Plozasiran (ARO-APOC3), an Investigational RNAi Therapeutic, Demonstrates Profound and Durable Reductions in APOC-3 and Triglycerides (TG) in Patients With Severe Hypertriglyceridemia (SHTG), SHASTA-2 Final Results

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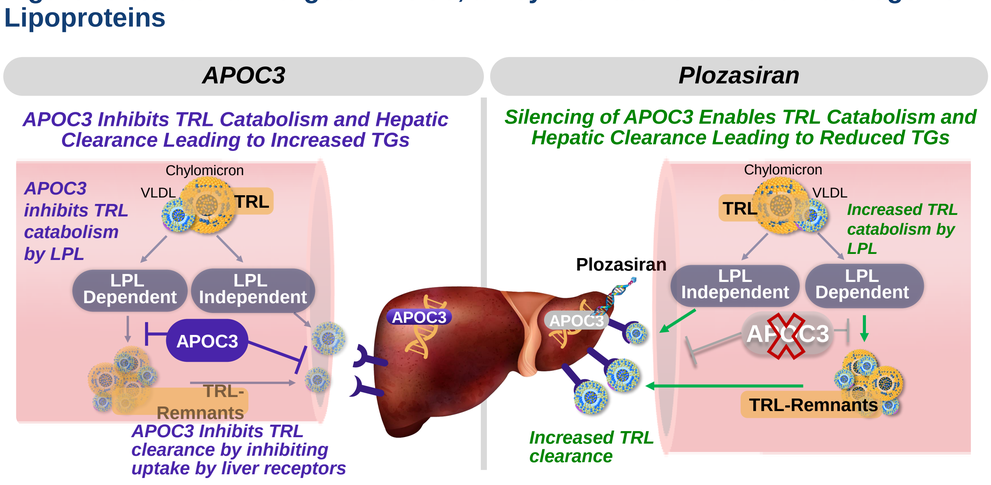
BACKGROUND

- Severe hypertriglyceridemia (SHTG) is characterized by triglyceride (TG) levels > 500 mg/dL[1-3]
  - Very severe forms (TG> 880 mg/dL) include familial and multifactorial chylomicronemia syndrome (FCS and MCS)[4-6]
  - FCS (2-9 cases per million) is a rare recessive condition caused by bi-allelic or digenic pathogenic variants in the lipoprotein lipase (LPL) pathway
  - MCS is far more frequent (1/600) and is usually multifactorial
- Individuals with SHTG have an increased acute pancreatitis (AP) risk[1-3,6]
- Current treatments fail to lower TGs below a threshold that exposes patients to the risk of AP[1-3]
- Plozasiran is a highly specific, potent RNAi molecule with deep and durable gene silencing that requires infrequent dosing.
- Plozasiran, a hepatocyte-targeted RNAi that reduces circulating TGs by reducing APOC3, a key regulator of TG metabolism (**Figure 1**)

Figure 1. Plozasiran Targets APOC3, a Key Mediator of TG and Atherogenic Lipoproteins



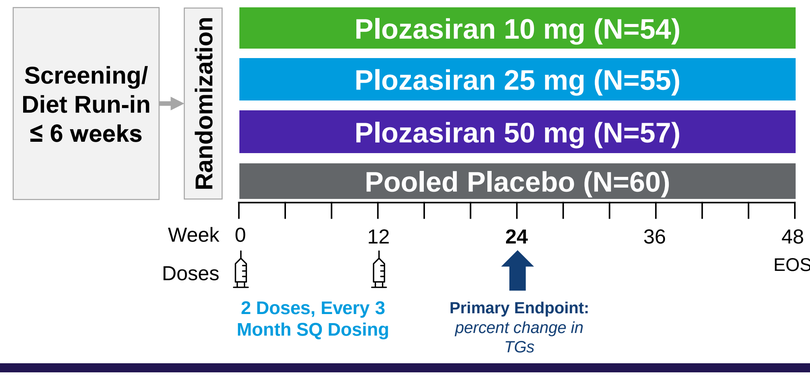
OBJECTIVES

- The objectives of this study were to evaluate safety and efficacy for lowering TG and atherogenic lipoproteins below pancreatitis risk threshold, thereby lowering severity/occurrences of AP in patients with SHTG, and to explore optimal dosing

METHODS

- SHASTA-2, a randomized, placebo-controlled, Phase 2b study (NCT04720534) evaluated efficacy and safety of plozasiran in patients with SHTG and in the open label extension period
- Eligible patients (n=229) randomized 3:1, received a total of 2 doses (SQ 10, 25, or 50 mg plozasiran) or matched placebo on Day 1 and at Week 12 and followed through Wk48 (**Figure 2**)
- The primary endpoint was percent change from baseline in fasting TGs at Week 24
- Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling.

Figure 2. Study Schema



RESULTS

- Plozasiran produced LS mean % change from baseline reductions in APOC3 to -78% and TGs to -74%, at Wk 24 representing trough effect with quarterly dosing (p<0.0001)
- % change from baseline reductions in APOC3 and TGs were –48% and –58%, respectively at Wk48 (p <0.0001)
- The majority (>90%) of patients achieved TGs <500 mg/dL by Wk24 and 78% persisted through Wk48
- Durable reductions in other lipoprotein parameters (remnant cholesterol, non-HDL-C, ApoB) were also observed through Wk48
- All patients transitioned to 25 mg in the OLE and achieved similar reductions in APOC3 and Triglycerides as in the double-blind period
- There were no deaths
- All serious TEAEs were deemed not related to plozasiran and resolved without sequelae (except 2 patients with malignancies)
- Data includes exposure out to 48 weeks in the double-blind period and out to 15 months in the open label extension period
- All patients who enrolled in OLE are receiving 25 mg plozasiran

Table 1. Baseline Characteristics

	Pooled Placebo (N=61)	Plozasiran 10 mg (N=54)	Plozasiran 25 mg (N=55)	Plozasiran 50 mg (N=56)
Mean (SD) age, years	56 (11)	53 (10)	56 (11)	54 (11)
Female, n (%)	14 (23)	8 (15)	12 (22)	16 (28)
White, n (%)	55 (92)	47 (87)	48 (87)	53 (93)
Mean (SD) BMI, kg/m²	31 (4)	33 (5)	32 (5)	32 (5)
Mean (SD) APOC3,[a] mg/dL	31 (16)	33 (15)	34 (17)	32 (16)
Median (Q1, Q3) triglyceride, mg/dL	679 (540, 929)	696 (559, 1088)	598 (517, 982)	663 (531, 1028)
Mean (SD) Triglyceride, mg/dL	851 (507)	890 (577)	942 (756)	908 (653)
Mean (SD) non-HDL-C, mg/dL	185 (79)	209 (74)	206 (91)	196 (88)
Mean (SD) ApoB, mg/dL	95 (29)	103 (44)	103 (32)	110 (55)
Mean (SD) remnant cholesterol,[b] mg/dL	115 (82)	134 (88)	132 (98)	124 (92)
Mean (SD) LDL-C, UC, mg/dL	69 (39)	75 (44)	74 (40)	72 (42)
Mean (SD) HDL-C, mg/dL	30 (12)	28 (9)	30 (11)	31 (13)

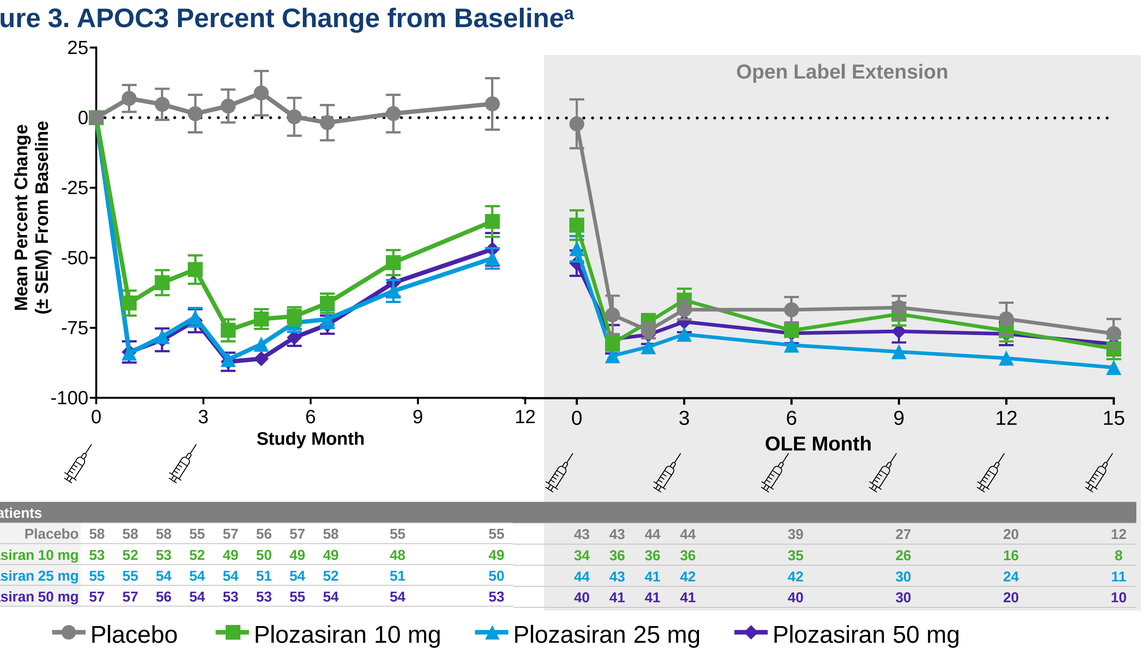
[a]Analysis removed 2 participants with baseline values BLOQ (ad hoc); [b]Based on calculation: Total cholesterol – HDL-C – LDL-C (UC). Data are shown for the full analysis set of 226, ie all randomized patients who received at least 1 dose of plozasiran.

Table 2. Summary of Adverse Events at 48 Weeks

	Pooled Placebo (N=61)	Plozasiran 10 mg (N=54)	Plozasiran 25 mg (N=55)	Plozasiran 50 mg (N=56)
TEAEs	43 (71)	43 (80)	36 (66)	49 (88)
TEAEs occurring in ≥ 5 patients				
COVID-19	10 (16.7)	10 (18.5)	8 (14.5)	8 (14.0)
Worsening glycemic control*	7 (11.7)	12 (22.2)	9 (16.4)	11 (19.6)
Diarrhea	5 (8.3)	3 (5.6)	1 (1.8)	1 (1.8)
Urinary tract infection	5 (8.3)	3 (5.6)	1 (1.8)	2 (3.5)
Headache	3 (5.0)	8 (14.8)	5 (9.1)	2 (3.5)
Serious TEAEs	10 (16.4)	4 (7.4)	2 (3.6)	7 (12.5)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0	1 (1.9)	0	0
Local Injection Site Reactions	0	0	0	1 (2)[a]
Acute pancreatitis, adjudicated cases, No. (%)	2 (3)	0 (0)	0 (0)	1 (2)[b]
Death	0	0	0	0

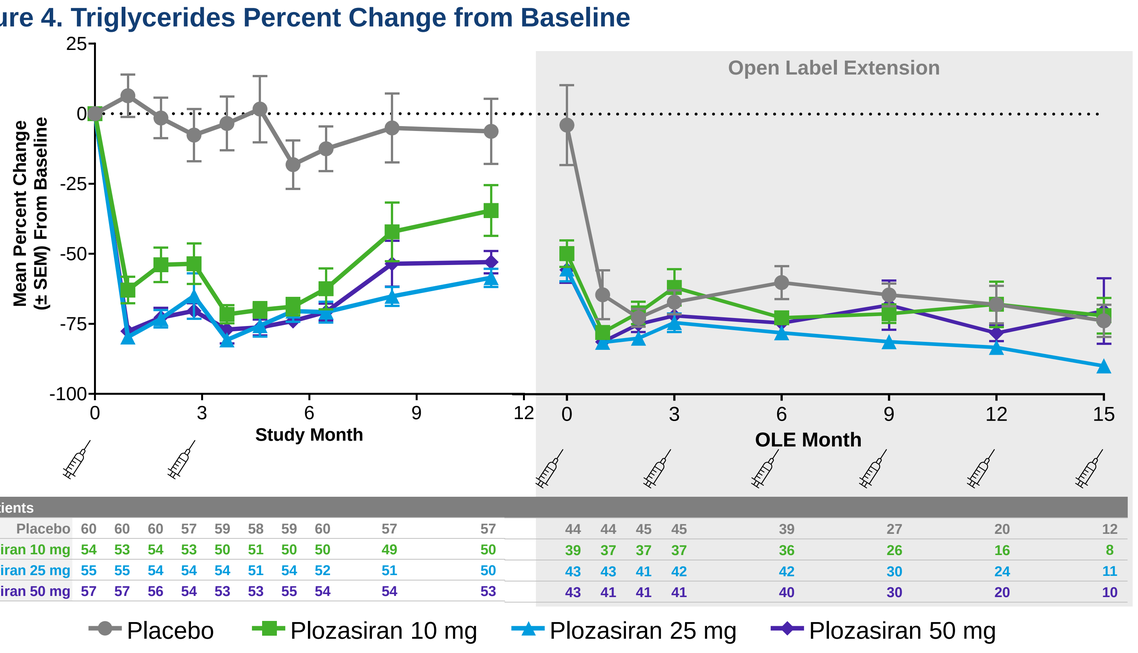
*Worsening glycemic control defined by multiple glycemic control parameters including but not limited to hemoglobic A1c, new onset diabetes mellitus, type 2 diabetes mellitus, diabetes mellitus, hyperglycemia, insulin resistance. n (%); Worsening glycemic control was only observed in patients with uncontrolled diabetes at baseline. [a]local injection site reactions only include events that start on the day of injection and persist for at least 48 hours post injection. [b]The event in the patient assigned to the 50-mg plozasiran cohort occurred during the safety observation period, at which time the patient's triglyceride levels had returned to baseline level of greater than 2000 mg/dL from an on-treatment nadir of 106 mg/dL.

Figure 3. APOC3 Percent Change from Baseline[a]



[a]Analysis removed 2 participants with baseline values below limits of quantitation, BLOQ (ad hoc).

Figure 4. Triglycerides Percent Change from Baseline



CONCLUSIONS

- **In patients with SHTG, plozasiran decreased LS mean % change from baseline APOC3, TGs, and remnant cholesterol while increasing HDL-C at 24 weeks (persisting at 48 weeks) for all dose levels:**
  - **APOC3 ↓ to -78%, (-48%)**
  - **TG ↓ to -74%, (-58%)**
  - **Remnant cholesterol ↓ to -62%, (-45%)**
  - **HDL-C ↑ up to +68%, (+38%)**
- **Half of patients reached TG values below 150 mg/dL at 24 weeks, thereby normalizing their fasting triglycerides**
- **>90% of patients treated with plozasiran achieved TGs < 500 mg/dL at Week 24, below the risk threshold for Acute Pancreatitis**
- **Plozasiran was well tolerated with a favorable safety profile in this study**
- **Consistency of PD effect with minimal interpatient variability was seen in all patients in the open label extension**
- **Based on these results, RNAi-mediated silencing of hepatic APOC3 expression via plozasiran is a promising potential treatment for patients with SHTG and a phase 3 program in SHTG is currently underway (ClinicalTrials.gov: NCT06347003, NCT06347016, NCT06347133)**

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