#AHA23

ARO-APOC3, an Investigational RNAi Therapeutic, Silences APOC3 and Reduces TG to Near Normal Levels in Patients With SHTG: SHASTA-2 Study Results

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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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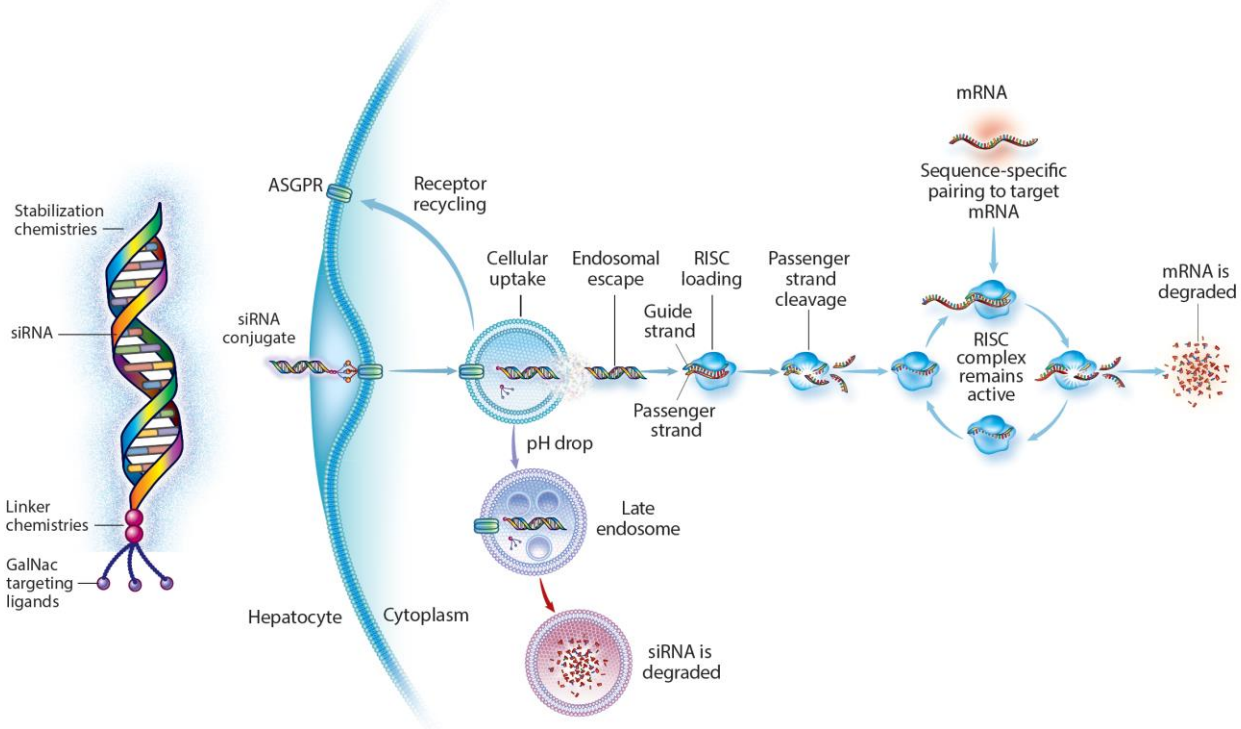
Goal Of SHTG Therapy Is To Reduce TGs Below Pancreatitis Risk

- **Severe hypertriglyceridemia (SHTG) is characterized by circulating triglycerides (TG) > 500 mg/dL[1-3]**
- **In the United States (US), there are ~2-4 million adults with SHTG[4-5]**
- **The etiology of SHTG is multi-factorial[4-6]**
  - Risk factors can include genetic disorders, obesity, untreated or poorly controlled diabetes, and certain medications
  - Very severe forms include FCS and MCS
    - FCS, the ultra-rare form, is due to monogenic mutations and is prevalent in >500 cases in the US
    - MCS is far more frequent than FCS and is usually associated with multigenic mutations and aggravating factors
- **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]**
- **Limited treatment options exist to reduce TGs below the threshold at which pancreatitis occurs[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; **AP**, acute pancreatitis; **ASCVD**, atherosclerotic cardiovascular disease; **FCS**, familial chylomicronemia syndrome; **MCS**, multifactorial chylomicronemia syndrome; **SHTG**, severe hypertriglyceridemia; **TG**, triglycerides.

Key Features Of Using RNAi As A Therapeutic Modality

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

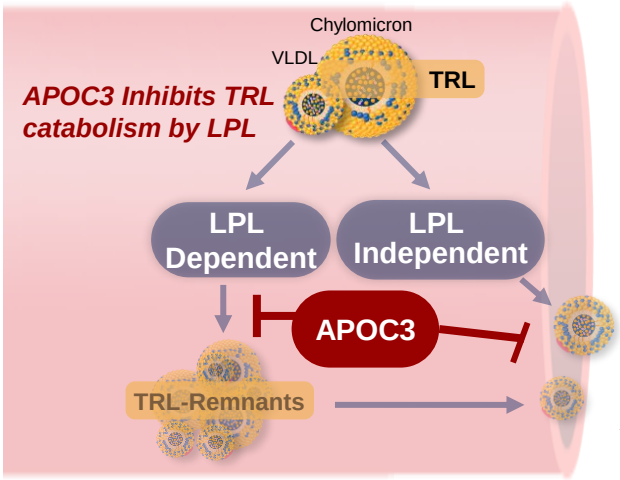
Infrequent Dosing:
Long tissue PK/PD, on target effect

ASGPR, asialoglycoprotein receptor**; GalNAc**, N-Acetylgalactosamine; **mRNA**, messenger ribonucleic acid; **PD**, pharmacodynamic; **pH**, potential of Hydrogen; **PK**, pharmacokinetic; **RISC**, RNA-induced silencing complex; **RNA**, ribonucleic acid; **RNAi**, ribonucleic acid interference; **siRNA**, small interfering ribonucleic acids

Plozasiran (ARO-APOC3) Is An Investigational RNAi Therapeutic Targeting ApoC3, A Key Mediator Of TG And Atherogenic Lipoproteins

APOC3[1]

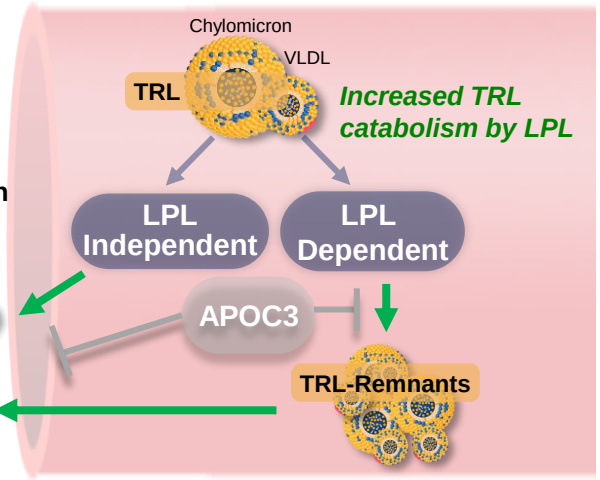
APOC3 Inhibits TRL Catabolism and Hepatic Clearance Leading to Increased TGs

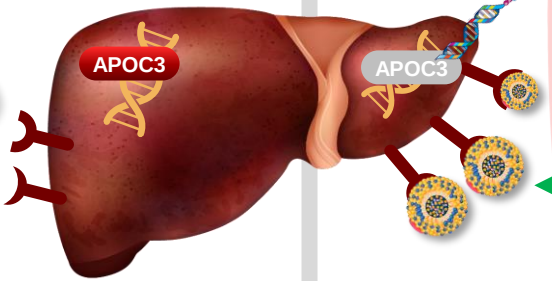


APOC3 Inhibits TRL clearance by inhibiting uptake by liver receptors

Plozasiran

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



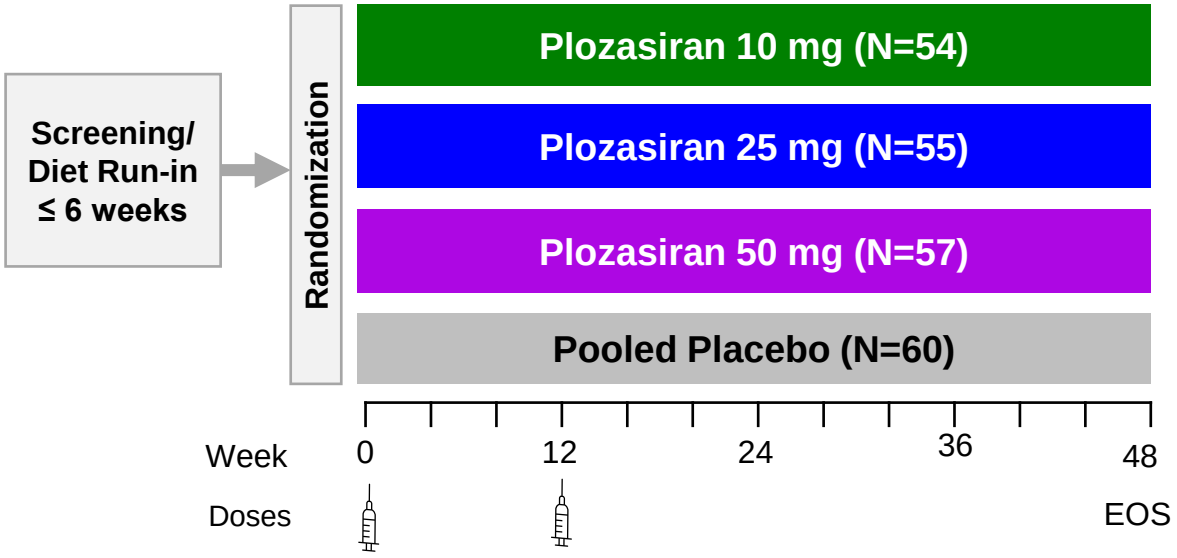


Increased TRL clearance

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. **APOC3**, apolipoprotein C3; **LPL**, lipoprotein lipase; **RNAi**, ribonucleic acid interference; **TG**, triglycerides; **TRL**, triglyceride rich lipoproteins; **VLDL**, very low-density lipoprotein.

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 when all subjects had reached Week 24 cutoff date of April 14, 2023.

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

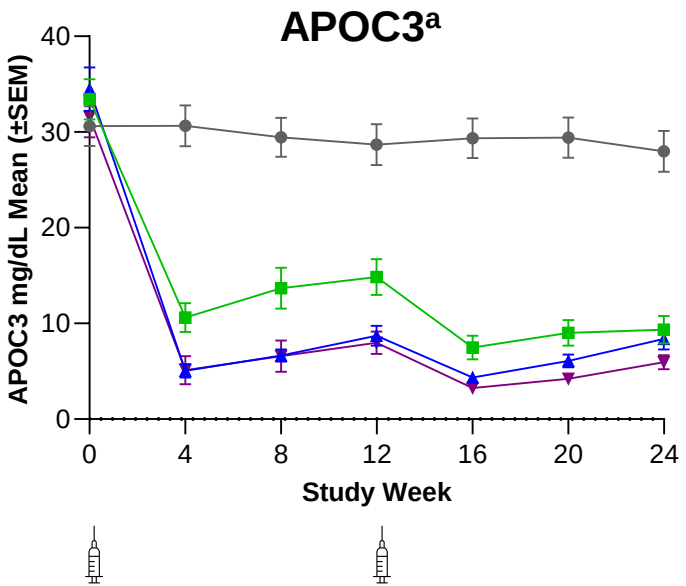
SHASTA-2: Data cutoff 14 Apr 2023. *All samples taken after ≥ 10 hour fast. **AP**, acute pancreatitis; **ApoB**, apolipoprotein B; **APOC3**, apolipoprotein C3; EOS, end of study; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **LP**, lipoproteins; **OLE**, open label extension; **SHTG**, severe hypertriglyceridemia; **TG**, triglycerides.

Baseline Characteristics

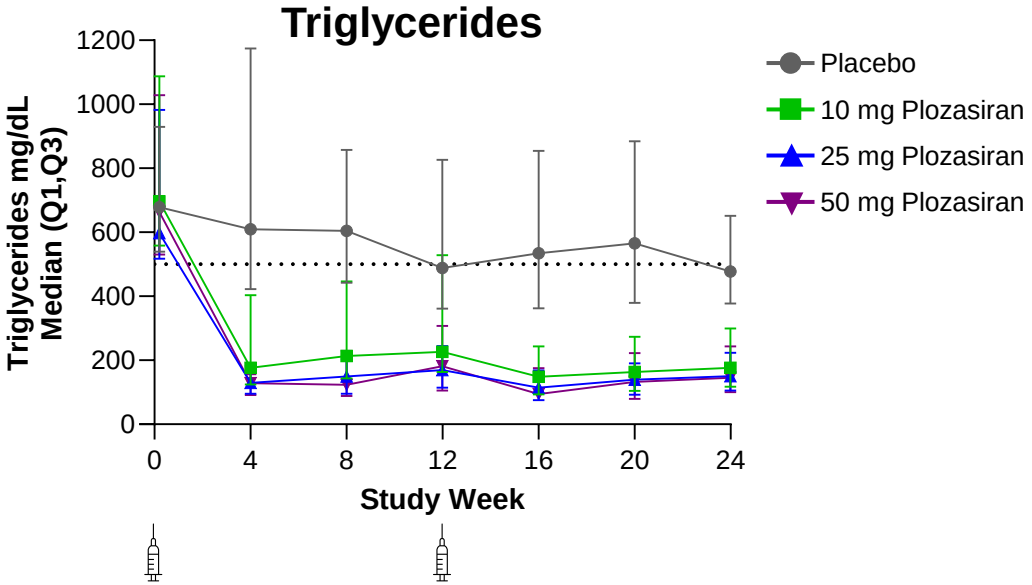
	Pooled Placebo (N=60)	Plozasiran 10 mg (N=54)	Plozasiran 25 mg (N=55)	Plozasiran 50 mg (N=57)
Mean (SD) age, years	56.2 (11.0)	53.0 (9.6)	56.0 (10.6)	54.3 (11.0)
Female, n (%)	14 (23.3)	8 (14.8)	12 (21.8)	16 (28.1)
White, n (%)	55 (91.7)	47 (87.0)	48 (87.3)	53 (93.0)
Mean (SD) BMI, kg/m^2	30.6 (3.8)	32.5 (4.9)	31.8 (5.1)	31.5 (5.3)
Mean (SD) APOC3,[a] mg/dL	30.6 (15.9)	33.4 (15.4)	34.5 (16.8)	31.6 (16.1)
Median (Q1, Q3) triglyceride, mg/dL	678.6 (539.6, 929.1)	696.0 (558.8, 1087.6)	597.7 (517.3, 982.1)	663.1 (530.8, 1028.3)
Mean (SD) non-HDL-C, mg/dL	184.8 (78.7)	208.8 (73.6)	206.3 (91.3)	195.7 (87.6)
Mean (SD) ApoB, mg/dL	94.91 (28.6)	103.10 (44.4)	103.44 (31.8)	109.80 (54.5)
Mean (SD) remnant cholesterol,[b] mg/dL	115.4 (82.2)	134.1 (87.9)	132.1 (98.3)	123.8 (91.5)
Median (Q1, Q3) LDL-C, UC, mg/dL	62.0 (42.0, 92.0)	65.0 (46.0, 96.0)	71.0 (44.0, 97.0)	65.0 (41.0, 96.0)
Mean (SD) HDL-C, mg/dL	29.7 (11.6)	28.3 (8.8)	29.5 (11.2)	30.5 (12.6)

SHASTA-2: Data cutoff 14 Apr 2023. [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). **ApoB**, apolipoprotein B; **APOC3**, apolipoprotein C3; **BMI**, body mass index; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **N**, number; **Q**, quartile; **SD**, standard deviation; **UC,** ultracentrifuge

Plozasiran Demonstrates Substantial And Durable Decreases In Serum APOC3 Restoring TG Homeostasis



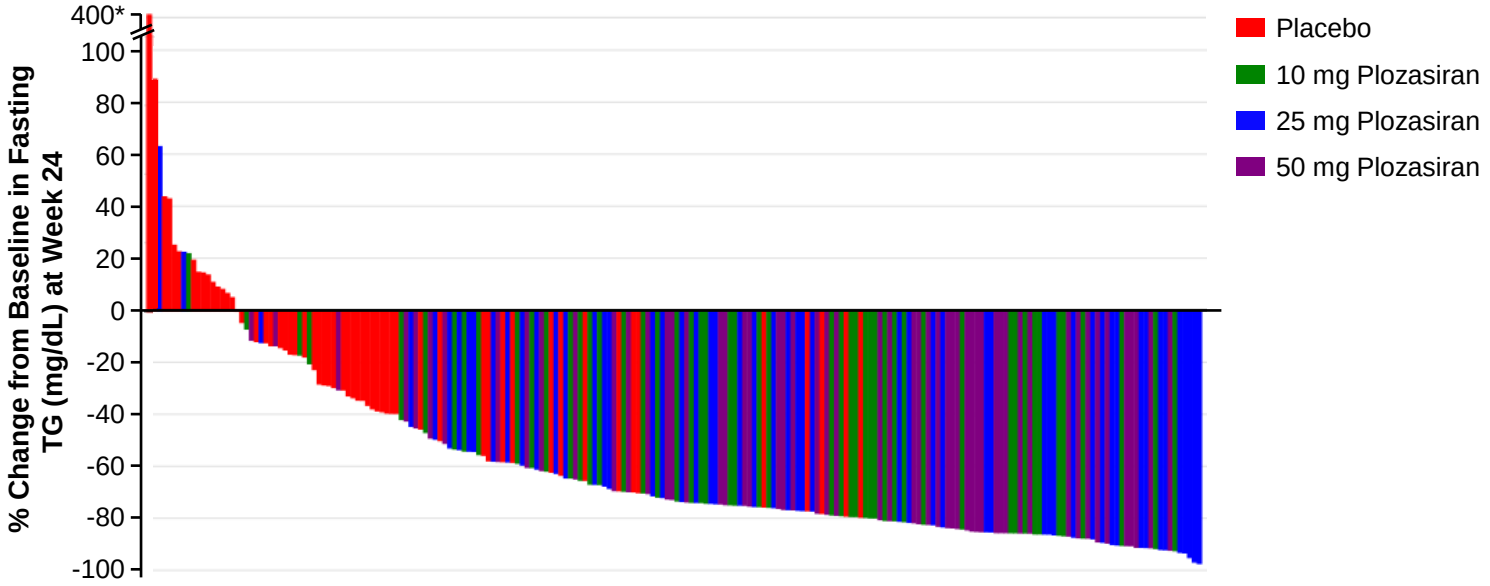
Least Squares Mean*[a] % Change from Baseline at Week 24			
-2%	-69% p<0.0001	-73% p<0.0001	-79% p<0.0001



Least Squares Mean* % Change from Baseline at Week 24			
-17%	-66% p<0.0001	-70% p<0.0001	-74% p<0.0001

SHASTA-2: Data cutoff 14 Apr 2023; [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. **APOC3**, apolipoprotein C3; **SEM**, standard error of the mean; **Q**, quartile; **TG**, triglycerides.

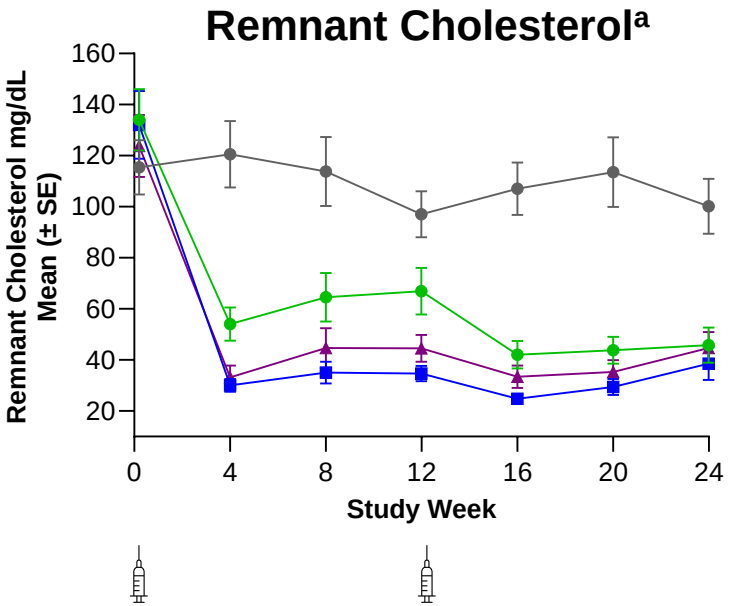
Most Subjects Treated With Plozasiran Achieved Triglyceride Levels < 500 mg/dL, Below the Risk Threshold For Acute Pancreatitis

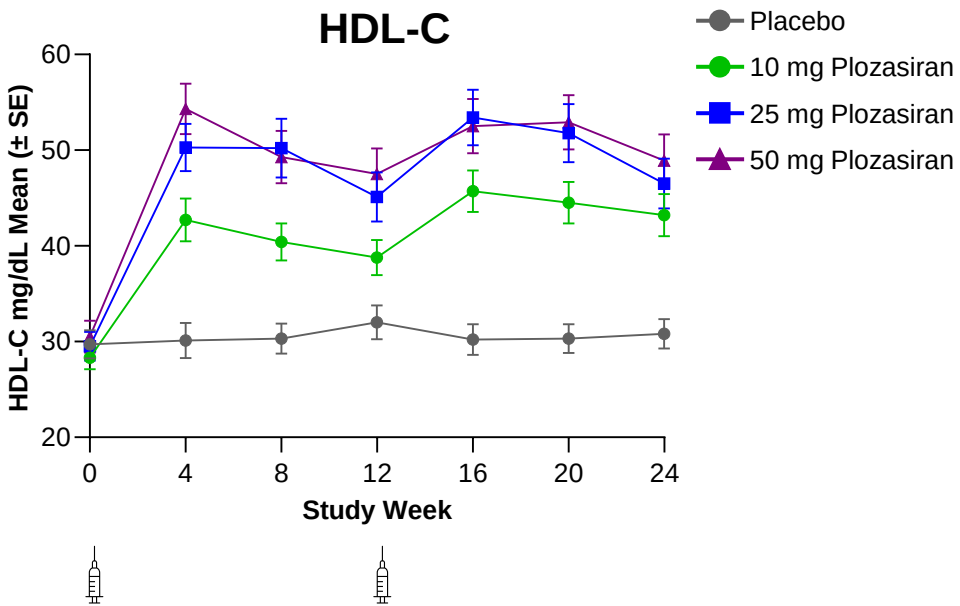


n/N (%)	Placebo (Pooled)	Plozasiran 10 mg	Plozasiran 25 mg	Plozasiran 50 mg
All Patients Who Reached TG < 150 mg/dL at Wk 24	4/59 (7%)	22/50 (44%)	27/54 (50%)	28/55 (51%)
All subjects Who Reached TG < 500 mg/dL at Wk 24	**32/59 (54%)**	**44/50 (88%)**	**50/54 (93%)**	**50/55 (91%)**
Subjects with Baseline TG > 880 mg/dL Who Reached TG < 500 mg/dL at Wk 24	5/15 (33%)	9/14 (64%)	13/16 (81%)	14/17 (82%)

SHASTA-2: Data Cutoff 14 APR 2023. *Axis adjusted for one subject in Placebo group as outlier (percent change >400%).
N, number; **TG**, triglycerides; Wk, week.

Plozasiran Decreases Remnant Cholesterol And Increases HDL-C





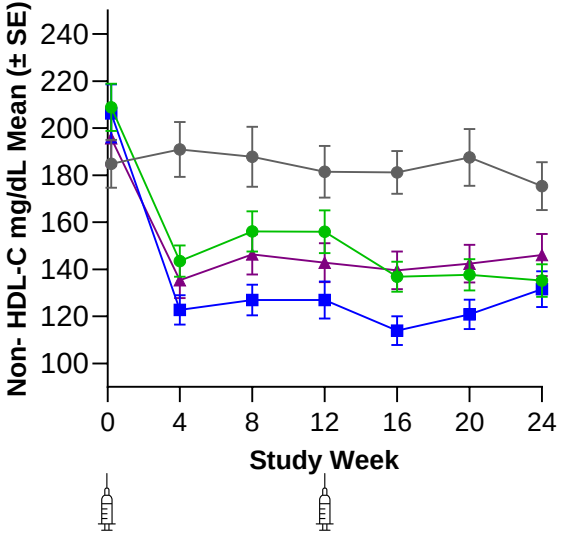
LS Mean*[a] % Change from Baseline at Week 24			
1%	-61% p<0.0001	-63% p<0.0001	-58% p<0.0001

LS Mean* % Change from Baseline at Week 24			
10%	54% p<0.0001	63% p<0.0001	68% p<0.0001

SHASTA-2: Data cutoff 14 Apr 2023; [a]Based on calculation: Total cholesterol – HDL-C – LDL-C (ultracentrifugation) *Statistical significance was determined using Mixed Model Repeat Measures (MMRM) analysis. **HDL-C**, high density lipoprotein cholesterol; **LS**, least squares; **SE**, standard error; **UC**, ultracentrifuge

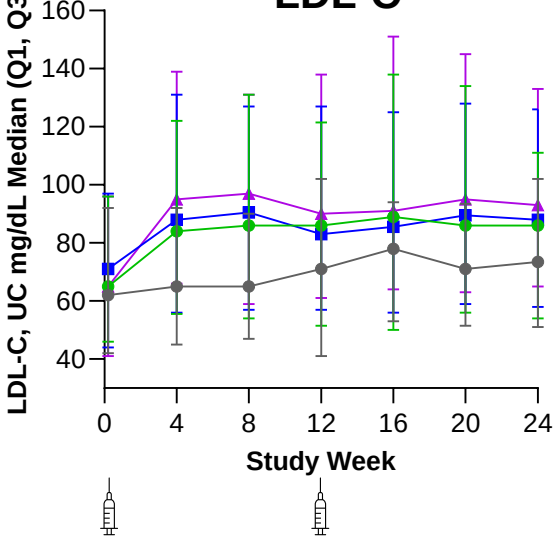
Plozasiran Impact On Additional Lipid Parameters

Non-HDL-C



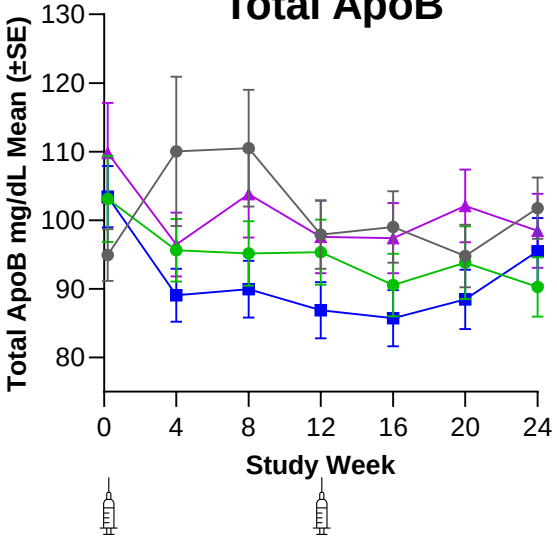
LS Mean* % Change from Baseline at Week 24			
-2%	-30% p<0.0001	-29% p<0.0001	-22% p<0.05

LDL-C



LS Mean* % Change from Baseline at Week 24			
17%	47% p<0.05	42% NS	76% p<0.0001

Total ApoB



LS Mean* % Change from Baseline at Week 24			
6%	-8% p<0.05	-5% p<0.05	0% NS

Placebo 10 mg Plozasiran 25 mg Plozasiran 50 mg Plozasiran

SHASTA-2: Data cutoff 14 Apr 2023. *Statistical significance was determined using Mixed Model Repeat Measures (MMRM) analysis.
ApoB, apolipoprotein B; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**; low density lipoprotein cholesterol; **LS**, least squares; **SE**, standard error.

Summary Of Adverse Events

	Pooled Placebo (N=60)	Plozasiran		
		10 mg (N=54)	25 mg (N=55)	50 mg (N=57)
TEAEs	42 (70.0)	41 (75.9)	35 (63.6)	48 (84.2)
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 (19.3)
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	7 (11.7)	4 (7.4)	2 (3.6)	5 (8.8)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0	1 (1.9)	0	0

TEAEs reported to date reflect the comorbidities and underlying conditions of the study population

Serious TEAEs were not related to Plozasiran

All serious TEAEs were resolved without sequelae (except 2 subjects with malignancies), with none with an outcome of death

Data includes exposure out to 48 weeks

SHASTA-2: Data cutoff 14 Apr 2023. *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.
TEAEs, treatment emergent adverse events.

Plozasiran Reduces Triglycerides And Triglyceride Rich Lipoproteins in Subjects With SHTG

- **Plozasiran durably decreases serum APOC3, TGs, and remnant cholesterol while increasing HDL-C at 24 weeks for all dose levels:**
  - APOC3 reductions to -79%
  - TG reductions to -74%
  - Remnant cholesterol reductions to -63%
  - HDL-C increase up to +68%
- **Over 90% of subjects treated with plozasiran achieved TG levels < 500 mg/dL, below the risk threshold for Acute Pancreatitis**
- **Plozasiran has a favorable safety profile to date**
- **These data support further development of plozasiran in planned phase 3 programs for the treatment of FCS and SHTG**
- **Based on these results, RNAi-mediated silencing of hepatic APOC3 expression via plozasiran is a promising potential treatment for subjects with SHTG**

SHASTA-2: Data cutoff 14 Apr 2023. **APOC3**, apolipoprotein C3; **FCS**, familial chylomicronemia syndrome; **HDL-C**, high density lipoprotein cholesterol; **RNAi**, ribonucleic acid interference; **SHTG**, severe hypertriglyceridemia; **TGs**, triglycerides.

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THANK YOU

WE WOULD LIKE TO THANK THE PATIENTS AND CAREGIVERS WHO PARTICIPATED IN THIS STUDY

American Heart Association.

Scientific Sessions

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