#AHA24

MUIR SHASTA

PLOZASIRAN AND TRIGLYCERIDE LEVELS IN HYPERTRIGLYCERIDEMIA: DATA FROM SUBJECTS IN AN OPEN-LABEL EXTENSION TRIAL - A GLIMPSE INTO 18-MONTH RESULTS

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on behalf of the SHASTA-2 and MUIR Study Teams

American Heart Association.

American Heart Association. 100 YEARS Bold Hearts

AUTHORS AND MY DISCLOSURE

Presenter

- **CM Ballantyne** reports grants and/or honoraria from Abbott Diagnostic, Akcea, Althera, Amarin, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Esperion, Genentech, Gilead, Illumina, Ionis, Matinas BioPharma Inc, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo.

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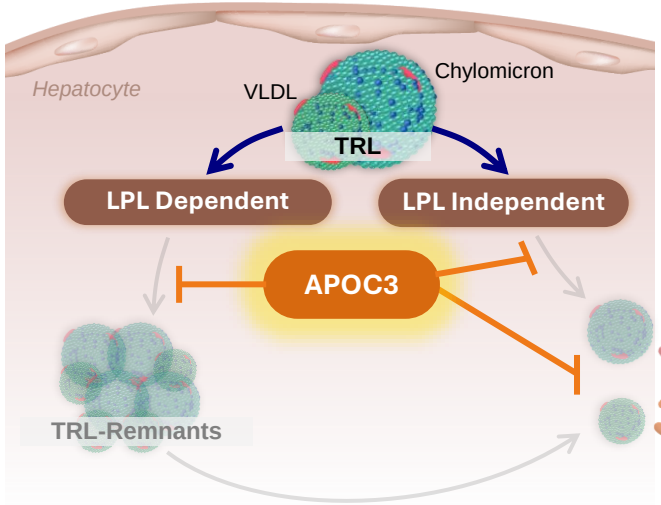
BACKGROUND

- Despite current modestly effective triglyceride (TG) lowering therapies, more effective agents are needed to lower persistently elevated TGs and risk of acute pancreatitis
- More recently identified triglyceride-rich lipoproteins (TRLs), specifically remnant cholesterol (RC)-rich particles, are important drivers of ASCVD risk independent of LDL-C, driving development of more effective TG-directed therapies
- Apolipoprotein C3 (APOC3) raises TGs by inhibiting lipoprotein lipase (LPL) dependent and independent pathways
- Plozasiran, an investigational RNAi agent targeting APOC3 mRNA in hepatocytes, demonstrated large reductions in circulating APOC3, TGs, TRL-RC with a good safety profile in placebo-controlled trials

PLOZASIRAN (ARO-APOC3) IS AN INVESTIGATIONAL SIRNA THERAPEUTIC TARGETING APOC3, A KEY REGULATOR OF TG AND TRL METABOLISM

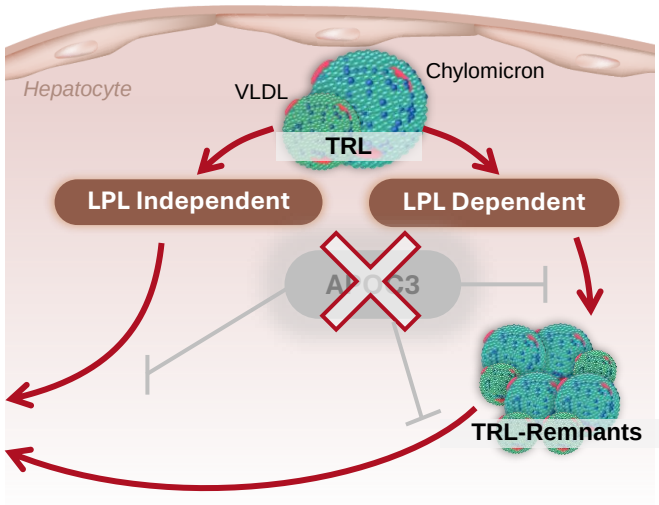
CHYLOMICRONEMIA[1,2]

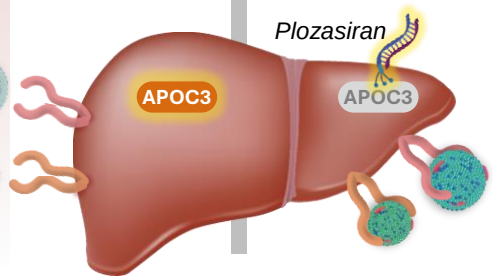
APOC3 inhibits lipolysis and hepatic clearance of TRLs, increasing TGs



PLOZASIRAN[2]

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

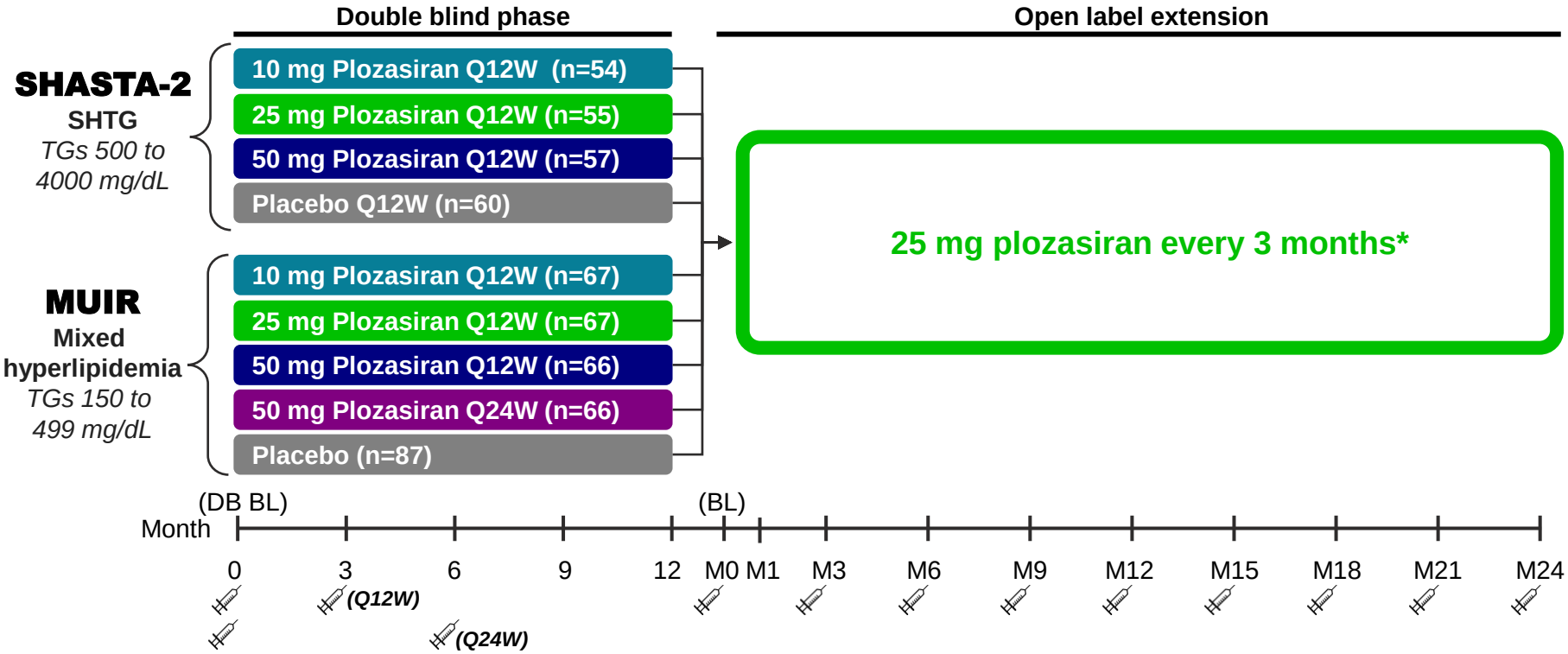




APOC3, apolipoprotein C3; **HL**, hepatic lipase; **LPL**, lipoprotein lipase; **TG**, triglycerides; **TRL**, triglyceride rich lipoproteins; **VLDL**, very low-density lipoprotein.

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.

STUDY DESIGN



*Until final dose decision, participants were dosed according to their assigned dose in the parent study
DB, double-blind; **BL**, baseline, **M**, Month; **Q12W**, every 12 weeks; **Q24W**, every 24 weeks; **SHTG**, severe hypertriglyceridemia; **TG**, triglyceride.

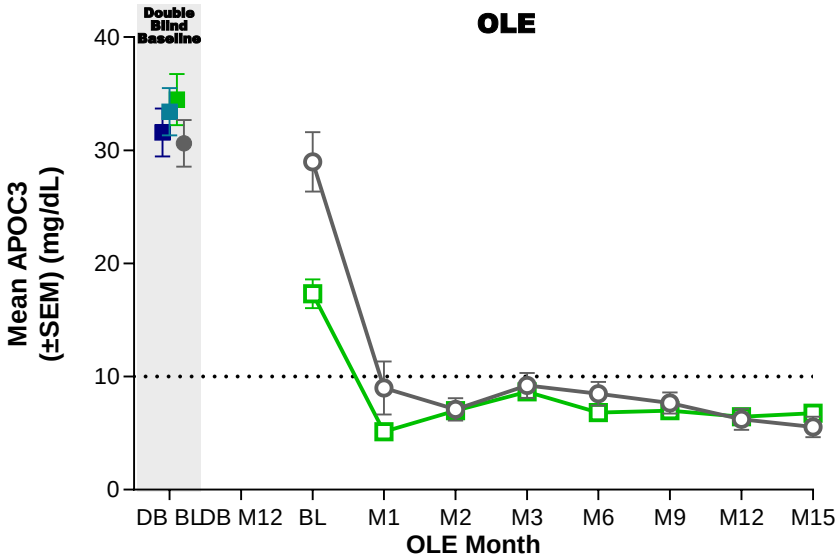
BASELINE CHARACTERISTICS OF PARENT STUDY

	OLE Patients from SHASTA-2 (AROAPOC3-2001)		OLE Patients from MUIR (AROAPOC3-2002)	
Parent Study	Placebo/Plozasiran (N=45)	Plozasiran/Plozasiran (N=124)	Placebo/Plozasiran (N=57)	Plozasiran/Plozasiran (N=192)
Mean (SD) age, years	55.4 (10.9)	55.0 (10.6)	59.6 (9.9)	62.3 (11.0)
Male, n (%)	34 (75.6)	97 (78.2)	32 (56.1)	108 (56.3)
White, n (%)	41 (91.1)	112 (90.3)	51 (89.5)	180 (93.8)
Mean (SD) BMI, kg/m^2	30.3 (3.7)	31.70 (4.6)	30.7 (5.5)	32.06 (6.4)
Lab Measures, mean (SD) mg/dL				
APOC3[a]	32.971 (16.6)	33.723 (16.4)	15.010 (4.8)	15.347 (5.5)
Triglyceride	893.6 (553.5)	947.42 (711.1)	241.64 (73.1)	242.1 (75.0)
Triglyceride, median (Q1, Q3)	685.1 (583.2, 923.7)	664.2 (550.5, 1017.8)	222.1 (185.0, 275.7)	221.7(179.0, 297.7)
LDL-C[b]	85.5 (42.5)	105.7 (47.9)	110.8 (35.8)	115.3 (41.4)
non-HDL-C	187.5 (82.4)	210.7 (91.6)	147.0 (40.9)	152.1 (47.3)
ApoB	95.1 (29.9)	107.1 (47.5)	102.0 (27.6)	102.1 (26.0)
ApoB48	6.8 (6.5)	8.1 (7.5)	2.7 (2.0)	2.8 (2.0)
VLDL-C[c]	60.1 (20.02)	60.8 (14.54)	45.2 (13.24)	45.7 (15.06)
HDL-C	28.5 (11.6)	29.5 (10.5)	41.4 (10.9)	43.4 (11.9)
Clinical Characteristics, n (%)				
ASCVD history or elevated risk[d]	10 (22.2)	32 (25.8)	4 (7.0)	26 (13.5)
History of acute pancreatitis	4 (8.89)	8 (6.45)	1 (1.75)	2 (1.04)
Diabetes[a]	30 (66.7)	75 (60.5)	31 (54.4)	121 (63.0)
Concomitant Statin Use, n (%)				
Any use	32 (71.1)	87 (70.2)	55 (96.5)	177 (92.2)
High intensity	23 (51.1)	63 (50.8)	31 (54.4)	109 (56.8)
Moderate intensity	8 (17.8)	17 (13.7)	21 (36.8)	60 (31.3)

[a]Analysis that removed n=2 participants with baseline values of BLOQ (ad hoc).[b]Martin-Hopkins methodology. [c]Calculated. [d]Or at elevated risk, ie. 10 yr risk of CHD of >20%. Clinical data cutoff 23Sept2024. **APOC3**, apolipoprotein C3; **ApoB**, apolipoprotein-B; **ASCVD**, atherosclerotic cardiovascular disease; **BLOQ**, below limits of quantification; **BMI**, body mass index; **CHD**, congenital heart disease; **HDL**, high-density lipoprotein; **LDL**, low-density lipoprotein; **OLE**, open label extension; **SD**, standard deviation; **VLDL**, very low-density lipoprotein.

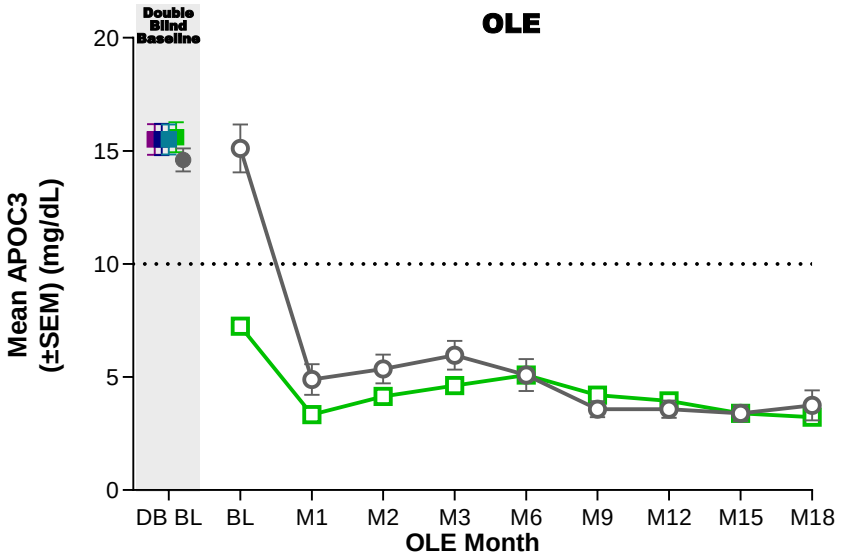
CONSISTENT REDUCTIONS IN APOC3 WITH PLOZASIRAN

SHASTA APOC3



Placebo➞ Plozasiran	58	43	43	44	44	43	40	37	25	17
Plozasiran ➞ Plozasiran	165	114	120	118	120	119	118	113	85	60

MUIR APOC3



Placebo➞ Plozasiran	60	54	52	50	53	53	50	50	38	16
Plozasiran ➞ Plozasiran	166	185	186	185	184	182	173	170	133	52

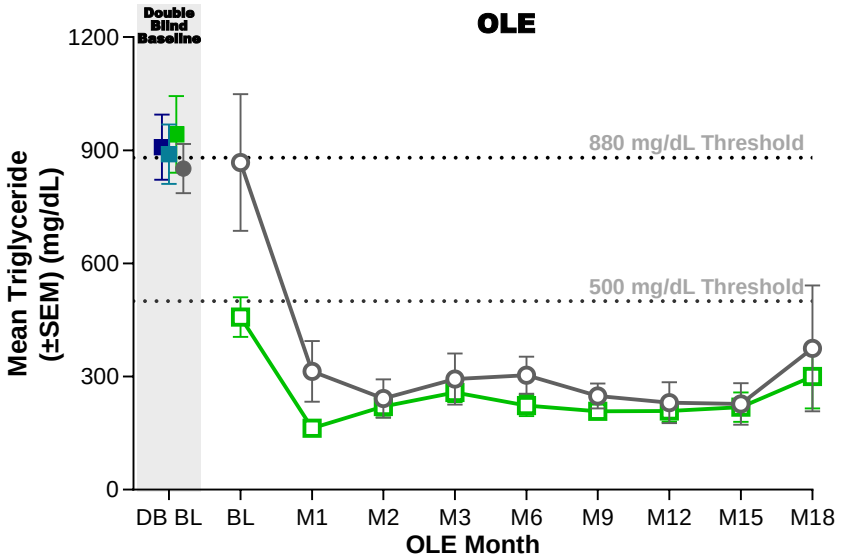
Double-blind Period Placebo; Plozasiran 10 mg; Plozasiran 25 mg; Plozasiran 50 mg; Plozasiran 50 mg Q24W | **OLE Period** Placebo/ Plozasiran; Plozasiran/ Plozasiran

Data cut as of 23SEP2024. Last dose from double blind for each study was at least 9 months prior, except for the Q24W arm in MUIR which was at least 6 months prior.

APOC3, apolipoprotein C3; **D**, Day; **DB**, double-blind; **BL**, baseline, **M**, Month; **OLE,** open-label extension; **SEM**, standard error of the mean,

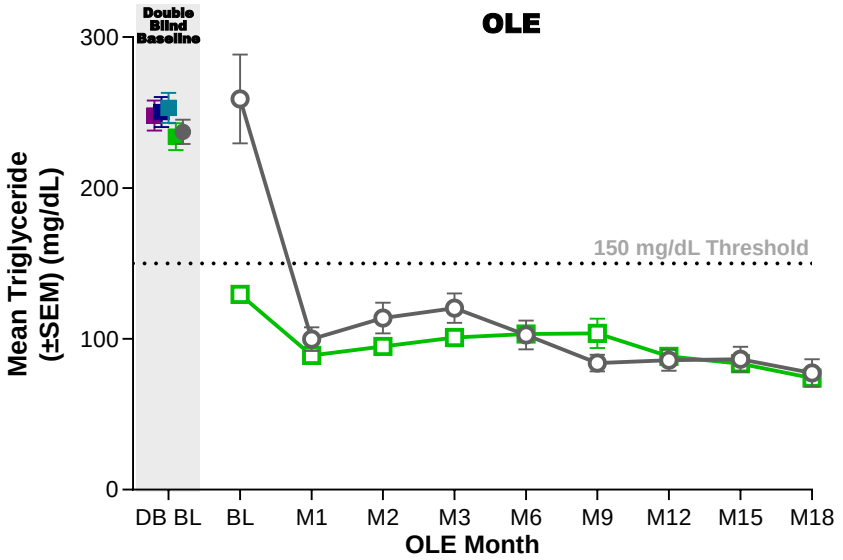
CONSISTENT REDUCTIONS IN TG WITH PLOZASIRAN

SHASTA Triglycerides



	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
Placebo➞ Plozasiran	60	45	44	45	45	44	41	38	25	17
Plozasiran ➞ Plozasiran	166	124	121	119	121	120	119	114	85	60

MUIR Triglycerides



	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
Placebo➞ Plozasiran	60	57	54	52	55	55	52	52	39	17
Plozasiran ➞ Plozasiran	166	191	189	188	187	185	176	173	134	53

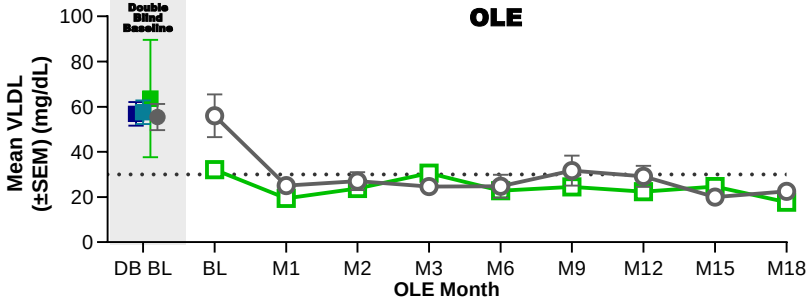
Double-blind Period Placebo; Plozasiran 10 mg; Plozasiran 25 mg; Plozasiran 50 mg; Plozasiran 50 mg Q24W

OLE Period Placebo/ Plozasiran; Plozasiran/ Plozasiran

[a]Analysis removed 1 participant with baseline value below limits of quantitation, BLOQ. [b] Data cut as of 23SEP2024. Last dose from double blind for each study was at least 9 months prior, except for the Q24W arm in MUIR which was at least 6 months prior.
D, Day; **DB**, double-blind; **BL**, baseline, **M**, month; **OLE,** open-label extension; **SEM**, standard error of the mean.

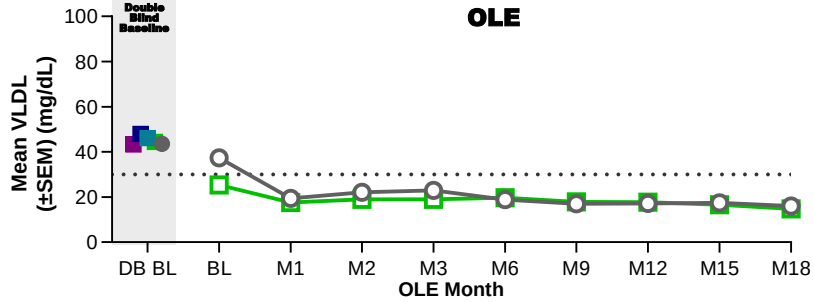
CONSISTENT REDUCTIONS IN REMNANT CHOLESTEROL AND NON-HDL-C WITH PLOZASIRAN

SHASTA Remnant Cholesterol (VLDL-C)*



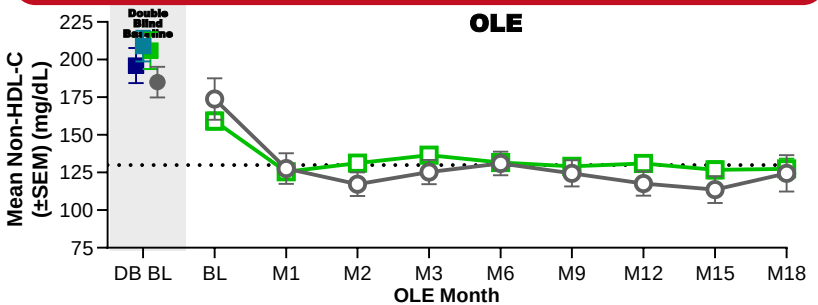
Placebo➔ Plozasiran	13	5	7	7	7	6	6	5	3	2
Plozasiran ➔ Plozasiran	38	23	25	24	25	23	23	22	14	9

MUIR Remnant Cholesterol (VLDL-C)*



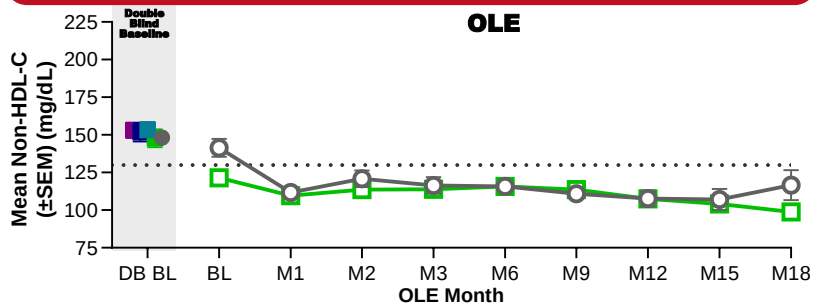
Placebo➔ Plozasiran	78	49	47	50	49	47	47	35	16	3
Plozasiran ➔ Plozasiran	242	173	173	171	170	160	159	126	51	13

SHASTA Non-HDL Cholesterol



Placebo➔ Plozasiran	60	44	44	45	45	44	41	38	25	17
Plozasiran ➔ Plozasiran	166	120	120	118	120	119	118	113	85	60

MUIR Non-HDL Cholesterol



Placebo➔ Plozasiran	87	57	54	52	55	55	52	52	39	17
Plozasiran ➔ Plozasiran	266	191	189	188	187	185	176	173	134	53

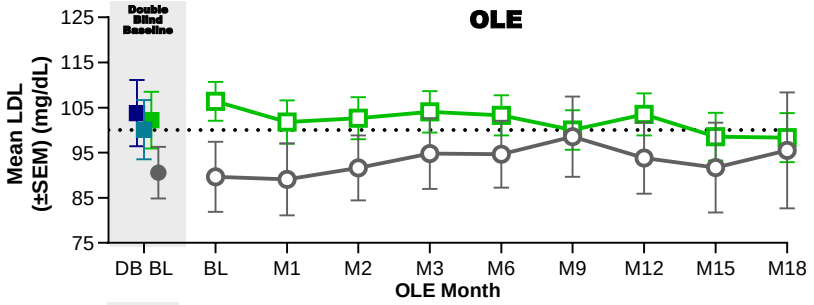
Double-blind Period Placebo | Plozasiran 10 mg | Plozasiran 25 mg | Plozasiran 50 mg | Plozasiran 50 mg Q24W

OLE Period Placebo/ Plozasiran | Plozasiran/ Plozasiran

Data cut as of 23SEP2024. Last dose from double blind for each study was at least 9 months prior, except for the Q24W arm in MUIR which was at least 6 months prior. *Remnant cholesterol (VLDL-C) = Total cholesterol - LDL-C (UC) - HDL-C. **DB**, double-blind; **BL**, baseline; **HDL**, high-density lipoprotein; **M**, month; **OLE,** open-label extension; **SEM**, standard error of the mean; **VLDL=C**, very low-density lipoprotein cholesterol.

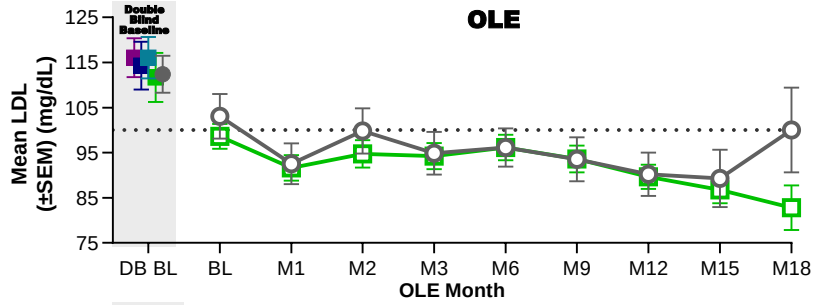
PLOZASIRAN: FAVORABLE CHANGES IN APOB LEVELS WITH NO ADVERSE EFFECTS ON LDL-C

SHASTA LDL Cholesterol*



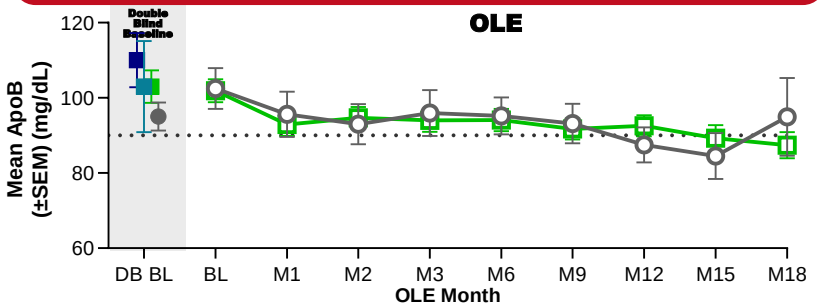
	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
Placebo→ Plozasiran	60	37	39	40	40	39	36	34	21	14
Plozasiran → Plozasiran	166	107	109	106	108	108	107	101	76	50

MUIR LDL Cholesterol*



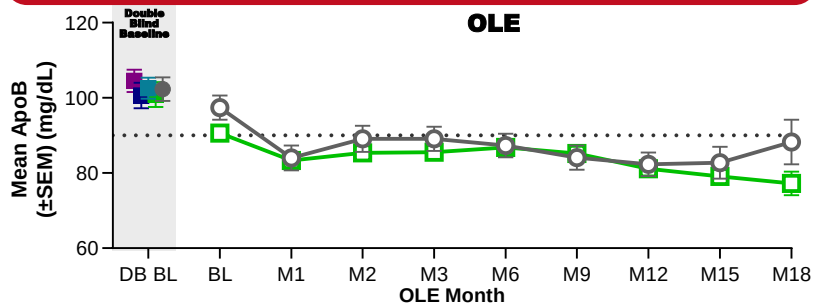
	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
Placebo→ Plozasiran	87	57	57	54	52	55	55	52	52	39
Plozasiran → Plozasiran	266	192	191	189	188	187	185	176	173	134

SHASTA ApoB



	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
Placebo→ Plozasiran	60	35	34	37	45	44	41	38	25	17
Plozasiran → Plozasiran	166	92	93	103	113	119	118	113	85	59

MUIR ApoB



	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
Placebo→ Plozasiran	87	52	51	50	54	54	51	51	37	16
Plozasiran → Plozasiran	266	176	180	185	186	184	175	172	130	52

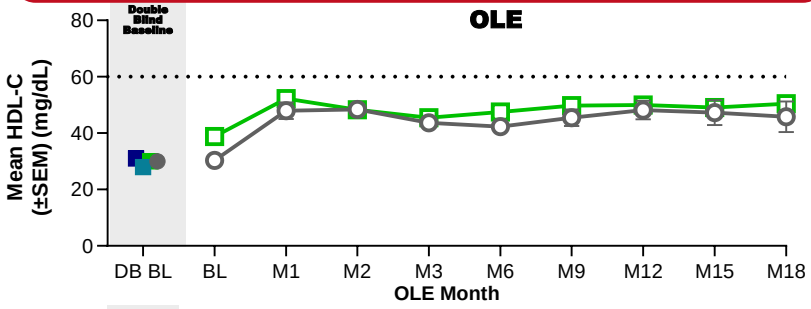
Double-blind Period: Placebo; Plozasiran 10 mg; Plozasiran 25 mg; Plozasiran 50 mg; Plozasiran 50 mg Q24W

OLE Period: Placebo/ Plozasiran; Plozasiran/ Plozasiran

Data cut as of 23SEP2024. Last dose from double blind for each study was at least 9 months prior, except for the Q24W arm in MUIR which was at least 6 months prior. *LDL cholesterol using Martin-Hopkins methodology. **ApoB**, apolipoprotein-B; **DB**, double-blind; **BL**, baseline; **LDL**, low-density lipoprotein; **M**, month; **OLE,** open-label extension; **SEM**, standard error of the mean.

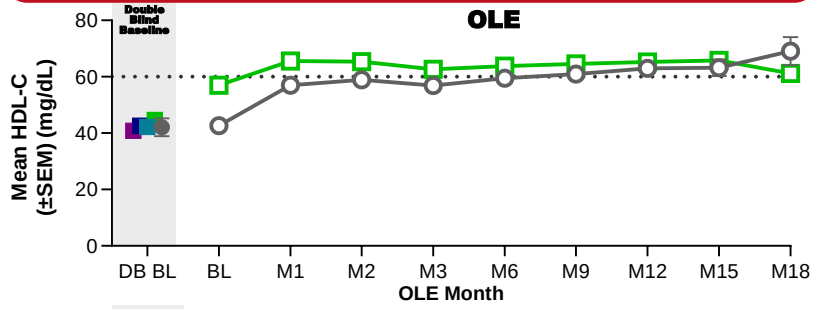
CONSISTENT INCREASES FROM BL IN HDL-C AND NO WORSENING FROM BL IN LP(A) WITH PLOZASIRAN

SHASTA HDL Cholesterol



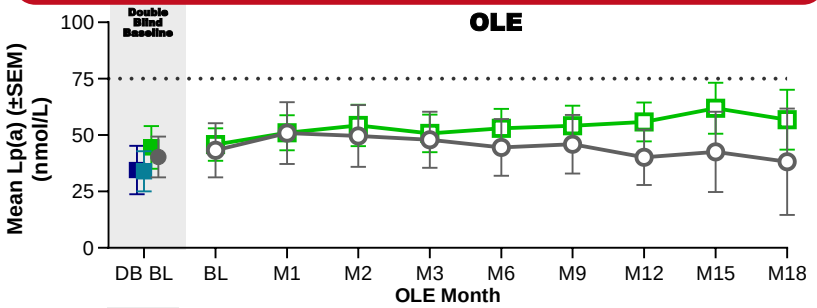
Placebo→ Plozasiran	60	44	44	45	45	44	41	38	25	17
Plozasiran → Plozasiran	166	120	120	118	120	119	118	113	85	60

MUIR HDL Cholesterol



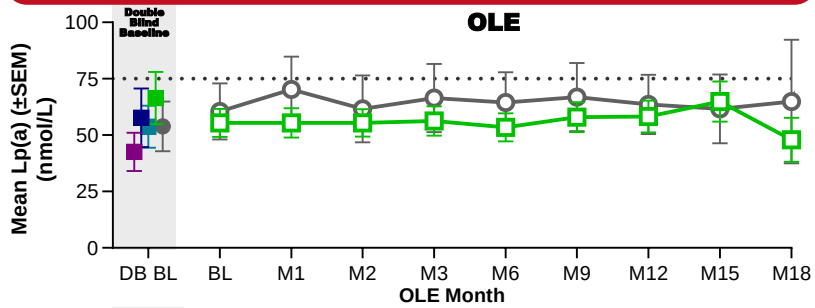
Placebo→ Plozasiran	87	57	54	52	55	55	52	52	39	17
Plozasiran → Plozasiran	266	191	189	188	187	185	176	173	134	53

SHASTA Lp(a)



Placebo→ Plozasiran	60	45	44	45	45	44	41	38	25	17
Plozasiran → Plozasiran	166	122	120	118	120	119	118	113	85	59

MUIR Lp(a)



Placebo→ Plozasiran	87	56	53	51	54	54	51	51	37	16
Plozasiran → Plozasiran	266	191	189	188	187	185	176	173	131	53

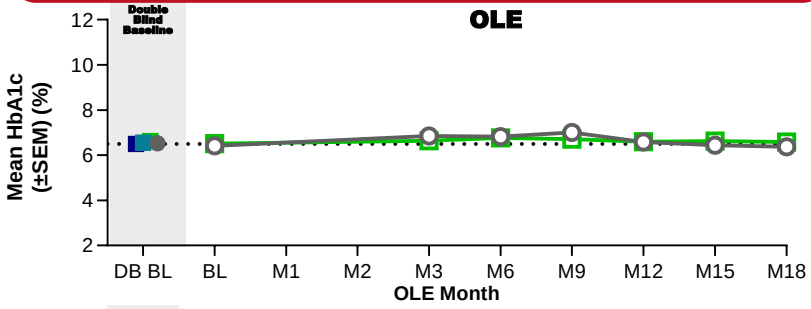
Double-blind Period — Placebo; Plozasiran 10 mg; Plozasiran 25 mg; Plozasiran 50 mg; Plozasiran 50 mg Q24W

OLE Period — Placebo/ Plozasiran; Plozasiran/ Plozasiran

Data cut as of 23SEP2024. Last dose from double blind for each study was at least 9 months prior, except for the Q24W arm in MUIR which was at least 6 months prior. *VLDL calculated. **DB**, double-blind; **BL**, baseline; **HDL**, high-density lipoprotein; **M**, month; **OLE,** open-label extension; **SEM**, standard error of the mean; **VLDL**, very low-density lipoprotein.

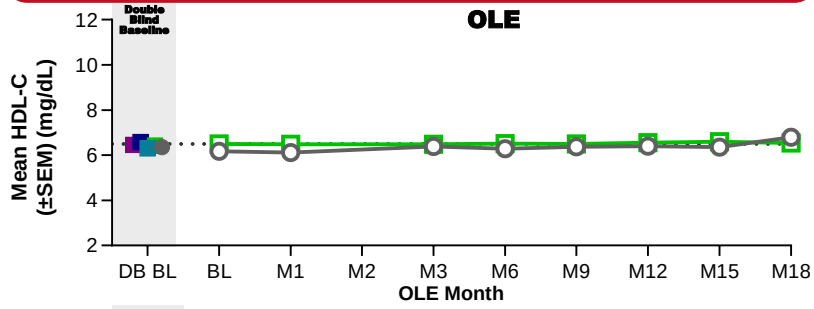
WITH SELECTED STUDY DOSE OF 25 MG, NO WORSENING IN INSULIN RESISTANCE OR HBA1C, NO NEW ONSET DM IN OLE

SHASTA HbA1c



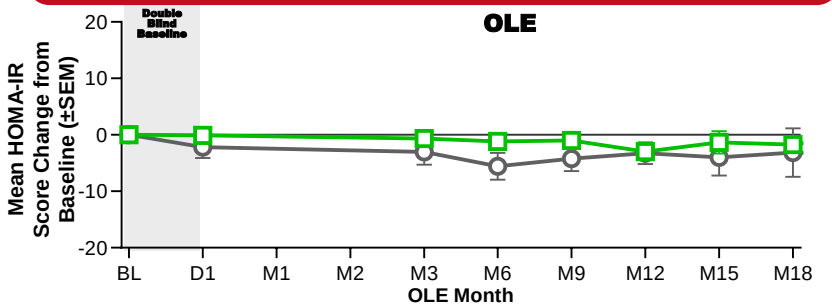
Placebo➞ Plozasiran	61	45	24	33	46	46	42	38	25	17
Plozasiran ➞ Plozasiran	165	122	67	75	120	119	118	115	85	60

MUIR HbA1c



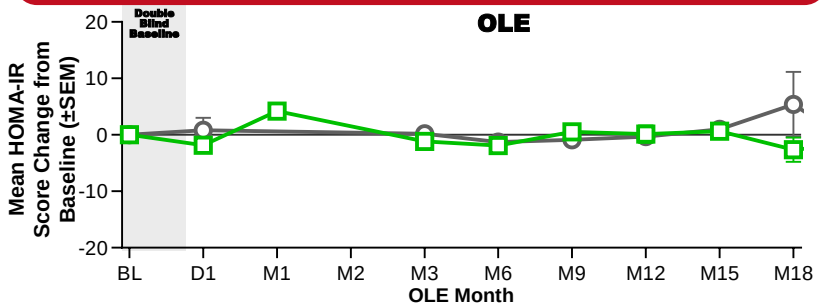
Placebo➞ Plozasiran	87	56	42	41	55	55	52	52	39	17
Plozasiran ➞ Plozasiran	266	189	144	160	187	185	176	173	135	53

SHASTA HOMA-IR



Placebo➞ Plozasiran	61	45	46	46	42	37	25	16
Plozasiran ➞ Plozasiran	165	123	120	117	118	115	85	60

MUIR HOMA-IR



Placebo➞ Plozasiran	87	53	54	55	52	52	39	17
Plozasiran ➞ Plozasiran	266	186	185	185	176	171	134	52

Double-blind Period Placebo; Plozasiran 10 mg; Plozasiran 25 mg; Plozasiran 50 mg; Plozasiran 50 mg Q24W | **OLE Period** Placebo/Plozasiran; Plozasiran/Plozasiran

Data cut as of 23SEP2024. Last dose from double blind for each study was at least 9 months prior, except for the Q24W arm in MUIR which was at least 6 months prior. **DB**, double-blind; **BL**, baseline; **HbA1c**, glycosylated hemoglobin; **HOMA-IR,** homeostatic model assessment for insulin resistance; **M**, month; **OLE,** open-label extension; **SEM**, standard error of the mean.

SAFETY OVERVIEW OPEN LABEL EXTENSION

TEAEs, n (%)	OLE Patients from SHASTA-2 and MUIR N=418
TEAEs	261 (62)
TEAEs experienced by at least 5% patients	
COVID-19	25 (6)
Type 2 diabetes	23 (5.5)
Back pain	16 (3.8)
Upper respiratory tract infection	16 (3.8)
Headache	13 (3)
Diabetes mellitus	13 (3)
Influenza	13 (3)
Urinary tract infection	12 (2.9)
Serious TEAEs*	44 (10.5)
TEAEs leading to treatment discontinuation, dose interruptions, or study discontinuation	23 (5.5)
Deaths	2 (0.5)

Clinical Data Cutoff 23 Sept 2024. *All serious TEAEs were not study drug related.
Deaths, not related to study drug: sudden cardiac death and MODS. **Withdrawn, may be related to study drug:** 2 T1DM, 2 T2DM, 1 HbA1C increase and 1 rash (all were mild to moderate in severity). **Withdrawn, not related to study drug:** 1 drug abuse, 2 HbA1c increase, 5 T1DM, 2 T2DM (all mild to moderate in severity) and CRC and small intestine adenocarcinoma (severe). **Interrupted, may be related to study drug:** Pain, LFT increase (mild to moderate in severity). **Interrupted, not related to study drug:**
2 HbA1c, 2 T2DM, 1 external ear cellulitis, 1 influenzas (all mild to moderate in severity) and schizophrenia, large intestine polyp, and AV block complete (severe).
AV, atrioventricular; **CRC**, colorectal cancer; **HbA1c**, glycosylated hemoglobin; **LFT**, liver function test; **OLE**, open-label extension;
MODS, Multiple organ dysfunction syndrome; **T1DM**, type 1 diabetes mellitus; **T2DM**, type 2 diabetes mellitus; **TEAE**, treatment-emergent adverse event.

CONCLUSION

- 418 subjects from MUIR and SHASTA-2 entered the extension in which all received plozasiran 25 mg SC dosed quarterly
- 10, 25 or 50 mg of plozasiran under blinded conditions produced mean reductions in triglycerides up to -64% (MUIR) and up to -74% (SHASTA-2), 12 weeks (trough) after the second dose
- Corresponding trough reductions in the extension were maintained up to -73% (MUIR) and -86% (SHASTA-2) through 15 months follow-up
- Common reported AEs were consistent with the index studies and patient populations
- No worsening of HbA1c, no new onset DM, providing further evidence that long-term safety remains favorable with repeated dosing and longer observation periods
- Extended open-label treatment with 25 mg plozasiran in subjects with moderate to severely elevated TGs continue to show reductions in TG and safety consistent with the blinded index studies; results that are encouraging for the ongoing Phase 3 program
- Favorable sustained reductions in TGs and APOC3, decreases in remnant cholesterol, non-HDL-C, favorable changes in apoB, increases in HDL-C, and no changes in LDL-C, Lp(a), HbA1c, results that remain durable over the duration of the open-label extension

AE, adverse event; **HbA1c**, glycosylated hemoglobin; **OLE**, open-label extension; **SC**, subcutaneously; **TG**, triglycerides.