TITLE:

RNA Inhibitors

SESSION:

Triglyceride Rich Lipoproteins Trials

NAME:

Jennifer Hellawell, MD

Disclosures

Dr. Hellawell is an employee of Arrowhead Pharmaceuticals

MUIR SHASTA

Plozasiran and Triglyceride Levels in Hypertriglyceridemia: Data From Subjects in an Open-Label Extension Trial - A Glimpse into 18-month Results

arrowhead pharmaceuticals

Authors and Affiliations

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Plozasiran is an investigational drug in late-stage development.

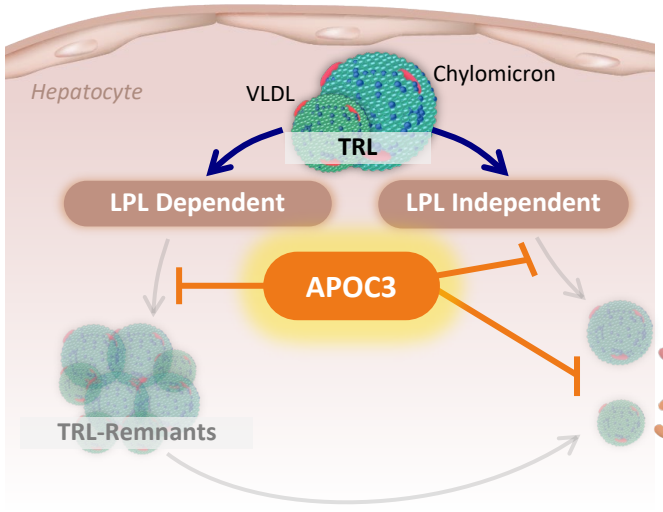
Background

- 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

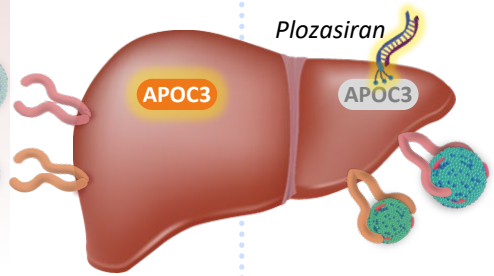
1. Brunzell JD, Bierman EL. *Med Clin North Am*. 1982;66(2):455–6. **2.** Pallazola VA, et al. *Eur J Prev Cardiol*. 2020;27(19):2276-8. **3.** Warden BA, et al. *J Clin Lipidol*. 2020;14(2):201-6. **4.** M Paquette, et al. *J Clin Endocrin Metab*. 2021;106(9):e3473–e3482. **5.** Gelrud A, et al. *Expert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

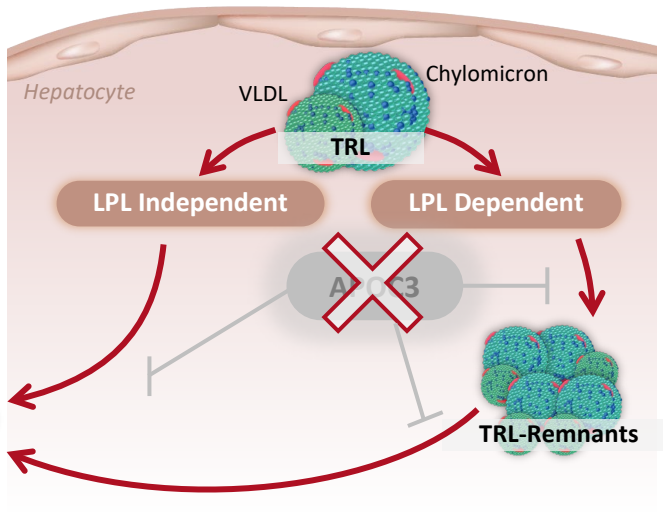
CHYLOMICRONEMIA[1,2]



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



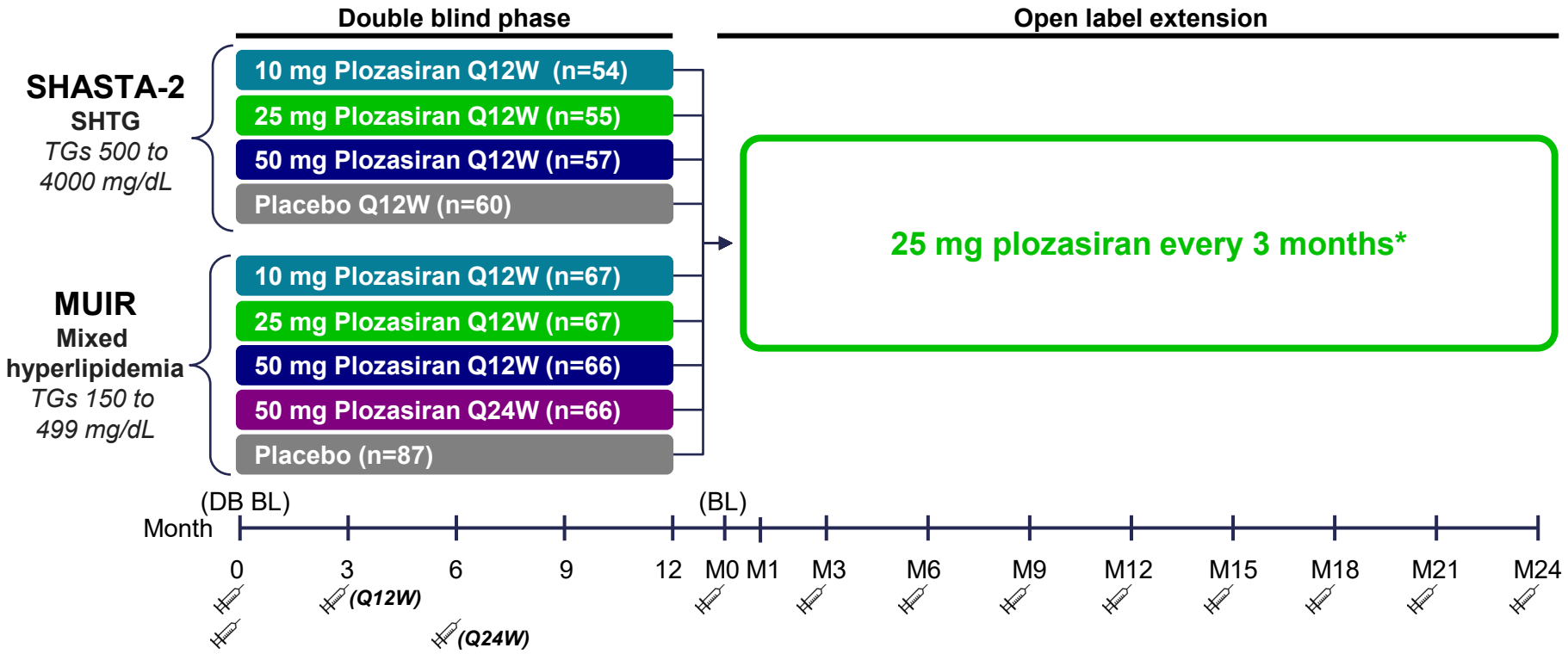
PLOZASIRAN[2]



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.

Study Design



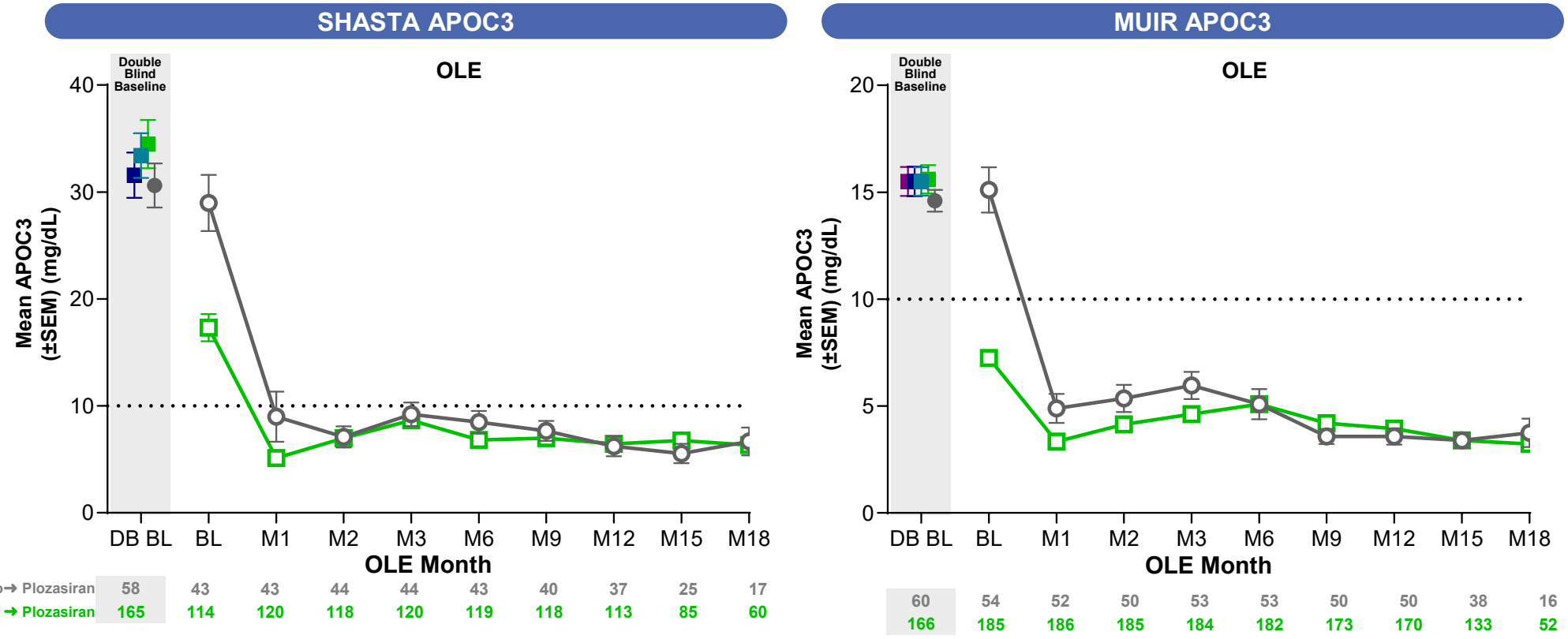
*Until final dose decision, participants were dosed according to their assigned dose in the parent study
DB, double-blind; **BL**, baseline, **M**, Month; **Q12W**, every 12 weeks; **Q24W**, every 24 weeks; **SHTG**, severe hypertriglyceridemia; **TG**, triglyceride.

Baseline Characteristics of Parent Study

Parent Study	OLE Patients from SHASTA-2 (AROAPOC3-2001) Placebo/Plozasiran (N=45)	OLE Patients from SHASTA-2 (AROAPOC3-2001) Plozasiran/Plozasiran (N=124)	OLE Patients from MUIR (AROAPOC3-2002) Placebo/Plozasiran (N=57)	OLE Patients from MUIR (AROAPOC3-2002) 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/m²	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.

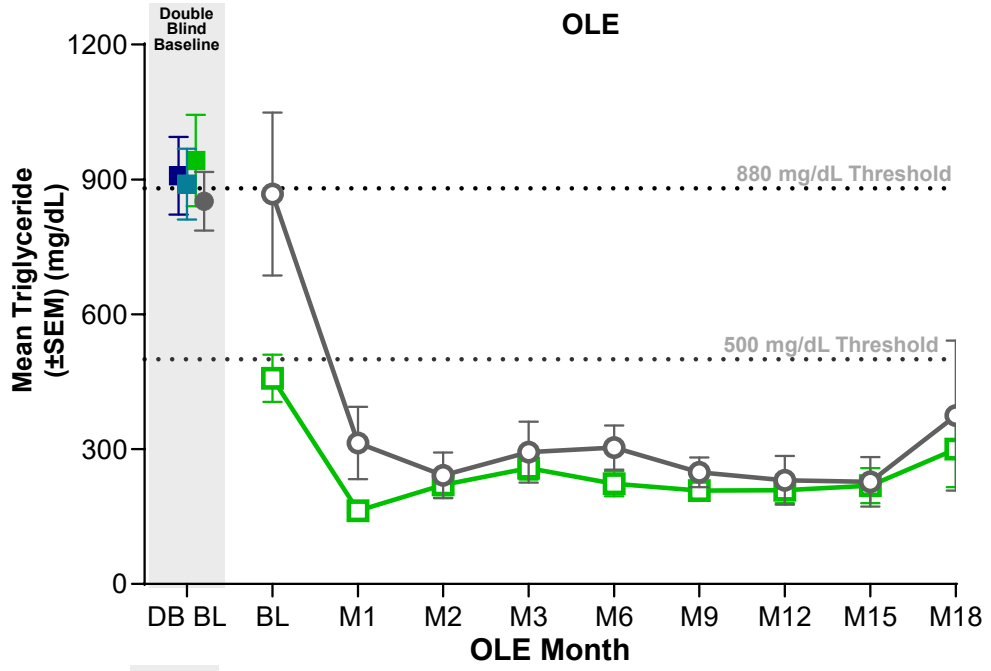
Consistent reductions in APOC3 with plozasiran



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,

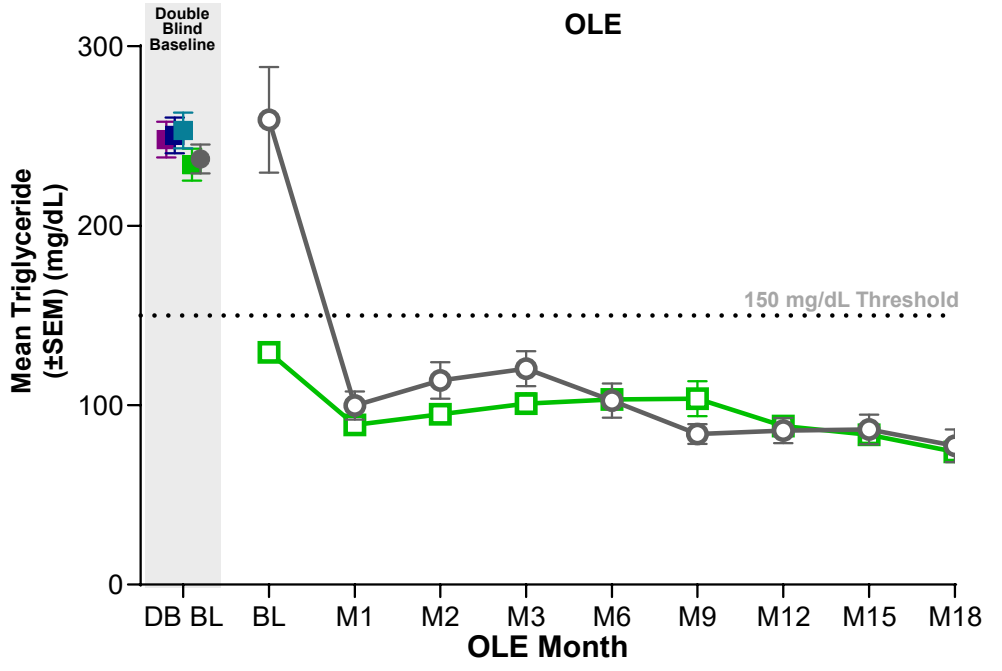
Consistent reductions in TG with plozasiran

SHASTA Triglycerides

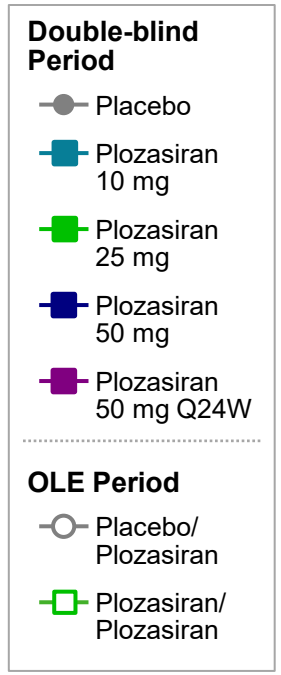


	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
Placebo→ Plozasiran	60	45	44	45	45	44	41	38	25	17
Plozasiran → Plozasiran	166	124	121	119	121	120	119	114	85	60

MUIR Triglycerides



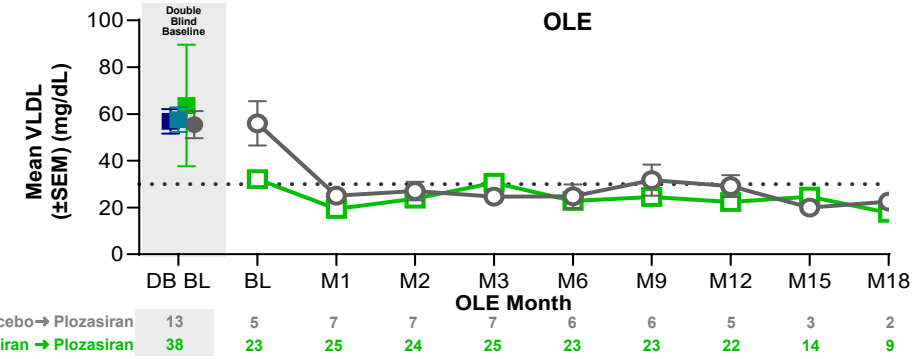
DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
60	57	54	52	55	55	52	52	39	17
166	191	189	188	187	185	176	173	134	53



[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.

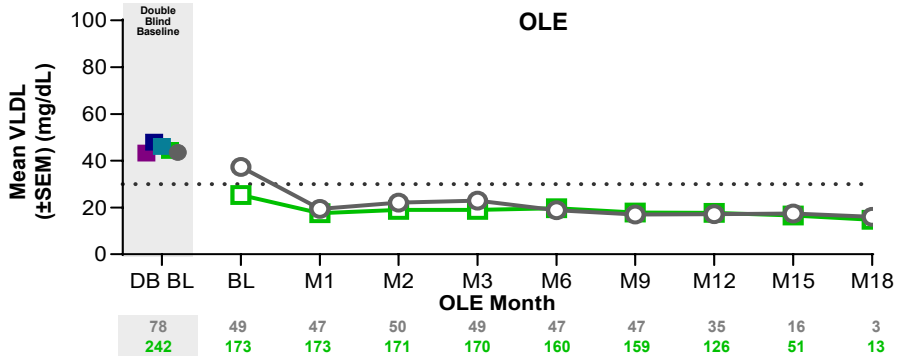
Consistent reductions in remnant cholesterol and non-HDL-C with plozasiran

SHASTA Remnant Cholesterol (VLDL-C)*



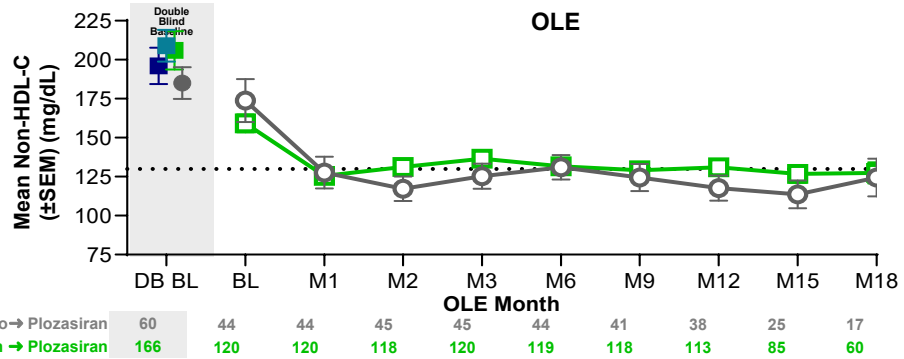
	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
Placebo→ Plozasiran	13	5	7	7	7	6	6	5	3	2
Plozasiran → Plozasiran	38	23	25	24	25	23	23	22	14	9

MUIR Remnant Cholesterol (VLDL-C)*



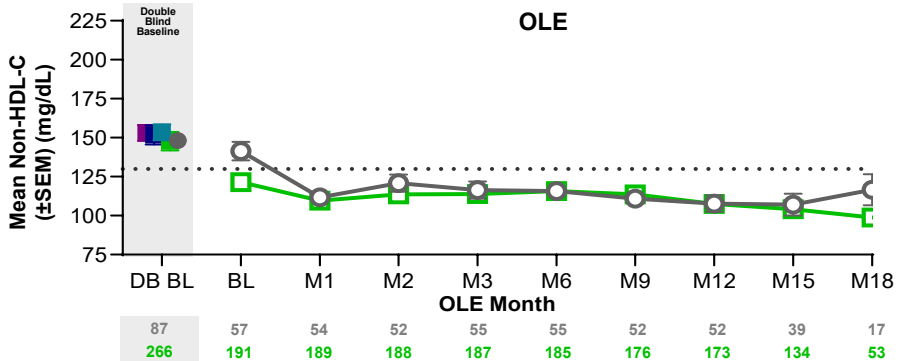
	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
	78	49	47	50	49	47	47	35	16	3
	242	173	173	171	170	160	159	126	51	13

SHASTA Non-HDL Cholesterol



	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
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



	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
	87	57	54	52	55	55	52	52	39	17
	266	191	189	188	187	185	176	173	134	53

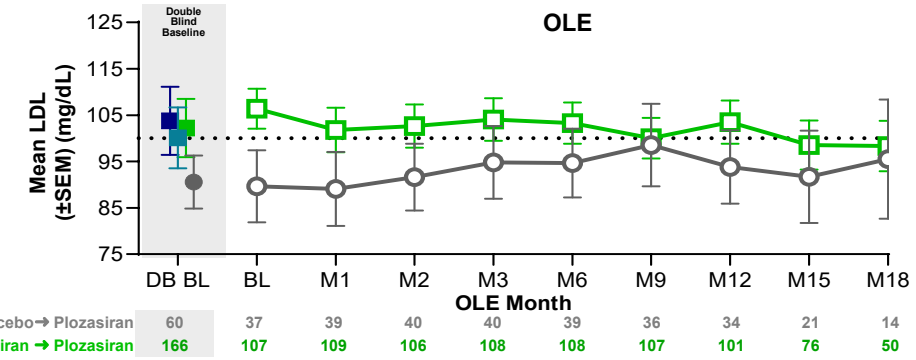
Double-blind Period
- Placebo
- Plozasiran 10 mg
- Plozasiran 25 mg
- Plozasiran 50 mg
- Plozasiran 50 mg Q24W

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.

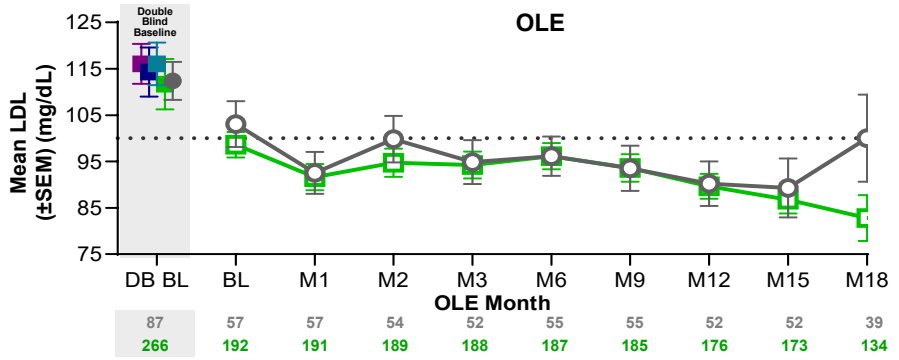
Favorable changes in ApoB with no adverse effects on LDL-C with plozasiran

SHASTA LDL Cholesterol*



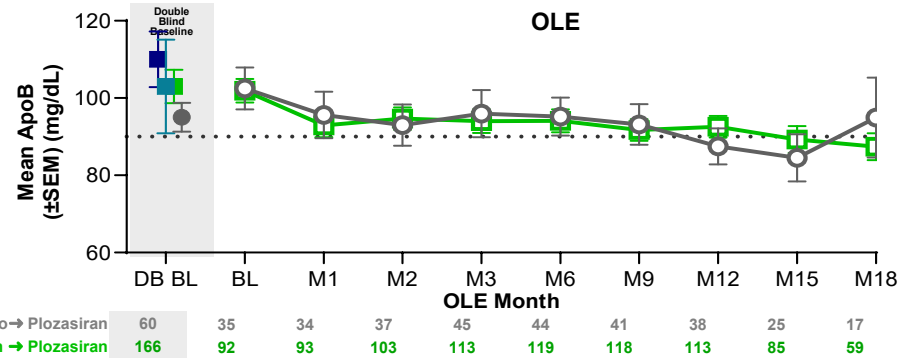
	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
Placebo→ Plozasiran	60	37	39	40	40	39	36	34	21	14
Plozasiran → Plozasiran	166	107	109	106	108	108	107	101	76	50

MUIR LDL Cholesterol*



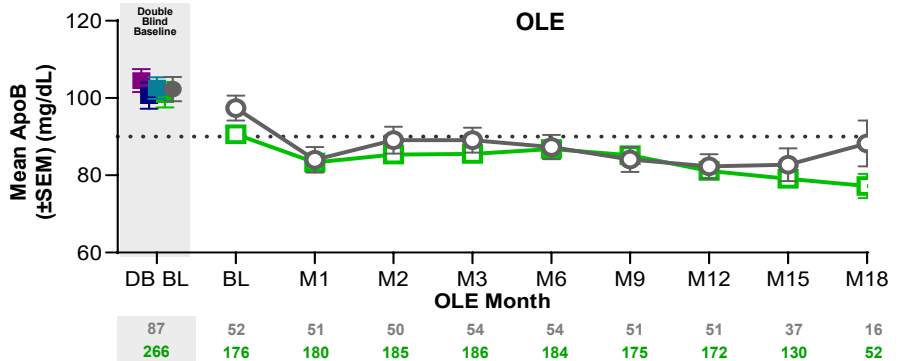
	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
	87	57	57	54	52	55	55	52	52	39
	266	192	191	189	188	187	185	176	173	134

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
	87	52	51	50	54	54	51	51	37	16
	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

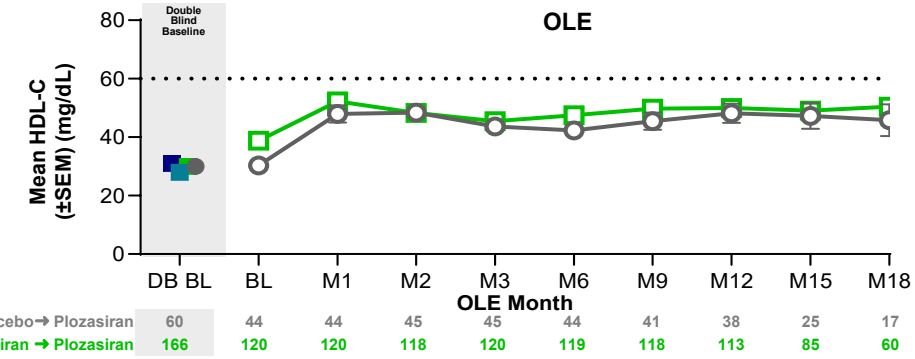
OLE Period

- 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.

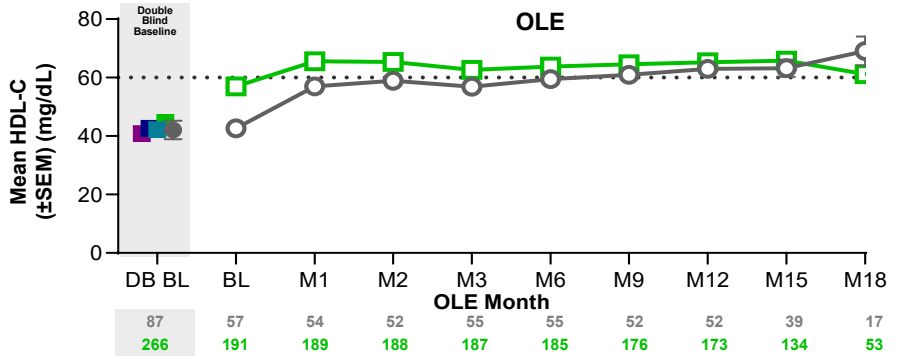
Favorable changes in HDL-C with no adverse effects on Lp(a) with plozasiran

SHASTA HDL Cholesterol



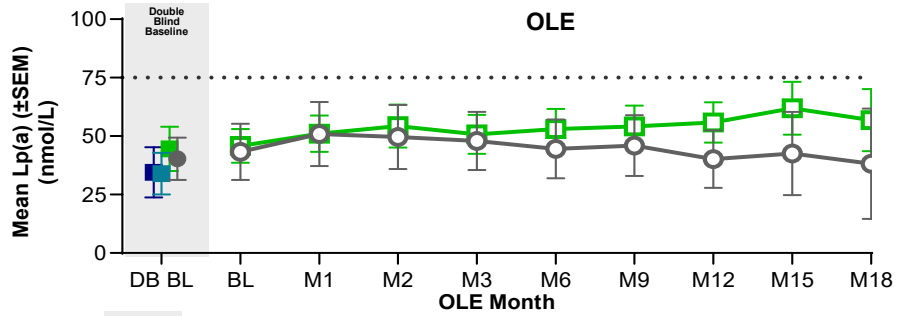
Placebo→ Plozasiran	60	44	44	45	45	44	41	38	25	17
Plozasiran → Plozasiran	166	120	120	118	120	119	118	113	85	60

MUIR HDL Cholesterol



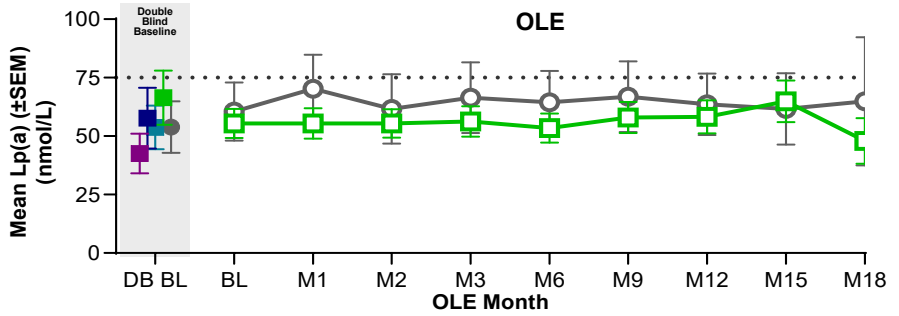
Placebo→ Plozasiran	87	57	54	52	55	55	52	52	39	17
Plozasiran → Plozasiran	266	191	189	188	187	185	176	173	134	53

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

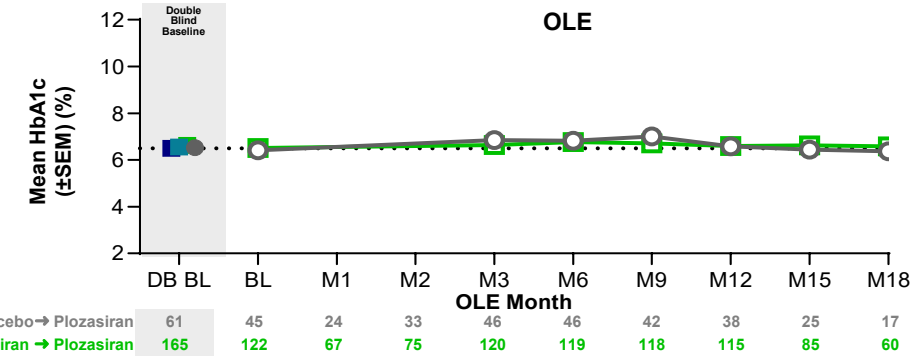
Double-blind Period
- Placebo
- Plozasiran 10 mg
- Plozasiran 25 mg
- Plozasiran 50 mg
- Plozasiran 50 mg Q24W

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.

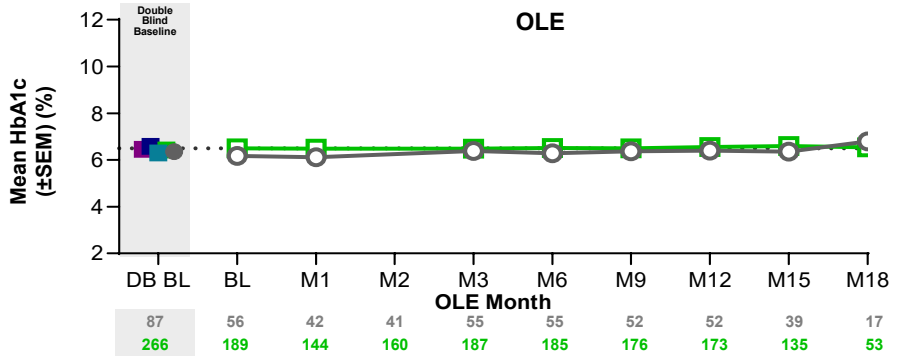
With selected clinical dose of 25 mg, no worsening insulin resistance or HbA1c, no new onset DM in OLE

SHASTA HbA1c



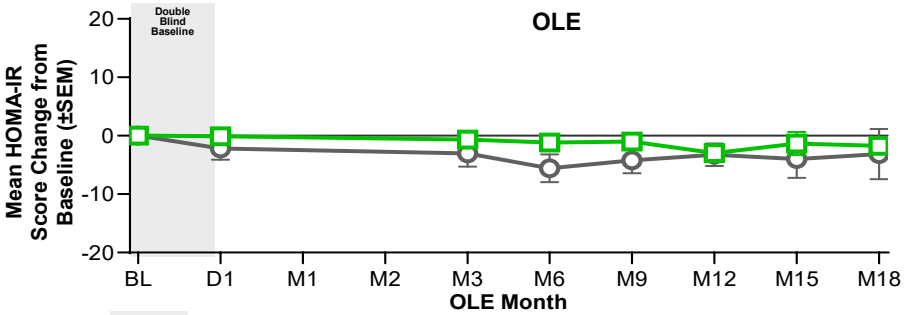
	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
Placebo→ Plozasiran	61	45	24	33	46	46	42	38	25	17
Plozasiran → Plozasiran	165	122	67	75	120	119	118	115	85	60

MUIR HbA1c



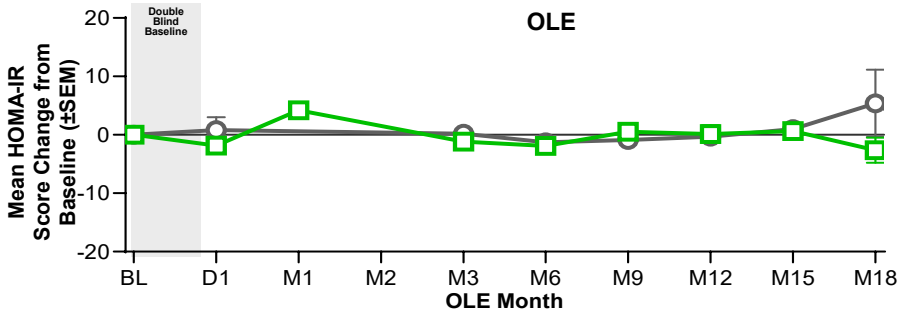
	DB BL	BL	M1	M2	M3	M6	M9	M12	M15	M18
	87	56	42	41	55	55	52	52	39	17
	266	189	144	160	187	185	176	173	135	53

SHASTA HOMA-IR



	BL	D1	M1	M2	M3	M6	M9	M12	M15	M18
Placebo→ Plozasiran	61	45			46	46	42	37	25	16
Plozasiran → Plozasiran	165	123			120	117	118	115	85	60

MUIR HOMA-IR



	BL	D1	M1	M2	M3	M6	M9	M12	M15	M18
	87	53			54	55	52	52	39	17
	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)

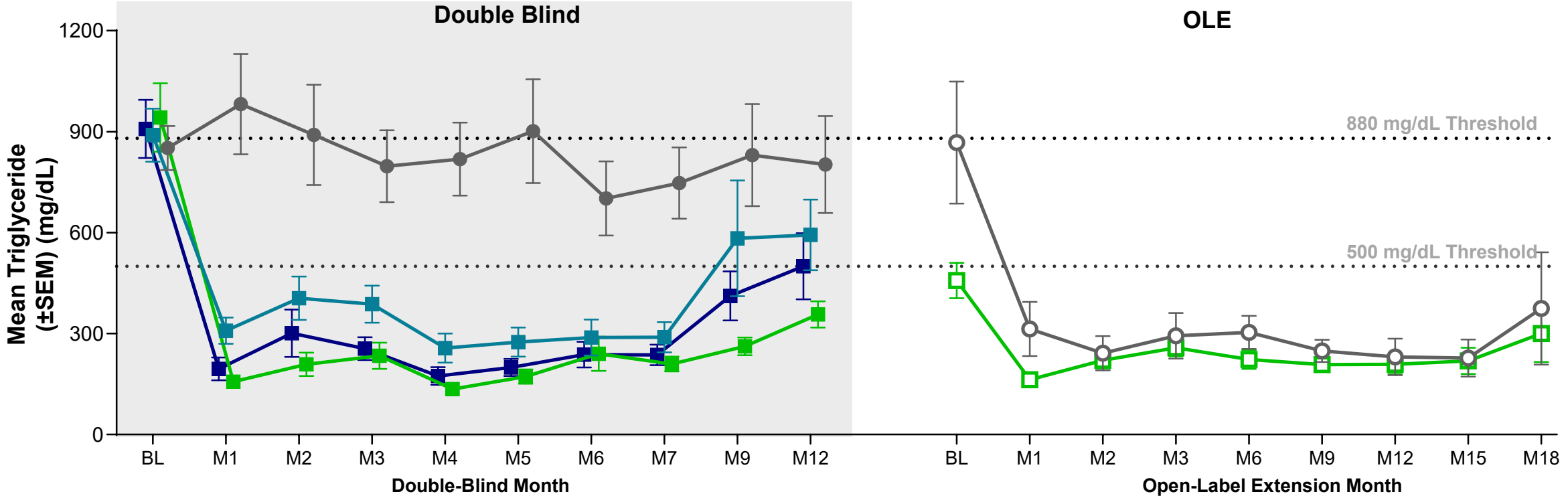
Clinical Data Cutoff 23 Sept 2024. *All serious TEAEs were not study drug related. **Deaths, not related to study drug**: sudden cardiac death and MODS. **Withdrawn, may be related to study drug:** 2 T1DM, 2 T2DM, 1 HbA1C increase and 1 rash (all were mild to moderate in severity). **Withdrawn, not related 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 q3m
- 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 OLE

Back-up slides

SHASTA Triglycerides



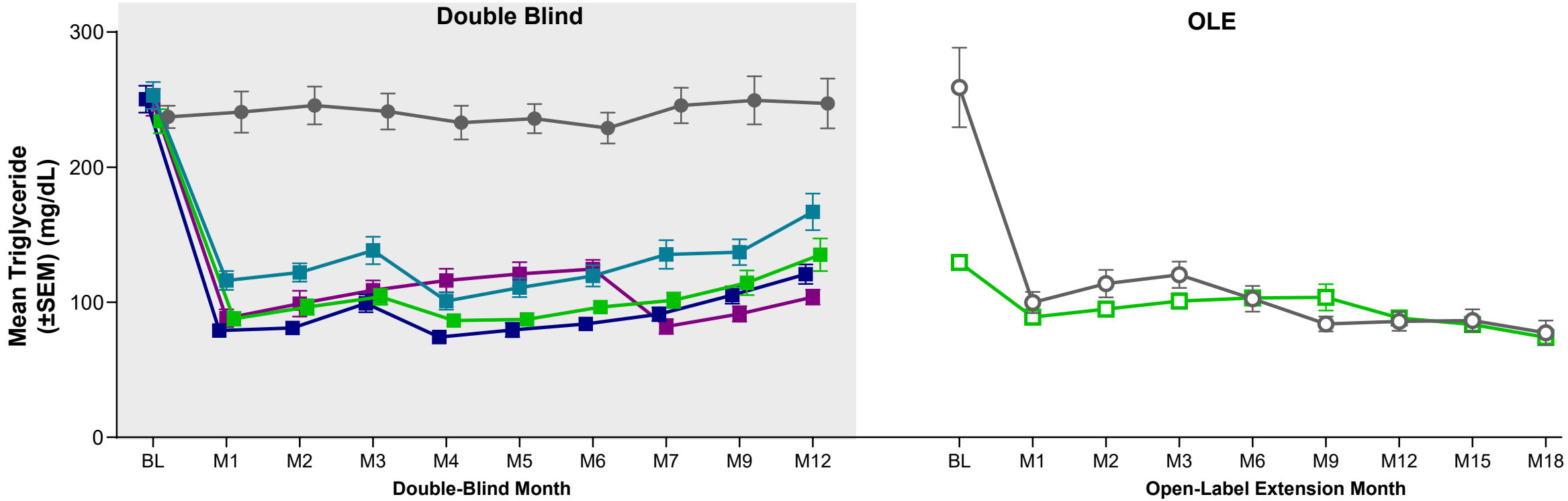
	BL	M1	M2	M3	M4	M5	M6	M7	M9	M12
Placebo	60	60	60	57	59	58	59	60	57	57
Plozasiran 10 mg	54	53	54	53	50	51	50	50	49	50
Plozasiran 25 mg	55	55	54	54	54	51	54	52	51	50
Plozasiran 50 mg	57	57	56	54	53	53	55	54	54	53

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

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

OLE Period: Placebo/ Plozasiran; Plozasiran/ Plozasiran

MUIR Triglycerides



	BL	M1	M2	M3	M4	M5	M6	M7	M9	M12
Placebo	87	85	83	80	77	82	81	82	80	78
Plozasiran 10 mg	67	62	64	63	63	59	61	61	61	60
Plozasiran 25 mg	67	67	66	61	63	61	63	64	63	64
Plozasiran 50 mg	66	63	64	64	63	61	62	62	60	61
Plozasiran 50 mg Q24W	66	63	64	61	65	63	61	61	61	61

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

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

OLE Period: Placebo/ Plozasiran; Plozasiran/ Plozasiran