ARO-APOC3, an Investigational RNAi Therapeutic, Shows Similar Efficacy and Safety in Genetically Confirmed FCS and Non-FCS Participants with Severe Hypertriglyceridemia

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American Heart Association. Scientific Sessions

Financial Disclosure

Presenter: C Ballantyne

Grant/Research Support- All significant. (All paid to institution, not individual): Abbott Diagnostic, Akcea, Amgen, Esperion, Novartis, Regeneron, Roche Diagnostic, NIH, AHA, ADA.

Consultant- Abbott Diagnostics, Althera, Amarin*, Amgen, Arrowhead, Astra Zeneca, Biotech, Corvidia, Denka Seiken*, Esperion, Genentech, Gilead, Matinas BioPharma Inc, New Amsterdam*, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, Sanofi-Synthelabo* (*Significant where noted (>$10,000))

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P. Clifton, J. Baker, C. Schwabe, S. Thackwray and R. Scott report no relevant disclosures

D. Sullivan reports grants and/or consulting fees from Regeneron, Amgen, Astra-Zeneca, Amarin, Espirion, Arrowhead, Sanofi, and Novartis

J Hamilton, A Lira Pineda, B. Given, S Melquist, I Chen and J San Martin are all current or former employees of Arrowhead Pharmaceuticals

GF Watts reports consulting fees from Amgen, Novartis, Arrowhead, Kowa and Astra Zeneca

D.Gaudet reports grants and personal fees from Arrowhead during the conduct of the study; and grants and/or personal fees from Acasti, Akcea, Amryt Pharma, Esperion, Gemphire, Ionis, HDL Therapeutics, Kowa, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi and UniQure outside the submitted work.

I Goldberg has been on a scientific advisory boards for Arrowhead, Esperion and Amgen. He has received funds from Arrowhead for preclinical studies.

JW Knowles reports consulting fees from Arrowhead

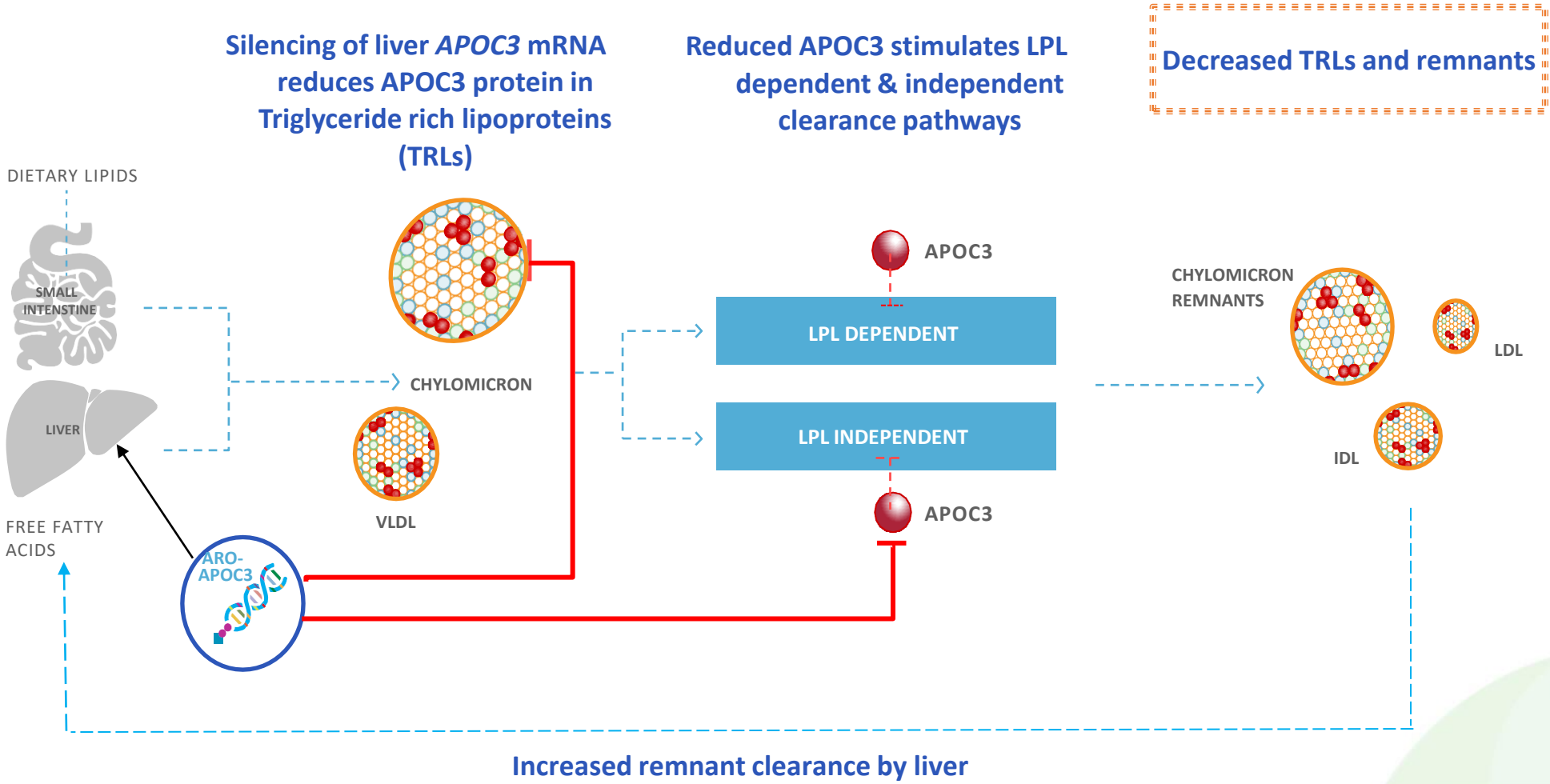
RA Hegele reports consulting fees from Acasti, Aegerion, Akcea/Ionis, Amgen, Arrowhead, HLS Therapeutics, Novartis, Pfizer, Regeneron and Sanofi

APOC3 is a key regulator of triglyceride-rich lipoproteins (TRLs) through lipoprotein lipase (LPL)-dependent and -independent pathways

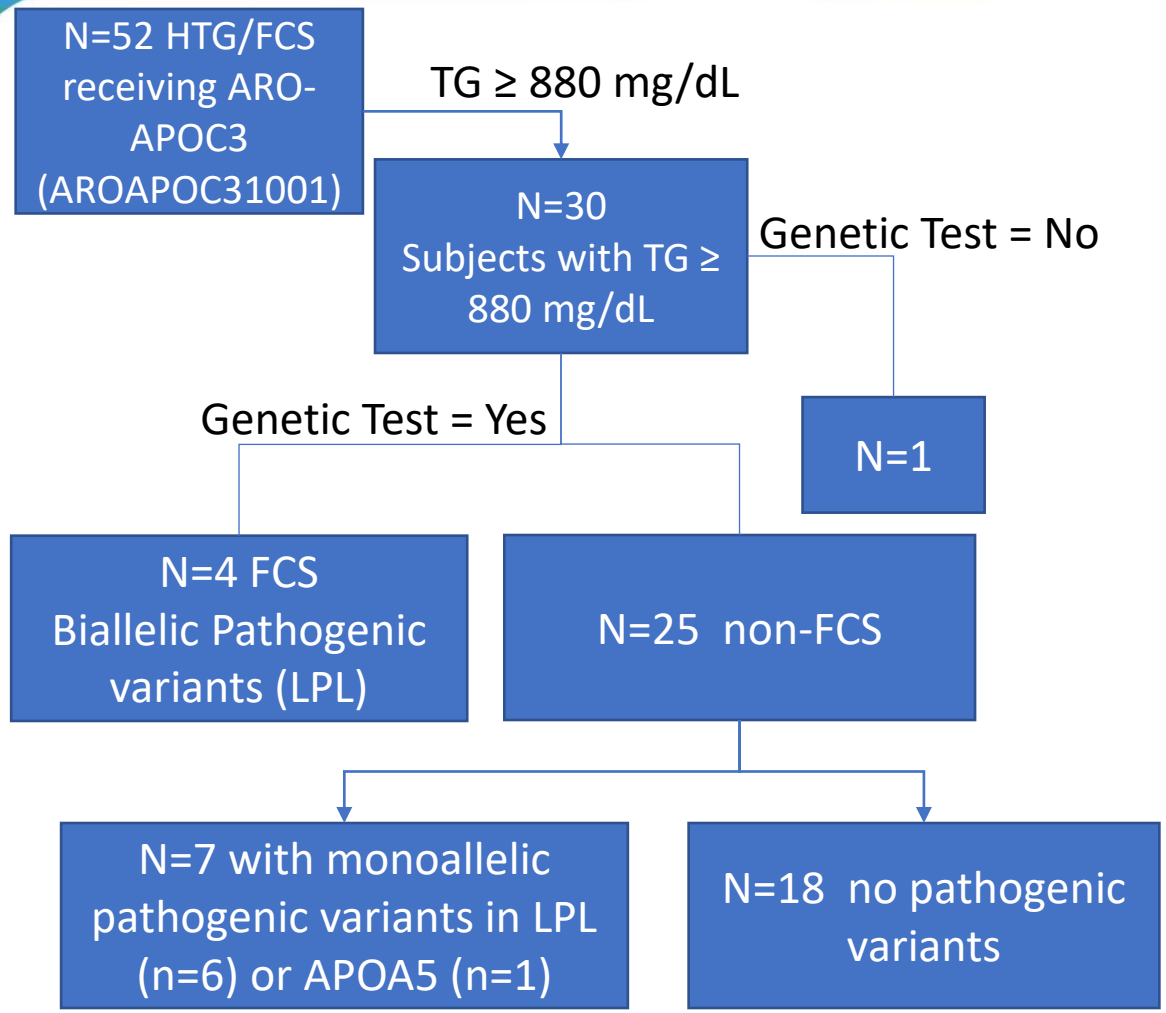
- **Familial Chylomicronemia Syndrome (FCS) is an ultra-rare genetic disease with severe hypertriglyceridemia and high risk for pancreatitis**
  - FCS patients harbor biallelic pathogenic DNA variants in lipolysis-associated genes
- **APOC3 is a key regulator of TG metabolism**
  - SHTG is characterized by excess levels of Apolipoprotein C3 (APOC3)-containing particles, such as chylomicrons or VLDL
  - Loss-of-function mutations in APOC3 are associated with lower TG, lower post-prandial lipemia and decreased incidence of coronary artery disease
- **ARO-APOC3 is designed to specifically target and silence the APOC3 gene, thereby reducing TG levels**
- **ARO-APOC3 resulted in robust and sustained reductions in APOC3, TGs and Non-HDL-C with HDL-C increases in subjects with HTG and chylomicronemia[1]**
- **The effect of ARO-APOC3 on FCS participants compared with non-FCS participants with similar baseline TG levels is currently undetermined**

[1]Clifton P. et al, AHA Scientific Sessions 2020

ARO-APOC3 specifically targets and silences the APOC3 gene, reducing TG levels



Participant Disposition and Baseline Characteristics



Parameter (SD)	FCS n=4	Non-FCS n=25
Age (years)	44.0 (13.5)	46.8 (13.2)
Male (%)	50	60
White (%)	75	76
Asian (%)	25	16
BMI (kg/m^2)**	22.1 (0.8)	30.7 (4.6)
APOC3 (mg/dL)	48.1 (18.0)	74.3 (22.6)
TG (mg/dL)	1650 (1387, 4791)*	1381 (324-5577)*
HDL-C** (mg/dL)	12.5 (1.0)	22.1 (7.6)
Non-HDL-C (mg/dL)	319 (178)	338 (209)

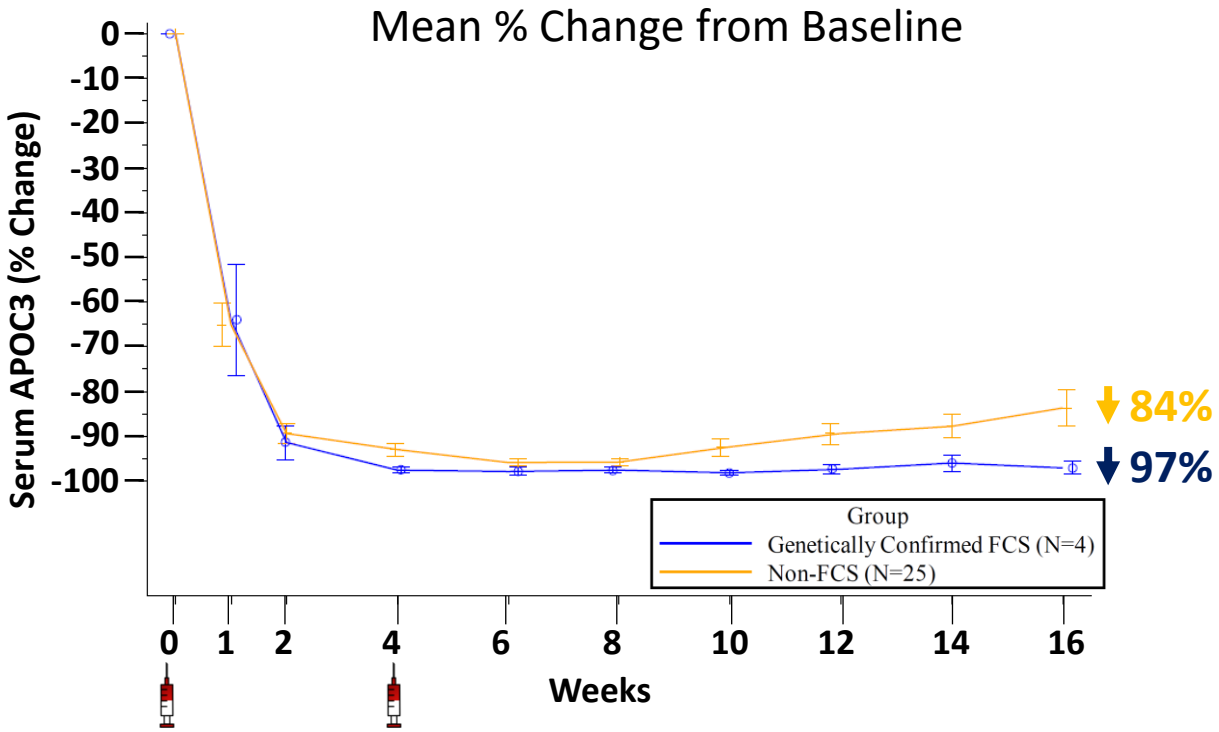
* TG values reported as median (min, max)

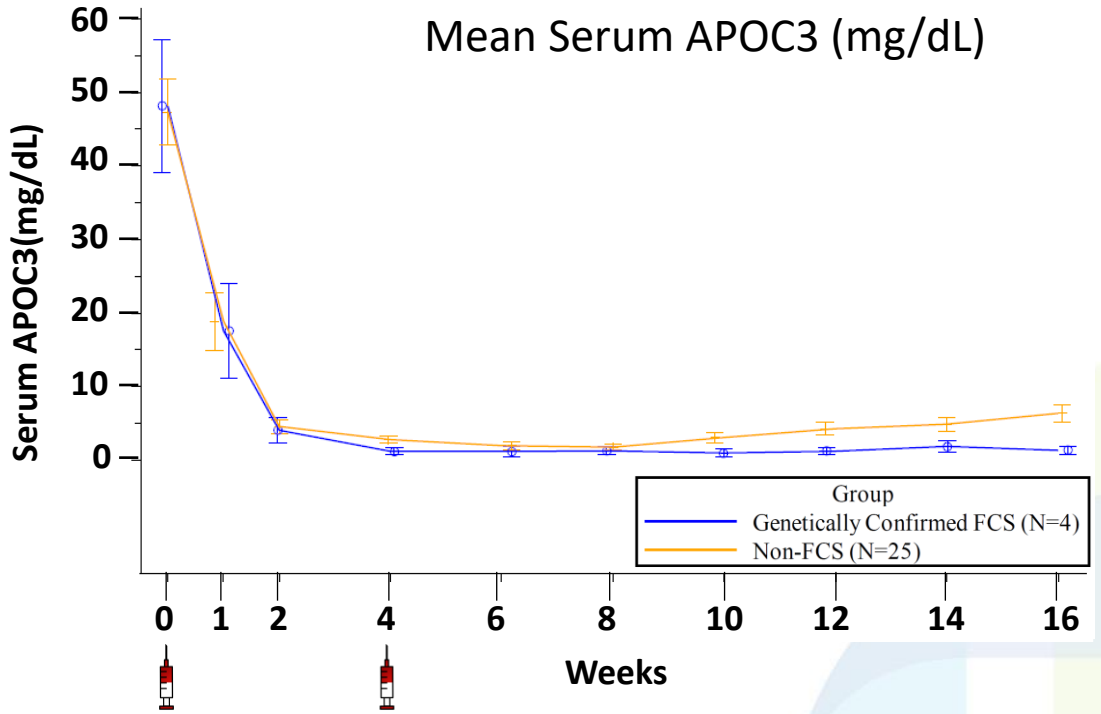
** p<0.001

Clinical Cutoff = 29 Mar 2021 (DBL)

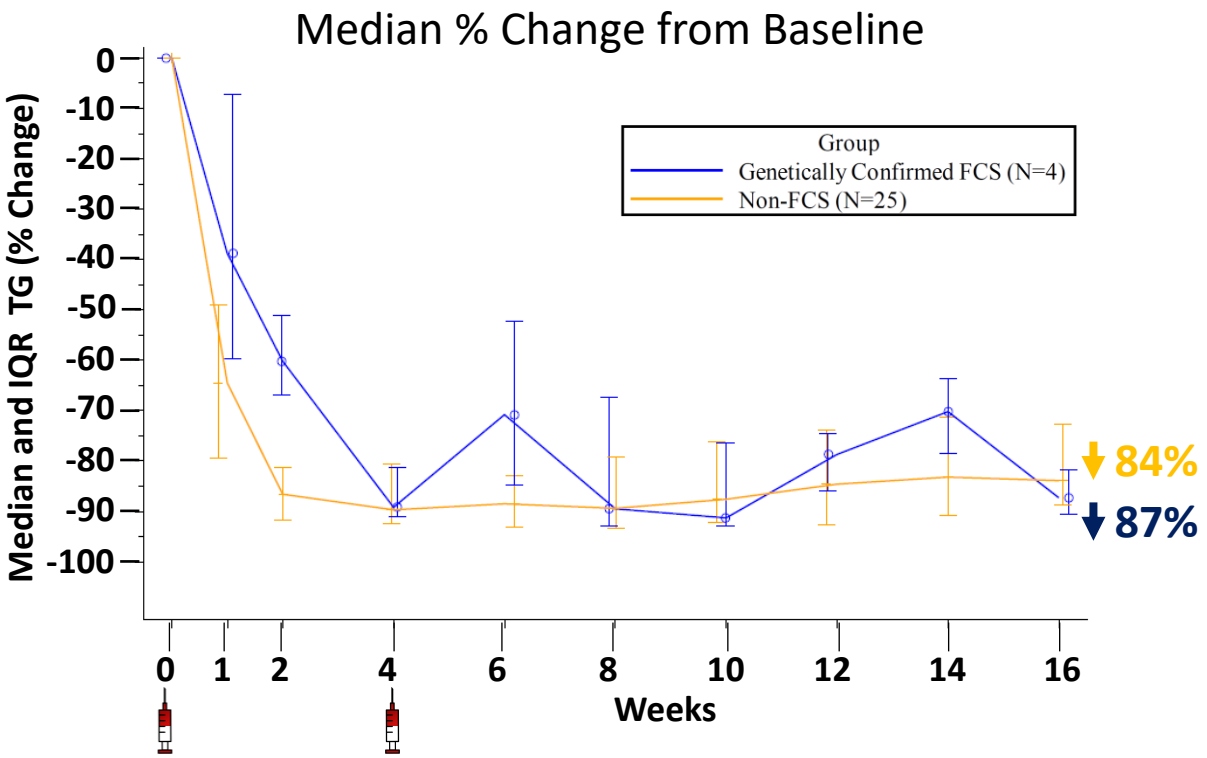
Given similar pharmacodynamic activity, all ARO-APOC3 doses were pooled in non-FCS group

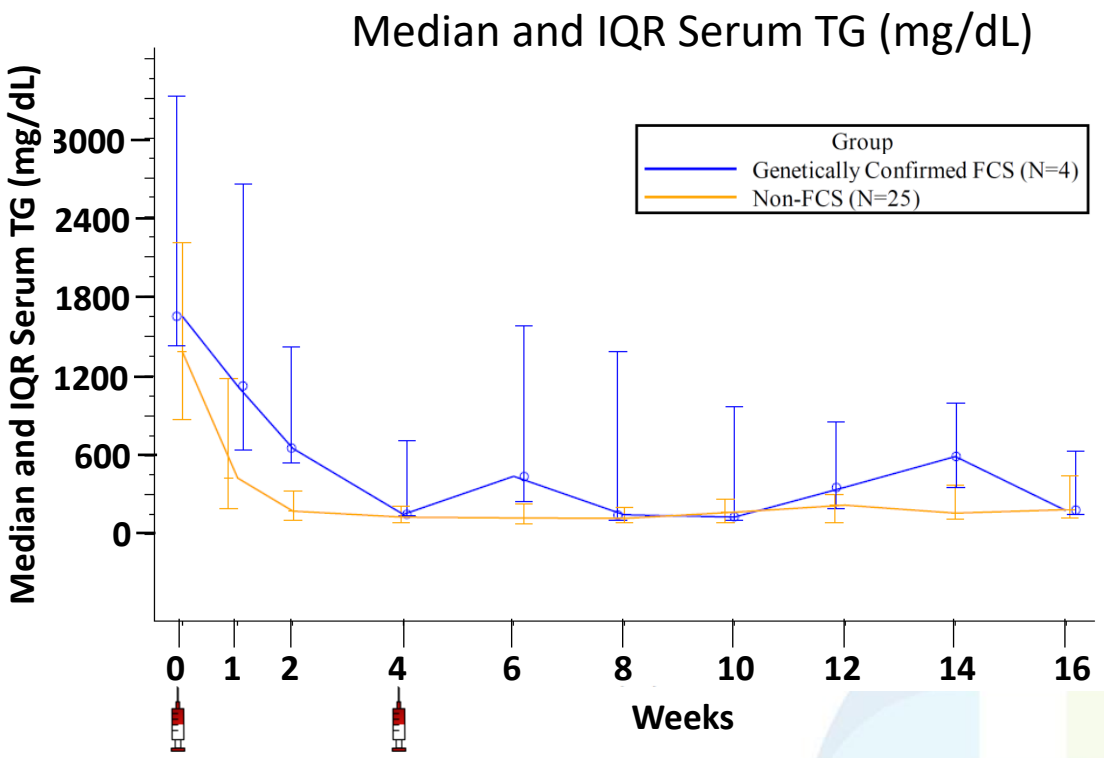
ARO-APOC3 results in similar, sustained reduction in baseline serum APOC3 in FCS and non-FCS participants





ARO-APOC3 results in similar sustained reduction of triglycerides in FCS and non-FCS participants





Summary Safety Findings Between FCS and Non-FCS Participants

# of Subjects Reporting ≥ 1 Event, n (%)	ARO-APOC3 FCS (N=4)	ARO-APOC3 Non-FCS (N=25)	All (N=29)
Treatment-emergent AEs (TEAEs) in MedDRA PT	3 (75%)	19 (76%)	22 (76%)
TEAEs in 2 or more subjects			
Headache	1 (25%)	5 (20%)	6 (21%)
Upper respiratory tract infection	0 (0%)	4 (16%)	4 (14%)
Alanine aminotransferase increased	1 (25%)	2 (8%)	3 (10%)
Abdominal distension	0 (0%)	2 (8%)	2 (7%)
Constipation	0 (0%)	2 (8%)	2 (7%)
Diarrhoea	1 (25%)	1 (4%)	2 (7%)
Fatigue	0 (0%)	2 (8%)	2 (7%)
Injection site bruising	1 (25%)	1 (4%)	2 (7%)
Injection site pain	1 (25%)	1 (4%)	2 (7%)
Nasopharyngitis	1 (25%)	1 (4%)	2 (7%)
Treatment-related TEAEs	2 (50%)	10 (40%)	12 (41%)
Serious TEAEs	0 (0%)	2 (8%)	2 (7%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0 (0%)	0 (0%)	0 (0%)
TEAEs causing deaths	0 (0%)	0 (0%)	0 (0%)

- TEAEs and the safety parameters were similar and comparable with FCS compared to non-FCS subjects.
- ARO-APOC3 was generally well tolerated.
- No TEAE-related study drug discontinuation, dose interruptions, or premature study withdrawals.
- No clear pattern of an increased frequency or intensity of AEs with increasing dose level.
- 2 SAEs (chest pain and acute pancreatitis) not related to ARO-APOC3 in 2 subjects in the non-FCS group. Both subjects completed the study.

Summary

- In patients with FCS compared with non-FCS, ARO-APOC3 SC achieves similar levels of reduction of APOC3 and changes in key lipid parameters
- In patients with FCS compared with non-FCS, safety parameters were similar and comparable
- In patients with severe HTG (TG>880 mg/dL), ARO-APOC3 was well tolerated, and consistently decreased APOC3, TG, and non-HDL-C, and increased HDL-C, independent of underlying genetic cause of HTG.
- ARO-APOC3 may represent a promising RNAi therapeutic for the treatment of severe HTG with infrequent dosing (Q3M or greater)