PALISADE

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A Randomised, Placebo-Controlled Phase 3 Study of Plozasiran in Patients with Familial Chylomicronemia Syndrome

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Financial Disclosures

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Persistent Chylomicronemia

- **Extremely high plasma triglycerides** (> 10 mmol/L, 880 mg/dL) in which the fat you eat and then absorbed as particles, called chylomicrons, cannot be cleared from the circulation[1].

- **Due to ultrarare bi-allelic recessive variants** (Familial Chylomicronemia Syndrome, FCS) **or more common genetic variants** (Multifactorial Chylomicronemia Syndrome) that **impair the lipolytic enzyme, lipoprotein lipase (LPL)**[1-4].
  - Adults with extreme chylomicronemia, a high-risk subset of which, can phenocopy classical FCS

- **Chylomicronemia causes multiple symptoms** (physical, cognitive, emotional), the most severe being **acute pancreatitis** and its life-threatening sequelae[5-8].
  - Directly related to Triglyceride levels > 5.5 mmol/L (>500 mg/dL)

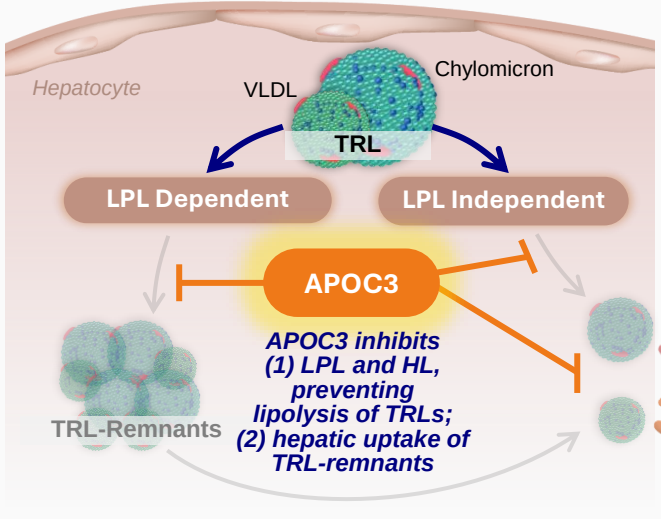
- **Current therapeutic agents** (fibrates, n-3 fatty acids, statins, niacin) are **generally ineffective**

1. Brunzell JD, Bierman EL. Med Clin North Am. 1982;66(2):455–6 2. Pallazola VA, et al. *Eur J Prev Cardiol*. 2020;27(19):2276-8. 3. Warden BA, et al. *J Clin Lipidol*. 2020;14(2):201-6. 4. M Paquette et al. Journal of Clinical Endocrinology & Metabolism, Volume 106, Issue 9, September 2021, Pages e3473–e3482, 5. Gelrud A, et al. Expert Rev Cardiovasc Ther 2017;15(11):879-887. 6. Murphy MJ, et al. JAMA Intern Med. 2013;173(2):162–4. 7. Yuan G, Al-Shali KZ, Hegele RA. CMAJ. 2007;176(8):1113–20. 8. Nawaz H, et al. Am J Gastroenterol. 2015 Oct;110(10):1497-503. 9. Dron JS, Hegele RA. Front Endocrinol (Lausanne) 2020;11:455.10. Hansen SEJ et al. Clinical Gastroenterology and Hepatology 2021;19(8):1652-1660.e6

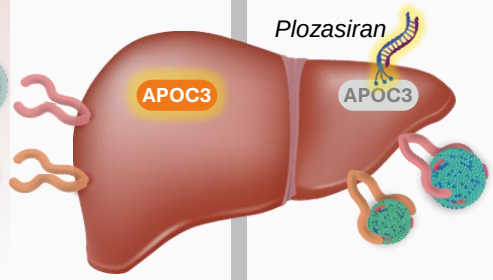
Plozasiran (ARO-APOC3) is an Investigational siRNA Therapeutic Targeting APOC3, a Key Regulator of TG and TRL Metabolism

CHYLOMICRONEMIA[1,2]

APOC3 inhibits lipolysis and hepatic clearance of TRLs, increasing TGs

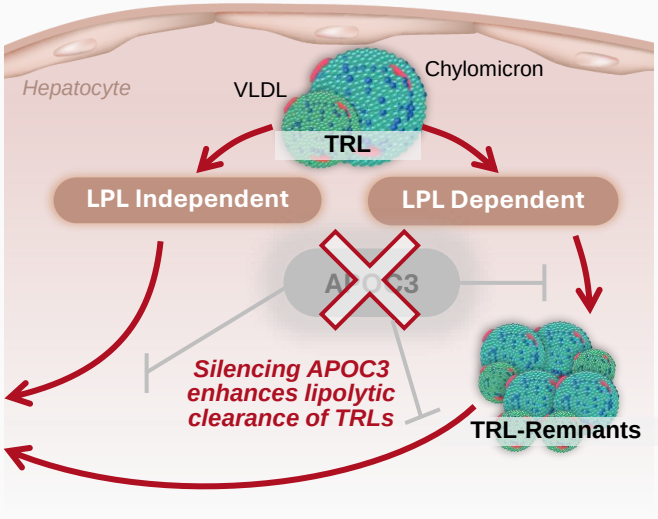


APOC3 inhibits LPL and delays clearance of TRL-remnants by preventing uptake by liver receptors, increasing plasma TGs



PLOZASIRAN[2]

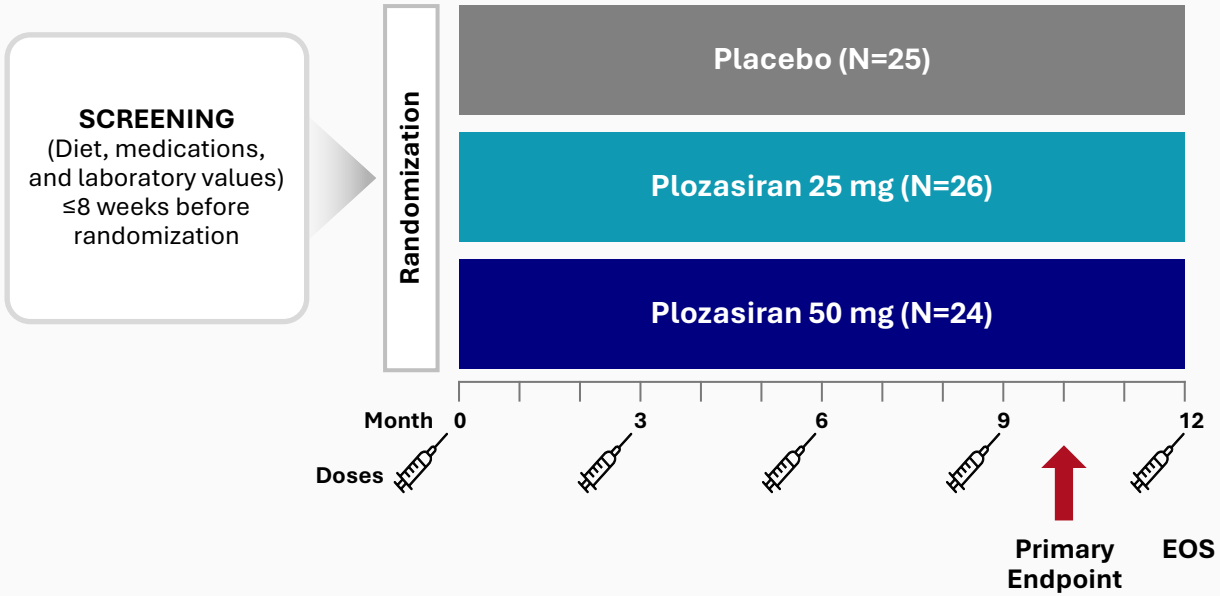
Silencing of APOC3 enhances lipolysis and hepatic clearance of TRLs, reducing TGs



Silencing APOC3 enhances TG lipolysis and TRL-remnant clearance by hepatic receptors, reducing plasma TGs

1. Van Zwol W et al. *J Clin Med*. 2019; 8:1085. 2. Ballantyne CM, et al. *New Engl J Med*. 2024; Published online: May 28, 2024. DOI: 10.1056/NEJMoa2404143. **APOC3**=apolipoprotein C3; **HL**=hepatic lipase; **LPL**=lipoprotein lipase; **TG**=triglycerides; **TRL**=triglyceride rich lipoproteins; **VLDL**=very low-density lipoprotein.

PALISADE: Randomized Placebo-Controlled Phase 3 Study of Plozasiran in Patients with FCS



Primary Endpoint:

- Placebo-adjusted median percent change in triglycerides at Month 10

Multiplicity-controlled key secondary endpoints:

1. Percent change from baseline at Months 10 and 12 (averaged) in fasting triglycerides
2. Percent change from baseline at Month 10 in fasting APOC3
3. Percent change from baseline at Month 12 in fasting APOC3
4. Incidence of positively adjudicated events of acute pancreatitis during the randomized period

APOC3=apolipoprotein C3; **FCS**=familial chylomicronemia syndrome; **EOS**=end of study.

PALISADE Enrolled Patients with FCS Defined Clinically or Genetically Confirmed

Criteria included history of multiple TG measurements above 11.3 mmol/L (1000 mg/dL), despite best standard of care; plus at least one of the following:

1. **Prior genetic testing diagnostic of FCS* OR**
2. **Recurrent episodes of acute pancreatitis§ OR**
3. **Recurrent hospitalizations for severe abdominal pain without other explainable cause OR**
4. **History of childhood pancreatitis OR**
5. **Family history of HTG-induced acute pancreatitis**

Genetic testing was done on all patients without prior testing for FCS variants

*Supportive genetic testing includes but is not limited to homozygous, compound heterozygous, or double heterozygote for loss-of-function or otherwise inactivating mutations in genes affecting lipoprotein lipase activity including LPL, APOC2, APOA5, GPIHBP1, GPD1, or LMF1; or evidence of low LPL activity (<20% of normal) based on source-verifiable documentation; § not caused by alcohol or cholelithiasis; HTG=hypertriglyceridemia

PALISADE Baseline Characteristics

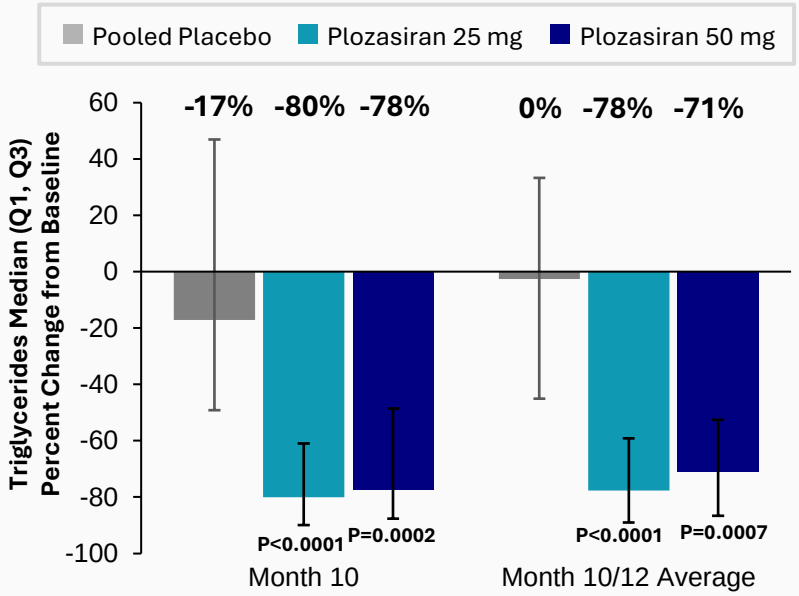
Characteristic	Pooled Placebo (N=25)	Plozasiran 25 mg (N=26)	Plozasiran 50 mg (N=24)
Mean (SD) Age, years	47 (14)	48 (14)	43 (11)
Female, n (%)	11 (44)	14 (54)	13 (54)
Male, n (%)	14 (56)	12 (46)	11 (46)
White, n (%)	19 (76)	19 (73)	17 (71)
Mean (SD) BMI, kg/m^2	25 (4)	26 (4)	25 (5)
Median (Q1, Q3) APOC3, mg/dL	39 (29, 50)	39 (27, 44)	30 (18, 37)
Mean (SD) APOC3, mg/dL	40 (18)	39 (17)	33 (20)
Median (Q1, Q3) Triglyceride, mg/dL	2053 (1435, 2755)	2008 (1204, 3361)	1902 (1434, 2948)
Median (Q1, Q3) Triglyceride, mmol/L	23 (16, 31)	23 (14, 38)	22 (16, 33)
Mean (SD) Triglyceride, mg/dL	2272 (1141)	2350 (1375)	2492 (1523)
Mean (SD) Triglyceride, mmol/L	26 (13)	27 (16)	28 (17)
Receiving Statins n (%)	11 (44)	11 (42)	12 (50)
Fibrates, n (%)	16 (64)	19 (73)	15 (63)
Omega-3 fatty acids, n (%)	6 (24)	9 (35)	7 (29)
Diabetes or Pre-diabetes, n (%)	11 (44)	10 (39)	7 (29)
Genetic Confirmation of FCS, n (%)	14 (56)	14 (54)	16 (67)
Previous episode of pancreatitis, n (%)	22 (88)	23 (89)	22 (92)

Data are reported as mean (±SD) unless otherwise noted. Note: Diabetic patients are defined as having HbA1c ≥6.5% or fasting glucose ≥126 mg/dL or with medical history of 'diabetes' or receiving diabetic medications at baseline. *% = 100 x n/N', N' is the number of diabetic or prediabetic patients at baseline.**APOC3**=apolipoprotein C3; **BMI**=body mass index; **FCS**=familial chylomicronemia syndrome; **N**=number; **Q**=quartile; **SD**=standard deviation; **W**=week.

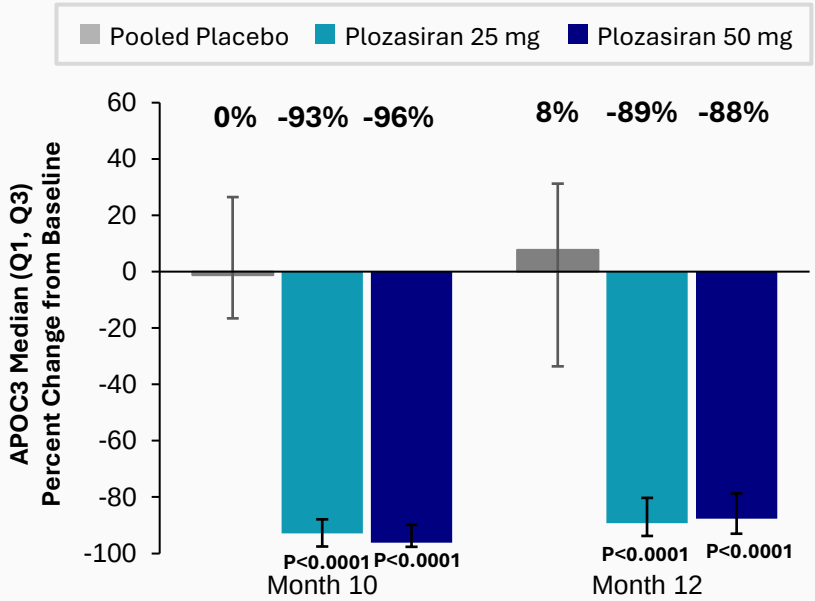
Plozasiran Reduced Plasma Triglycerides and APOC3 Relative to Placebo in Persistent Chylomicronemia

PALISADE

Median Triglycerides†



Median APOC3



*P<0.001 vs placebo; †Primary and first key secondary endpoints

APOC3=apolipoprotein C3; **Q1**=1st quartile; **Q3**=3rd quartile.

Plozasiran Response at 1 Month Persisted to 12 Month Endpoint for Median Change in Triglycerides and APOC3

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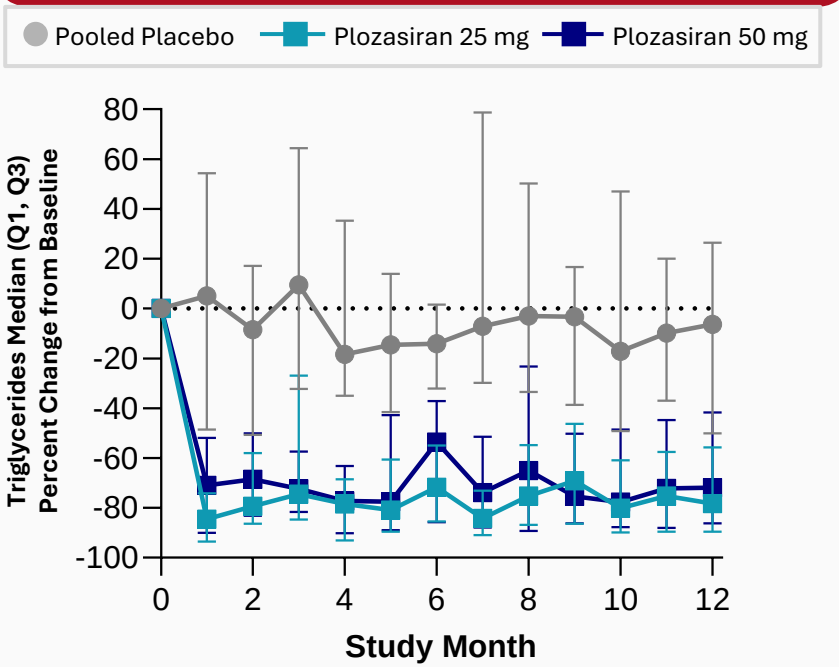
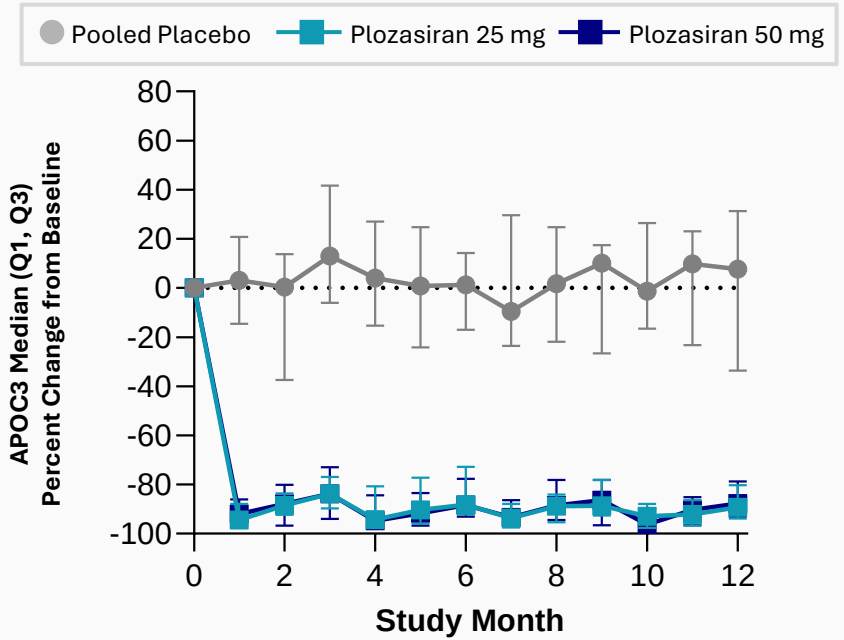
Median Triglycerides



Median APOC3



APOC3=apolipoprotein C3; **Q1**=1st quartile; **Q3**=3rd quartile.

Reductions in Triglyceride and APOC3 Levels According to Genetically Confirmed FCS

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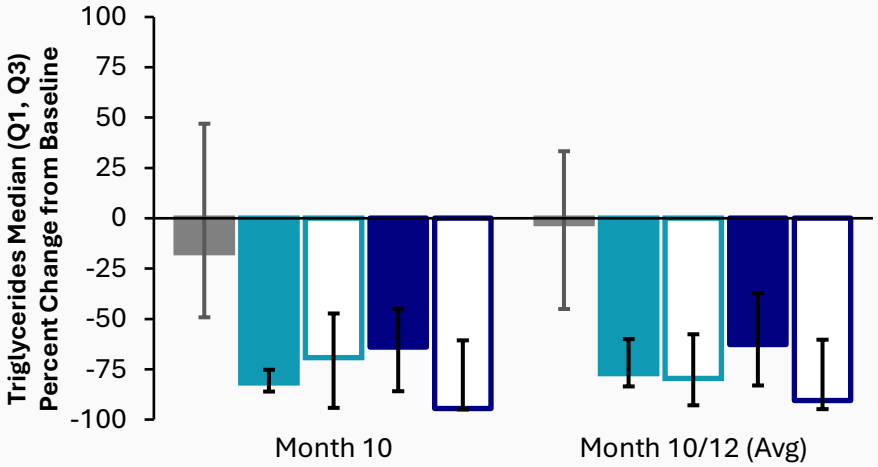
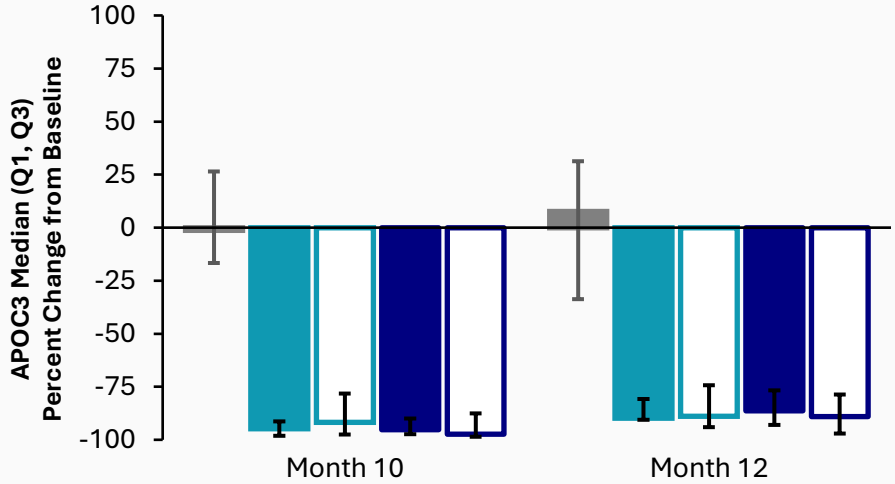
Triglycerides



APOC3



Pooled Placebo

With Genetic Confirmation of FCS

Plozasiran 25 mg

Plozasiran 50 mg

Without Genetic Confirmation of FCS

Plozasiran 25 mg

Plozasiran 50 mg

APOC3=apolipoprotein C3; **FCS**=familial chylomicronemia syndrome; **Q1**=1st quartile; **Q3**=3rd quartile.

Plozasiran Reduced Plasma Triglyceride Levels to Below Thresholds for Risk of Acute Pancreatitis

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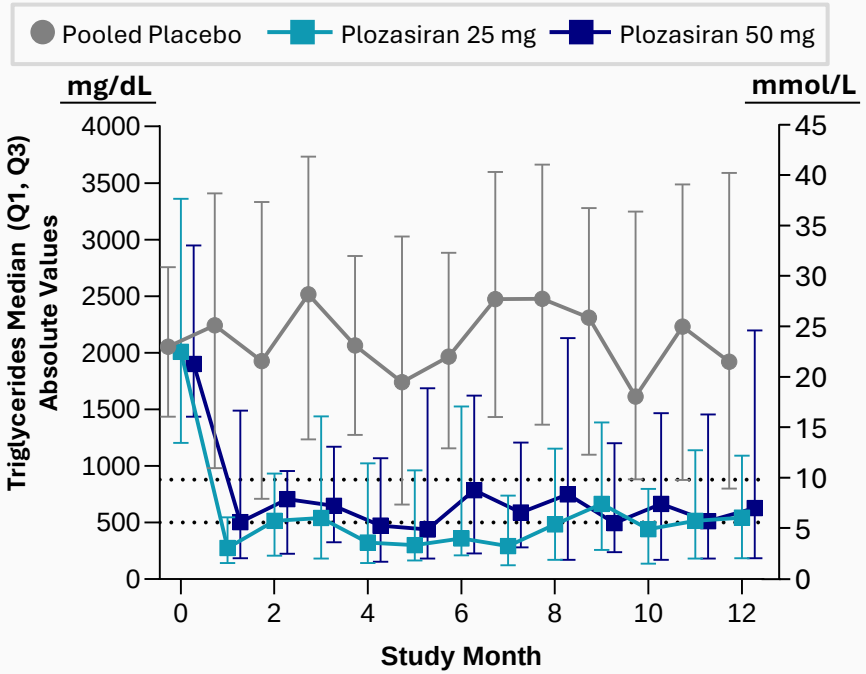
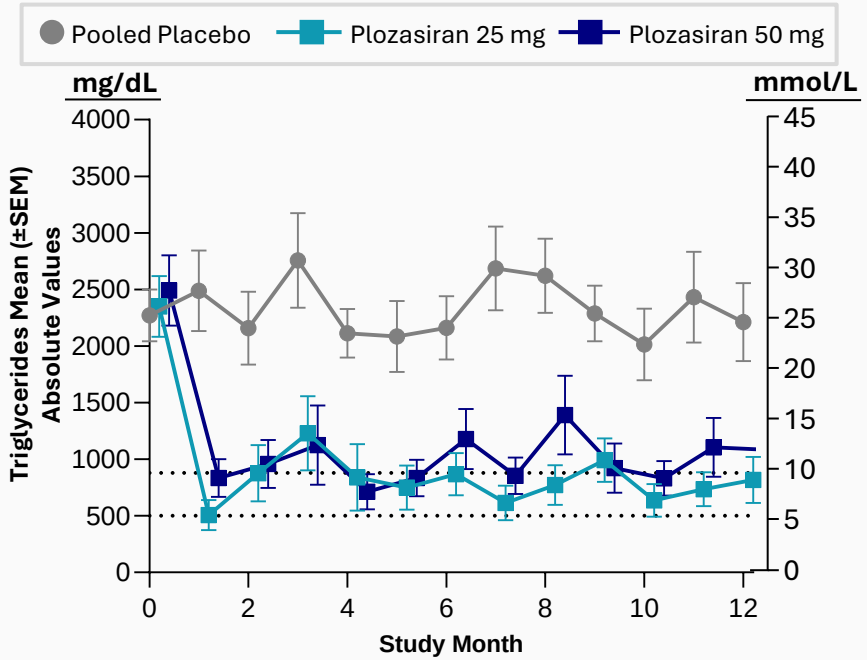
Median Absolute Triglyceride Levels

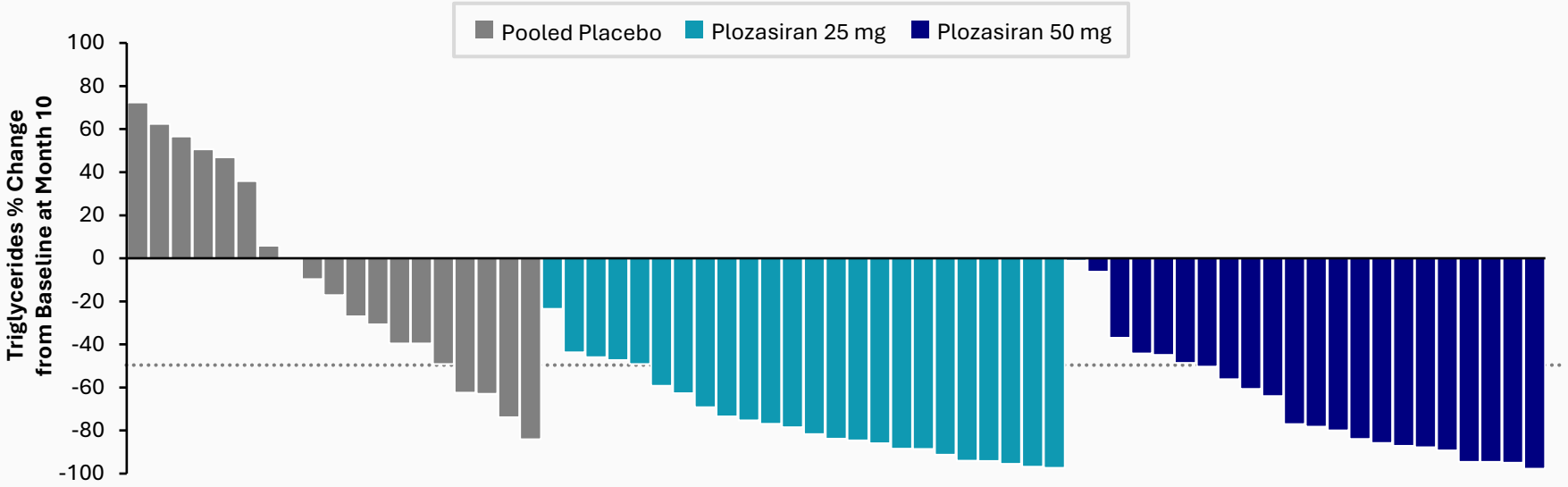


Mean Absolute Triglyceride Levels



Q1=1st quartile; **Q3**=3rd quartile; **SEM**=standard error of mean.

Reductions in Plasma Triglycerides and Percentage of Patients Attaining TGs Below Risk Thresholds for Pancreatitis

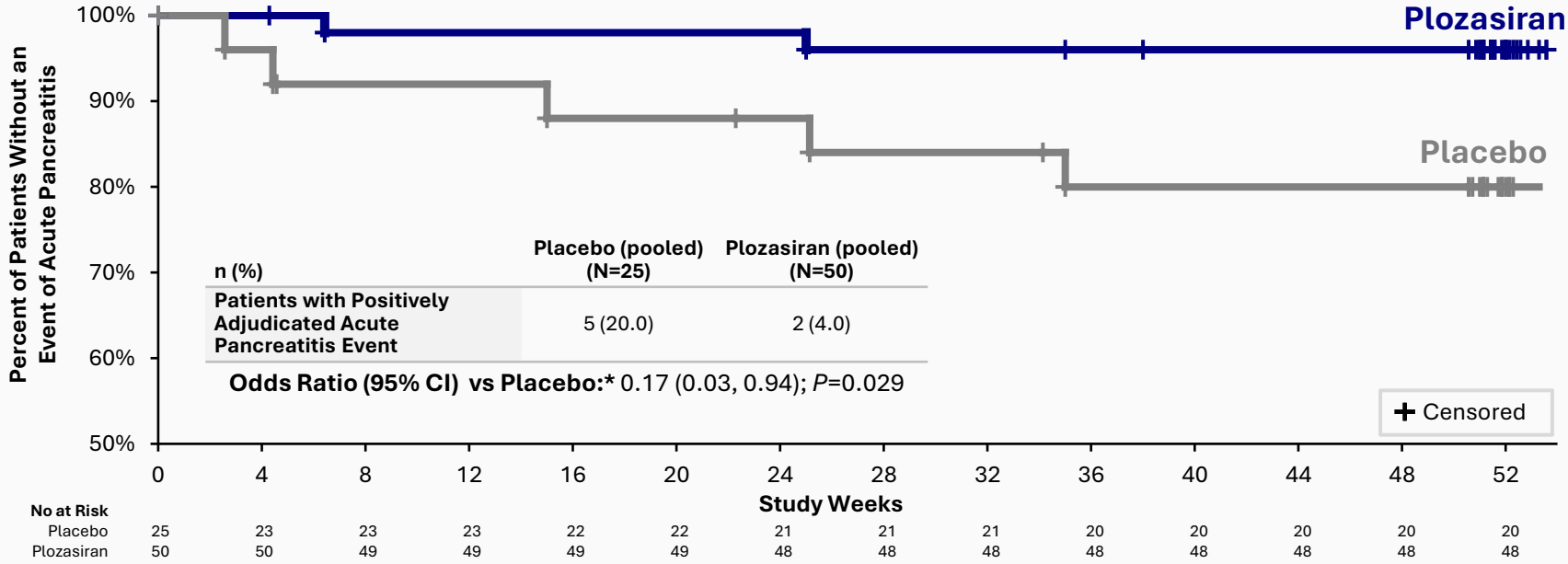


n (%)	Placebo (Pooled) (n=19)	Plozasiran 25 mg (n=24)	Plozasiran 50 mg (n=22)
All patients who reached triglycerides < 5.5 mmol/L (500 mg/dL) at month 10	1 (5%)	12 (50%)	10 (46%)
All patients who reached triglycerides < 10 mmol/L (880 mg/dL) at month 10	**4 (21%)**	**18 (75%)**	**12 (55%)**
All patients who reached triglycerides < 11 mmol/L (1000 mg/dL) at month 10	6 (32%)	20 (83%)	15 (68%)

Thresholds above 500 and 880 mg/dL increase risk of AP and CVD; Extremely high TG levels >1000 mg/dL can lead to "chylomicron syndrome," causing AP; **APOC3**=apolipoprotein C3.

Plozasiran Reduced the Incidence of Acute Pancreatitis

Time to First Pancreatitis Event



n (%)	Placebo (pooled) (N=25)	Plozasiran (pooled) (N=50)
Patients with Positively Adjudicated Acute Pancreatitis Event	5 (20.0)	2 (4.0)

Odds Ratio (95% CI) vs Placebo:* 0.17 (0.03, 0.94); *P*=0.029

No at Risk														
Placebo	25	23	23	23	22	22	21	21	21	20	20	20	20	20
Plozasiran	50	50	49	49	49	49	48	48	48	48	48	48	48	48

*Odds ratio, 95% CI, and P-value were based on CMH test stratified by baseline TG category.
7 incident cases occurred in 5 of 25 (20%) participants receiving placebo and 2 incident cases occurred in 2 of 50 (4%) participants in the plozasiran-treated group.**CI**=confidence interval; **CMH**=Cochran-Mantel-Haenszel; **TG**=triglyceride.

Summary of Adverse Events

	Pooled Placebo (N=25)	Plozasiran	
		25 mg (N=26)	50 mg (N=24)
Patients with Any TEAEs	20	23	20
Most Common TEAEs, N (%)			
Abdominal Pain	5 (20)	7 (27)	6 (25)
COVID-19 Infection*	0 (0)	5 (19)	7 (29)
Nasopharyngitis	3 (12)	5 (19)	2 (8)
Headache	2 (8)	3 (12)	5 (21)
Nausea	2 (8)	4 (15)	3 (13)
Back Pain	2 (8)	3 (12)	2 (8)
Upper respiratory tract infection	2 (8)	3 (12)	2 (8)
Diarrhea	2 (8)	1 (4)	4 (17)
Severe TEAEs	5 (20)	3 (12)	3 (13)
Serious TEAEs	7 (28)	5 (19)	2 (8)
Deaths	0 (0)	0 (0)	0 (0)
Premature Discontinuations	6 (24)	3 (12)	2 (8)
HbA1c, mean (SD)			
Baseline	6.1 (1.33)	5.7 (0.90)	5.59 (1.15)
Month 12	6.2 (1.17)	5.98 (1.00)	5.83 (1.56)
Platelet count, 10^9/liter, mean (SD)			
Baseline	217.9 (80.5)	204.4 (70.4)	192.9 (50.7)
Mean change from baseline at Month 10	25.9 (38.2)	28.7 (61.2)	-4.4 (48.2)
Mean change from baseline at Month 12	8.6 (47.5)	-4.3 (40.8)	-8.7 (50.8)

- A greater proportion of placebo-treated patients experienced SAEs
- Fewer premature discontinuations with plozasiran
- No reductions in platelet counts
- Hyperglycemia with plozasiran confined to patients with pre-diabetes and diabetes
- No deaths

*The observed difference in COVID-19 occurrence in this trial was not seen in the larger phase 2b trials in mixed hyperlipidemia and severe hypertriglyceridemia also conducted during the COVID-19 pandemic, and likely was a chance finding.
HbA1c=glycosylated hemoglobin; **SD**=standard deviation; **SAE**=serious adverse event; **TEAE**=treatment emergent adverse event.

Conclusions

PALISADE met all trial endpoints (alpha-controlled)

- Plozasiran (quarterly dosing) significantly reduced triglycerides in patients with persistent chylomicronemia (FCS or FCS-like syndrome*) at 10 months; over half of patients achieved TG treatment goals
- Reductions in TGs and APOC3 apparent at 1 month and sustained thereafter with comparable efficacy in genetically and clinically defined patients
- Plozasiran significantly reduced acute pancreatitis at 12 months
- Favorable safety and tolerability similar to placebo
- Plozasiran is a novel therapeutic candidate for reducing plasma TG levels and risk of acute pancreatitis in patients with persistent chylomicronemia

*High risk MCS (patients with prior AP events and exceptionally high TGs)

APOC3=apolipoprotein C3; **FCS**=familial chylomicronemia syndrome; **mRNA**=messenger RNA; **siRNA**=small interfering RNA.

The study sponsors would like to thank

the patients who participated and their families,

and all investigators and staff who completed the trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk

Gerald F. Watts, D.Sc., M.D., Ph.D., Robert S. Rosenson, M.D., Robert A. Hegele, M.D., Ira J. Goldberg, M.D., Antonio Gallo, M.D., Ph.D., Ann Mertens, M.D., Ph.D., Alexis Baass, M.D., Rong Zhou, Ph.D., Ma'an Muhsin, M.D., Jennifer Hellawell, M.D., Nicholas J. Leeper, M.D., and Daniel Gaudet, M.D., Ph.D., for the PALISADE Study Group*