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SHASTA-2 Final Study Results

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

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on behalf of the SHASTA-2 Study Team

Financial Disclosures

Presenter

D Gaudet reports grants and/or honoraria from Alnylam, Amgen, Arrowhead, AstraZeneca, Boehringer-Ingelheim, CRISPR Therapeutics, Dalcor Pharma, Eli Lilly, Esperion, Ionis, Kowa, Novartis, Pfizer, Regeneron, Sanofi, Ultragenyx and Verve Therapeutics.

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- **D Pall** reports grants and/or honoraria from (all paid to institution, not individual) Arrowhead Pharmaceuticals Inc., AstraZeneca, Boehringer Ingelheim, Eli Lilly, Esperion, Ionis, Kowa, Novartis, NovoNordisk, Pfizer.
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- **J Hellawell,** is a current employee of Arrowhead Pharmaceuticals
- **J San Martin and K. Modesto** were former employees of Arrowhead Pharmaceuticals

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SHTG Therapy Goal is to Sustainably Reduce TGs Below Pancreatitis Risk

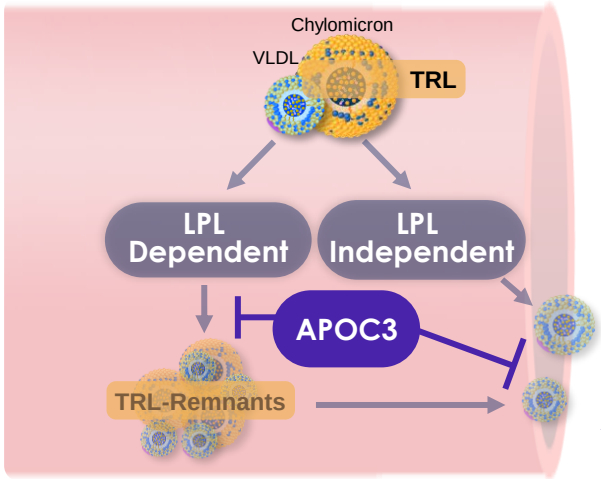
- Severe hypertriglyceridemia (SHTG) is characterized by TG levels > 500 mg/dL[1-3]
- Very severe forms (TG> 880 mg/dl = chylomicronemia) include **FCS** and **MCS**[4-6]
  - **FCS** (2-9 cases per million) is a rare recessive condition caused by bi-allelic or digenic pathogenic variants in the lipoprotein lipase (LPL) pathway;
  - **MCS** is far more frequent (1/600) and is usually multifactorial;
- SHTG significantly increases the risk of ASCVD and acute pancreatitis (AP), often with recurrent attacks requiring repeat hospital admissions and worsening outcomes[1-3,6]
- AP risk is proportional to number, characteristics, and concentration of triglyceride rich lipoproteins (TRLs), particularly chylomicrons, and increases linearly as TGs rise[7]
- Limited treatment options exist to sustainably reduce TGs below pancreatitis risk threshold [1-3]

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, A.L. et al., Pancreatology, 2020. 20(5): p. 795 800.

In this Phase 2 Study, Plozasiran (ARO-APOC3) Reduces APOC3, A Key Mediator of Elevated TG, Chylomicronemia and Atherogenic Lipoproteins

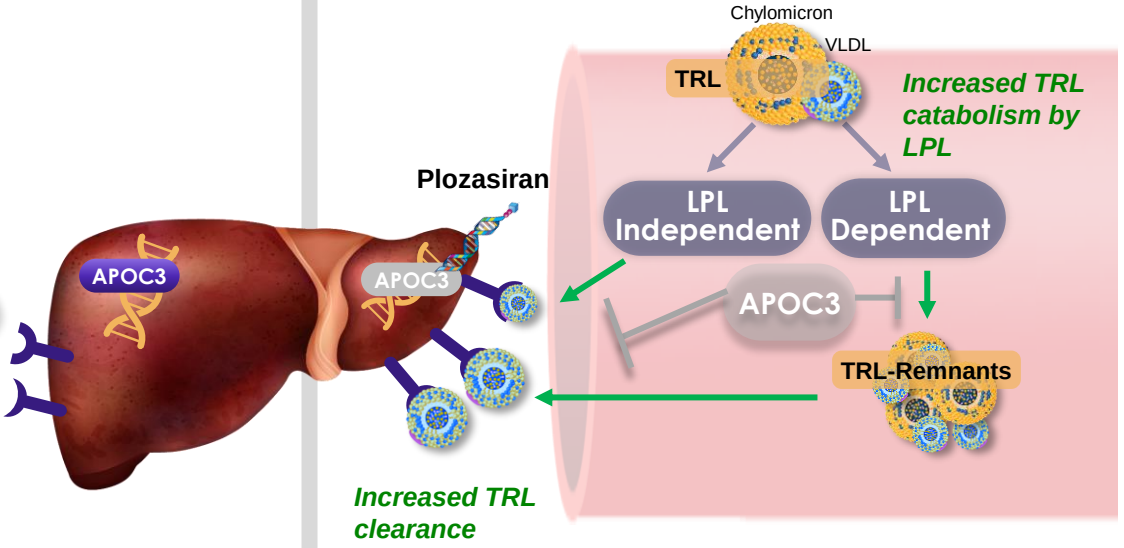
APOC3[1]

APOC3 Inhibits TRL Catabolism and Hepatic Clearance Leading to Increased TGs



Plozasiran

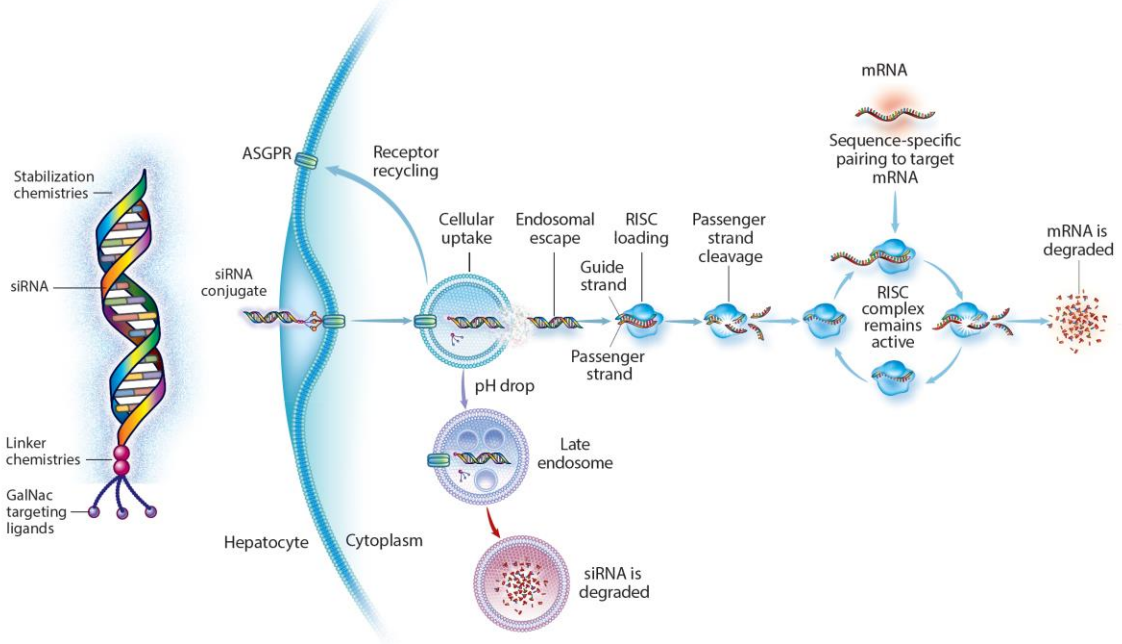
Silencing of APOC3 Enables TRL Catabolism and Hepatic Clearance Leading to Reduced TGs



1. Van Zwol W et al. *J Clin Med*. 2019; 8:1085. Chylomicrons are large triglyceride rich lipoproteins produced in enterocytes from dietary lipids. Remnant cholesterol is a very atherogenic lipoprotein composed primarily of very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL). It represents the amount of cholesterol in remnant lipoproteins.

Key Features Of Using RNAi As A Therapeutic Modality

- Arrowhead's Targeted RNAi Molecule (TRiM™) technology leverages the RNAi mechanism
- RNAi is a natural process that uses short fragments of RNA molecules to interfere with mRNA translation into associated proteins.



High Specificity:
Allowing to suppress the expression of a specific gene

Potent Activity:
Deep and consistent silencing of target genes

Safety:
Minimal off target adverse effects due to targeted delivery (GalNAc) and sequence specificity

Infrequent Dosing:
Long tissue PK/PD, on target effect

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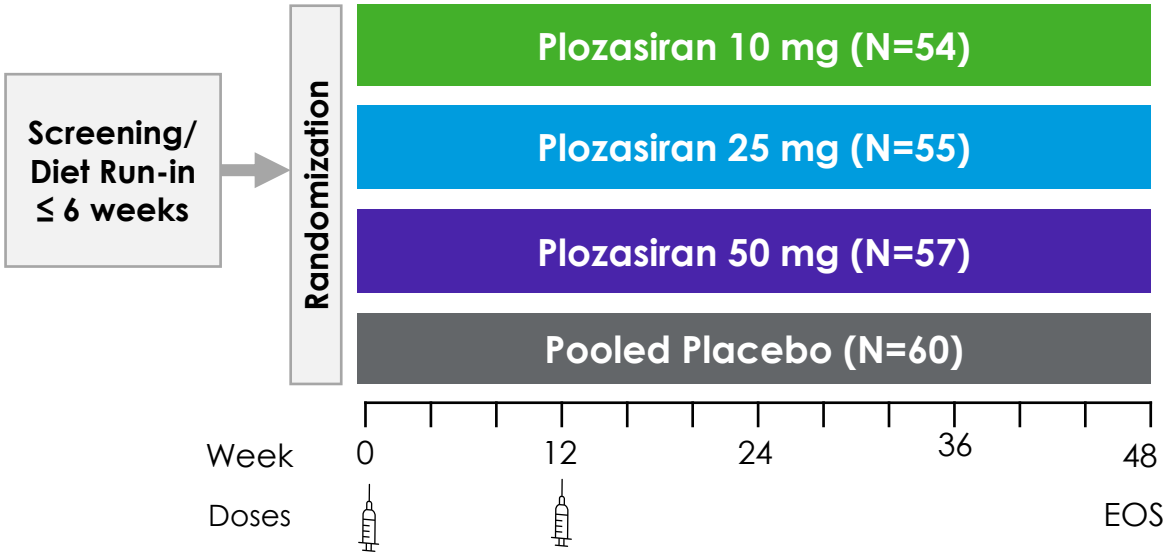
SHASTA-2: A Double-blind, Phase 2b Placebo-Controlled, Dose Ranging Study Of Plozasiran In Subjects With SHTG

- **Study Objectives:** To evaluate safety and efficacy for lowering TG and atherogenic lipoproteins and severity/occurrences of AP in subjects with SHTG, and to explore optimal dosing



Study Population: SHTG history of TG ≥ 500 mg/dL and fasting TG of 500 – 4,000 mg/dL during screening period

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**

Data Analysis: Phase 2 study data evaluated at Week 24 and Week 48

All subjects were eligible to enroll in an Open Label Extension (OLE) at end of the study.

SHASTA-2. *All samples taken after ≥ 10 hour fast.

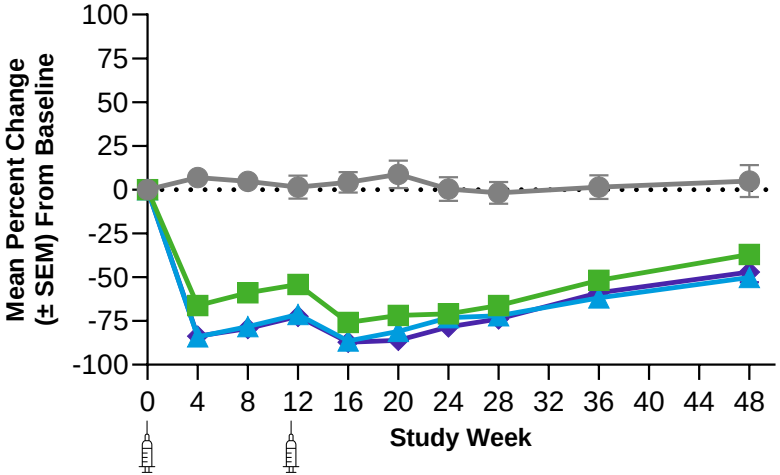
Baseline Characteristics

	Pooled Placebo (N=60)	Plozasiran 10 mg (N=54)	Plozasiran 25 mg (N=55)	Plozasiran 50 mg (N=57)
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 that removed n=2 participants with baseline values of 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 investigational product.

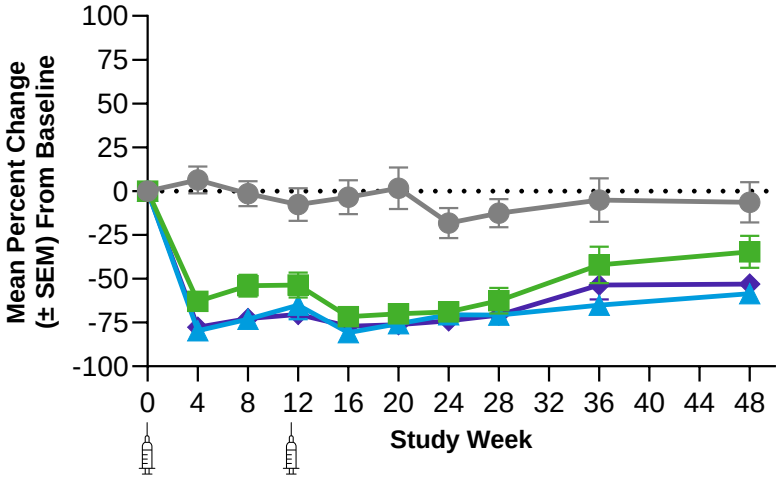
Plozasiran Demonstrates Significant Decreases in APOC3 and Contributes to Restoration of Triglyceride Homeostasis

APOC3[a]



LS Mean*[a] % Change from Baseline at Week 24 & 48				
Week 24	-1%	-69% p<0.0001	-72% p<0.0001	-78% p<0.0001
Week 48	4%	-34% p<0.0001	-48% p<0.0001	-47% p<0.0001

Triglycerides



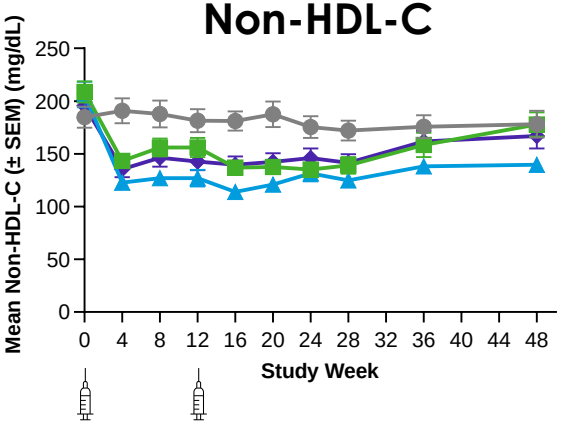
LS Mean* % Change from Baseline at Week 24 & 48				
Week 24	-17%	-66% p<0.0001	-70% p<0.0001	-74% p<0.0001
Week 48	-7%	-31% p<0.05	-58% p<0.0001	-53% p<0.0001

Placebo | Plozasiran 10 mg | Plozasiran 25 mg | Plozasiran 50 mg

[a]Analysis that removed n=2 participants with baseline values of BLOQ (ad hoc). *Statistical significance was determined using Mixed Model Repeat Measures (MMRM) analysis. Nadir achieved at 16 weeks where Placebo corrected LSM of 77% difference achieved, i.e. 135 mg/dL from 942 mean baseline

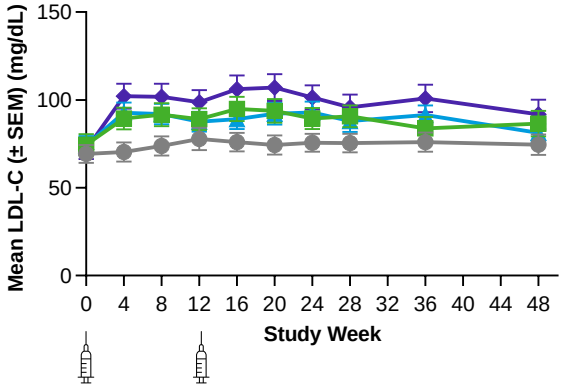
Plozasiran Impact on Additional Lipid Parameters

Non-HDL-C



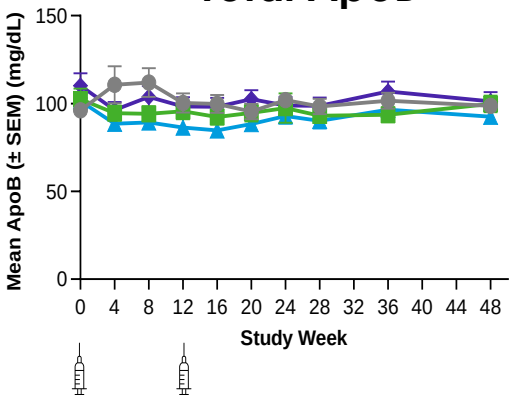
LS Mean* % Change from Baseline at Week 24 & 48				
Week 24	-2%	-29% p<0.0001	-28% p<0.0001	-22% P=0.0001
Week 48	1%	-10% NS	-24% P=0.0003	-14% p<0.05

LDL-C



LS Mean* % Change from Baseline at Week 24 & 48				
Week 24	18%	49% p<0.05	44% NS	78% p<0.0001
Week 48	21%	34% p<0.05	34% NS	45% p<0.05

Total ApoB



LS Mean* % Change from Baseline at Week 24 & 48				
Week 24	8%	6% NS	-5% NS	1% NS
Week 48	6%	6% NS	0% NS	2% NS

Placebo Plozasiran 10 mg Plozasiran 25 mg Plozasiran 50 mg

*Statistical significance was determined using Mixed Model Repeat Measures (MMRM) analysis.

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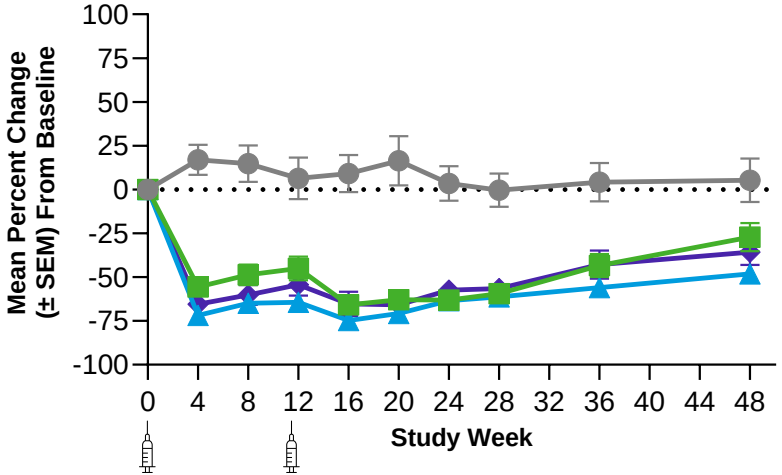
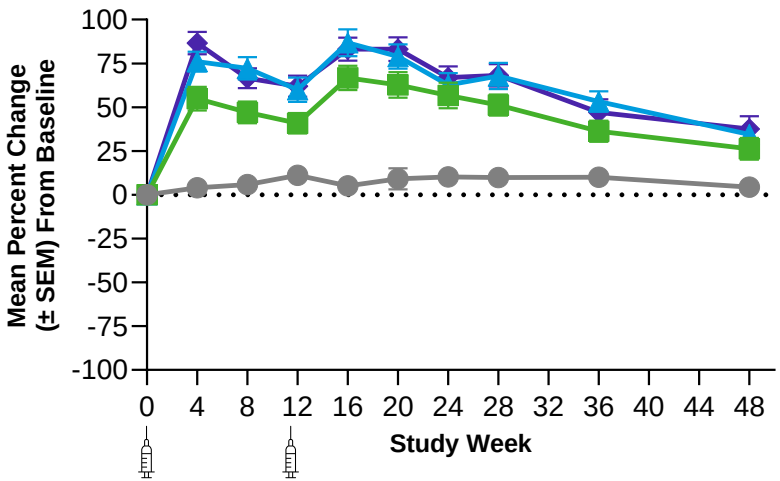
Plozasiran Decreases Remnant Cholesterol and Increases HDL-C

Remnant Cholesterol



LS Mean* % Change from Baseline at Week 24 & 48				
Week 24	2%	-60% p<0.0001	-62% p<0.0001	-57% p<0.0001
Week 48	2%	-24% p<0.05	-45% p<0.0001	-34% p=0.002

HDL-C

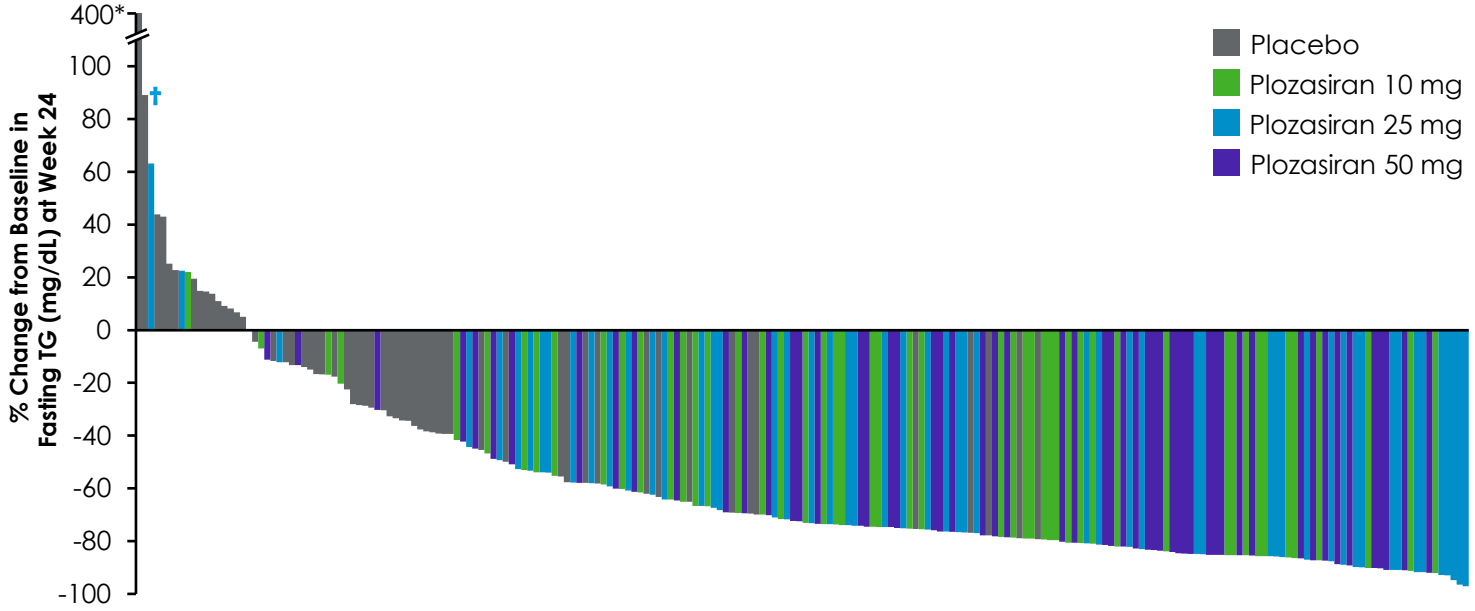


LS Mean* % Change from Baseline at Week 24 & 48				
Week 24	11%	54% p<0.0001	63% p<0.0001	68% p<0.0001
Week 48	6%	24% p<0.05	32% p=0.0007	38% p<0.0001

Placebo | Plozasiran 10 mg | Plozasiran 25 mg | Plozasiran 50 mg

For all panels: *Statistical significance was determined using Mixed Model Repeat Measures (MMRM) analysis.

Most Subjects Treated With Plozasiran (>90%) Achieved Triglyceride Levels < 500 mg/dL, Below the Risk Threshold for Acute Pancreatitis



All Patients Who Reached TG < 150 mg/dL at Wk 24, n/N (%)	4/59 (7%)	22/50 (44%)	27/54 (50%)	28/55 (51%)
All subjects Who Reached TG < 500 mg/dL at Wk 24, n/N (%)	**32/59 (54%)**	**44/50 (88%)**	**50/54 (93%)**	**50/55 (91%)**
Subjects with Baseline TG > 880 mg/dL Who Reached TG < 500 mg/dL at Wk 24, n/N (%)	5/15 (33%)	9/14 (64%)	13/16 (81%)	14/17 (82%)

*Axis adjusted for one patient in placebo group as outlier (percent change greater than 400%). †In this patient who was randomized to 25 mg plozasiran, the absence of decrease in triglyceride at Week 24 was later found to be caused by a causal mutation for glycerol kinase deficiency, an X linked recessive disorder, where free glycerol concentrations are most often >2.0 mmol/L. These markedly elevated free glycerol levels cause significant over estimations of triglyceride levels, ie "pseudo hypertriglceridemia", due to enzymatic techniques used in conventional triglyceride laboratory measures. This patient was found to be a responder. Data are from highest dose group.

Pardo, J.F., et al. *Atherosclerosis*, 2019. 287: p. e237

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Summary of Adverse Events at 48 Weeks

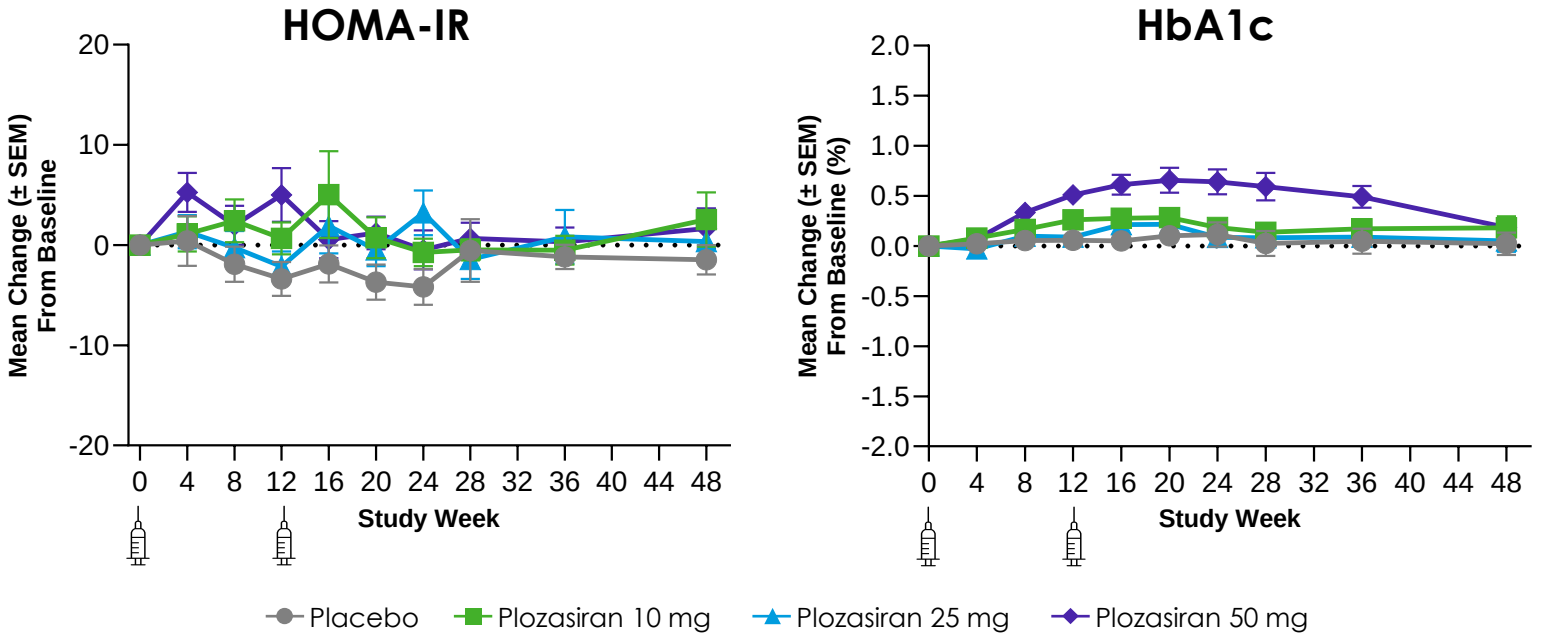
	Pooled Placebo (N=61)	Plozasiran		
		10 mg (N=54)	25 mg (N=55)	50 mg (N=56)
TEAEs	43 (71)	43 (80)	36 (66)	49 (88)
TEAEs occurring in ≥ 5 subjects				
COVID-19	10 (16.7)	10 (18.5)	8 (14.5)	8 (14.0)
Worsening glycemic control*	7 (11.7)	12 (22.2)	9 (16.4)	11 (19.6)
Diarrhea	5 (8.3)	3 (5.6)	1 (1.8)	1 (1.8)
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)
Treatment related adverse events	8 (13.3)	14 (25.9)	8 (14.5)	10 (17.5)
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[a]	0	0	0	1 (2)
Acute pancreatitis,[b] adjudicated cases, No. (%)	2 (3)	0 (0)	0 (0)	1 (2)
Death	0	0	0	0

- TEAEs reflect the comorbidities and underlying conditions of the study population
- Serious TEAEs were deemed not related to Plozasiran
- All serious TEAEs resolved without sequelae (except 2 subjects with malignancies), with no deaths
- Data includes exposure out to 48 weeks

*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 (%) [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 c, 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.

No Changes in HOMA-IR and HbA1c Observed With Plozasiran at the 25 mg Dose Chosen To Move Forward in Subsequent Phase 3 Trials

HbA1c increases observed in diabetics were transient, reversible, manageable, and not associated with significant clinical symptoms or discontinuation



Note: Diabetic patients are defined as having HbA1c ≥6.5% or Fasting Glucose ≥126 mg/dL or with medical history of 'diabetes' or receiving diabetic medications at baseline.

SHASTA-2 Study Conclusion

- **Plozasiran decreases LS mean serum 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%)

- **Over 90% of subjects at 24 weeks treated with plozasiran achieved TGs < 500 mg/dL and below the risk threshold for Acute Pancreatitis**
- **Plozasiran has a favorable safety profile at 48 weeks**
- **These data support further development of plozasiran in planned phase 3 programs for the treatment of chylomicronemia and SHTG**
- **Based on these results, RNAi-mediated silencing of hepatic APOC3 expression via plozasiran is a promising potential treatment for subjects with SHTG**

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Gaudet D, Pall D, Watts G, et al.

Plozasiran (ARO-APOC3) for Severe Hypertriglyceridemia

The SHASTA-2 Randomized Clinical Trial

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THANK YOU

We Would Like To Thank The Patients And Caregivers Who Participated In This Study

Acronyms

ALT= alanine transaminase; **AP**, acute pancreatitis; **ApoA**=apolipoprotein A; **ApoB**, apolipoprotein B; **ApoC**=apolipoprotein C; **APOC3,** apolipoprotein C3; **ASCVD**, atherosclerotic cardiovascular disease; **ASGPR**, asialoglycoprotein receptor **AST**=aspartate aminotransferase; **BLOQ**, below limits of quantitation; **BMI**, body mass index; **EOS**, end of study; **FCS**, familial chylomicronemia syndrome; **GalNAc**, N-Acetylgalactosamine **HbA1C**=hemoglobin A1C; **HDL-C**, high density lipoprotein cholesterol; **HOMA-IR**=homeostasis model assessment-estimated insulin resistance; **hsCRP**=high-sensitivity C-reactive protein; **LDL-C**, low density lipoprotein cholesterol; **LP**, lipoproteins; **Lp(a)**=lipoprotein (a); **LPL**, lipoprotein lipase; **LS**, least squares; **MCS**, multifactorial chylomicronemia syndrome; **MRI-PDFF**= magnetic resonance imaging-proton density fat fraction; **mRNA**, messenger ribonucleic acid; **N**, number; **OLE**, open label extension; **PD**, pharmacodynamic; **pH**, potential of Hydrogen; **PK**, pharmacokinetic; **Q**, quartile; **RISC,** RNA-induced silencing complex; **RNA**, ribonucleic acid; **RNAi**, ribonucleic acid interference; **SD**, standard deviation; **SE**, standard error; **SEM**, standard error of the mean; **SHTG**, severe hypertriglyceridemia; **siRNA**, small interfering ribonucleic acids; **TEAEs**, treatment emergent adverse events. **TG**, triglycerides. **TRL**, triglyceride rich lipoproteins; **UC**, ultracentrifuge; **VLDL**, very low-density lipoprotein.