Pharmacodynamic effect of ARO-APOC3, an investigational hepatocyte-targeted RNA interference therapeutic targeting apolipoprotein C3, in patients with hypertriglyceridemia and multifactorial chylomicronemia

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arrowhead pharmaceuticals

Abstract: 12594

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, T Chang, B. Given, J San Martin, S Melquist and N Rajicic 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

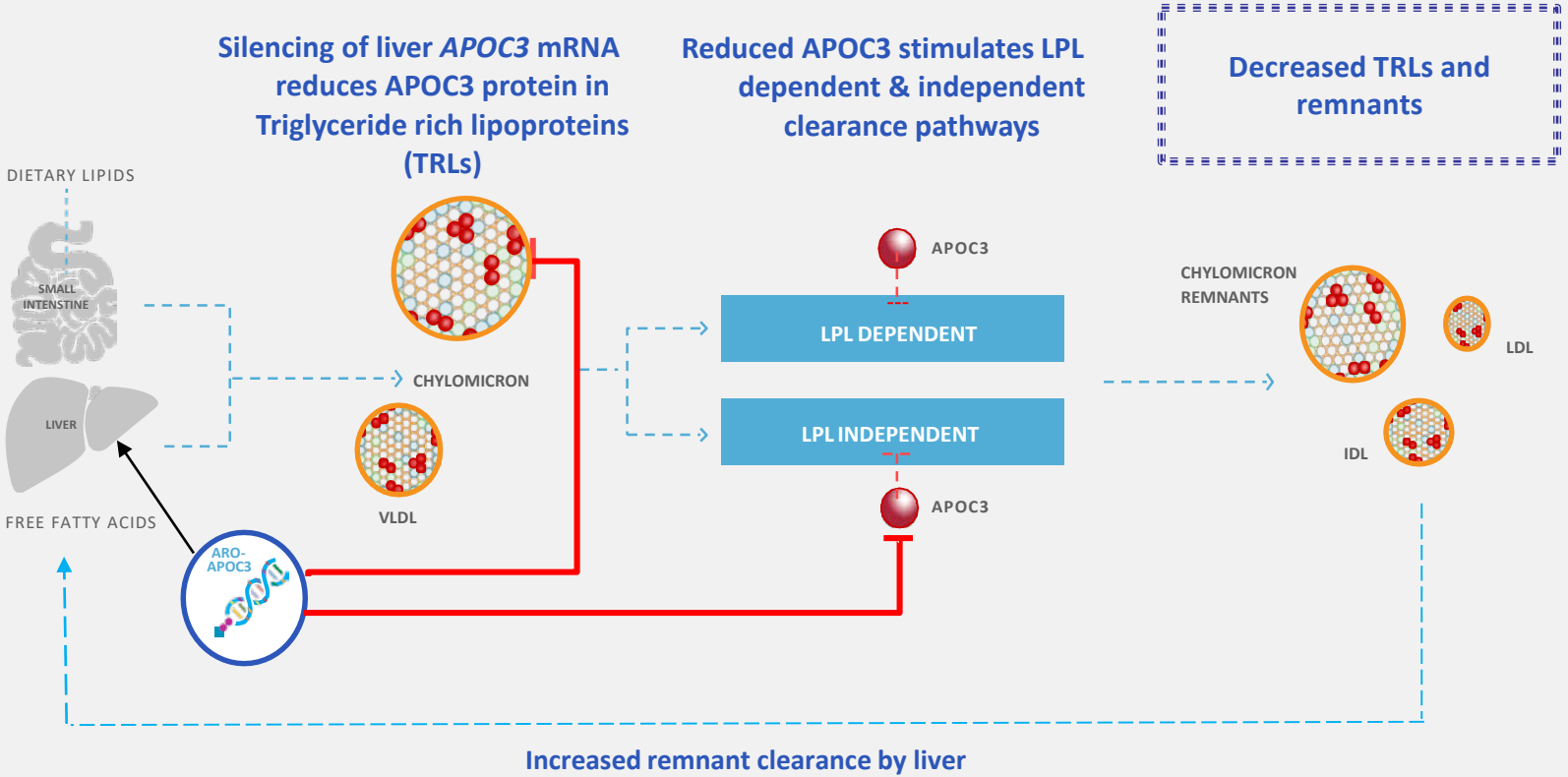
- **Severe hypertriglyceridemia (SHTG) is characterized by triglyceride (TG) levels ≥ 500 mg/dL, which can lead to acute pancreatitis**
  - SHTG may be caused by a combination of genetics (i.e., chylomicronemia), diet, and comorbid conditions (e.g., metabolic syndrome, diabetes)
  - Reduction and maintenance of TG levels below 500 mg/dL can reduce the risk of acute pancreatitis and is a goal of therapy[1]

- **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

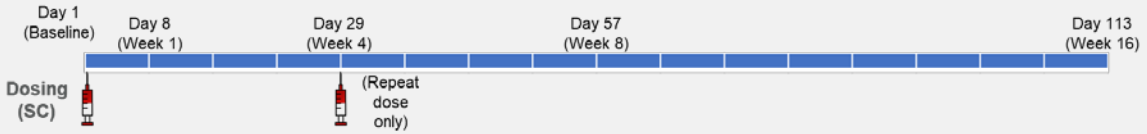
- **ARO-APOC3 is designed to specifically target and silence the *APOC3* gene, thereby reducing TG levels**
  - ARO-APOC3 is an investigational synthetic, double-stranded, hepatocyte-targeted RNA interference trigger designed to specifically target *APOC3* mRNA transcripts

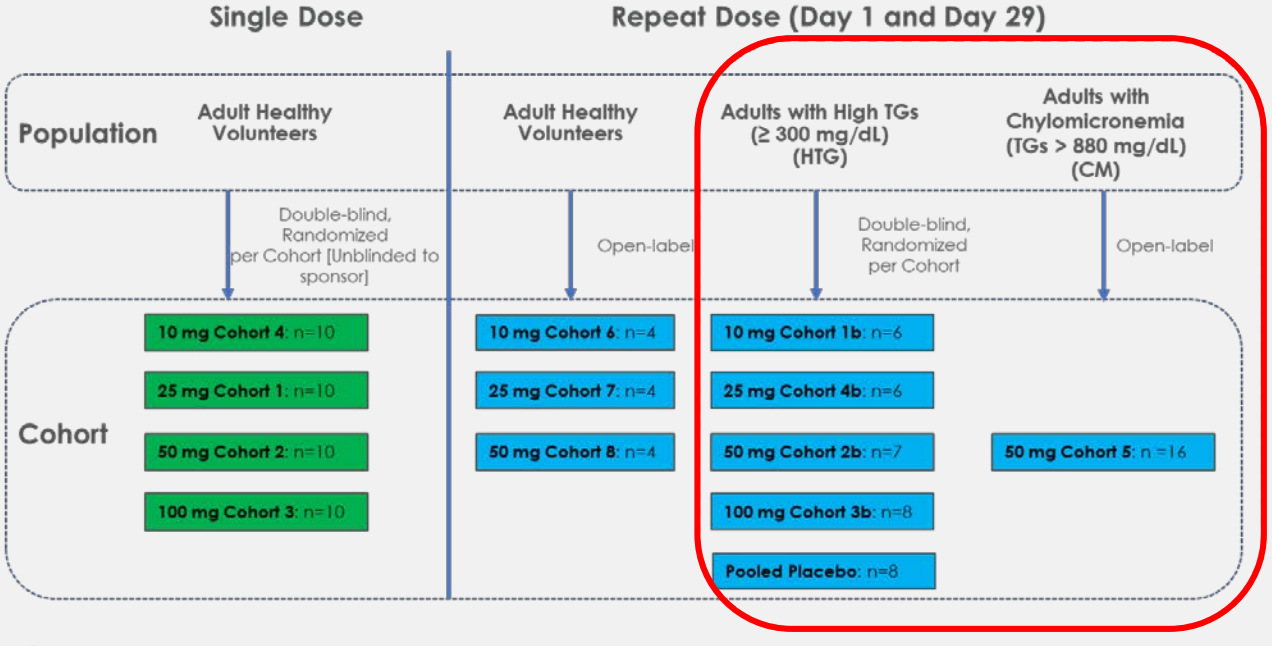
[1]NCEP 2002. Circulation 106:3143-3421

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



Phase 1 study to evaluate the effect of ARO-APOC3 in patients with hypertriglyceridemia (HTG) or chylomicronemia (CM)





Study Endpoints

Safety (Primary):

- Incidence and frequency of adverse events

Key Pharmacodynamics (PD) and Lipid Parameters:

- Change from baseline over time in APOC3
- Change from baseline over time in the following key parameters: Triglyceride, HDL-C, non-HDL-C

Data cut date: 31 Aug 2020

Baseline characteristics of HTG and CM patient cohorts

	HTG (TG≥ 300 mg/dL)					Chylomicronemia
Mean (range) Fasting values	**Pooled Placebo n=8**	**10 mg ARO-APOC3 n = 6**	**25 mg ARO-APOC3 n = 6**	**50 mg ARO-APOC3 n = 7**	**100 mg ARO-APOC3 n = 8**	**50 mg ARO-APOC3 n=16 (all active)**
Age (years)	47.6 (30-68)	50.2 (40-55)	53.8 (36-62)	48.1 (19-64)	55.0 (36-70)	46.8 (20-65)
% Male	75	100	67	43	75	56
BMI (kg/m^2)	30.7 (21.8-39.5)	32.7 (25.3-39.2)	30.5 (25.8-34.7)	30.7 (20.1-40.0)	32.2 (27.3-36.3)	29.6 (20.3-35.3)
APOC3 (mg/dL)	23 (13-34)	25 (15-42)	45 (25-88)	25 (13-49)	30 (18-63)	50 (19-88)
Triglycerides (mg/dL)	618 (262-1746)	596 (318-1381)	1659 (459-3546)	671 (294-1593)	616 (283-1448)	2015 (344-4636)
VLDL-C (mg/dL)*	88 (40-200)	128 (62-372)	321 (94-645)	98 (51-253)	104 (61-162)	259 (58-542)
LDL-C (mg/dL) (direct assay)	80 (15-144)	87 (56-130)	87 (16-150)	76 (23-117)	95 (12-184)	25 (2-77)
HDL-C (mg/dL)	28 (16-38)	28 (12-38)	28 (18-38)	29 (22-44)	33 (18-64)	18 (10-36)
non-HDL-C (mg/dL)	168 (81-231)	213 (110-443)	347 (188-696)	210 (126-332)	204 (139-314)	302 (123-598)

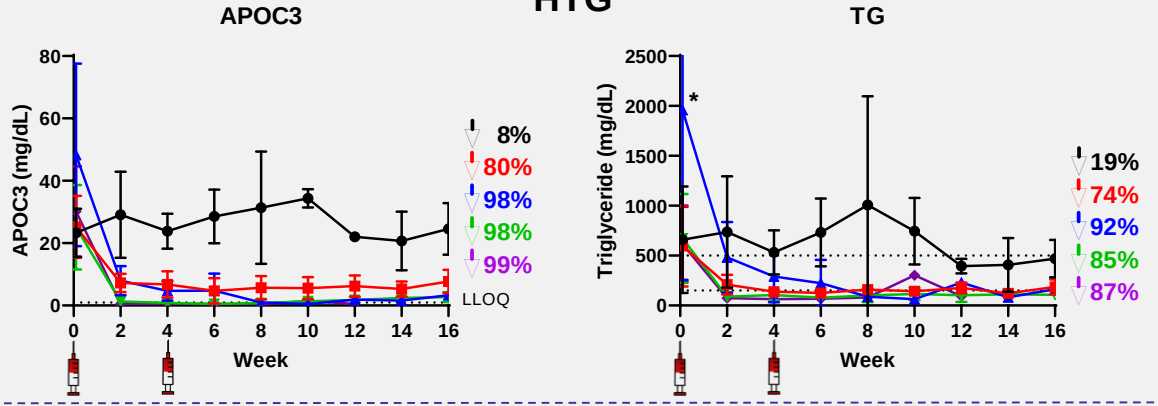
* VLDL-C is not calculated when TG > 400 mg/dL

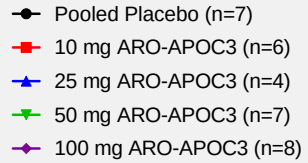
Data cut date: 31 Aug 2020

ARO-APOC3 results in substantial and sustained reduction of APOC3 and TG

HTG

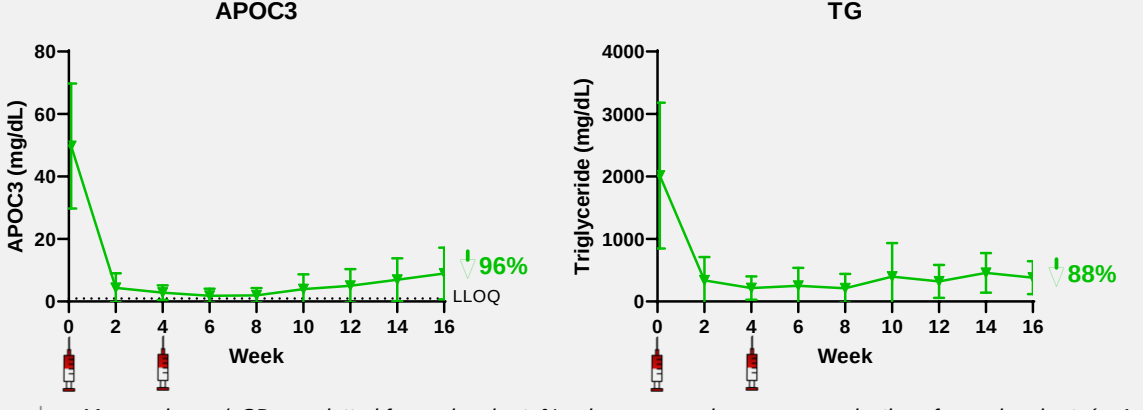
Data cut date: 31 Aug 2020

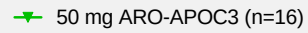




* Vertical error bar is truncated for 25 mg ARO-APOC3 cohort, Vertical error bars are truncated if they cross below zero

Chylomicronemia





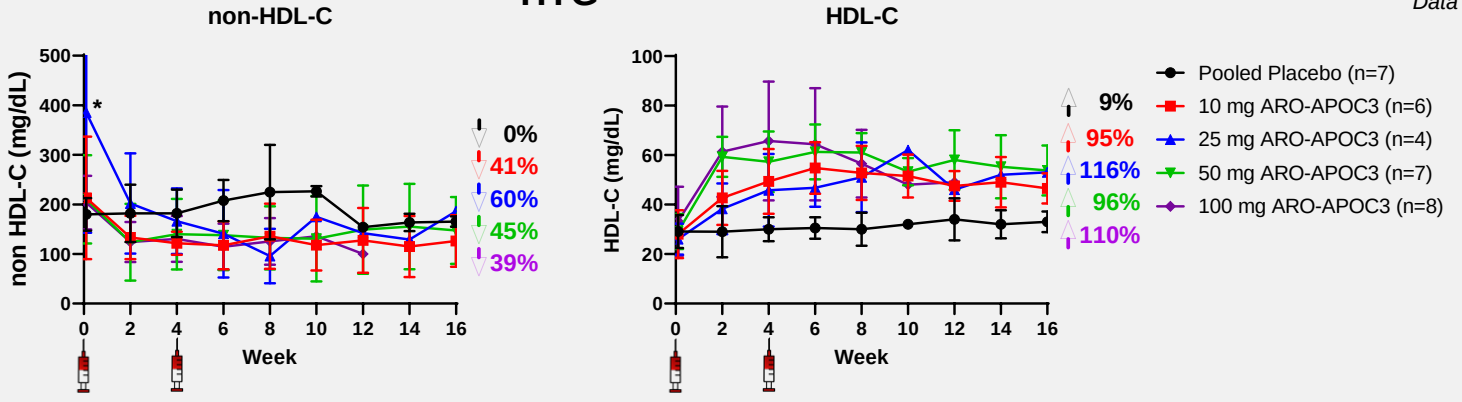
Only subjects with baseline + >1 additional visit are included in graphs

Mean values +/- SD are plotted for each cohort ;% values are maximum mean reductions for each cohort (n>1 subject at a visit date)

ARO-APOC3 substantially reduces non-HDL-C and increases HDL-C

HTG

Data cut date: 31 Aug 2020



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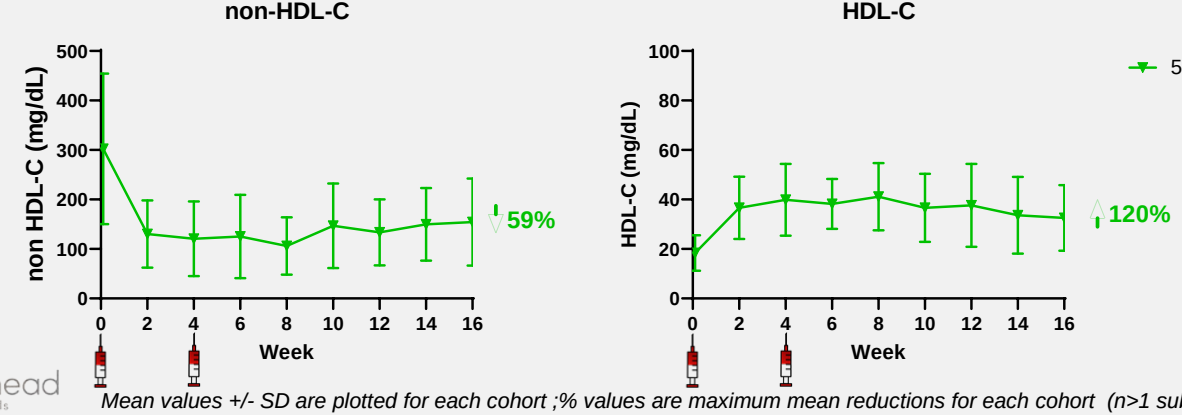
Chylomicronemia



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Mean values +/- SD are plotted for each cohort ;% values are maximum mean reductions for each cohort (n>1 subject at a visit date)

Summary interim safety findings in HTG and CM patients

	HTG Cohorts (TG>300 mg/dL)					CM TG>880mg/dL	
TEAEs Reported in > 1 subject, AE Term (MedDRA Preferred Term)	**10 mg Cohort 1b n = 5**	**25 mg Cohort 4b n = 5**	**50 mg Cohort 2b n = 7**	**100 mg Cohort 3b n=8**	**Pooled Placebo N=8**	**50 mg Cohort 5 n=16**	**Total Active n = 41**
Injection site reaction – erythema, rash, discoloration, pain, bruising	0	2 (40%)	2 (28.5%)	2 (25%)	0	2 (12.5%)	8 (19.5%)
ALT, LFT, transaminase increased, Liver function test increased	0	1 (20%)	1 (14%)	2 (25%)	0	3 (19%)	7 (17%)
Headache	1 (20%)	2 (40%)	2 (28.5%)	1 (12.5%)	0	0	6 (15%)
Upper respiratory tract infection	0	1 (20%)	2 (28.5%)	0	0	1 (6%)	4 (10%)
Rash	0	0	0	2 (25%)	0	1 (6%)	3 (7%)
Abdominal distention	0	2 (40%)	0	0	0	0	2 (5%)
Diarrhea	1 (20%)	0	1 (14%)	0	0	0	2 (5%)
Hyperglycemia	0	1 (20%)	1 (14%)	0	0	0	2 (5%)
Paresthesia	1 (20%)	0	0	1 (12.5%)	0	0	2 (5%)

Safety data cutoff 11 Sep 2020

- **AEs at injection site were all mild**
- **ALT elevations were generally asymptomatic and transient, returning towards baseline by end of study**
  - Only two subjects had ALT >3X ULN at two sequential visits with return to pre-dose baseline by Day 113 (EOS).
  - The highest ALT was in a subject with a history of cholelithiasis and biliary colic. Baseline ALT of 22 U/L, elevation on Day 85 to 230 U/L with return to 36 U/L on Day 99 and 33 U/L at Day 113 (EOS) Subject subsequently underwent elective cholecystectomy
- **No clinically significant adverse changes in platelets, total bilirubin or creatinine**
- **No drug discontinuations**
- **1 SAE of pancreatitis**
  - Not related to ARO-APOC3
  - History of pancreatitis, type 2 diabetes mellitus and gall stones
  - MRCP/endoscopic ultrasound indicated pancreatolithiasis as probable cause

ARO-APOC3, an investigational RNAi therapeutic that silences *APOC3* mRNA transcripts results in favorable lipid changes in patients

- In patients with **hypertriglyceridemia**, 10 mg, 25 mg, 50 mg and 100 mg SC doses of ARO-APOC3, resulted in **robust and sustained reductions in TGs and Non-HDL-C with HDL-C increases**
  - Maximal mean reduction of -80% to -99% in APOC3
  - Maximal mean reduction of -74% to -92% in TG, -39% to -62% in non-HDL-C
  - Maximal mean increase of +95% to +116% in HDL-C
- In patients with **chylomicronemia,** 50 mg ARO-APOC3 SC achieves similar levels of **reduction of APOC3 and changes in key lipid parameters**
  - Maximal mean reduction of -98% in APOC3
  - Maximal mean reduction of -88% in TG, -59% in non-HDL-C
  - Maximal mean increase of +120% in HDL-C
- The effect of ARO-APOC3 is **maintained >12 weeks post second dose** regardless of patient population
- ARO-APOC3 **safety profile** supportive of later stage clinical development based on interim Phase 1 study results

ARO-APOC3 may prove useful as a therapeutic option in patients with hypertriglyceridemia, severe hypertriglyceridemia and chylomicronemia