PALISADE

WCIRDC 2024

A Phase 3 Study to Assess the Efficacy and Safety of Plozasiran in Adults with Genetically or Clinically-Defined Familial Chylomicronemia Syndrome at High Risk of Acute Pancreatitis

Ira J Goldberg: NYU School of Medicine, NYU Langone Health, New York City, NY, USA

arrowhead pharmaceuticals

Authors and Financial Disclosure

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[1]Gerald F. Watts, D.Sc., M.D., Ph.D., [2]Robert S. Rosenson, M.D., [3]Robert A. Hegele, M.D., ***[4]Ira J. Goldberg, M.D.***, [5]Antonio Gallo, M.D., Ph. D., [6]Ann Mertens, M.D., Ph.D., [7]Alexis Baass, M.D., M.Sc., [8]Rong Zhou, Ph.D., [8]Ma'an Muhsin, M.D., [8]Jennifer Hellawell, M.D., [9]Nicholas J. Leeper, M.D., [10]Daniel Gaudet, M.D., Ph.D., on behalf of the PALISADE Study Group*

Affiliations

[1]School of Medicine, University of Western Australia and Department of Cardiology, Royal Perth Hospital, Perth, Australia (G.F.W.); [2]Metabolism and Lipids Program, Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mt Sinai, Mount Sinai, New York, NY, USA (R.S.R.); [3]Robarts Research Institute, London, Ontario, Canada (R.A.H.); [4]NYU School of Medicine, NYU Langone Health, New York City, NY, USA (I.J.G); [5]Sorbonne University, INSERM UMR1166, Lipidology and Cardiovascular Prevention Unit, Department of Nutrition, Pitie-Salpetriere Hospital, AP-HP, Paris, France (A.G.); [6]Department of Endocrinology, University Hospitals Leuven – KU Leuven, Leuven, Belgium (A.M.); [7]Department of Medicine, McGill University and Genetic Dyslipidemia Clinic, Montréal Clinical Research Institute (IRCM), Montréal, Québec, Canada (A.B.); [8]Arrowhead Pharmaceuticals, Pasadena, CA, USA (R.Z., M.M, J.H.); [9]Stanford University, Palo Alto, CA, USA (N.J.L.); [10]Université de Montréal and ECOGENE-21, Montréal, Québec, Canada (D.G).

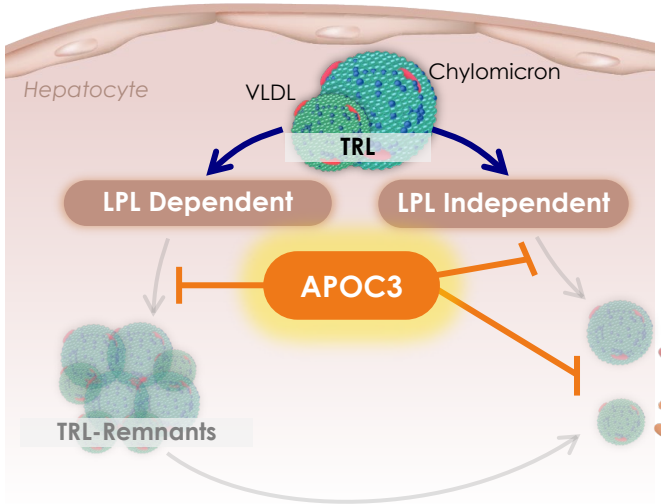
Persistent Chylomicronemia

- **Is reflected by extremely high plasma triglycerides** (>880 mg/dL) caused by impaired circulatory clearance of chylomicrons containing TGs derived from the diet[1]
- **Due to ultrarare bi-allelic recessive variants of lipoprotein lipase** (LPL; Familial Chylomicronemia Syndrome, FCS) **or more common genetic variants** (Multifactorial Chylomicronemia Syndrome) that **impair triglyceride lipolysis**[1-4]
  - Adults with extreme chylomicronemia 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 (>500 mg/dL)
- **Current therapeutic agents** (fibrates, n-3 fatty acids, statins, niacin) are **generally ineffective**

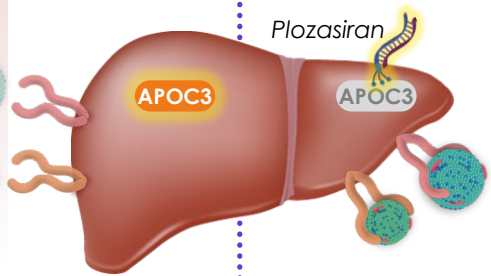
1. Brunzell JD, Bierman EL. *Med Clin North Am.* 1982;66(2):455–6. **2.** Pallazola VA, et al. *Eur J Prev Cardiol.* 2020;27(19):2276-8. **3.** Warden BA, et al. *J Clin Lipidol.* 2020;14(2):201-6. **4.** M Paquette et al. *J Clin Endocrin Metab*. 2021;106(9):e3473–e3482. **5.** Gelrud A, et al. *Expert 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. *Clin Gastro Hep.* 2021;19(8):1652-1660.e6.

Plozasiran: an Investigational SiRNA Therapeutic Targeting APOC3, a Key Regulator of TG and TRL Metabolism

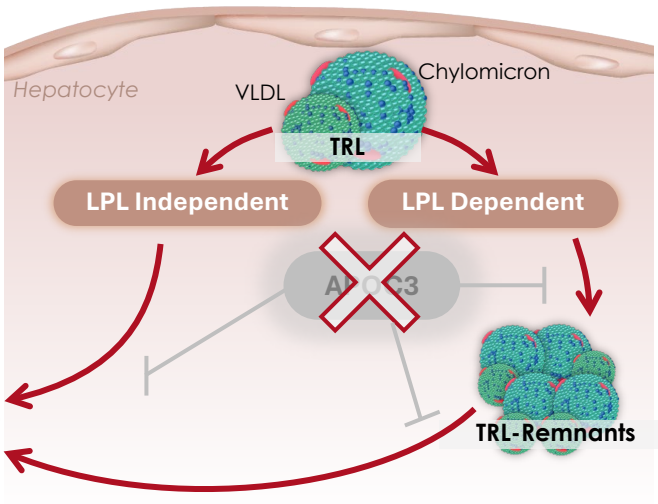
CHYLOMICRONEMIA[1,2]



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



PLOZASIRAN[2]



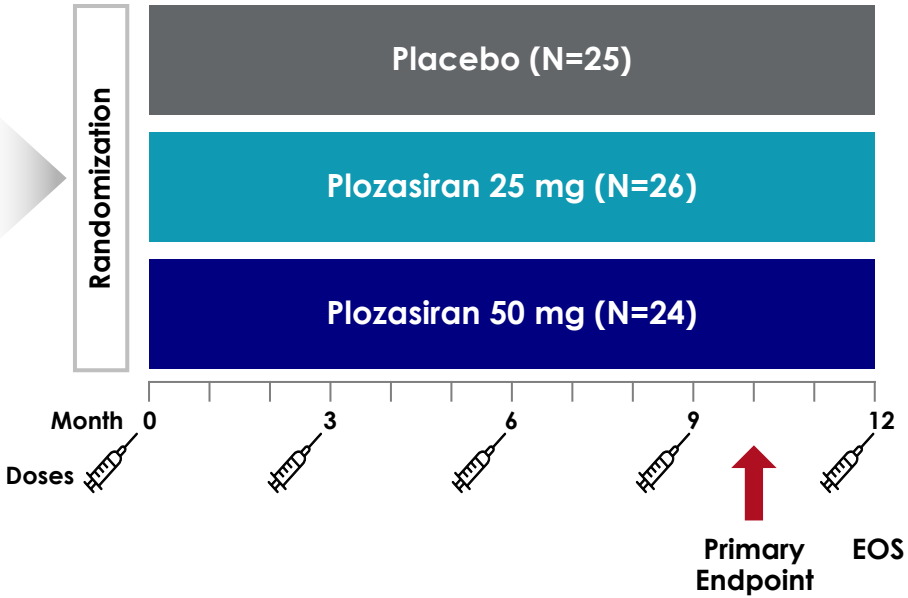
Silencing APOC3 enhances TG lipolysis and TRL-remnant clearance by hepatic receptors, reducing plasma TGs

APOC3, apolipoprotein C3; **HL**, hepatic lipase; **LPL**, lipoprotein lipase; **TG**, triglycerides; **TRL**, triglyceride rich lipoproteins; **VLDL**, very low-density lipoprotein.

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.

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

SCREENING
(Diet, medications, and laboratory values)
≤8 weeks before randomization



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 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 not previously tested 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. **FCS**, familial chylomicronemia syndrome; **HTG**, hypertriglyceridemia; **TG**, triglycerides.

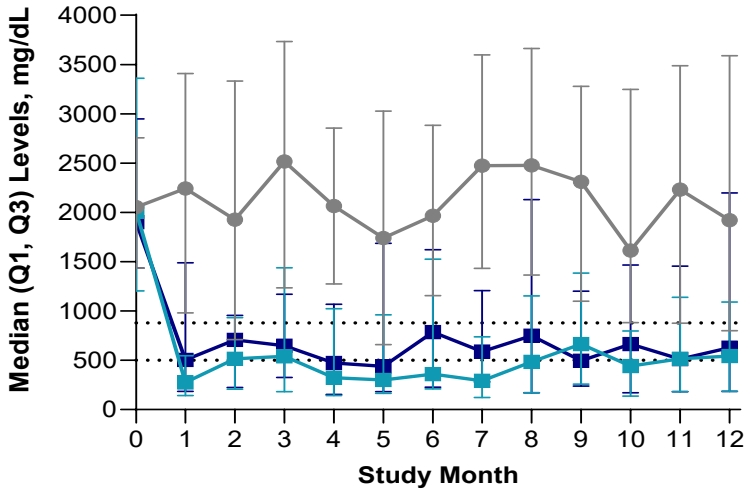
PALISADE Baseline Characteristics

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)
Mean (SD) triglyceride, mg/dL	2272 (1141)	2350 (1375)	2492 (1523)
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)

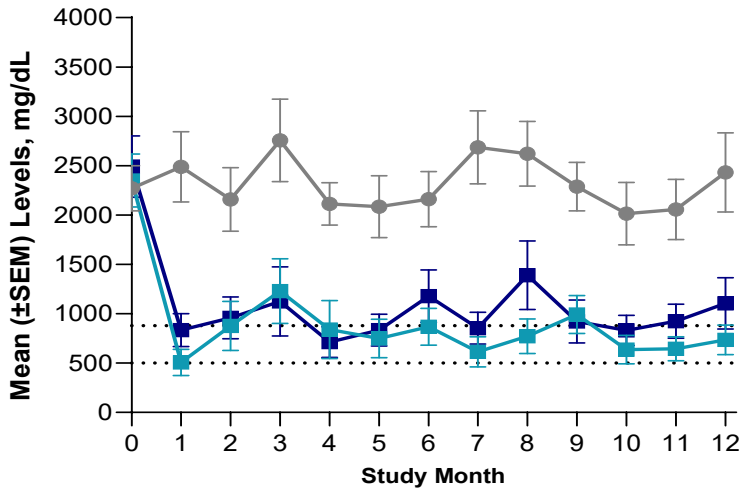
Data are reported as mean (±SD) unless otherwise noted. Note: Diabetic patients are defined as having HbA1c ≥6.5% or fasting glucose ≥126 mg/dL or with medical history of 'diabetes' or receiving diabetic medications at baseline. *% = 100 x n/N', N' is the number of diabetic or prediabetic patients at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

Plozasiran TG Response at 1 Month Persisted Below Thresholds for Risk of Pancreatitis Over 12 Months

Median Triglyceride



Mean Triglyceride



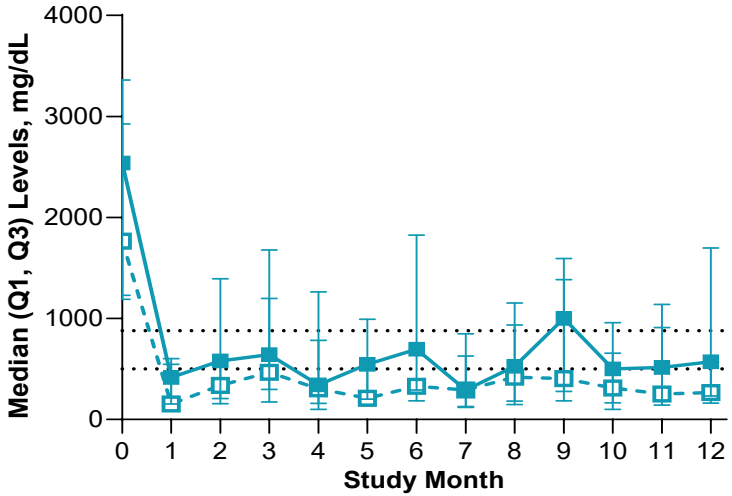
Pooled Placebo | Plozasiran 25 mg | Plozasiran 50 mg

75% of patients reached triglycerides < 880 mg/dL and 50% reached < 500 mg/dL at 10 months

AP, acute pancreatitis; **Q1**, 1st quartile; **Q3**, 3rd quartile; **SEM**, standard error of mean; **TG**, triglycerides.

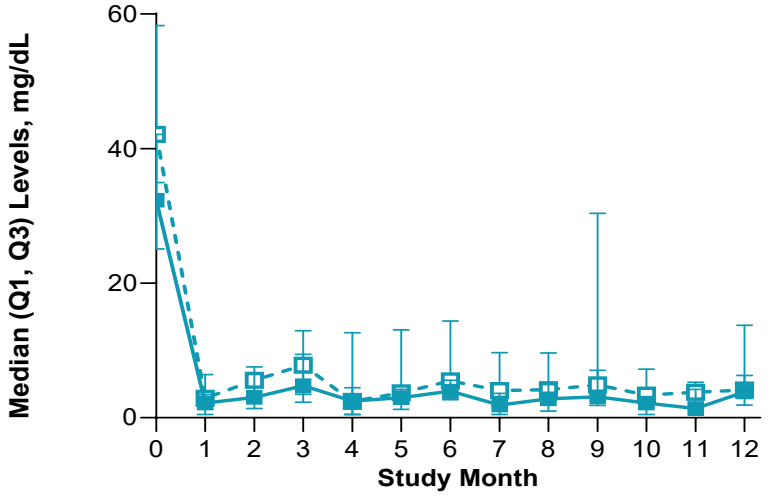
Plozasiran TG and APOC3 Responses Persisted Over 12 Months with no Significant Difference by FCS Genotype

Median Triglyceride



With FCS Genetic Confirmation	14	14	14	14	13	14	14	14	13	14	13	13	13
Without FCS Genetic Confirmation	12	11	11	11	11	10	10	10	12	11	11	9	11

Median APOC3



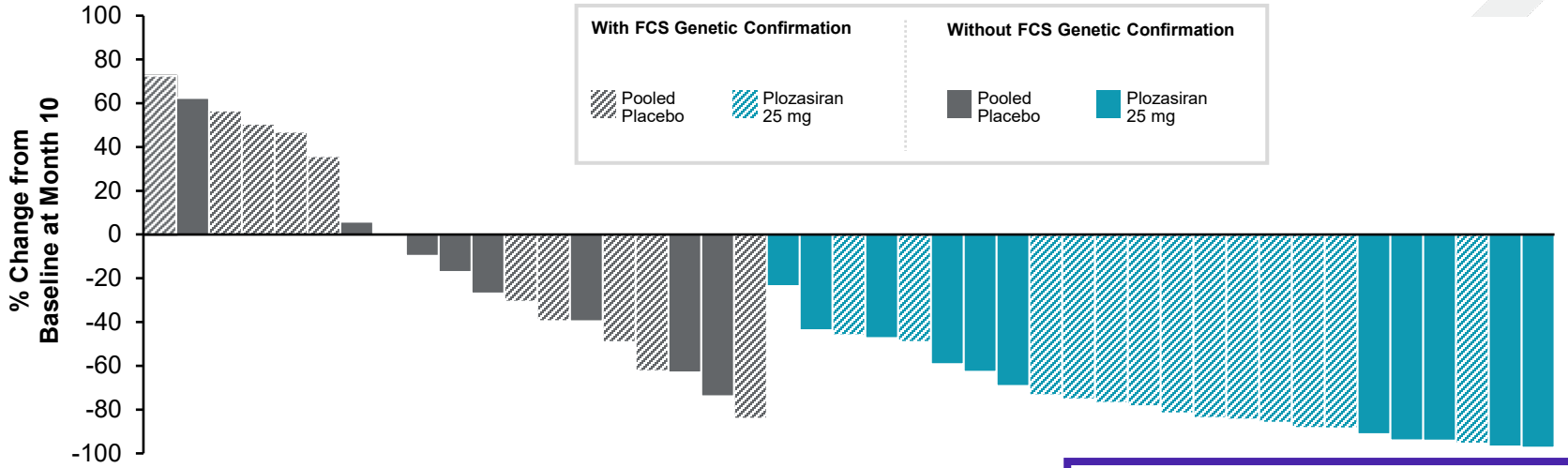
With FCS Genetic Confirmation	14	14	14	14	13	14	14	14	13	14	13	13	13
Without FCS Genetic Confirmation	12	11	11	11	11	10	10	10	12	11	11	9	11

With FCS Genetic Confirmation — Plozasiran 25 mg

Without FCS Genetic Confirmation — Plozasiran 25 mg

Between group differences are not statistically significant through all time points.
APOC3, apolipoprotein C3; **FCS**, familial chylomicronemia syndrome; **Q1**, 1st quartile; **Q3**, 3rd quartile; **TG**, triglycerides.

Reductions in TG and % of Patients Attaining TG Below Risk Thresholds for Pancreatitis by FCS Genotype



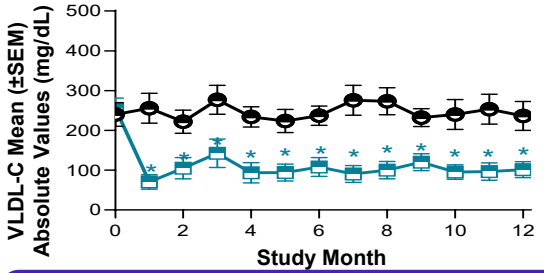
Primary Endpoint:
80 % change in median TG at 10 month

	Placebo (Pooled)		Plozasiran 25 mg	
	With FCS Genetic Confirmation (n=10)	Without FCS Genetic Confirmation (n=9)	With FCS Genetic Confirmation (n=13)	Without FCS Genetic Confirmation (n=11)
Patients attaining triglycerides < 500 mg/dL at month 10	1 (10%)	0 (0)	6 (46%)	6 (55%)
Patients attaining triglycerides < 880 mg/dL at month 10	**1 (10%)**	**3 (33%)**	**10 (77%)**	**8 (73%)**
Patients attaining triglycerides < 1000 mg/dL at month 10	1 (10%)	5 (56%)	11 (85%)	9 (82%)

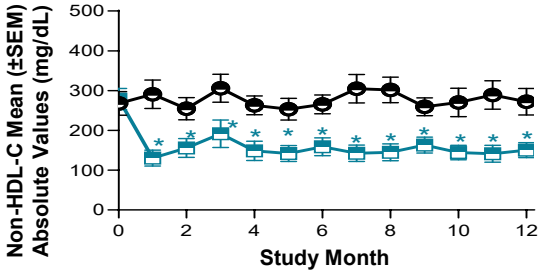
Thresholds above 500 and 880 mg/dL increase risk of AP and CVD; Extremely high TG levels >1000 mg/dL can lead to "chylomicron syndrome," causing AP.

Plozasiran Lowered TG-Rich Lipoproteins and Increased LDL-Cholesterol and HDL-Cholesterol Levels

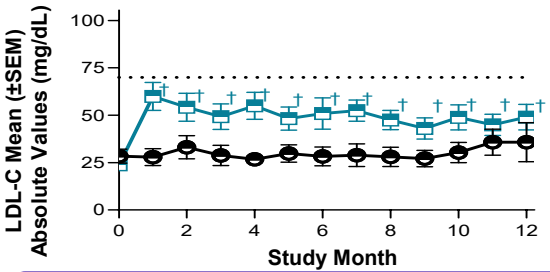
Remnant Cholesterol



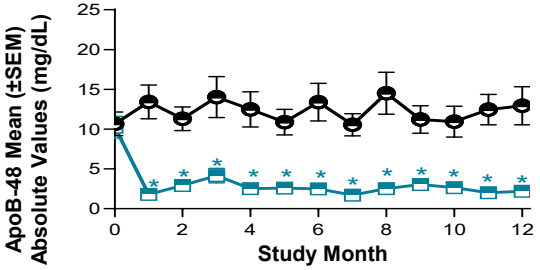
Non-HDL-Cholesterol



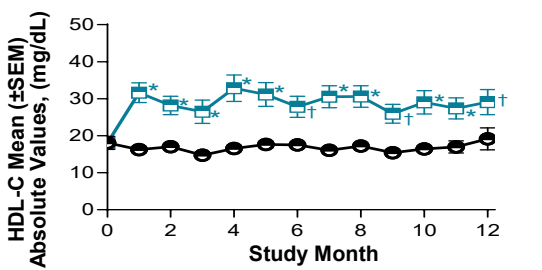
LDL-Cholesterol



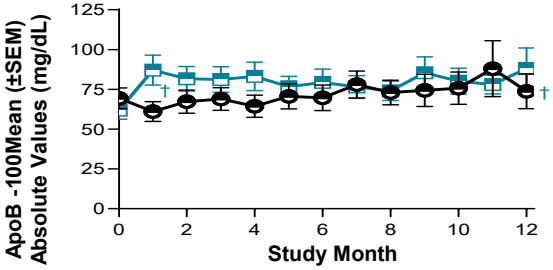
ApoB-48



HDL-Cholesterol



ApoB-100

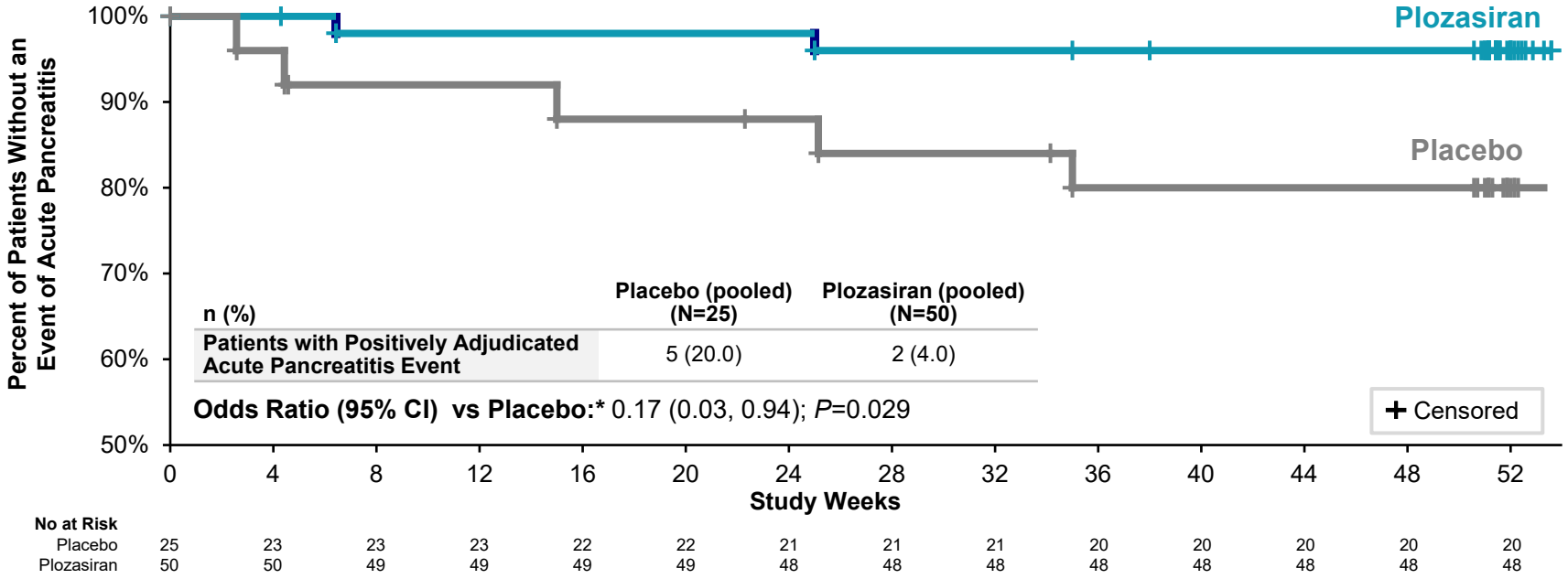


Responses Were Similar By FCS Genotype

SEM=standard error of mean.
*P<0.0001; †P<0.05.With Plozasiran Vs Placebo.

Plozasiran Significantly 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. †4 patients with AP events were FCS genotype negative.
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 from blinded therapy 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 alpha-controlled trial endpoints

- Plozasiran (quarterly dosing) significantly reduced acute pancreatitis
- Plozasiran substantially reduced triglycerides in patients with persistent chylomicronemia (FCS or FCS-like syndrome*) and over half achieved TG treatment goals (75% <880 mg/dL,
  50% <500 mg/dL), invariant of FCS genotype
- Reductions in TGs and APOC3 were apparent at 1 month and sustained thereafter over 12 months with comparable efficacy in genetically and clinically-defined patients
- Reductions in atherogenic TRLs and minor increase in LDL-C with no change in ApoB
- Favorable safety and tolerability comparable 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 acute pancreatitis events and exceptionally high TGs).
APOC3, apolipoprotein C3; **FCS,** familial chylomicronemia syndrome; **HDL-C,** high-density lipoprotein cholesterol;
MCS, Multifactorial Chylomicronemia Syndrome; **TG,** triglycerides; **VLDL-C,** very low-density lipoprotein cholesterol.

Circulation

Temporal Effects of Plozasiran on Lipids and Lipoproteins in Persistent Chylomicronemia

Gerald F. Watts, DSc, MD, PhD; Robert A. Hegele, MD; Robert S. Rosenson, MD; Ira J. Goldberg, MD; Antonio Gallo, MD, PhD; Ann Mertens, MD, PhD; Alexis Baass, MD, MSc; Rong Zhou, PhD; Ma'an Muhsin, MD; Jennifer Hellawell, MD; Daniel Gaudet, MD, PhD; Nicholas J. Leeper, MD; on behalf of the PALISADE Study Group

Circulation

https://www.ahajournals.org/doi/ 10.1161/CIRCULATIONAHA.124.072860

PALISADE

The study sponsors would like to thank the patients who participated and their families, and all investigators and staff who completed the trial

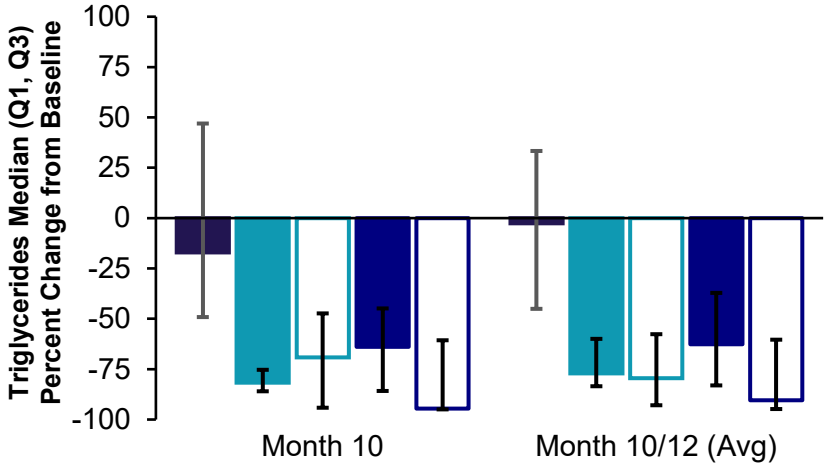
PALISADE Study Patients: Genotype Analysis

Genotype, N (%)	Pooled Placebo (N=25)	Plozasiran	
		25 mg (N=26)	50 mg (N=24)
LPL			
Homozygote	7 (28.0)	5 (19.2)	8 (33.3)
Compound Heterozygote	6 (24.0)	4 (15.4)	6 (25.0)
APOA5			
Homozygote	0 (0)	1 (3.8)*	0 (0)
GPIHBP1			
Homozygote	0 (0)	1 (3.8)	2 (8.3)
Compound Heterozygote	0 (0)	1 (3.8)	0 (0)
LMF1			
Homozygote	0 (0)	3 (11.5)	0 (0)
APOC2			
Homozygote	1 (4.0)	0 (0)	0 (0)
Not Genetically Confirmed	11 (44)	12 (46)	8 (33)

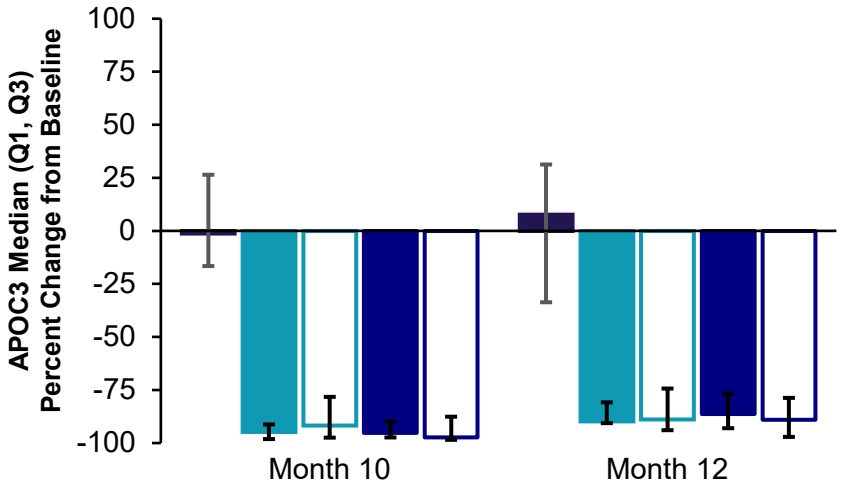
*APOA5: This patient was already homozygous pathogenic stopgain variant in LMF1, confirmed FCS diagnosis. Also reported homozygous APOA5 mutation of unknown pathogenicity.
APOA5, apolipoprotein A5 gene; **APOC2**, apolipoprotein C2 gene; **GPIHBP1**, glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 gene; **LMF1**, lipase maturation factor 1 gene; **LPL**, lipoprotein lipase gene.

Reductions in Triglyceride and APOC3 Levels According to Genetically Confirmed FCS

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

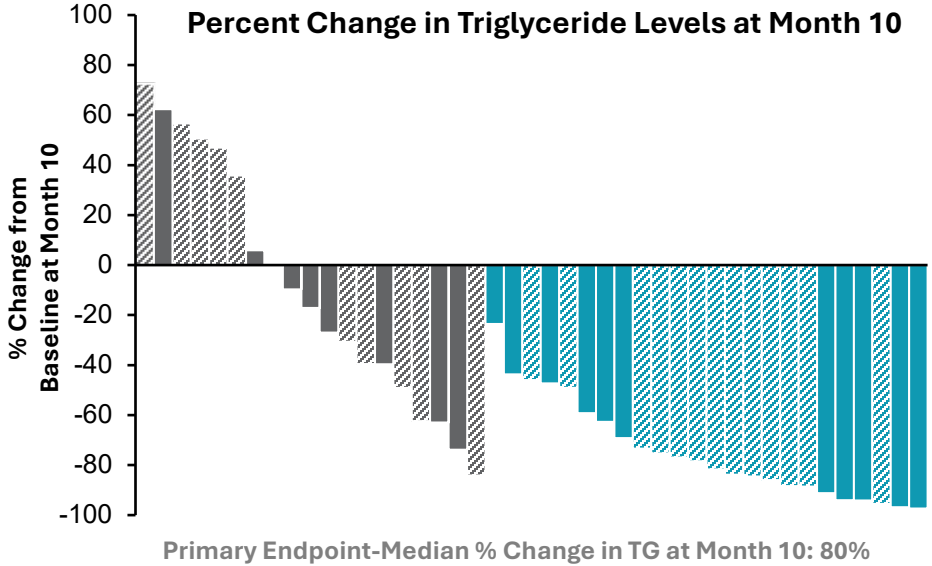
APOC3=apolipoprotein C3; **FCS**=familial chylomicronemia syndrome; **Q1**=1st quartile; **Q3**=3rd quartile.

PALISADE Baseline Characteristics

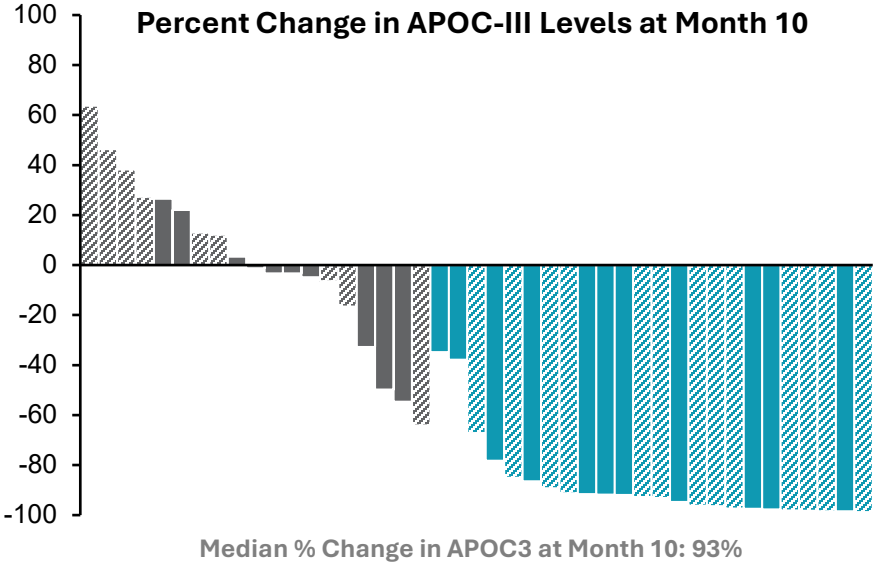
	With FCS Confirmation		Without FCS Confirmation	
	Placebo (N=14)	Plozasiran (N=14)	Placebo (N=11)	Plozasiran (N=12)
Mean Age	45.5	48.8	49.7	46.9
Female, n (%)	8 (57.1)	9 (64.3)	3 (27.3)	5 (41.7)
Male, n (%)	6 (42.9)	5 (35.7)	8 (72.7)	7 (58.3)
White, n (%)	10 (71.4)	10 (71.4)	9 (81.8)	9 (75.0)
Mean BMI	22.74	25.3	27.8	27.0
Median APOC3 (mg/dL)	32.1	32.3	56.8	42.1
Mean APOC3 (mg/dL)	30.2	32.2	52.2	45.9
Median triglycerides (mg/dL)	2153.7	2540.5	1787.7	1766.5
Mean triglycerides, (mg/dL)	2326.6	2500.4	2202.3	2173.5
Receiving statins, n (%)	5 (35.7)	5 (35.7)	6 (54.5)	6 (50.0)
Fibrates, n (%)	7(50.0)	12 (85.7)	9 (81.8)	7 (58.3)
Omega 3 fatty acids, n (%)	3 (21.4)	5 (35.7)	3 (27.3)	4 (33.3)
Diabetes or pre-diabetes, n (%)	2 (14.3)	2 (14.3)	9 (81.8)	8 (66.7)
Previous episode of pancreatitis, n (%)	12 (85.7)	13 (92.9)	10 (90.9)	10 (83.3)
Mean LDL-C (mg/dL)	18.4	22.1	41.1	25.8
Mean ApoB-100 (mg/dL)	50.1	51.3	83.5	72.6
Mean HbA1C	5.3	5.4	7.1	6.1

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; **CVD**, cardiovascular disease; **FCS**, familial chylomicronemia syndrome; **HbA1c**, glycated hemoglobin; **LDL-C**, low-density lipoprotein cholesterol; **N**, number; **Q**, quartile; **SD**, standard deviation; **W**, week.

REDUCTIONS IN TG AND APOC-III AND % OF PATIENTS ATTAINING TG BELOW RISK THRESHOLDS FOR PANCREATITIS BY FCS GENOTYPE



Primary Endpoint-Median % Change in TG at Month 10: 80%



Median % Change in APOC3 at Month 10: 93%

With FCS Genetic Confirmation
Pooled Placebo | Plozasiran 25 mg

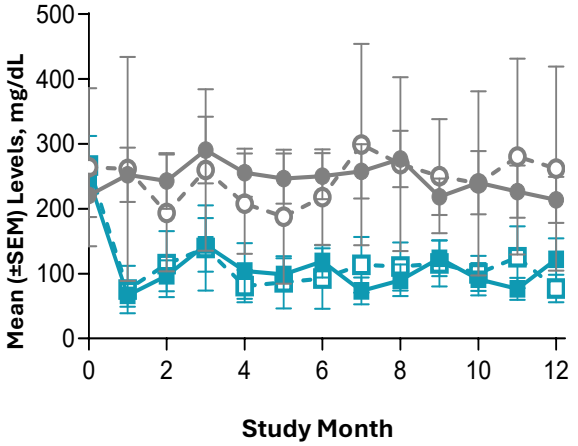
Without FCS Genetic Confirmation
Pooled Placebo | Plozasiran 25 mg

	Placebo (Pooled)		Plozasiran 25 mg	
	With FCS Genetic Confirmation (n=10)	Without FCS Genetic Confirmation (n=9)	With FCS Genetic Confirmation (n=13)	Without FCS Genetic Confirmation (n=11)
Patients attaining triglycerides < 500 mg/dL at month 10	1 (10%)	0 (0)	6 (46%)	6 (55%)
Patients attaining triglycerides < 880 mg/dL at month 10	**1 (10%)**	**3 (33%)**	**10 (77%)**	**8 (73%)**
Patients attaining triglycerides < 1000 mg/dL at month 10	1 (10%)	5 (56%)	11 (85%)	9 (82%)

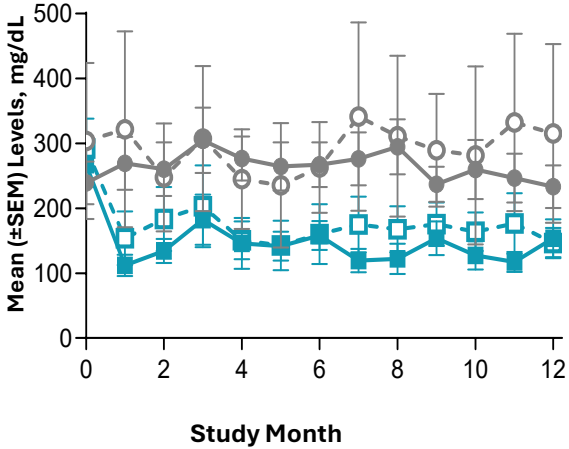
Thresholds above 500 and 880 mg/dL increase risk of AP and CVD; Extremely high TG levels >1000 mg/dL can lead to "chylomicron syndrome," causing AP

PLOZASIRAN LOWERED TG-RICH LIPOPROTEINS AND NON-HDL-C WITH NO DIFFERENCE BY FCS GENOTYPE

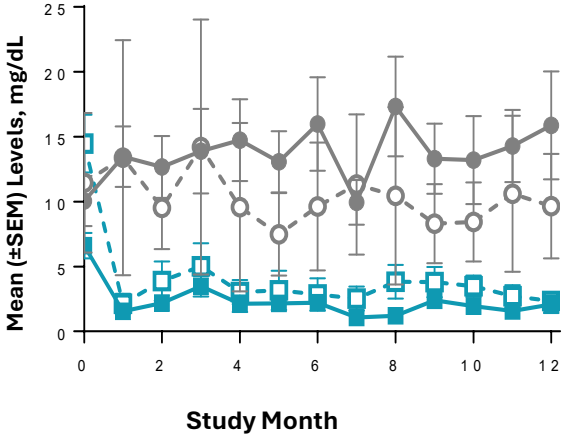
Remnant Cholesterol[§]



Non-HDL-Cholesterol[§]



Apo B-48[§]



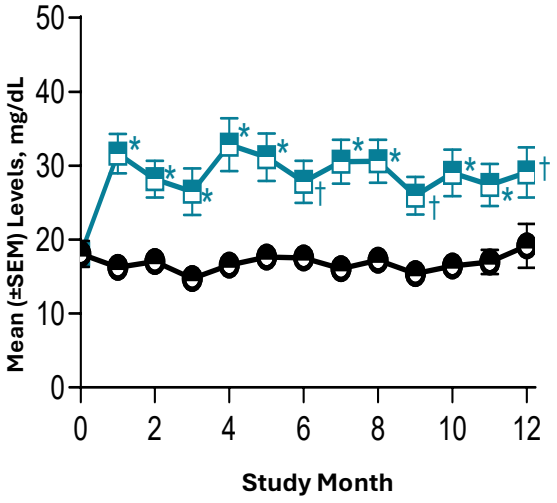
With FCS Genetic Confirmation — Plozasiran 25 mg — Placebo

Without FCS Genetic Confirmation — Plozasiran 25 mg — Placebo

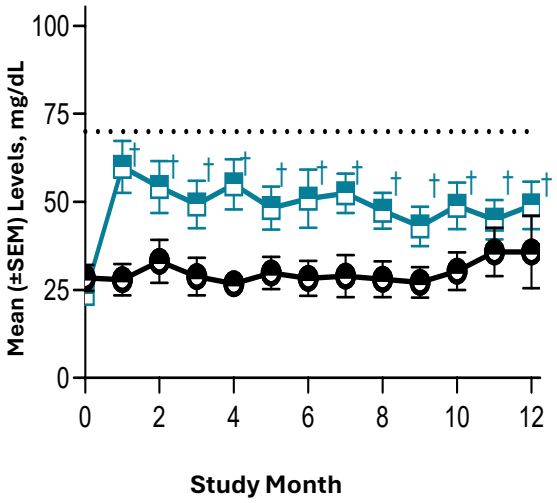
[§]Not significant for between group differences; significant vs placebo, $P<0.05$.
Remnant cholesterol = Total cholesterol - LDL-C (UC) - HDL-C
FCS, familial chylomicronemia syndrome; **HDL**, high-density lipoprotein; **LS**, least squares; **SEM**, standard error of the mean.

PLOZASIRAN INCREASED HDL-C AND LDL-C WITH NO CHANGE IN TOTAL APOB OR APOB-100

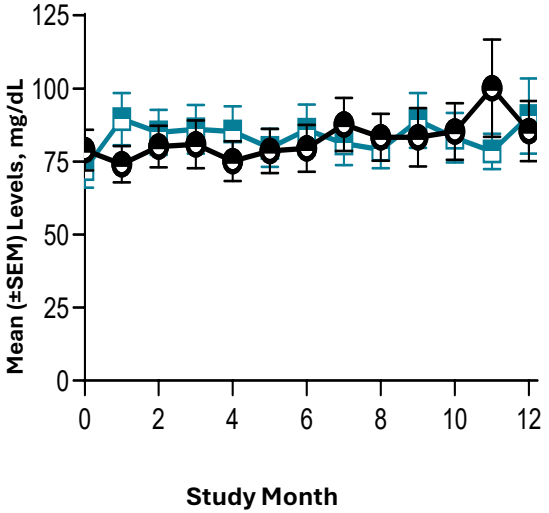
HDL-C



LDL-C



Total Apo B



Pooled Placebo Plozasiran 25 mg

*P<0.0001; †P<0.05.
FCS, familial chylomicronemia syndrome; **HDL**, high-density lipoprotein; **LS**, least squares; **LDL**, low-density lipoprotein; **SEM**, standard error of the mean.