#AHA22

ARO-APOC3, an Investigational RNAi Therapeutic, Decreases Serum Apolipoprotein C3, Triglyceride, and Non-HDL-C Concentrations While Increasing HDL-C in Patients With Severe Hypertriglyceridemia

Christie M Ballantyne, MD
Baylor College of Medicine
on behalf of the SHASTA-2 Study Team

American Heart Association.

Financial Disclosure

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.

Co-Authors

GF Watts reports grants and/or honoraria from Amgen, Novartis, and Sanofi-Regeneron.

D Gaudet reports grants and/or honoraria from Acasti, Akcea, Allergan, Amryt pharma, Amgen, Applied Therapeutics, Arrowhead, AstraZeneca, Boehringer-Ingelheim, Dalcor Pharma, Eli Lilly, Esperion, Institut de Cardiologie de Montréal, Ionis, Kowa, the Medicine Company, NovoNordisk, Pfizer, Regeneron, UniQure, and Verve Therapeutics.

S Vasas has no disclosures.

R Fu, S Melquist, H Moradi and J San Martin are all current employees of Arrowhead Pharmaceuticals

RA Hegele reports honoraria and/or speaker's fees from Acasti, Akcea/Ionis, Amgen, HLS Therapeutics, and Sanofi.

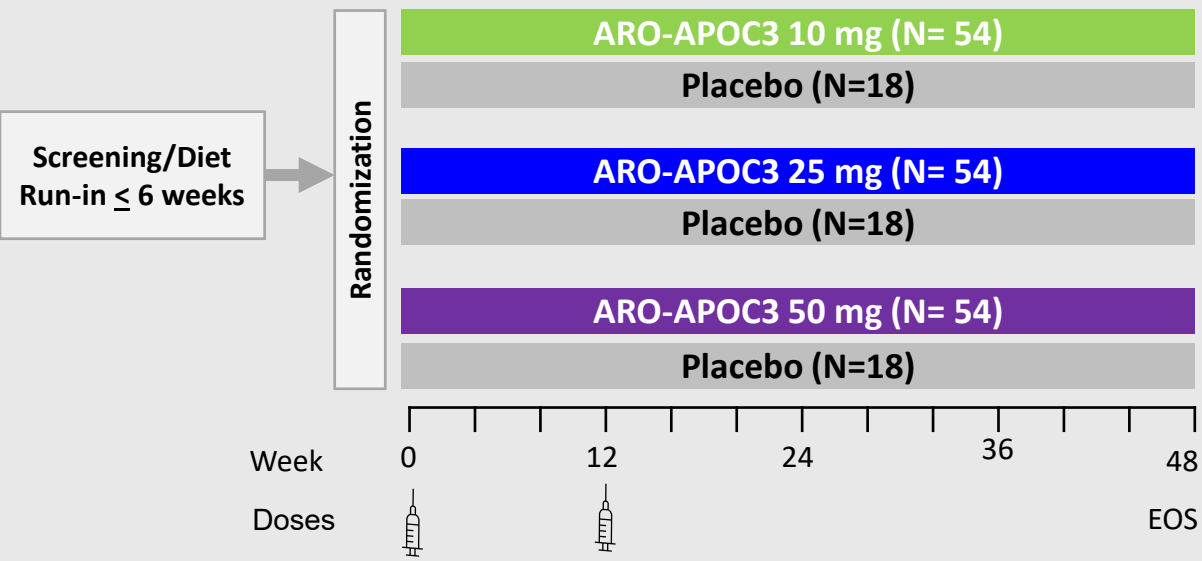
RS Rosenson reports grant/research support from (all paid to institution, not individual): Amgen, Arrowhead, Novartis, Eli Lilly, Regeneron; consulting fees from Amgen, Arrowhead, CRISPR Therapeutics, Eli Lilly, Lipigon, Novartis, Precision Biosciences, Regeneron, UltraGenyx, Verve; non-promotional speaking fee from Amgen and Kowa; other support from MediMergent, LLC (significant); and is an UpToDate, Inc. stock shareholder (significant).

SJ Nicholls reports grants and/or honoraria from Akcea, Amarin, Amgen, Anthera, Arrowhead Pharmaceuticals Inc, AstraZeneca, Boehringer Ingelheim, Cerenis, CSL Behring, Eli Lilly, Esperion, InfraReDx, LipoScience, The Medicines Company, Merck, New Amsterdam Pharma, Novartis, Omthera, Resverlogix, Roche, Sanofi-Regeneron, and Takeda.

Role of Apolipoprotein C3-Targeted Therapies in Severe Hypertriglyceridemia

- Severe hypertriglyceridemia (SHTG) significantly increases risk of acute pancreatitis.
- Currently, there are limited effective therapies to treat SHTG.
- Apolipoprotein C3 (APOC3) regulates circulating levels of triglycerides (TGs) and lipoprotein metabolism by inhibiting lipoprotein lipase-dependent and –independent pathways.
- Loss of function mutations in *APOC3* are associated with:
  - Low TG, chylomicrons, VLDL-C, remnant cholesterol and increased levels of HDL-C
  - Reduced risk of cardiovascular disease (CVD)
  - No known adverse phenotype associated with genetic deficiency in *APOC3*
- ARO-APOC3 is an investigational, hepatocyte-targeted RNA interference (RNAi) therapeutic designed to specifically silence hepatic *APOC3* mRNA expression and reduce circulating APOC3 and TGs.
- Phase 1 studies of ARO-APOC3 in subjects with hypertriglyceridemia resulted in robust and sustained reductions in TGs and non-HDL-C, increases in HDL-C, and with a safety profile supportive of later stage clinical development

SHASTA 2: An Ongoing Double-blind, Placebo-controlled, Dose Ranging Study of ARO-APOC3 in Subjects With SHTG



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 in

- TG
- APOC3
- non-HDL-C
- LDL-C
- HDL-C

Data Analysis: Ongoing Phase 2 study data evaluated when ≥50% of subjects had reached Week 12 and received both doses. 177 subjects had entered the study at the time of the data cutoff (25 Jul 2022). Data available to the Week 16 visit are presented.

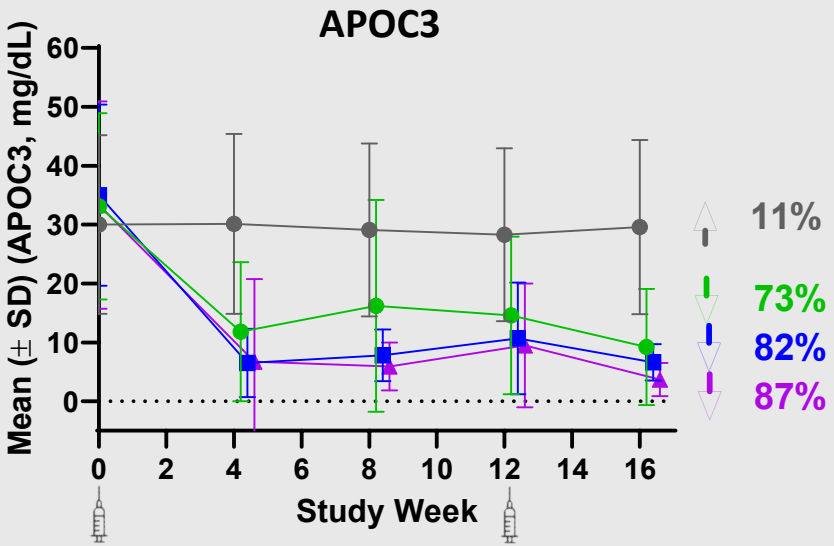
* All samples taken after ≥ 10 hour fast

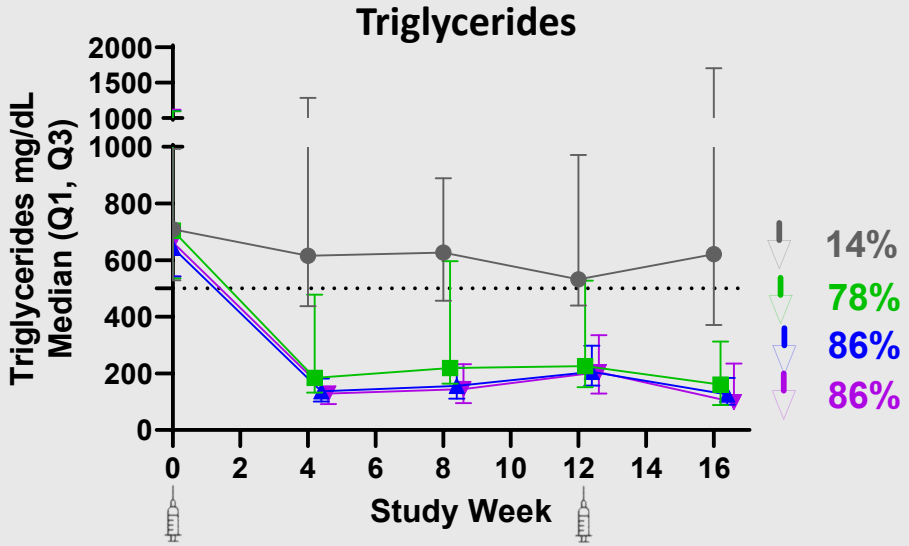
Baseline Characteristics

	Pooled Placebo	ARO-APOC3		
	(N=46)	10 mg (N=43)	25 mg (N=43)	50 mg (N=45)
Mean (SD) age, years	56.3 (11.17)	53.9 (9.29)	56.0 (11.70)	54.8 (10.52)
Female, n (%)	11 (24)	4 (9)	12 (28)	13 (29)
White, n (%)	42 (91)	37 (86)	37 (86)	41 (91)
Mean (SD) BMI, kg/m^2	30.4 (3.8)	32.9 (5.1)	31.4 (5.0)	31.3 (5.3)
Mean (SD) APOC3 µg/L	31.3 (17.4)	33.1 (15.8)	35.0 (15.4)	32.6 (17.5)
Median (Q1, Q3) TG, mg/dL	708.5 (528.5, 993.0)	704.4 (535.8, 1097.7)	643.9 (542.7, 1099.2)	663.1 (527.4, 1134.9)
Mean (SD) LDL-C (ultracentrifugation), mg/dL	68.7 (43.0)	75.5 (42.9)	73.81 (42.0)	70.1 (45.6)
Mean (SD) non-HDL-C, mg/dL	191.7 (85.8)	206.6 (78.4)	212.1 (98.1)	199.9 (88.1)
Mean (SD) HDL-C, mg/dL	29.6 (12.3)	28.4 (9.2)	28.6 (11.8)	29.4 (11.7)
Mean (SD) remnant cholesterol,* mg/dL	124.7 (90.5)	130.4 (88.3)	138.3 (103.9)	130.3 (93.7)

*Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C, ultracentrifugation)
SHASTA-2 : Data cutoff 25 Jul 2022

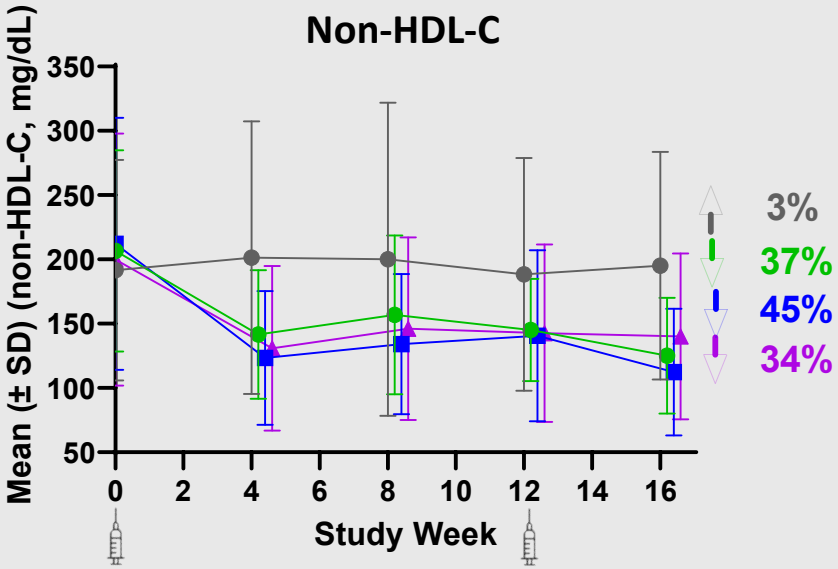
ARO-APOC3 Demonstrates Durable Decreases in Serum APOC3 and Triglycerides at All Doses Studied

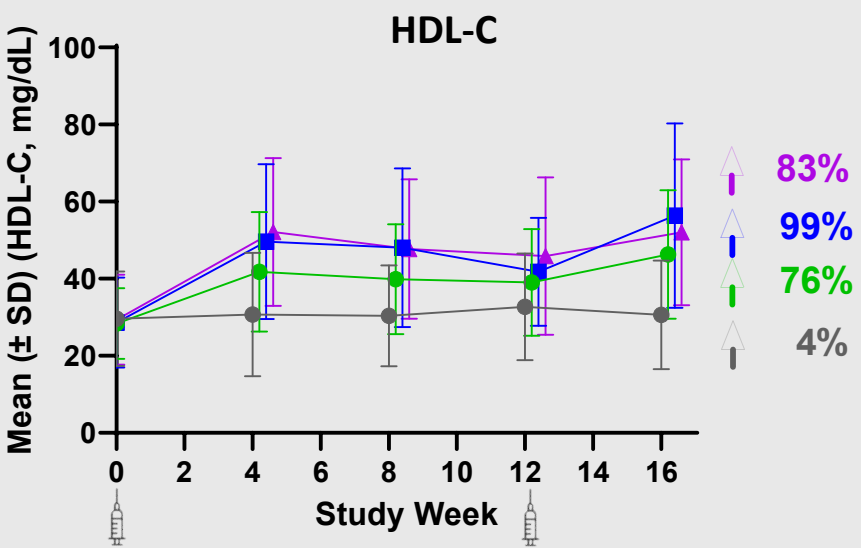




Placebo — 10 mg ARO-APOC3 — 25 mg ARO-APOC3 — 50 mg ARO-APOC3

ARO-APOC3 Decreases Serum Non-HDL-C and Increases HDL-C at All Doses Studied





Placebo — 10 mg ARO-APOC3 — 25 mg ARO-APOC3 — 50 mg ARO-APOC3

Changes In LDL-C and non-HDL-C at Week 16

	Pooled Placebo	ARO-APOC3		
		10 mg	25 mg	50 mg
LDL-C (Ultracentrifugation) (mg/dL)*				
Baseline median (Q1,Q3)	54.0 (31.0, 88.0)	62.0 (29.0, 100.0)	62.5 (44.0, 92.0)	60.0 (30.0, 106.0)
Median (Q1,Q3) at Week 16	72.5 (18.0, 90.0)	69.0 (38.0, 120.0)	64.5 (50.0, 126.0)	83.0 (63.0, 122.0)
Median % change at Week 16 (Q1, Q3)	**-6.6** (-32.8, 34.3)	**22.2** (-20.8, 86.8)	**13.3** (-15.2, 72.4)	**11.6** (0.0, 135.5)
N	(n=26)	(n=23)	(n=26)	(n=21)
Non-HDL Cholesterol(mg/dL)				
Baseline mean (SD)	198.8 (98.1)	213.2 (89.3)	224.6 (111.6)	225.1 (104.0)
Mean (SD) at Week 16	195.0 (88.6)	125.0 (45.1)	112.3 (49.3)	140.1 (64.5)
Mean % change at Week 16 (SD)	**2.8** (34.8)	**-36.5** (26.8)	**-45.0** (21.4)	**-33.5** (25.9)
N	(n=28)	(n=24)	(n=27)	(n=23)

*Median percent change reported due to non-normal distribution

Aggregated Summary of Adverse Events

# of Subjects Reporting ≥ 1 Treatment Emergent Adverse Event (TEAE) N (%)	77/177(44%)
TEAEs occurring in ≥ 4 subjects	N (%)
COVID-19	17 (10%)
Headache	12 (7%)
Urinary tract infection	7 (4%)
Diarrhea	5 (3%)
Hypertension	5 (3%)
Glycosylated hemoglobin increased	5 (3%)
Abdominal pain upper	4 (2%)
Non-Cardiac chest pain	4 (2%)
Type 2 diabetes mellitus	4 (2%)
Treatment-related TEAEs	16 (9%)
Serious TEAEs	10 (6%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0 (0%)
TEAEs causing deaths	0 (0%)

- TEAEs reported to date reflect the underlying comorbidities and conditions of the population under study
- All TEAEs were pooled regardless of treatment assignment
- Mean change from baseline in HbA1c at Week 16 across cohorts was 0.24% to 0.43% in subjects receiving ARO-APOC3, and 0.11% in subjects receiving placebo, driven by patients with baseline diabetes
- To date, 2 cases of pancreatitis have been reported (blinded)

Interim Analysis of SHASTA-2 Study Suggests Favorable Changes in Triglycerides and Non-HDL Cholesterol in Subjects With SHTG

- Analysis was performed in SHASTA-2 once 50% of subjects reached their Week 12 visit
- Interim results to date demonstrate that ARO-APOC3 durably decreases serum APOC3, TGs, and non-HDL-C while increasing HDL-C at all dose levels:
  - APOC3 up to -87% at Week 16
  - Triglycerides up to -86% at Week 16
  - Non-HDL-C up to -45% at Week 16
  - HDL-C up to +99% at Week 16
- ARO-APOC3 has been well tolerated in this ongoing Phase 2 study
- Based on these results, RNAi-mediated silencing of hepatic APOC3 expression via ARO-APOC3 appears to be a promising treatment for patients with SHTG

THANK YOU

American Heart Association.

Scientific Sessions

#AHA22