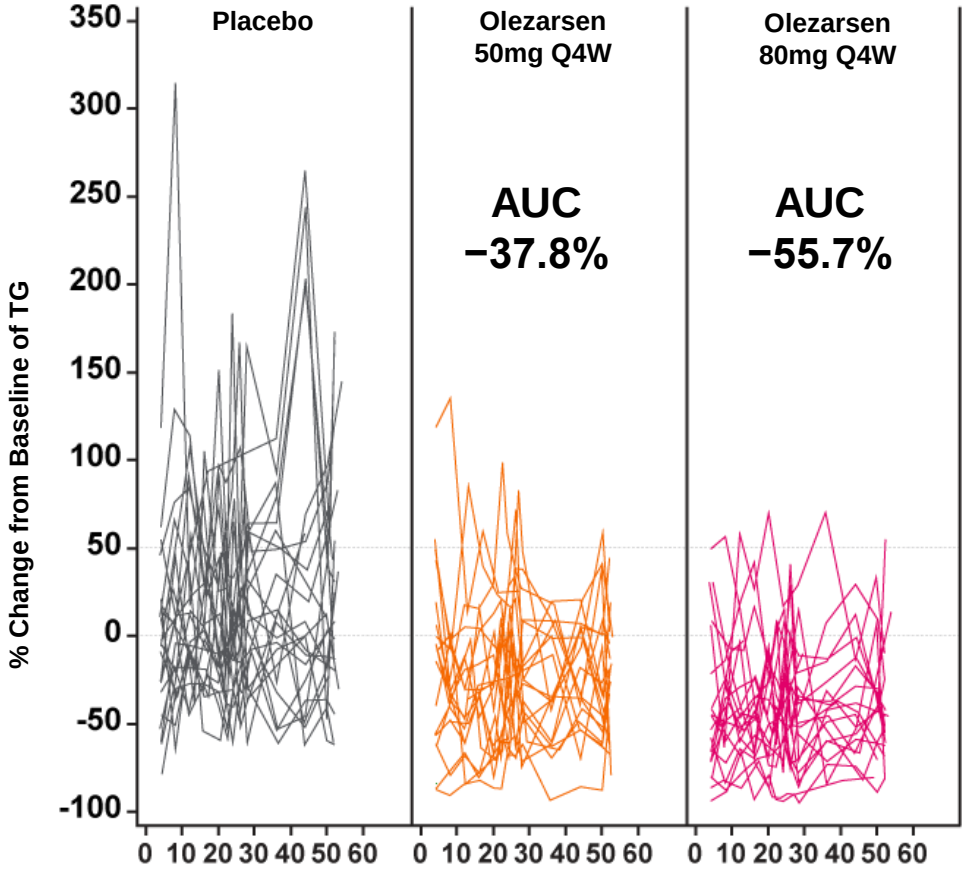
LSMD, Least squares mean difference

1. Olezarsen 80 mg dose (p<0.001); 50 mg dose (p=0.078). 2. Average of weeks 23, 25, and 27. 3. Average of weeks 51 and 53.

Olezarsen Substantially Reduced TG AUC Compared to Placebo through 12 Months of Treatment[1]

- 56% reduction in fasting triglyceride area under the curve[1] (AUC) from baseline compared to placebo
- Triglyceride levels in olezarsen treated patients were substantially lower compared to placebo patients after one year of treatment

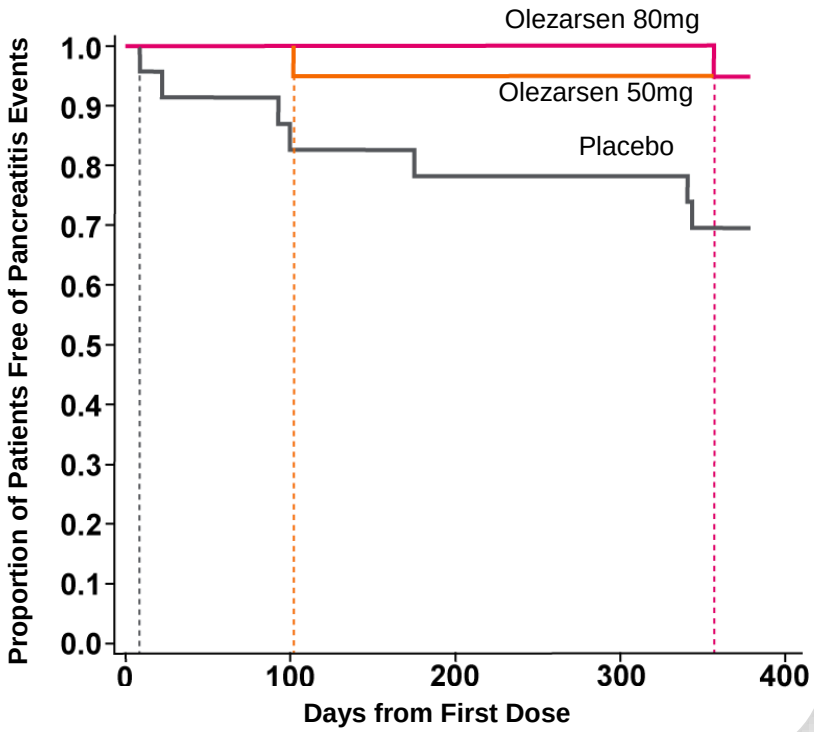
Increased triglyceride levels are associated with substantially increased risk of acute pancreatitis



1. AUC: non-pre-specified exploratory analysis of the area under the curve of triglyceride levels from week 1 to week 53.

Olezarsen Treatment Resulted in Substantial and Clinically Meaningful Difference in Acute Pancreatitis Events

Time to first pancreatitis event



Pancreatitis events

	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
Pancreatitis events, n	11	1	1
First Pancreatitis event, study day	9	102	357

Selected prespecified secondary endpoints

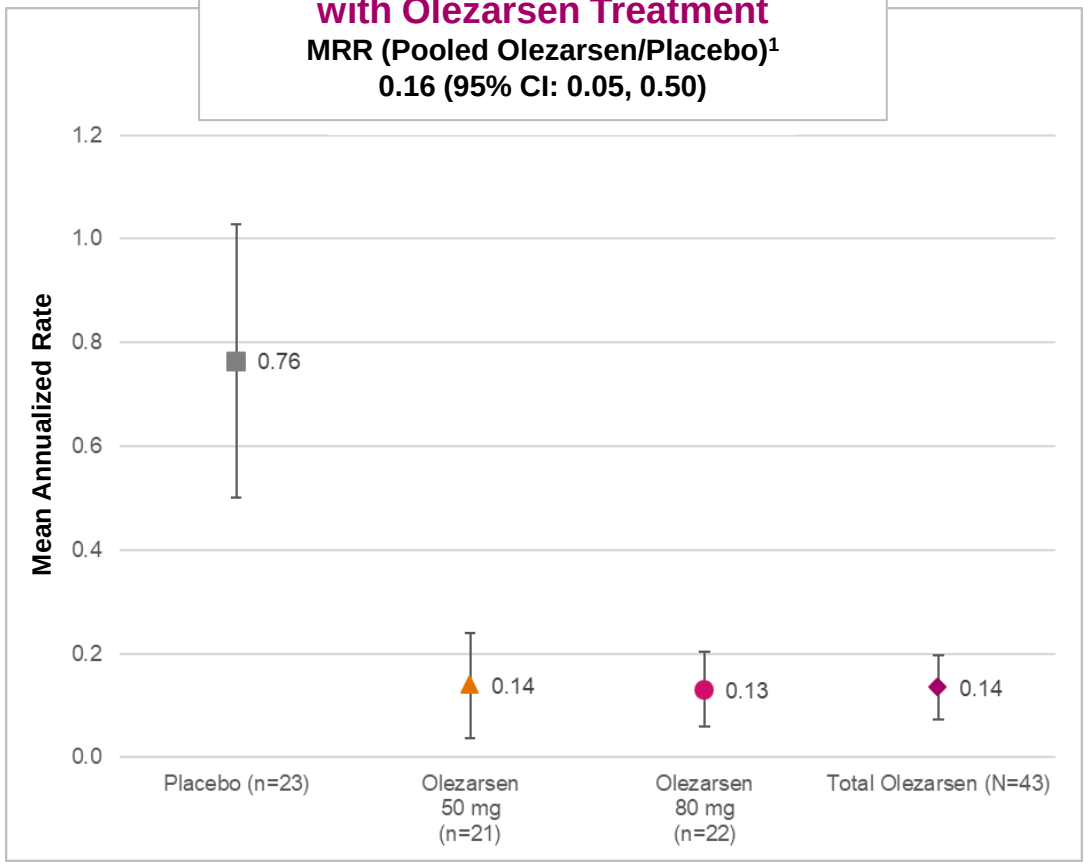
Adjudicated Acute Pancreatitis Endpoint (Week 1-53)	**Event Rate per 100 PY (95% CI)**		**Mean Rate Ratio* (95% CI)**
	Placebo (n=23)	**Pooled Olezarsen**	
Full analysis set	36.3 (14.7, 89.7)	4.37 (0.942, 20.3)	0.12 (0.022, 0.656)
Patients with previous history within 10 years prior to screening	66.2 (30.5, 144)	6.73 (1.61, 28.1)	0.10 (0.020, 0.506)
Patients with ≥2 events within previous 5 years prior to enrollment	119 (61.2, 230)	16.6 (4.05, 67.9)	0.14 (0.029, 0.669)

*Pooled olezarsen vs placebo; exposure-adjusted event rate in the treatment group divided by the exposure-adjusted event rate in the placebo group; a ratio of 1 would indicate no difference. Abbreviations: CI, confidence interval; PY, patient-year.

84% Reduction in All-Cause Hospitalizations and Inpatient Days Reduced by >6 Days with Olezarsen Treatment

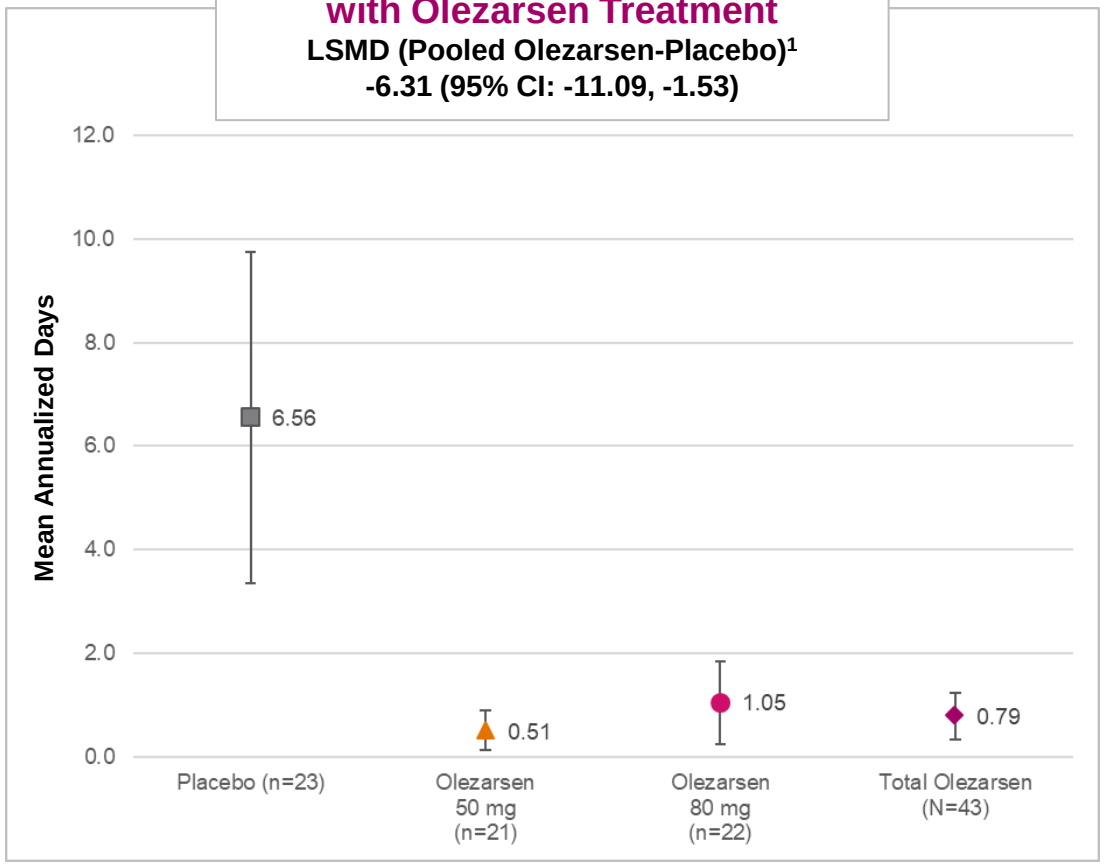
All-Cause Hospitalizations with Olezarsen Treatment

MRR (Pooled Olezarsen/Placebo)[1]
0.16 (95% CI: 0.05, 0.50)



Total Inpatient Days with Olezarsen Treatment

LSMD (Pooled Olezarsen-Placebo)[1]
-6.31 (95% CI: -11.09, -1.53)



MRR, mean rate reduction; LSMD, Least squares mean difference.

Favorable Safety and Tolerability Profile

- More TEAEs and SAEs in placebo-treated patients, primarily driven by more pancreatitis events in the placebo group
- No serious TEAEs related to study drug
- No clinically meaningful changes in platelet count or in measures of hepatic and renal function
- Low incidence of mild injection site reactions
- 1 death occurred in the 50 mg olezarsen group that was assessed as unrelated to study drug

TEAEs, n (%)	Placebo (n=23)	Olezarsen 50 mg (n=21)	Olezarsen 80 mg (n=22)
Any	22 (95.7)	18 (85.7)	19 (86.4)
Related to study drug	5 (21.7)	6 (28.6)	7 (31.8)
Mild	3 (13.0)	6 (28.6)	3 (13.6)
Moderate	0	0	4 (18.2)
Severe	2 (8.7)	0	0
Leading to treatment discontinuation	0	1 (4.8)	2 (9.1)
Leading to death	0	1 (4.8)	0
Any serious	9 (39.1)	4 (19.0)	3 (13.6)
Serious related to study drug	0	0	0

Phase 3 Balance Study: Clinically Meaningful Benefit with Olezarsen Treatment in Patients with FCS

- Treatment with olezarsen 80 mg resulted in clinically meaningful benefit in FCS patients, including:
  - Substantially reduced apoC-III, a key regulator of triglyceride metabolism, at 6 and 12 months
  - Statistically significant reductions in triglycerides at 6 months compared to placebo, which were sustained through 12 months
  - Substantially lower number of pancreatitis events and greater time to first event, compared to placebo, through 12 months of treatment
  - Favorable safety and tolerability

In conclusion, these data support the potential of olezarsen as a novel therapy to reduce plasma triglyceride levels and acute pancreatitis in patients with FCS

Delivering Olezarsen to FCS Patients in Need

Jonathan Birchall
Chief Commercial Officer

FCS: A Severe, Rare and Disease of High Unmet Need

- **Severe, rare disease often affecting people in the prime of life[7]**
- **Due to lack of awareness, patients are often misdiagnosed for years or decades**
- **Severe, potentially fatal pancreatitis, debilitating chronic symptoms, abdominal pain, crushing fatigue, brain fog, etc.**
- **Heavy economic burden driven by high under- and unemployment and high costs for medical care8**

~1-13 people/ million
affected by FCS in the U.S.[1-6]

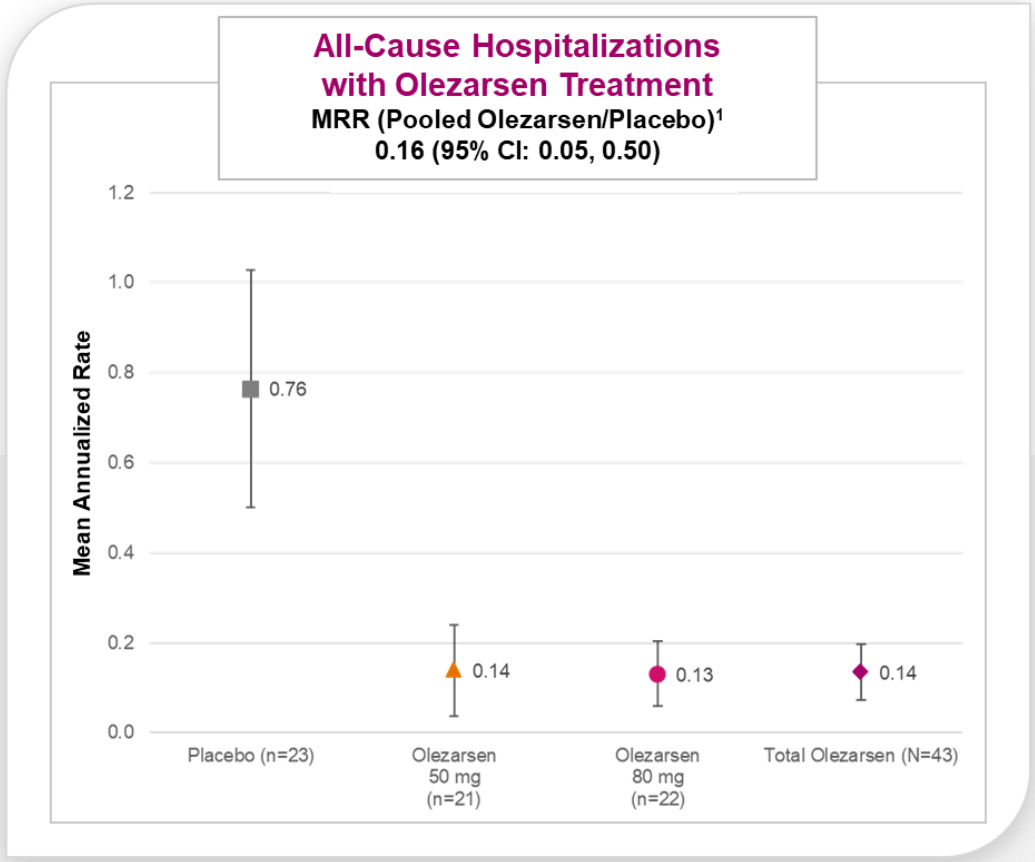
~24 years
Median age of diagnosis[7]

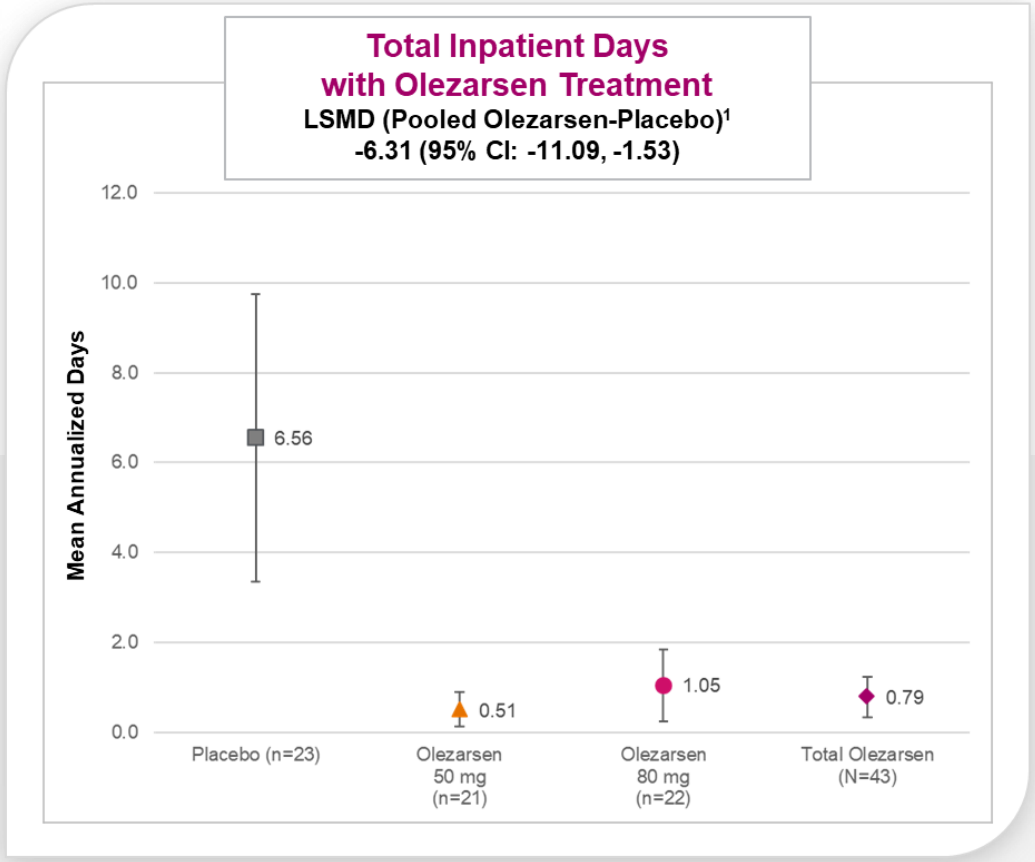
No approved treatments
in the U.S.[1]

Yang
Living with FCS

1. Moulin P, et al. *Atherosclerosis* 2018;275:265-72. 2. Brown EE, et al. *J Clin Lipidol* 2020;14(4):398-413. 3. Stroes E, et al. *Atheroscler Suppl* 2017:23:1-7. 4. Dron JS, et al. *BMC Med Genomics* 2020;13(1):23. 5. Hegele RA. *Nat Rev Genet* 2009;10(2):109-21. 6. Pallazola VA, et al. *Eur J Prev Cardiol* 2020;27(19):2276-8. 7. Gaudet D, et al. *N Engl J Med*. 2014;371:2200-2206. 8. Gaudet D, et al. *Lipids Health Dis.* 2020;19(1):120.

84% Reduction in All-Cause Hospitalizations and Inpatient Days Reduced by >6 Days with Olezarsen Treatment





Reductions in hospitalizations further demonstrate the profound difference olezarsen can make in the lives of people with FCS

MRR: mean rate reduction; LSMD: Least squares mean difference

Payers Understand the Need for an Effective Treatment to Prevent Acute Pancreatitis in Patients with FCS[1,2]

> We are very focused on reduction in hospitalization and other services.

> …reducing pancreatitis and persistent organ damage is key.

> A trend in improving acute pancreatitis would be great… outcomes data would be a homerun.

Payers understand the need to prevent acute pancreatitis and associated costs related to FCS and FCS-driven AP

1. Aquest FCS Research. 2. US Pricing Research

Poised to Make Olezarsen the Standard-of-Care for FCS

Substantial reduction in hospitalizations

Marked improvement in acute pancreatitis

Favorable safety and tolerability

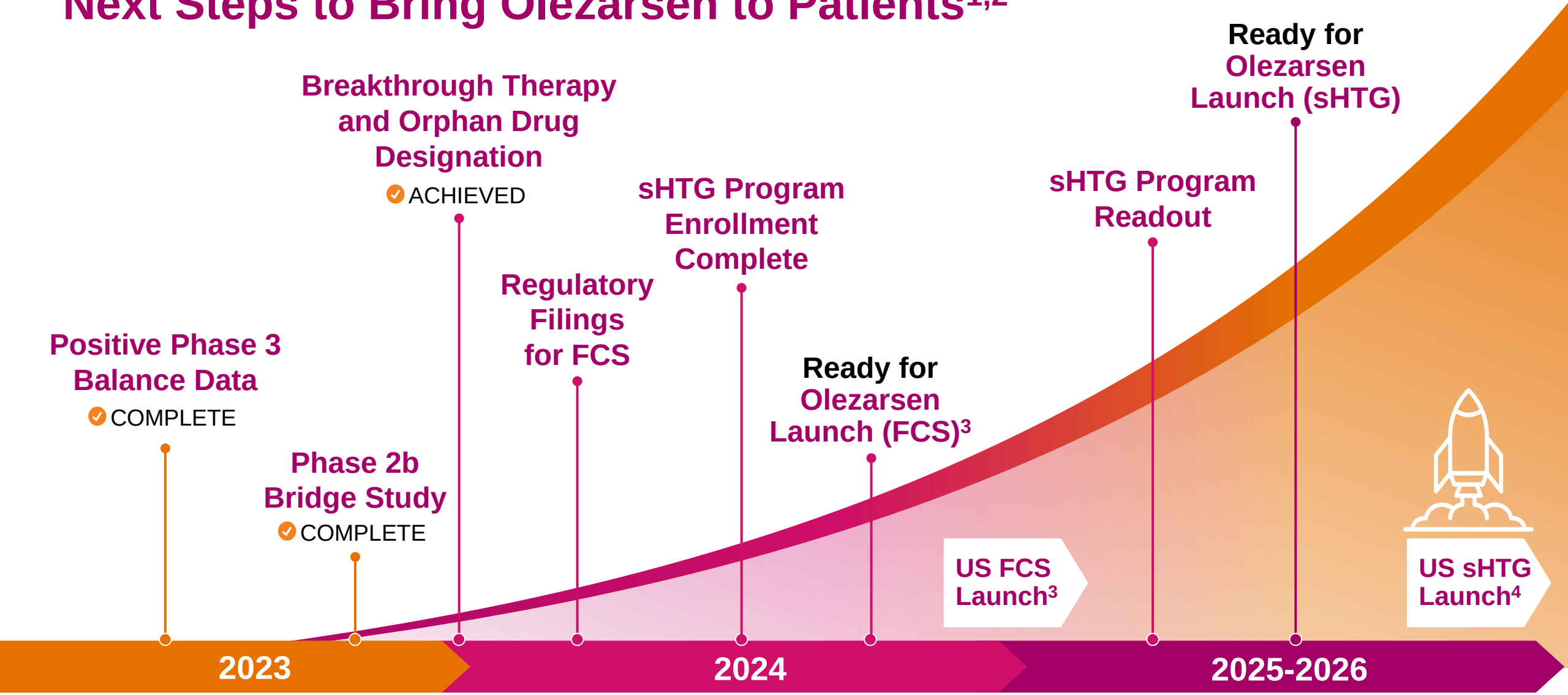
Self-administered auto-injector

Poised to Deliver Olezarsen to the Market…

Focused on the unique needs of patients, caregivers, physicians and payers

- **Building launch momentum through disease awareness and patient identification campaign**
- **Market research to identify physicians most likely to prescribe olezarsen**
- **Patient & caregiver support to assist patients through their treatment journey**
- **Efficient and targeted commercial team built to address HCP and patient needs**

Next Steps to Bring Olezarsen to Patients[1,2]



1. Timing expectations are based on current assumptions and are subject to change. 2 Assuming approval. 3. Assuming priority review.

Conclusion

Brett Monia, Ph.D.
Chief Executive Officer

Key Value-Driving Events Planned For 2024[1]

Phase 3 Clinical Data Events

Donidalorsen
✓ OASIS-HAE topline data

OASIS-HAE full data

OASIS-PLUS OLE + Switch data

Olezarsen
✓ Balance study full data, FCS

Phase 2 Clinical Data Events

Donidalorsen
3-year OLE, HAE

IONIS-FB-L$_{Rx}$
Geographic Atrophy

IgA nephropathy

ION224
✓ NASH

ION582
Angelman syndrome

ION541
ALS

Regulatory Actions

Eplontersen
OUS approval decisions, ATTRv-PN

OUS filings, ATTRv-PN

Olezarsen
NDA filing, FCS

FDA approval decision, FCS[2]

EU filing, FCS

Donidalorsen
NDA filing, HAE

QALSODY
EMA approval decision, SOD1-ALS

New Product Launches

WAINUA
✓ ATTRv-PN[3]

Olezarsen
FCS[4]

QALSODY
EU, SOD1-ALS[4]

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. 2. Assuming priority review.
3. WAINUA: www.wainua.com 4. Assuming approval in 2024.

Well-Positioned to Build on Momentum by Executing on Strategic Priorities

01

Wholly Owned Pipeline

Advancing and growing our wholly owned pipeline in focused therapeutic areas (neurology and cardiology)

02

Integrated Commercial Capabilities in Place

Steady cadence of new potentially **transformational medicines** to the **market**

03

Leading Technology

Advancing technology to **expand existing franchises and address new therapeutic areas**

04

Effective Financial Strategy Poised for Growth

Multi-billion-dollar revenue opportunity to enable future **positive cash flow**

Jackson,
Angelman Syndrome Patient

Driving Next-Level Value for Patients and All Ionis Stakeholders

Q&A


IONIS®