SHASTA-2

Final Study Results and a Glimpse into the OLE

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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Financial Disclosures

Presenter

- **CM Ballantyne** reports grants and/or honoraria from Abbott Diagnostic, Akcea, Althera, Amarin, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Esperion, Genentech, Gilead, Illumina, Ionis, Matinas BioPharma Inc, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo.

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- **K Modesto** and **J Hellawell,** are current employees of Arrowhead Pharmaceuticals
- **J San Martin** was a past employee of Arrowhead Pharmaceuticals

Goal of SHTG Therapy Is to Reduce TGs Below Pancreatitis Risk

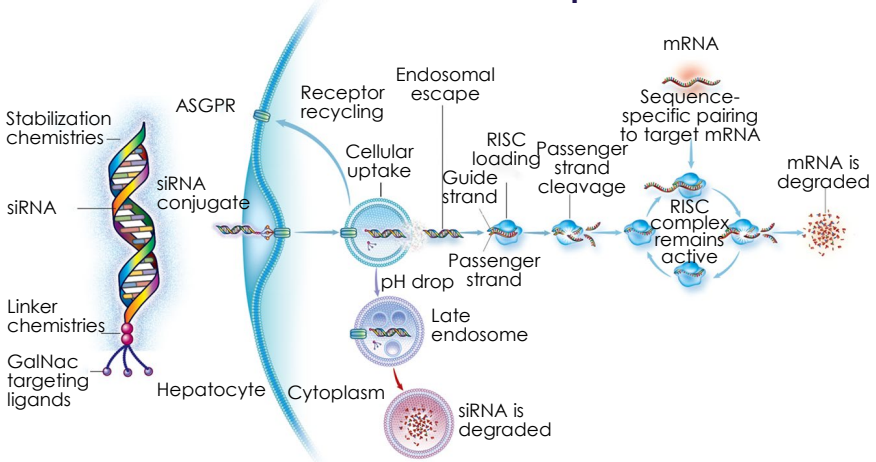
- Severe hypertriglyceridemia (SHTG) is characterized by TG levels > 500 mg/dL[1-3]
- Very severe forms (TG> 880 mg/dL = chylomicronemia) include **FCS** and **MCS**[4-6]
  - **FCS** (2-9 cases per million) is a rare recessive condition caused by bi-allelic or digenic pathogenic variants in the lipoprotein lipase (LPL) pathway
  - **MCS** is far more frequent (1/600) and is usually multifactorial
- 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]
- In Phase 2 studies, plozasiran has shown to be a highly specific RNAi molecule with deep and durable gene silencing that requires infrequent dosing

FCS, familial chylomicronemia syndrome; **MCS**, multifactorial chylomicronemia syndrome; TG, triglycerides.

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.

Plozasiran, an RNAi Targeting APOC3, is a Key Mediator of TG and Atherogenic Lipoproteins

RNAi is a natural process that uses short fragments of RNA molecules to interfere with mRNA translation into associated proteins



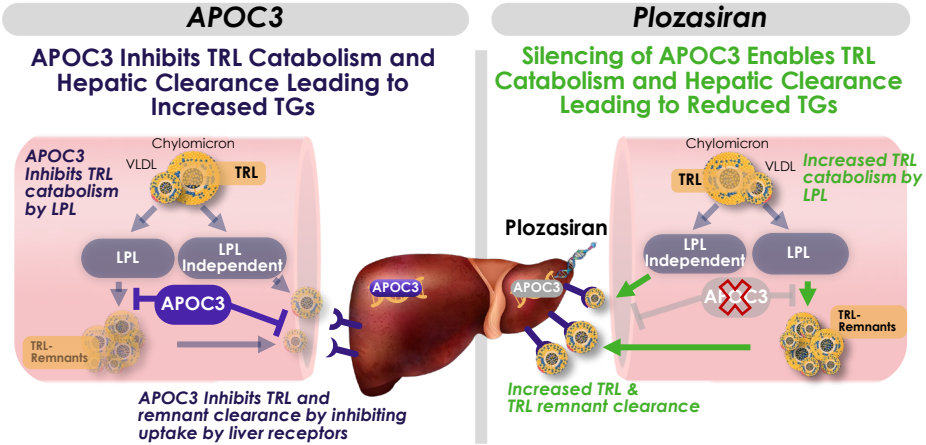
High Specificity
Allowing to suppress the expression of a specific gene

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

Plozasiran is an investigational RNAi therapeutic that substantially reduces TG and triglyceride rich lipoproteins (TRL) in patients with SHTG



APOC3, apolipoprotein C3; **ASGPR**, asialoglycoprotein receptor; **GalNAc**, N-Acetylgalactosamine; **LPL**, lipoprotein lipase; **mRNA**, messenger ribonucleic acid; **PD**, pharmacodynamic; **pH**, potential of Hydrogen; **PK**, pharmacokinetic; **RISC**, RNA-induced silencing complex; **RNA**, ribonucleic acid; **RNAi**, RNA interference; **siRNA**, small interfering ribonucleic acids; **TG**, triglycerides; **TRL**, triglyceride-rich lipoprotein; **VLDL**, very low-density lipoprotein.

SHASTA-2: A Double-blind, Phase 2b Placebo-Controlled, Dose Ranging Study of Plozasiran in Patients With SHTG

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

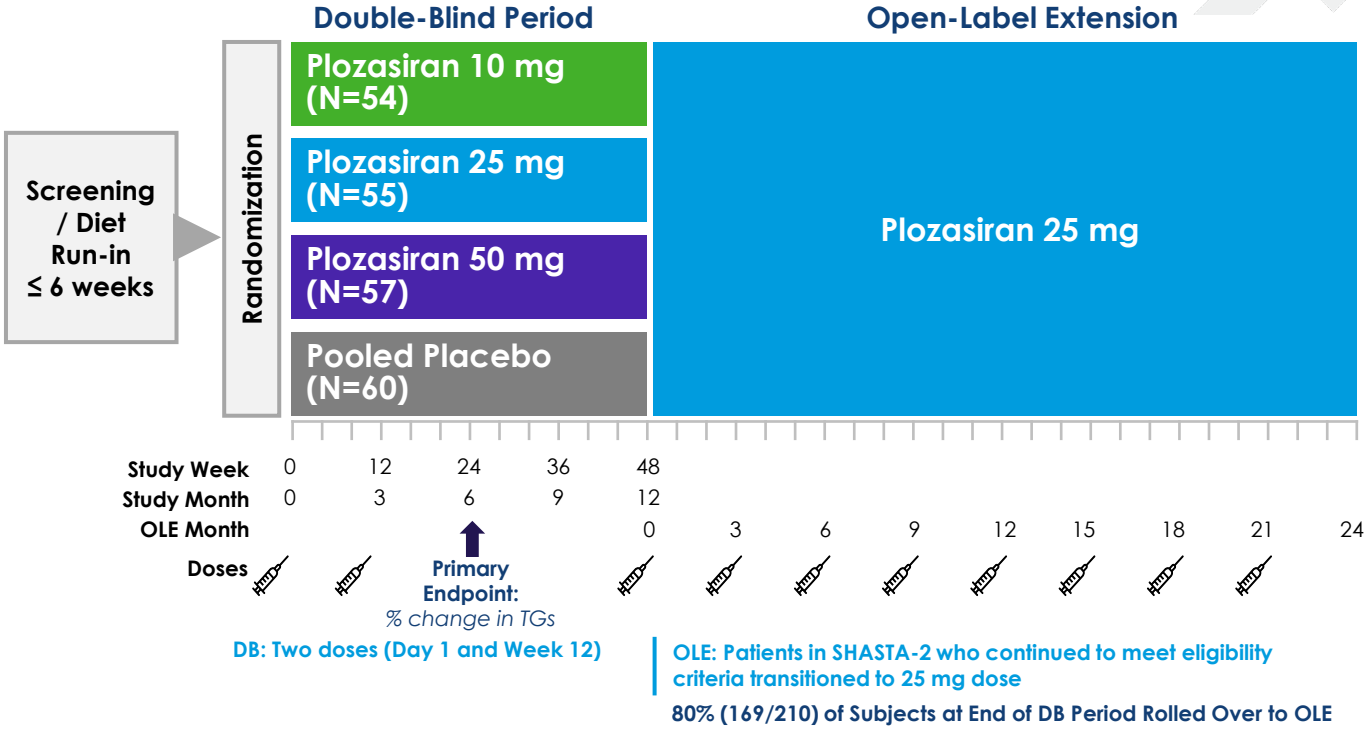
Study Population: SHTG history of TG ≥ 500 mg/dL and fasting TG of 500–4,000 mg/dL during screening period

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



*All samples taken after ≥ 10 hour fast.

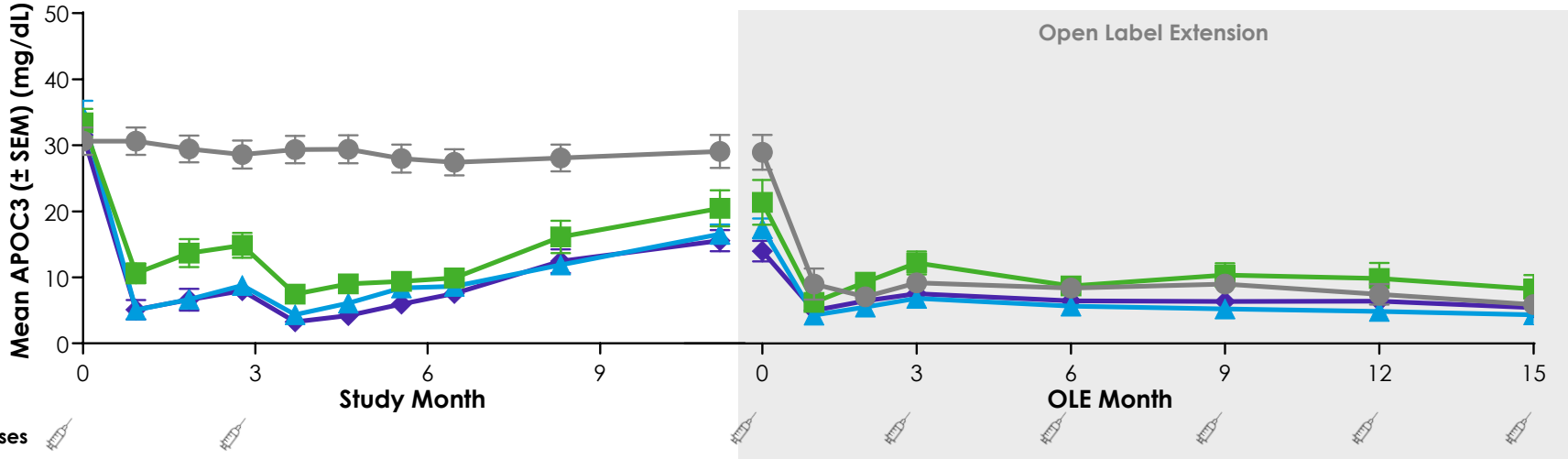
ApoB, apolipoprotein B; **APOC3**, apolipoprotein C3; **DB**: double blind; **EOS**, end of study; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **LP**, lipoprotein; **OLE**, open label extension; **TG**, triglycerides; **TRL**, triglyceride-rich lipoprotein; **VLDL-C**, very low-density lipoprotein cholesterol; **W**, week.

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/m^2	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 below limits of quantitation (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.
ApoB, apolipoprotein B; **APOC3**, apolipoprotein C3; **BMI**, body mass index; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **UC**, ultracentrifugation.

Plozasiran Had a Persistent Effect on APOC3[a] in All Study Periods

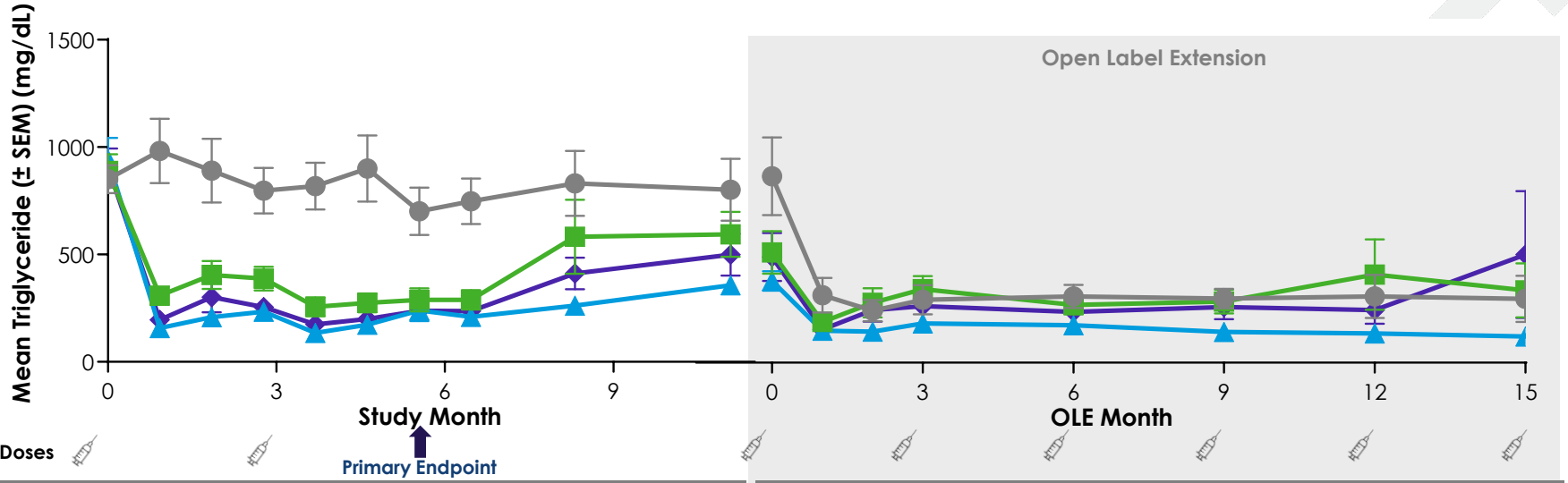


No. patients	DOUBLE-BLIND PERIOD (Weeks)										OPEN LABEL EXTENSION[b]							
	BL	W4	W8	W12	W16	W20	W24	W28	W36	W48	D0	M1	M2	M3	M6	M9	M12	M15
Placebo	58	58	58	55	57	56	57	58	55	55	43	43	44	44	39	27	20	12
Plozasiran 10 mg	53	52	53	52	49	50	49	49	48	49	34	36	36	36	35	26	16	8
Plozasiran 25 mg	55	55	54	54	54	51	54	52	51	50	44	43	41	42	42	30	24	11
Plozasiran 50 mg	57	57	56	54	53	53	55	54	54	53	40	41	41	41	40	30	20	10

Placebo Plozasiran 10 mg Plozasiran 25 mg Plozasiran 50 mg

[a]Analysis removed 2 participants with baseline values below limits of quantitation, BLOQ (ad hoc). [b]Data cut as of 29MAR2024.
APOC3, apolipoprotein C3; **D**, Day; **M**, Month; **OLE**, open-label extension; **SEM**, standard error of the mean; **W**, Week,

Plozasiran Had a Durable Effect on Triglycerides in All Study Periods



	DOUBLE-BLIND PERIOD (Weeks)									
No. patients	BL	W4	W8	W12	W16	W20	W24	W28	W36	W48
Placebo	60	60	60	57	59	58	59	60	57	57
Plozasiran 10 mg	54	53	54	53	50	51	50	50	49	50
Plozasiran 25 mg	55	55	54	54	54	51	54	52	51	50
Plozasiran 50 mg	57	57	56	54	53	53	55	54	54	53

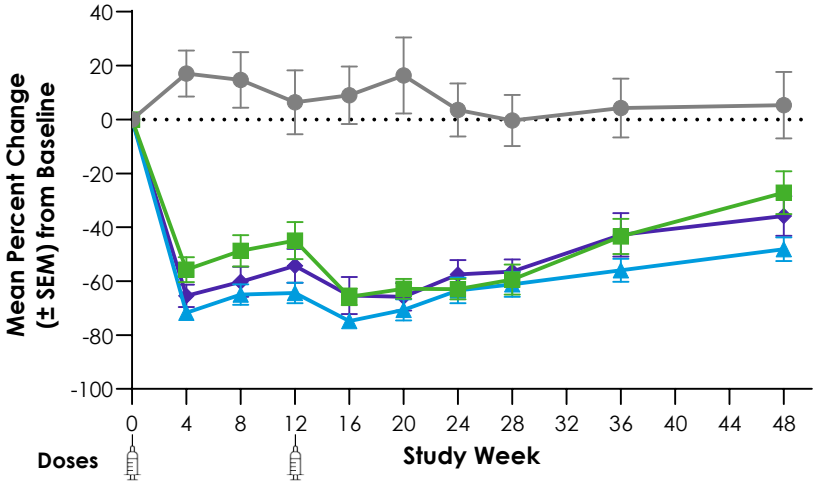
	OPEN LABEL EXTENSION[a]							
	D0	M1	M2	M3	M6	M9	M12	M15
Placebo	44	44	45	45	39	27	20	12
Plozasiran 10 mg	39	37	37	37	36	26	16	8
Plozasiran 25 mg	43	43	41	42	42	30	24	11
Plozasiran 50 mg	43	41	41	41	40	30	20	10

Placebo Plozasiran 10 mg Plozasiran 25 mg Plozasiran 50 mg

[a]Data cut as of 29MAR2024. **D**, Day; **M**, Month; **OLE**, open-label extension; **SEM**, standard error of the mean; **W**, Week,

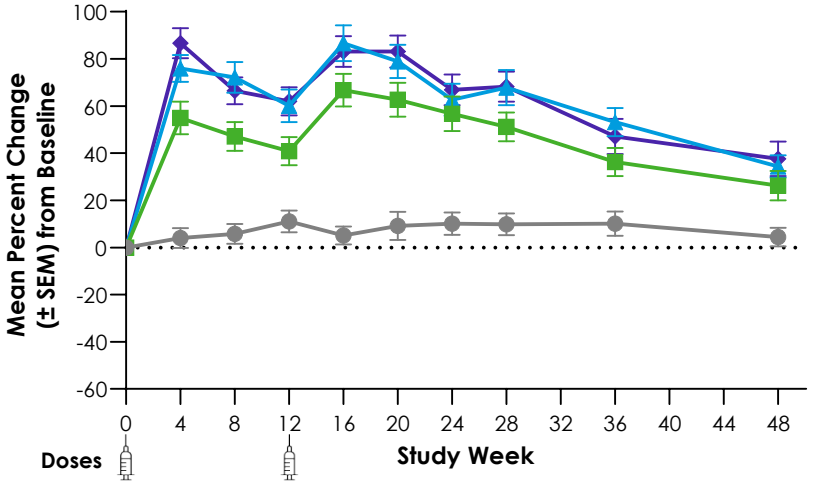
Plozasiran Decreased Remnant Cholesterol and Increased HDL-C

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



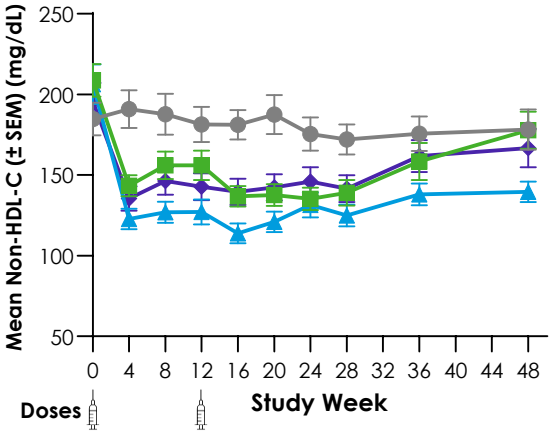
LS Mean* % Change from Baseline at Week 24 & 48				
Week 24	11%	54% p<0.0001	63% p<0.0001	68% p<0.0001
Week 48	6%	24% p<0.05	32% p=0.0007	38% p<0.0001

Placebo — Plozasiran 10 mg — Plozasiran 25 mg — Plozasiran 50 mg

For all panels: *Analysis of Covariance (ANCOVA) with repeated measures was used for statistical modeling. Nadir at 16 weeks where Placebo corrected LSM of 77% difference was achieved, i.e. 135 mg/dL from 942 mg/dL mean baseline .
HDL-C, high density lipoprotein cholesterol; **LS**, least squares; **SEM**, standard error of the mean.

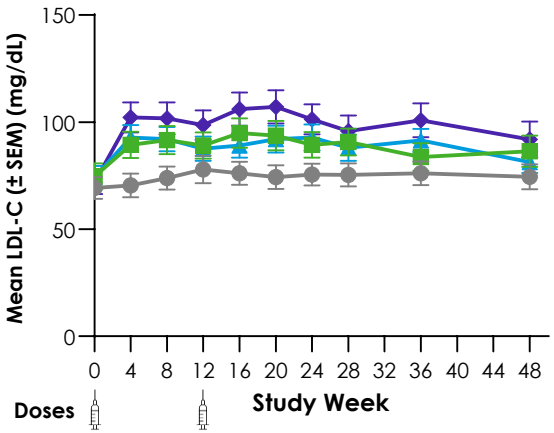
Plozasiran Impact on Additional Lipid Parameters

Non-HDL-C



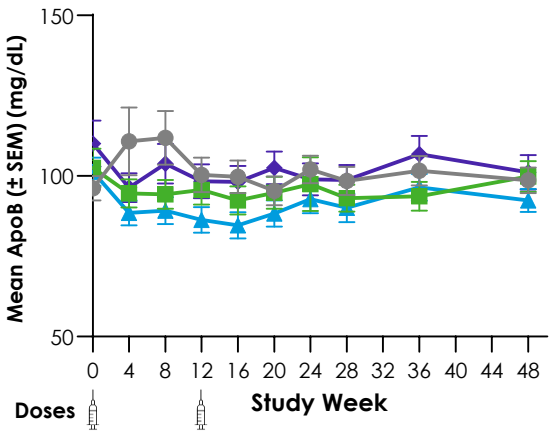
LS Mean* % Change from Baseline at Week 24 & 48				
Week 24	-2%	**-29%** p<0.0001	**-28%** p<0.0001	**-22%** P=0.0001
Week 48	1%	**-10%** NS	**-24%** P=0.0003	**-14%** p<0.05

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

*Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling.
ApoB, apolipoprotein B; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **LS**, least squares; **SEM**, standard error of the mean.

Summary of Adverse Events at 48 Weeks

No. (%)	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 subjects				
COVID-19	10 (16.7)	10 (18.5)	8 (14.5)	8 (14.0)
Worsening glycemic control[a]	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)[b]
Acute pancreatitis,[c] adjudicated cases	2 (3)	0 (0)	0 (0)	1 (2)
Death	0	0	0	0

- TEAEs reflect the comorbidities and underlying conditions of the study population
- There were no deaths
- Serious TEAEs were deemed not related to plozasiran and resolved without sequelae (except 2 subjects with malignancies)
- Data included exposure out to 48 weeks in the double-blind period

[a]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 observed in subjects with uncontrolled diabetes. [b]Local injection site reactions only include events that start on the day of injection and persist for at least 48 hours post injection. [c]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 >2000 mg/dL from an on-treatment nadir of 106 mg/dL. **TEAE**, treatment-emergent adverse event.

SHASTA-2 Study Conclusion

- In patients with SHTG, plozasiran decreased LS mean % change from baseline of 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%)
- The majority, >90% of patients treated with plozasiran achieved TGs < 500 mg/dL at Week 24, below the risk threshold for acute pancreatitis
- Half of patients reached TG values below 150 mg/dL at 24 weeks, thereby normalizing their triglycerides
- Consistency of PD with minimal interpatient variability and sustained effect seen with the OLE
- Plozasiran demonstrated a favorable safety profile in this study
- 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)

APOC3, apolipoprotein C3; **HDL-C**, high density lipoprotein cholesterol; **LS**, least squares; **OLE**, open-label extension; **PD**, pharmacodynamic; **RNAi**, RNA interference; **SHTG**, Severe hypertriglyceridemia; **TG**, triglycerides;

Plozasiran (ARO-APOC3) for Severe Hypertriglyceridemia

The SHASTA-2 Randomized Clinical Trial

Gaudet D, Pall D, Watts GF, Nicholls SJ, Rosenson RS, Modesto K, San Martin J, Hellawell J, Ballantyne CM. Plozasiran (ARO-APOC3) for Severe Hypertriglyceridemia: The SHASTA-2 Randomized Clinical Trial. JAMA Cardiol. 2024 Apr 7:e240959. doi: 10.1001/jamacardio.2024.0959. Epub ahead of print. PMID: 38583092; PMCID: PMC11000138.

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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.