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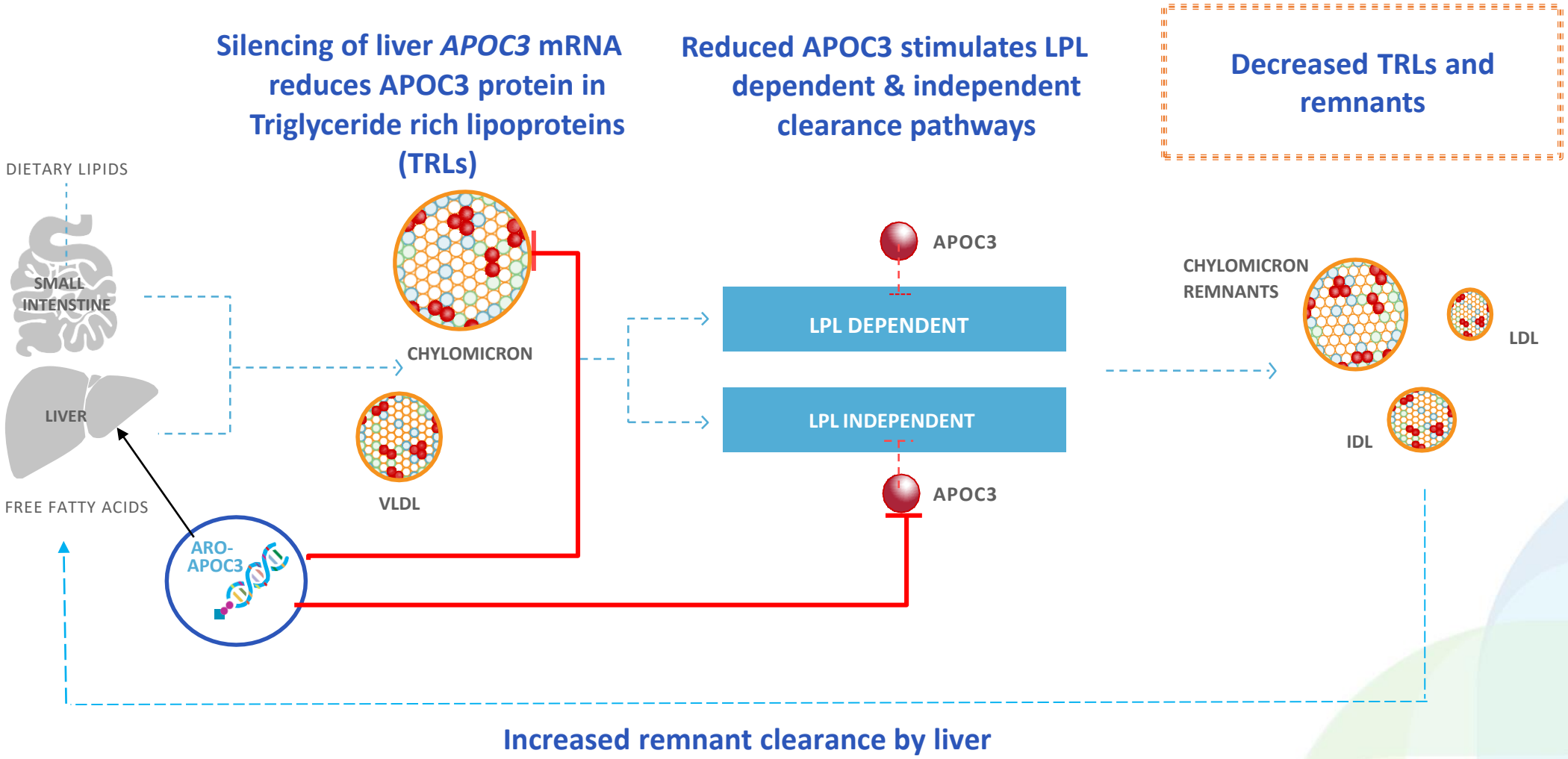
APOC3 is a key regulator of triglyceride-rich lipoproteins (TRLs) through lipoprotein lipase (LPL)-dependent and -independent pathways

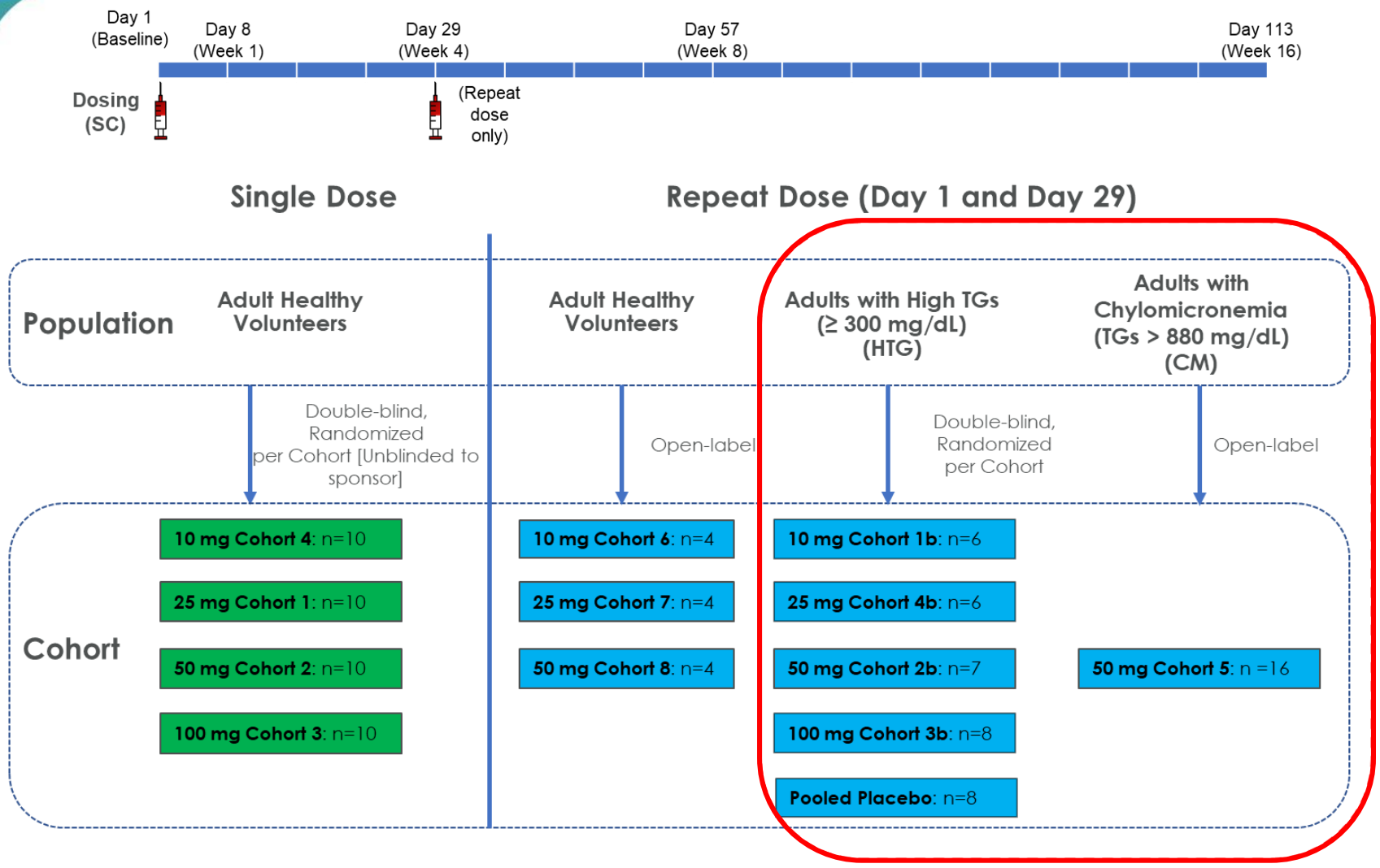
- **Severe hypertriglyceridemia (SHTG) is characterized by triglyceride (TG) levels ≥ 500 mg/dL, which can lead to acute pancreatitis**
  - SHTG may be caused by a combination of genetics (i.e., chylomicronemia), diet, and comorbid conditions (e.g., metabolic syndrome, diabetes)
  - Reduction and maintenance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

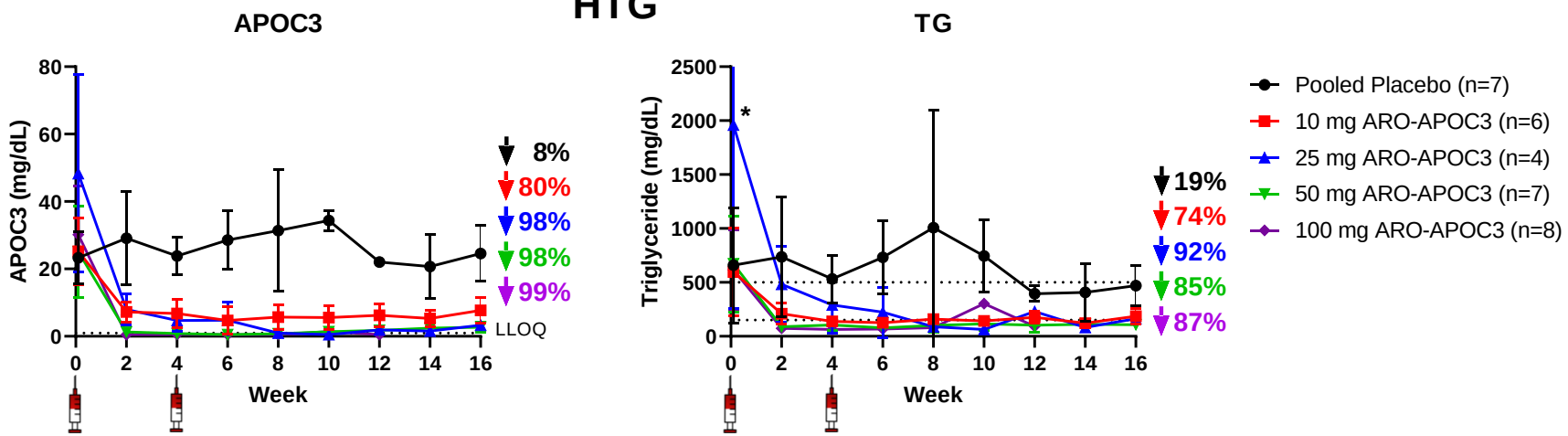
- Change from baseline over time in APOC3
- Change from baseline over time in the following key parameters: Triglyceride, HDL-C, non-HDL-C

Data cut date: 31 Aug 2020

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

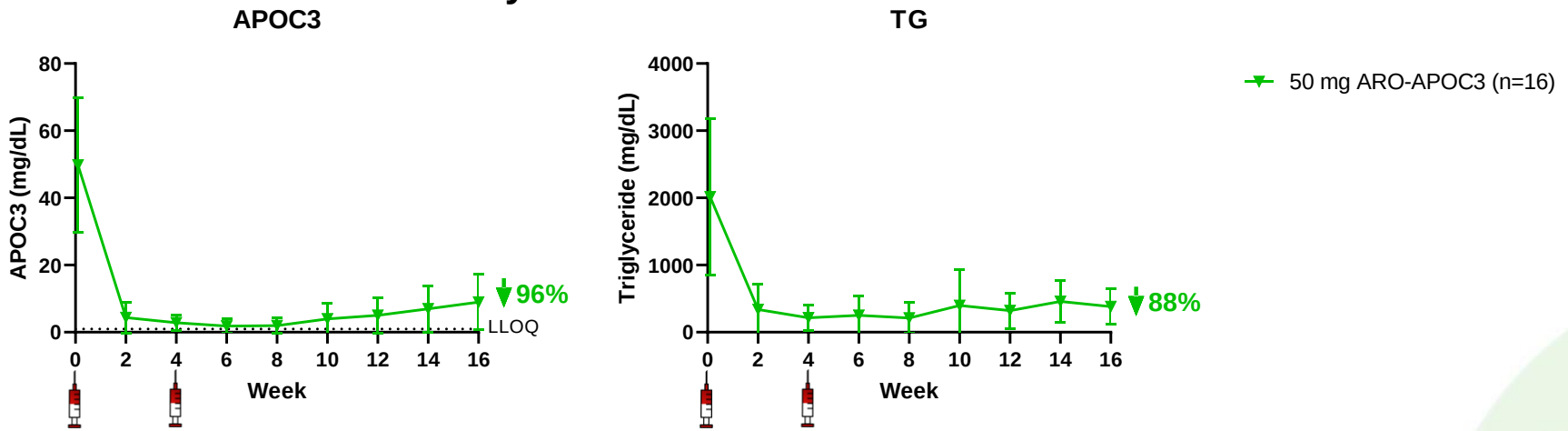
Data cut date: 31 Aug 2020

HTG



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

Chylomicronemia



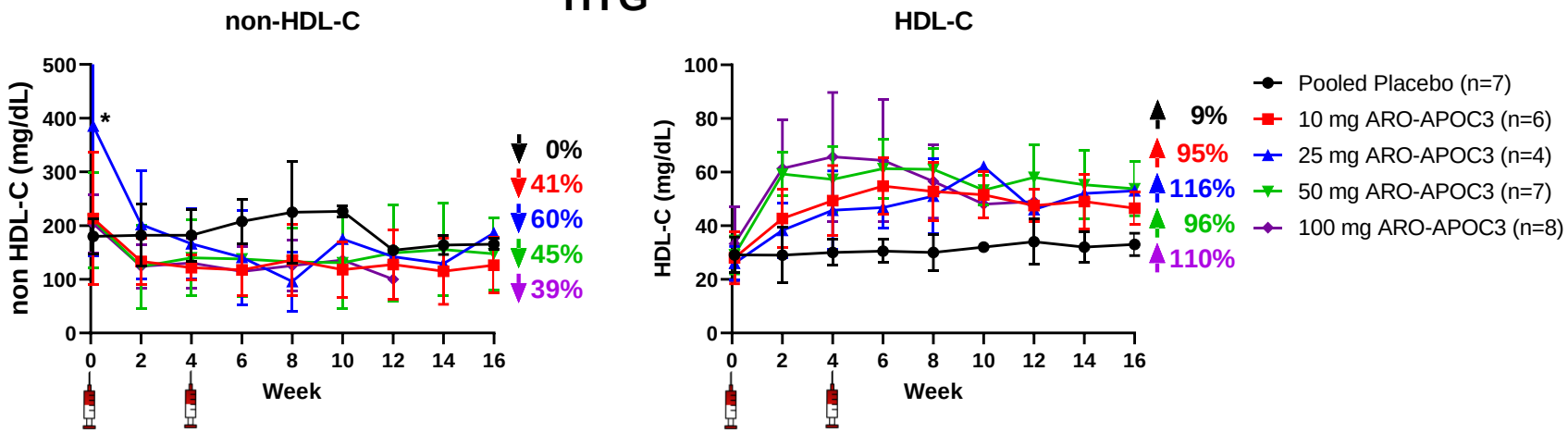
Only subjects with baseline + >1 additional visit are included in graphs

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

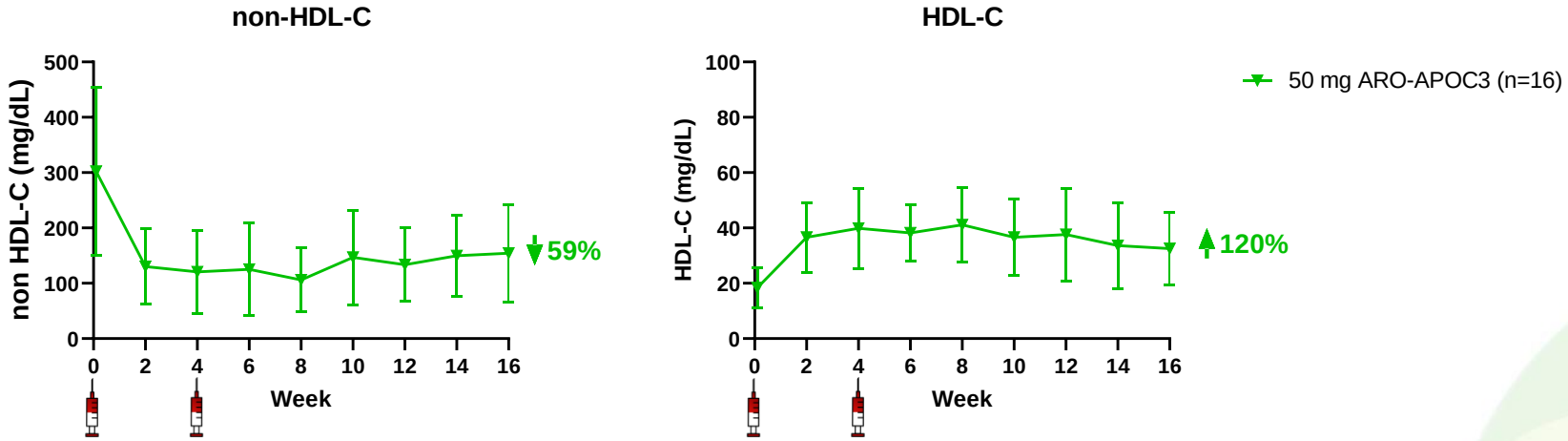
HTG

Data cut date: 31 Aug 2020



* Vertical error bar is truncated for 25 mg ARO-APOC3 cohort

Chylomicronemia



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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