MUIR Study Results: ARO-APOC3, an Investigational RNAi Therapeutic, Silences Apolipoprotein C3, and Reduces Atherosclerosis Associated Lipoproteins in Patients with Mixed Dyslipidemia

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BACKGROUND

Triglyceride Rich Lipoproteins (TRL) are a Genetically Validated Target Associated With Increased Atherogenic CVD

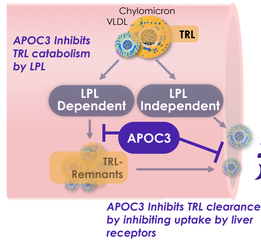
- Numerous epidemiologic studies have shown an association between higher TRL and an increased risk of ASCVD[1-2]
- A growing number of genome-wide association and Mendelian randomization studies support a causal role for TRL in ASCVD[3-7]
- Despite potent LDL-C-lowering therapies, residual ASCVD risk persists due to high levels of atherogenic TRL[8-11]

Plozasiran (ARO-APOC3) is an Investigational RNAi Therapeutic That Inhibits APOC3 Production and Thus Substantially Reduces TRL in Patients With Mixed Dyslipidemia

- Plozasiran is a highly specific, potent RNAi molecule with deep and durable gene silencing that requires infrequent dosing

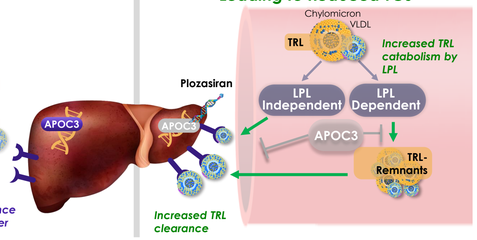
APOC3[13]

APOC3 Inhibits TRL Catabolism and Hepatic Clearance Leading to Increased TGs



Plozasiran

Silencing of APOC3 Enables TRL Catabolism and Hepatic Clearance Leading to Reduced TGs

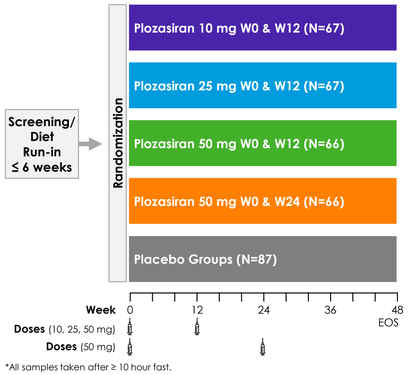


TRL-remnants are very atherogenic lipoproteins composed primarily of VLDL and IDL. It represents the amount of cholesterol in remnant lipoproteins.

METHODS

MUIR: A Double-Blind, Phase 2b Placebo-Controlled, Dose Ranging Study of Plozasiran (ARO-APOC3) in Subjects With Mixed Dyslipidemia

- Study Objectives: To evaluate safety and efficacy for lowering TG and atherogenic lipoproteins in subjects with Mixed Dyslipidemia, and to explore optimal dosing
- Data cutoff 24 Mar 2023



*All samples taken after ≥ 10 hour fast.

Study Population:

- Fasting TG between 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:

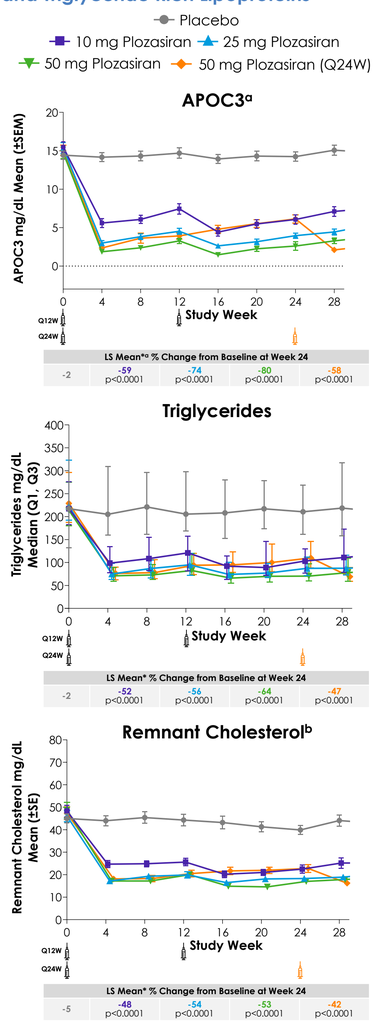
- Primary endpoint: TG
- Safety
- Key LP parameters: APOC3, non-HDL-C, LDL-C, HDL-C, APOB, VLDL-C

Data Analysis: Phase 2 study data evaluated when all subjects had reached Week 24 cutoff date of March 24, 2023

OLE: All subjects were eligible to enroll in the OLE at the end of the study

RESULTS

Figure 1. Plozasiran Demonstrates Substantial and Durable Decreases in APOC3 and Consequently in Triglycerides and Triglyceride Rich Lipoproteins



[a]Three subjects with BLOQ values at baseline were removed from the analysis; [b]based on calculation: remnant cholesterol = (total cholesterol) – (HDL-C) – (LDL-C, ultracentrifugation); *Statistical significance was determined using Mixed Model Repeat Measures (MMRM) analysis.

Table 1. Baseline Characteristics

	Pooled Placebo (N=87)	Plozasiran (W0 and W12) 10 mg (N=67)	25 mg (N=67)	50 mg (N=66)	Plozasiran (W0 & W24) 50 mg (N=66)
Mean (SD) age, years	58.9 (9.7)	60.2 (11.7)	61.3 (11.3)	62.6 (10.5)	61.3 (11.8)
Female, n (%)	41 (47.1)	31 (46.3)	30 (44.8)	29 (43.9)	23 (34.8)
White, n (%)	79 (90.8)	62 (92.5)	60 (89.6)	63 (95.5)	62 (93.9)
Mean (SD) BMI, kg/m²	31.2 (5.4)	30.5 (5.7)	32.4 (6.7)	32.6 (6.5)	32.0 (5.6)
Mean (SD) APOC3,[a] mg/L	14.6 (4.7)	15.5 (5.5)	15.6 (5.5)	15.0 (5.7)	15.0 (5.5)
Mean (SD) Remnant Cholesterol,[b] mg/dL	45.0 (18.9)	48.3 (20.5)	46.1 (20.3)	48.8 (27.2)	47.4 (23.1)
Median (Q1, Q3) Triglyceride, mg/dL	217.2 (182.7, 275.9)	222.9 (192.4, 323.1)	213.9 (180.2, 275.0)	228.9 (187.3, 296.4)	232.7 (182.1, 298.7)
Mean (SD) non-HDL-C, mg/dL	148.3 (43.4)	153.5 (42.0)	147.7 (48.4)	151.8 (49.3)	153.0 (42.7)
Mean (SD) ApoB, mg/dL	102.7 (29.5)	102.8 (23.3)	101.4 (23.3)	99.5 (26.1)	104.4 (24.3)
Mean (SD) HDL-C, mg/dL	42.1 (11.1)	42.2 (11.1)	44.7 (13.6)	42.7 (11.7)	40.8 (12.6)
Mean (SD) LDL-C (UC), mg/dL	101.6 (38.7)	105.1 (37.0)	101.6 (43.4)	103.0 (39.7)	105.6 (31.8)

[a]Analysis that removed n=3 participants with baseline values of BLOQ (ad hoc); [b]Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C, ultracentrifugation).

Table 2. Plozasiran Affects Multiple Lipid Parameters Demonstrating Robust Decreases in Atherogenic Lipoproteins and Increases in HDL-C

Percent Change From Baseline in Serum Lipid and Lipoprotein Concentrations at Week 24	Pooled Placebo (N=87)	Plozasiran (W0 and W12) 10 mg (n=67)	25 mg (n=67)	50 mg (n=66)	Plozasiran (W0 & W24) 50 mg (N=66)
LDL-C (Ultracentrifugation)					
Baseline mean, mg/dL (SD)	102 (39)	105 (37)	102 (43)	103 (40)	106 (32)
LS mean (SE) % change at Week 24	3 (3)	-1 (4)	0.5 (4)	-10 (4)*	6 (4)
Non-HDL-C					
Baseline mean, mg/dL (SD)	148 (43)	154 (42)	148 (48)	152 (49)	153 (43)
LS mean (SE) % change at Week 24	-3 (3)	-19 (3)**	-20 (3)**	-27 (3)**	-10 (3)*
ApoB					
Baseline mean, mg/dL (SD)	103 (30)	103 (23)	101 (27)	100 (26)	104 (24)
LS mean (SE) % change at Week 24	2 (3)	-9 (3)*	-11 (3)*	-19 (3)**	-5 (3)
HDL-C					
Baseline mean, mg/dL (SD)	42 (11)	42 (11)	45 (14)	43 (12)	41 (13)
LS mean (SE) % change at Week 24	5 (3)	38 (4)**	47 (4)**	51 (4)**	33 (4)**

*P<0.05; **P<0.0001. Statistical significance was determined using Mixed Model Repeat Measures (MMRM) analysis.

Table 3. Summary of Adverse Events

	Pooled Placebo (N=87)	Plozasiran (W0 and W12) 10 mg (N=67)	25 mg (N=67)	50 mg (N=66)	Plozasiran (W0 & W24) 50 mg (N=66)
Treatment-emergent adverse events (TEAEs)	52 (59.8)	42 (62.7)	45 (67.2)	47 (71.2)	48 (72.7)
TEAEs occurring in ≥ 5 subjects					
Covid 19	10 (11.5)	6 (9.0)	8 (11.9)	7 (10.6)	5 (7.6)
Worsening glycemic control*	7 (8.0)	7 (10.4)	5 (7.5)	12 (18.2)	14 (21.2)
Upper respiratory tract infection	7 (8.0)	3 (4.5)	5 (7.5)	1 (1.5)	8 (12.1)
Urinary tract infection	5 (5.7)	2 (3.0)	4 (6.0)	4 (6.1)	0
Headache	3 (3.4)	1 (1.5)	2 (3.0)	4 (6.1)	5 (7.6)
Bronchitis	0	4 (6.0)	1 (1.5)	2 (3.0)	5 (7.6)
Treatment-related adverse events	9 (10.3)	7 (10.4)	8 (11.9)	11 (16.7)	8 (12.1)
Serious TEAEs	3 (3.4)	1 (1.5)	5 (7.5)	7 (10.6)	4 (6.1)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	2 (2.3)	0	0	1 (1.5)	0
Deaths	0	0	1 (1.5)	2 (3.0)	1 (1.5)

*Worsening glycemic control defined by multiple glycemic control parameters including but not limited to hemoglobin A1c, new onset diabetes mellitus, type 2 diabetes mellitus, diabetes mellitus, hyperglycemia, insulin resistance.

- TEAEs reported to date reflect comorbidities and underlying conditions of the study population
- Most serious TEAEs recovered with no sequelae
- Data includes exposure out to 48 weeks

CONCLUSIONS

Plozasiran Demonstrates Potent and Durable Reductions of Atherogenic Lipoproteins in Mixed Dyslipidemia

- By silencing APOC3, plozasiran significantly reduced TGs and atherogenic triglyceride rich lipoproteins, across all dose levels at Week 24 in subjects with mixed dyslipidemia
  - APOC3 ↓ to -80%
  - TG ↓ to -64%
  - Remnant Cholesterol ↓ to -54%
  - ApoB ↓ to -19%
  - Non-HDL-C ↓ to -27%
  - HDL-C ↑ up to +51%
- Plozasiran has a favorable safety profile to date
- Plozasiran is the first RNAi investigational molecule that has demonstrated substantial reductions in triglyceride rich lipoproteins in this mixed dyslipidemia population
- Plozasiran is a promising potential treatment for subjects with increased risk for ASCVD due to elevated triglyceride rich lipoproteins and these data support further development of plozasiran in Phase 3 programs including a clinical outcomes trial

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ABBREVIATIONS

ApoB, apolipoprotein B; **APOC3**, apolipoprotein C3; **ASCVD**, atherosclerotic cardiovascular disease; **BLOQ**, below the limit of quantification; **BMI**, body mass index; **CHD**, coronary heart disease; **EOS**, end of study; **HDL-C**, high density lipoprotein cholesterol; **IDL**, intermediate-density lipoprotein; **LDL-C**, low density lipoprotein cholesterol; **LP**, lipoprotein; **LPL**, lipoprotein lipase; **LS**, least squares; **MD**, mixed dyslipidemia; **N**, number; **n**, number; **OLE**, open label extension; **Q**, quartile, **Q12W**, two doses given on day 1 and week 12; **Q24W**, Two doses given on day 1 and Week 24; **RNAi**, ribonucleic acid interference; **SAE**, severe adverse events; **SD**, standard deviation; **SE**, standard error; **SEM**, standard error of the mean; **SHTG**, severe hypertriglyceridemia; **TEAEs**, treatment emergent adverse events; **TG**, triglycerides; **TRL**, triglyceride rich lipoproteins; **UC**, ultracentrifuge; **VLDL**, very low density lipoprotein; **W**, week