Scientific Sessions 2019

RNA Interference Targeting Apolipoprotein C-III Results in Deep and Prolonged Reductions in Plasma Triglycerides

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Human Genetic Validation of Apolipoprotein C-III (APOC3) as a Target for Hypertriglyceridemia, Cardiovascular Disease

- Plasma triglyceride (TG) levels are an independent risk factor for cardiovascular disease and pancreatitis
- Apolipoprotein C-III (APOC3*)* is a component of VLDL, chylomicrons and functions to inhibit lipoprotein lipase (LPL) and non-LPL driven TG metabolism
- *APOC3* loss-of-function results in lower TG levels[1,2]
- *APOC3* targeted antisense oligonucleotide shown to be effective in lowering TG levels
  - toxicity profile was considered adverse, with Q1 wk dose intervals required
- APOC3 is predominantly synthesized in hepatocytes (~80-90%), an ideal target gene for RNAi therapeutic using Arrowhead's Targeted RNAi Molecule (TRiM™) platform
  - ARO-APOC3 is a hepatocyte targeted siRNA
  - Designed to induce deep and durable gene specific silencing while avoiding off-target effects

[1]Jorgensen AB *et al.*, NEJM 2014; 371:32-41
[2]TG and HDL Working Group of the Exome Sequencing Project; NEJM 2014; 371:22-31

Familial Chylomicronemia Syndrome, Severe Hypertriglyceridemia with Pancreatitis: Areas of High Unmet Medical Need

- Familial Chylomicronemia Syndrome (FCS) caused by impaired lipoprotein lipase (LPL) leading to extremely high TG levels [>880 mg/dL (10 mmol/L)]
  - Prevalence of approximately 1 in 1 million[1] with increased prevalence in populations such as French Canadians (founder effect)[2]
  - Symptoms include chronic daily abdominal pain, acute and chronic pancreatitis, diabetes mellitus
  - **Refractory to standard TG lowering therapies**, standard of care is very low fat (<20 g) diet

- Severe High Triglycerides (sHTG) with pancreatitis
  - Polygenic disorder exacerbated by comorbidities, diet and lifestyle
  - Prevalence of TG > 500 mg/dL (> 5.65 mmol/L) 1.7%[3,4]
  - 4% increased risk of acute pancreatitis for every 100 mg/dL (1.1 mmol/L) TG increase [5]

- For both conditions adherence to current therapies including strict diet/lifestyle changes is challenging

[1] Brahm and Hegele, Nat Rev Endocrinol. (2015) 11:352-362
[2] Gagné C *et al.,* CMAJ (1989) 140: 405-411.
[3] Ford *et al.,* Arch Intern Med. (2009) 169:572-578.
[3] Christian JB *et al.*, Am J Cardiol. (2011) 107:891-897.
[4] Murphy MJ *et al.*, JAMA Intern Med. (2013) 173:162-164.

AROAPOC31001 Study Design: Phase 1/2a clinical study

Primary Objective: Safety and Tolerability

Secondary/Exploratory Objectives: Pharmacokinetics and Pharmacodynamics

- Single and multiple dose PK of ARO-APOC3 in healthy volunteers
- Reduction in fasting serum APOC3 from baseline
- Changes in fasting serum lipids and lipoproteins

Cohort Description:

Single Dose:

- Cohorts 1-4 : Normal Healthy Volunteers (NHV) with fasting TG >80 mg/dL (6 active, 4 placebo (PBO) per cohort)

Multiple Dose (2 monthly doses):

- Cohorts 1b-4b: Dose ranging in subjects with history of fasting TG ≥ 500 mg/dL
- Cohort 5: Diagnosis of Familial Chylomicronemia Syndrome or Screening TG ≥ 880 mg/dL
- Cohort 6-8: NHV, multi-dose

Cohort 1-4 Baseline Characteristics

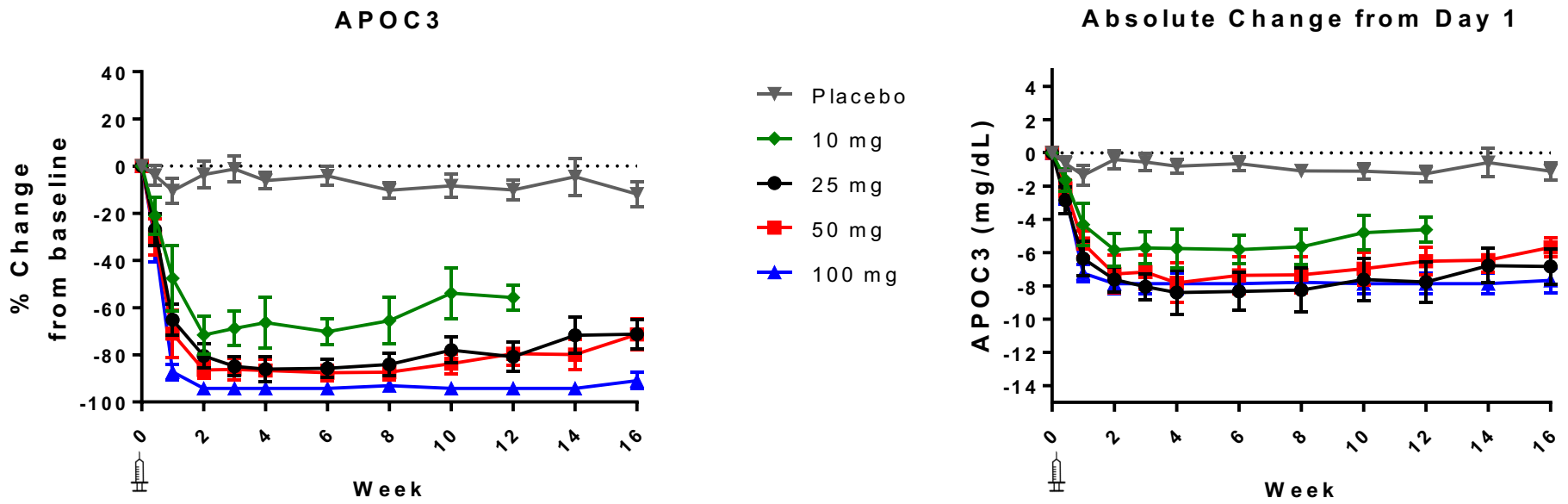
Mean (range) Fasting values	Cohort 1 (25 mg) n = 10 (6 active: 4 PBO)	Cohort 2 (50 mg) n = 10 (6 active: 4 PBO)	Cohort 3 (100 mg) n = 10 (6 active: 4 PBO)	Cohort 4 (10 mg) n = 10 (6 active: 4 PBO)
Age (years)	36 (23-51)	40.9 (20-61)	33.7 (22-65)	40.4 (24-62)
% Male	70%	60%	50%	70%
BMI (kg/m^2)	27.4 (22.8-32.0)	27.6 (22.3-34.1)	28.2 (21.0-34.1)	27.5 (20.6-36.6)
APOC3 (mg/dL)	11.5 (6.7-16.1)	9.2 (4.5-14.2)	9.7 (6.0-19.9)	7.7 (3.8-9.3)
Triglycerides (mg/dL)	189 (80-292)	134 (71-230)	141 (80-283)	120 (71-204)
VLDL-C (mg/dL)	32 (13-51)	24 (13-40)	25 (13-51)	21 (13-34)
LDL-C (mg/dL) (direct assay)	130 (101-158)	126 (74-195)	109 (84-135)	112 (67-158)
HDL-C (mg/dL)	32 (13-51)	41 (30-54)	40 (30-54)	41 (30-57)

Safety (NHV cohorts 1-4)

- 40 subjects enrolled and dosed (24 active, 16 placebo)
- No Serious AEs reported
- No Severe AEs reported
- One AE of moderate transient ALT elevation (peak of 210 U/L) in subject receiving ARO-APOC3 who had elevated ALT at baseline (65 U/L), with return to baseline by end-of-study (Day 113, 45 U/L).
- No other AEs from lab abnormalities in subjects receiving drug
- 8 Local Injection Site Reactions (LISRs) – all rated mild, more common at higher doses
  - LISR defined based on specific MedDRA preferred terms with duration of at least 48 hours.

Dose Dependent Reduction of APOC3

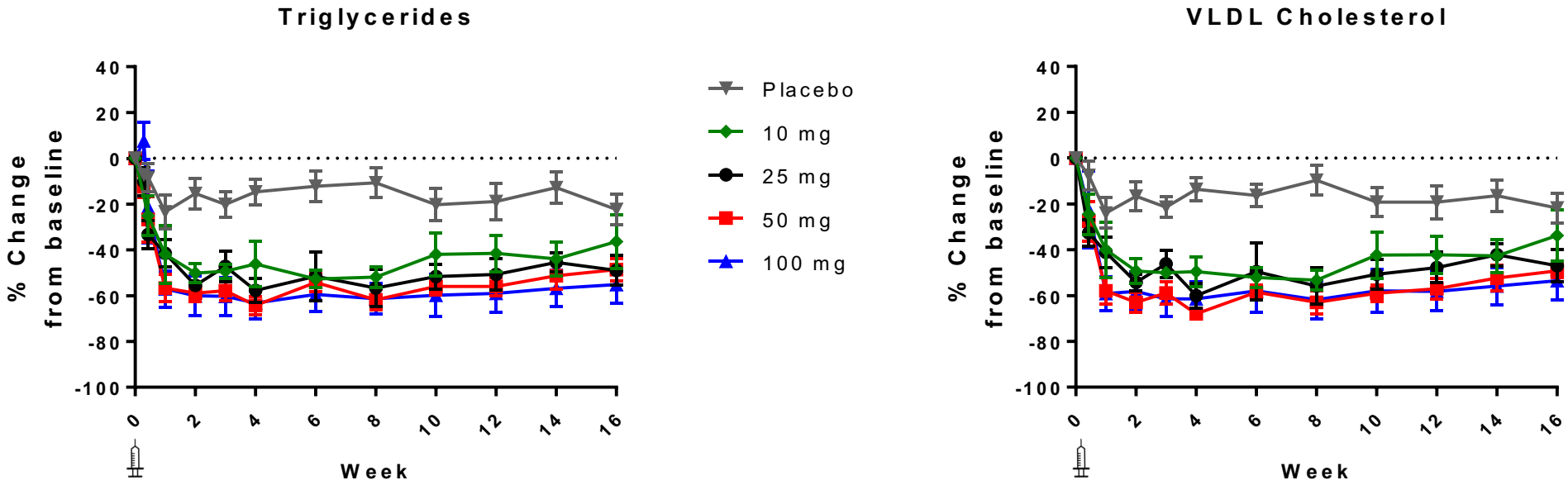
ARO-APOC3 or Placebo given on Day 1, Mean ± SEM



- Minimal dose response seen between 25 - 100 mg, therefore added 10 mg dose level
- Mean maximum reduction from baseline in serum APOC3 levels ranged from 72% [10 mg dose] ($p<0.0001$) to 94% [100 mg dose] ($p<0.0001$)
- Reduction in serum APOC3 levels was maintained through the end of study (Week 16), with Week 16 mean reductions of 70% [25 mg dose] to 91% [100 mg dose]

Reductions in Triglycerides and VLDL-C

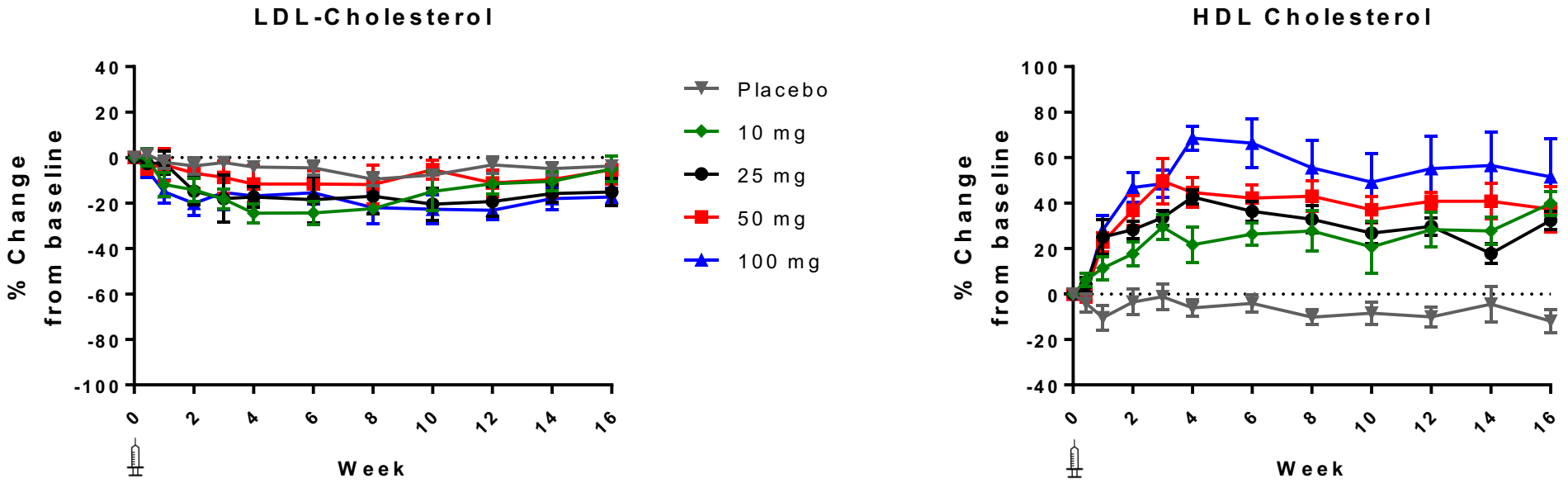
ARO-APOC3 or Placebo given on Day 1, Mean ± SEM



- Mean maximum reduction from baseline in serum TGs ranged from 53% (77 mg/dL) [10 mg dose] (p=0.002) to 64% (92 mg/dL) [100 mg dose] (p=0.0001)
- Mean maximum reduction from baseline in serum VLDL-C ranged from 53% (16 mg/dL) [10 mg dose] (p=0.0005) to 68% (19 mg/dL) [50 mg dose] (p<0.0001)
- Reduction in serum TG and VLDL-C was maintained through the end of study, with week 16 mean reductions of 41% to 55% for TG and 42-53% for VLDL-C

Changes in LDL-C and HDL-C

ARO-APOC3 or Placebo given on Day 1, Mean ± SEM



- Mean maximum reduction from baseline in serum LDL-C of 12% (19 mg/dL) [25 mg dose] (p=0.03) to 25% (35 mg/dL) [10 mg dose] (p=0.0004)
- Dose dependent increase in serum HDL-C with mean maximum increase from baseline in serum HDL-C from 30% (13 mg/dL) [10 mg dose] (p=0.0006) to 69% (32 mg/dL) [100 mg dose] (p<0.0001)
- Serum HDL-C increases were maintained through the end of study, with week 16 mean increases of 28% (12 mg/dL) [10 mg dose] to 52% (22 mg/dL) [100 mg dose]

Conclusions

- *APOC3* loss-of-function mutations have been associated with improved CV outcomes without identified phenotypic cost
  - Lipid phenotype includes reduced triglycerides, VLDL-C and increased in HDL-C
- ARO-APOC3, a RNAi therapeutic designed to silence hepatocyte *APOC3* mRNA shows after single doses in healthy volunteers:
  - Deep and durable reductions in serum APOC3 even at 10 and 25 mg dose levels.
  - Reductions in triglycerides, VLDL-C, LDL-C and increases in HDL-C similar to those reported in GWAS studies
  - A favorable safety and tolerability profile
- Opportunity for quarterly or Q6 month dose intervals, **ideal for populations with therapy adherence issues**
- Multiple dose evaluations in patients with severe hypertriglyceridemia and/or familial chylomicronemia syndrome are underway

Thank you!

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