Effect of Plozasiran Targeting APOC3 on Lipoprotein Particle Number and Size Measured by NMR in Patients with Hypertriglyceridemia

Poster #117

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INTRODUCTION

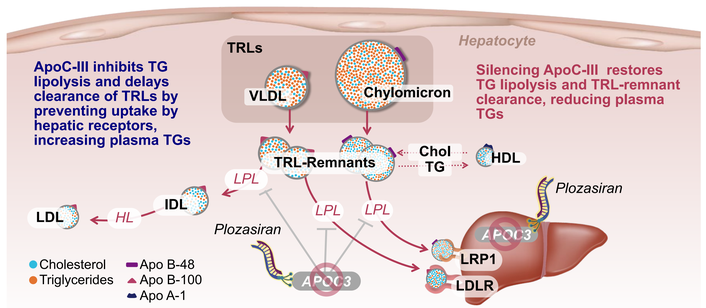
HTG Therapy Goal is to Sustainably Reduce TGs Below Pancreatitis Risk and Shift to Less Atherogenic Particles

- HTG and SHTG are characterized by TG levels >150 mg/dL and >500 mg/dL, respectively[1-3]
- HTG and SHTG significantly increase the risk of ASCVD and AP[1-6]
- AP risk is proportional to number, characteristics, and concentration of TRLs, particularly chylomicrons, and increases linearly as TGs rise[7]
- Despite potent LDL-C-lowering therapies, residual ASCVD risk is thought to persist due to high levels of atherogenic TRLs and limited treatment options exist to sustainably reduce TGs below the AP risk threshold[1-3,8-11]
- Plozasiran, an investigational siRNA targeting hepatic APOC3, deeply reduces TRLs[12,13]
- Impact of plozasiran on LP particle number and size distribution was unknown; but reductions in the number of TRL-P and a shift to possibly less atherogenic large LDL particles was expected

AP=acute pancreatitis; APOC3=apolipoprotein C3; ASCVD=atherosclerotic cardiovascular disease; HTG=hypertriglyceridemia; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; LP=lipoprotein; SHTG=severe hypertriglyceridemia; siRNA=small interfering ribonucleic acid; TG=triglyceride; TRL=triglyceride-rich lipoprotein; TRL-P=triglyceride-rich lipoprotein particle.

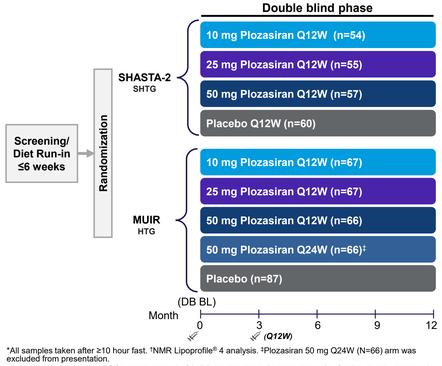
METHODS

Figure 1. Impact of Plozasiran on Triglycerides and Lipoprotein Metabolism



Apo A-1=apolipoprotein A-1; ApoB=apolipoprotein B; ApoC-III=apolipoprotein C3 gene; APOC3=apolipoprotein C3; Chol=cholesterol; HDL=high-density lipoproteins; HL=hepatic lipase; IDL=intermediate-density lipoprotein; LDL=low-density lipoprotein; LDLR=low-density lipoprotein receptor; LPL=lipoprotein lipase; LRP1=low-density lipoprotein receptor-related protein 1; TG=triglyceride; TRL=triglyceride-rich lipoprotein; VLDL=very low-density lipoprotein.

Figure 2. SHASTA-2 and MUIR: Double-blind, Phase 2b Placebo-Controlled, Dose Ranging Studies of Plozasiran in Subjects With Mixed Hyperlipidemia and SHTG[12,13]



*All samples taken after ≥10 hour fast. †NMR Lipoprofile® 4 analysis. ‡Plozasiran 50 mg Q24W (N=66) arm was excluded from presentation.

ApoB=apolipoprotein B; APOC3=apolipoprotein C3; DB=double-blind; BL=baseline; HDL-C=high-density lipoprotein cholesterol; HTG=hypertriglyceridemia; LDL-C=low-density lipoprotein cholesterol; LP=lipoprotein; NMR=nuclear magnetic resonance; PZN=plozasiran; Q12W=every 12 weeks; Q24W=every 24 weeks; SHTG=severe hypertriglyceridemia; TG=triglyceride.

Study Population:

SHTG fasting TG: 500–4000 mg/dL

Mixed Hyperlipidemia fasting TG 150–499 mg/dL and: Either LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL; Stable optimal statin therapy

Key Endpoints*: % change from baseline and over time in:

- **Primary endpoint:** TG
- **Key LP parameters:** APOC3, non-HDL-C, LDL-C, HDL-C, ApoB, Remnant Cholesterol
- **Safety**

Study Objectives: To determine the impact of plozasiran on LP particle concentration and subclass distribution using NMR† in two phase 2 studies

Data Analysis: Impact of PZN on LP particle concentration and size was measured by NMR in two phase 2 studies

403 patients from SHASTA-2 and MUIR who consented to additional analyses

RESULTS

Table 1. Baseline Characteristics[a]

	SHASTA-2		MUIR	
	Placebo pooled N=32	Active pooled N=99	Placebo pooled N=68	Active pooled N=204
Age, mean (SD), y	54 (10)	54 (10)	59 (10)	62 (11)
Male, n (%)	25 (78)	77 (78)	36 (53)	121 (59)
White, n (%)[b]	31 (97)	94 (95)	61 (90)	190 (93)
BMI, mean (SD)[c]	31 (4)	32 (5)	32 (5)	32 (6)
TG, mean (SD), mg/dL	686 (276)	723 (357)	235 (82)	252 (86)
TG, median (Q1, Q3), mg/dL	631 (532, 766)	613 (513, 805)	215 (176, 268)	230 (190, 307)
APOC3, mean (SD), mg/dL[d]	27 (11)	31 (13)	14 (5)	15 (6)
Non-HDL-C, mean (SD), mg/dL	163 (55)	177 (58)	144 (41)	149 (45)
ApoB, mean (SD), mg/dL	95 (25)	100 (30)	101 (29)	102 (25)
Remnant cholesterol UC, mean (SD), mg/dL[e]	92 (42)	103 (51)	44 (18)	48 (23)
LDL-C UC, mean (SD), mg/dL	71 (30)	74 (37)	97 (38)	101 (37)
HDL-C, mean (SD), mg/dL	31 (12)	30 (10)	42 (11)	42 (12)
Statins, n (%)	23 (72)	74 (75)	66 (97)	183 (90)
High-intensity statins, n (%)[f]	18 (56)	51 (52)	40 (59)	109 (53)
Fibrates, n (%)	16 (50)	47 (47)	13 (19.1)	23 (11.3)
Diabetes, n (%)[g]	19 (59)	69 (70)	41 (60)	127 (62)
10-year CHD risk >20%, n (%)	7 (22)	15 (15)	5 (7)	29 (14)

[a]Data are shown for the full analysis set, ie all randomized patients who received at least 1 dose of investigational product. [b]Other race not specified. [c]Calculated as weight in kilograms divided by height in meters squared. [d]Analysis that removed 2 participants from SHASTA and 3 participants from MUIR with baseline values below limits of quantitation (ad hoc). [e]Based on calculation: total cholesterol – HDL-C – LDL-C (UC). [f]High Intensity Statins=expected to lower LDL-C by ≥50% and consists of atorvastatin 40–80 mg or rosuvastatin 20–40 mg. [g]Participants were considered to have diabetes if they had a glycated hemoglobin level of 6.5% or higher or a fasting glucose level of 126 mg per deciliter or higher or if they had a medical history of diabetes or were receiving diabetic medications at baseline.

ApoB=apolipoprotein B; APOC3=apolipoprotein C3; BMI=body mass index; CHD=coronary heart disease; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; Q1, Q3=interquartile range; SD=standard deviation; TG=triglycerides; UC=ultracentrifugation.

Table 2. Lipid Results Summary, SHASTA-2 and MUIR[a]

Median (Q1, Q3) % Change from Baseline at Week 24

	SHASTA-2		MUIR	
	Placebo (pooled) N=32	Active (pooled) N=99	Placebo (pooled) N=68	Active (pooled) N=204
Triglycerides	-17.2 (-35.5, -2.2)	-76.6 (-84.6, -64.2)	-4.9 (-20.7, 6.8)	-58.6 (-69.4, -49.2)
APOC3[b]	3.7 (-28.0, 11.6)	-79.2 (-89.6, -67.4)	-7.1 (-22.7, 9.8)	-73.9 (-85.7, -58.5)
Non-HDL-C	6.9 (-12.8, 16.4)	-25.9 (-37.6, -6.5)	-2.8 (-15.1, 7.6)	-19.9 (-32.1, -5.6)
ApoB	10.7 (-3.3, 34.3)	-3.4 (-21.3, 10.1)	0.6 (-14.0, 9.3)	-11.6 (-25.5, -1.2)
Remnant cholesterol UC[c]	-4.9 (-24.7, 26.9)	-71.4 (-81.2, -56.1)	-12.4 (-31.9, 21.4)	-60.0 (-73.6, -42.5)
LDL-C UC	20.9 (0.0, 55.0)	27.9 (3.1, 59.4)	1.6 (-10.2, 20.2)	-3.1 (-16.3, 15.8)
HDL-C	3.3 (-7.6, 30.6)	50.0 (24.6, 77.3)	5.0 (-6.5, 15.4)	38.2 (19.4, 64.8)

[a]Data are shown for the NMR analysis set, ie all randomized patients who received at least 1 dose of investigational product and opted into this analysis. [b]Analysis that removed 2 participants from SHASTA and 3 participants from MUIR with baseline values below limits of quantitation (ad hoc). [c]Based on calculation: total cholesterol – HDL-C – LDL-C (UC).

ApoB=apolipoprotein B; APOC3=apolipoprotein C3; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; Q1, Q3=interquartile range; UC=ultracentrifugation.

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1. Pejic RN, et al. *J Am Board Fam Med.* 2006; 19:310-6. **2.** Grundy SM, et al. *J Am Coll Cardiol.* 2019; 73(24):e285-350. **3.** NCEP, ATPIII final report. NIH publication no.: 02–5215, 2002. **4.** Christian JB, et al. *Am J Cardiol.* 2011;107(6):891-897. **5.** Fan W, et al. *Cardiol Ther.* 2020;9(1):207-213. **6.** Okazaki H, *J Atheroscler Thromb.* 2021; 28(9): 883–904. **7.** Yang AL, et al. *Pancreatology.* 2020. 20(5): p. 795 800. **8.** Gugliucci A. *J Clin Med.* 2023;12:4399. **9.** Silverman MG, et al. *JAMA.* 2016;316(12):1289-1297. **10.** Langsted A, et al. *J Int Med.* 2020;288:116–127. **11.** Fu L, et al. *Diabetes Care.* 2022;45(9):2136-2143; **12.** Gaudet D, et al. *JAMA Cardiol.* 2024;9(7):620-630. **13.** Ballantyne CM, et al. *N Engl J Med.* 2024;391:899-912.

DISCLOSURES

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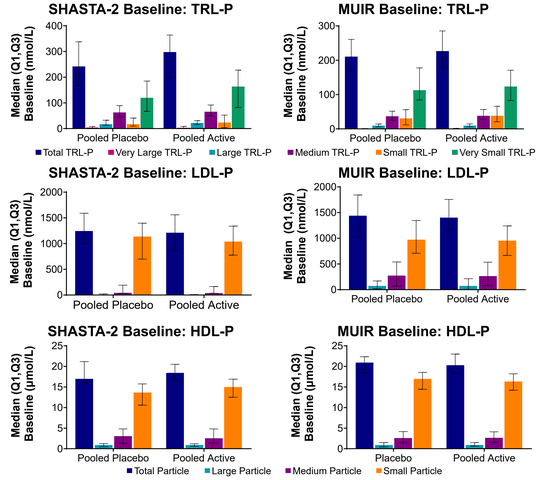
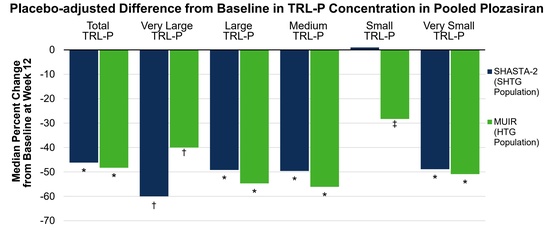
Figure 3. In SHASTA-2 and MUIR, There Was a Preponderance of Small or Very Small Lipoprotein Particles at Baseline



HDL-P=high density lipoprotein particle; LDL-P=low-density lipoprotein particle; TRL-P=triglyceride-rich lipoprotein particle.

Figure 4. In SHASTA-2 and MUIR, There Was a Reduction in Triglyceride Rich Lipoprotein Particles

Placebo-adjusted Difference from Baseline in TRL-P Concentration in Pooled Plozasiran

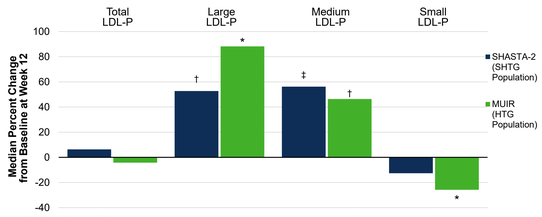


*$P \leq 0.0001$; †$P \leq 0.01$; ‡$P \leq 0.05$. Hodges-Lehmann method was used to estimate the median difference (location shift) for percent changes between plozasiran doses and placebo (pooled). P-values are from the Wilcoxon rank-sum test. Observed cases of the data are included. Baseline is the last observed value of the parameter collected on day-1 visit.

HTG=hypertriglyceridemia; SHTG=severe hypertriglyceridemia; TRL-P=triglyceride-rich lipoprotein particle.

Figure 5. While Total LDL-P Number was Unchanged, Larger LDL-P Levels Increased While Small LDL-Ps Decreased

Placebo-adjusted Difference from Baseline in LDL-P Concentration in Pooled Plozasiran



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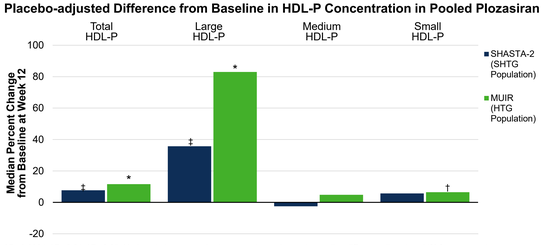
HTG=hypertriglyceridemia; LDL-P=low-density lipoprotein particle; SHTG=severe hypertriglyceridemia.

Figure 6. Total HDL-Ps Increased, Driven by an Increase in Large HDL-P

Placebo-adjusted Difference from Baseline in HDL-P Concentration in Pooled Plozasiran



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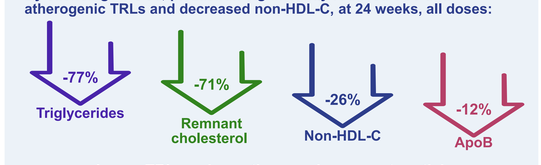
HDL-P=high-density lipoprotein particle; HTG=hypertriglyceridemia; SHTG=severe hypertriglyceridemia.

CONCLUSIONS

Plozasiran Demonstrated Potent and Durable Reductions of Atherogenic Lipoproteins in HTG Populations

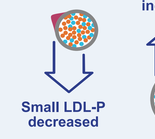
Reduction in TRLs

By silencing APOC3, plozasiran significantly reduced TGs and atherogenic TRLs and decreased non-HDL-C, at 24 weeks, all doses:



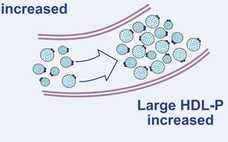
Lower TRLs reduce atherogenic remnant particles

Shift in LDL Particle Size



Larger LDL particles are potentially less atherogenic

Increase in HDL Particles



Higher HDL levels may improve cholesterol transport

- **Plozasiran had a favorable safety profile in these studies, with fewer severe AEs in the treatment groups than placebo[12,13]**
- **Plozasiran reduced APOC3 and showed potentially favorable quantitative and qualitative changes in LP particles evaluated by NMR in HTG patients**

Median % change from baseline.

AE=adverse event; ApoB=apolipoprotein B; APOC3=apolipoprotein C3; HDL=high-density lipoprotein; HDL-C=high-density lipoprotein cholesterol; HDL-P=high-density lipoprotein particle; HTG=hypertriglyceridemia; LDL=low-density lipoprotein; LDL-C=low-density lipoprotein cholesterol; LDL-P=low-density lipoprotein particle; LP=lipoprotein; NMR=nuclear magnetic resonance; TG=triglyceride; TRL=triglyceride-rich lipoprotein.

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