RNA Interference Targeting Apolipoprotein C-3 with ARO-APOC3 in Healthy Volunteers Mimics Lipid and Lipoprotein Findings Seen in Subjects With Inherited Apolipoprotein C-3 Deficiency

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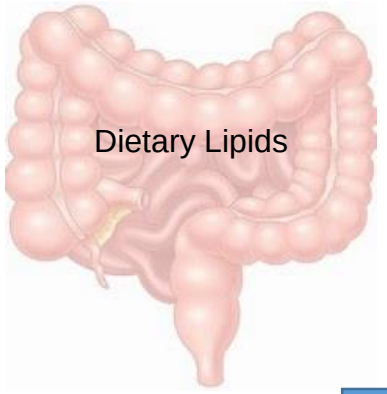
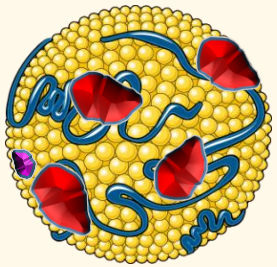
APOC3 Inhibits Lipoprotein Lipase and Inhibits Hepatocyte Triglyceride Rich Lipoprotein Clearance

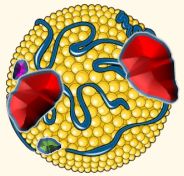
Triglyceride Synthesis

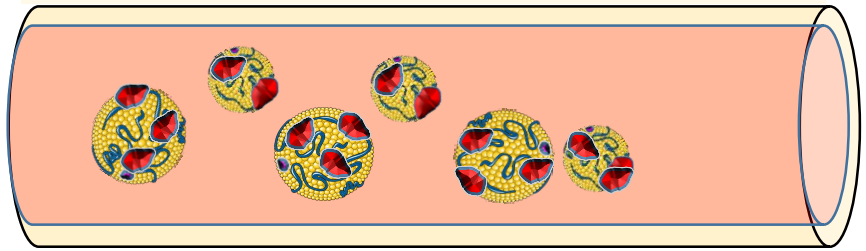


APOC3

Increased APOC3 Concentration







Circulating TGs

Reduced Triglyceride Clearance

Hydrolysis

LPL-Dependent

Uptake and Clearance of
Triglyceride-Rich Lipoprotein

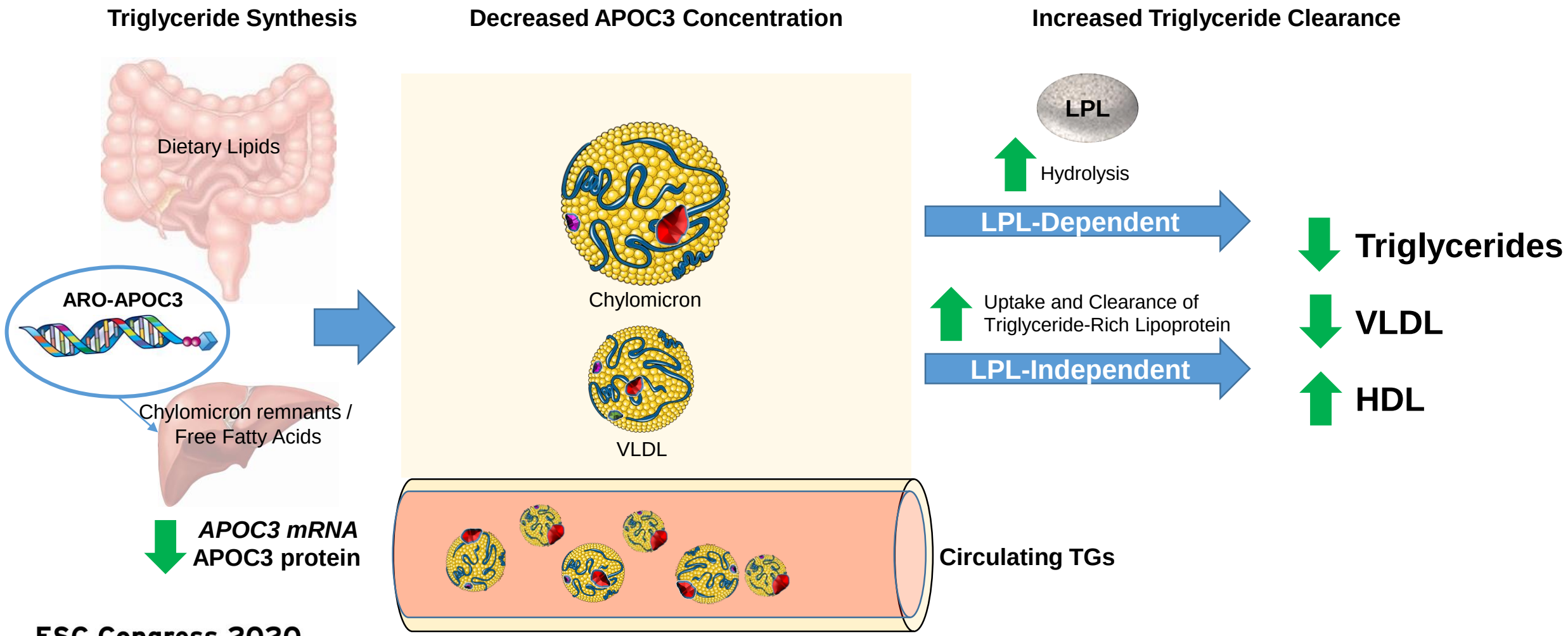
LPL-Independent

Triglycerides

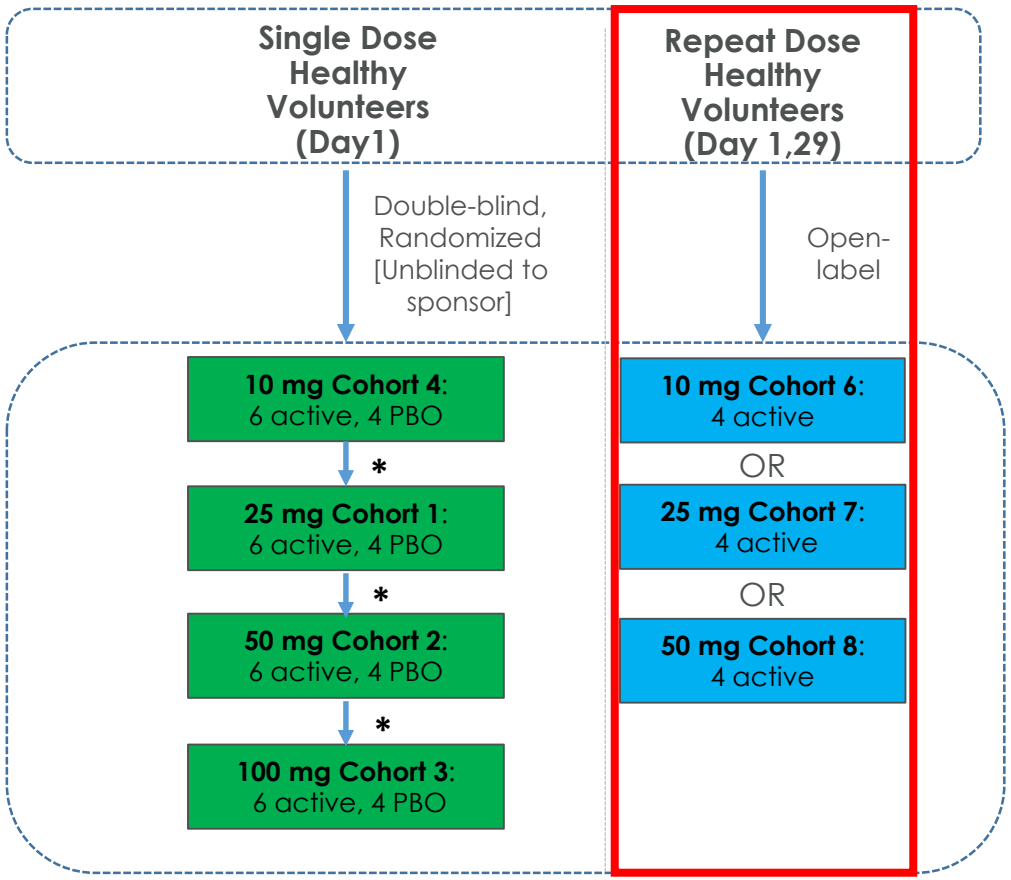
VLDL

HDL

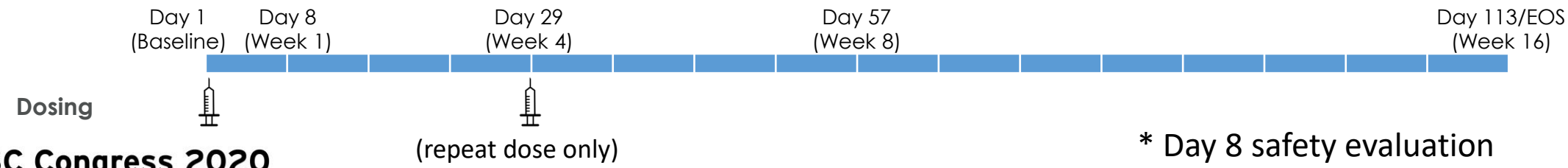
APOC3 Inhibits Lipoprotein Lipase and Inhibits Hepatocyte Triglyceride Rich Lipoprotein Clearance



AROAPOC31001 First-in-Human Study Design – Healthy Volunteers



- Results from single dose cohorts presented at AHA 2019
- Subcutaneous doses of ARO-APOC3 on days 1 and 29 for repeat dose healthy volunteer cohorts
- Repeat dose High TG and Chylomicronemia patient cohorts are enrolling and results will be presented in the future



* Day 8 safety evaluation

AROAPOC31001 Phase 1 study evaluated the safety and pharmacodynamic effects of ARO-APOC3

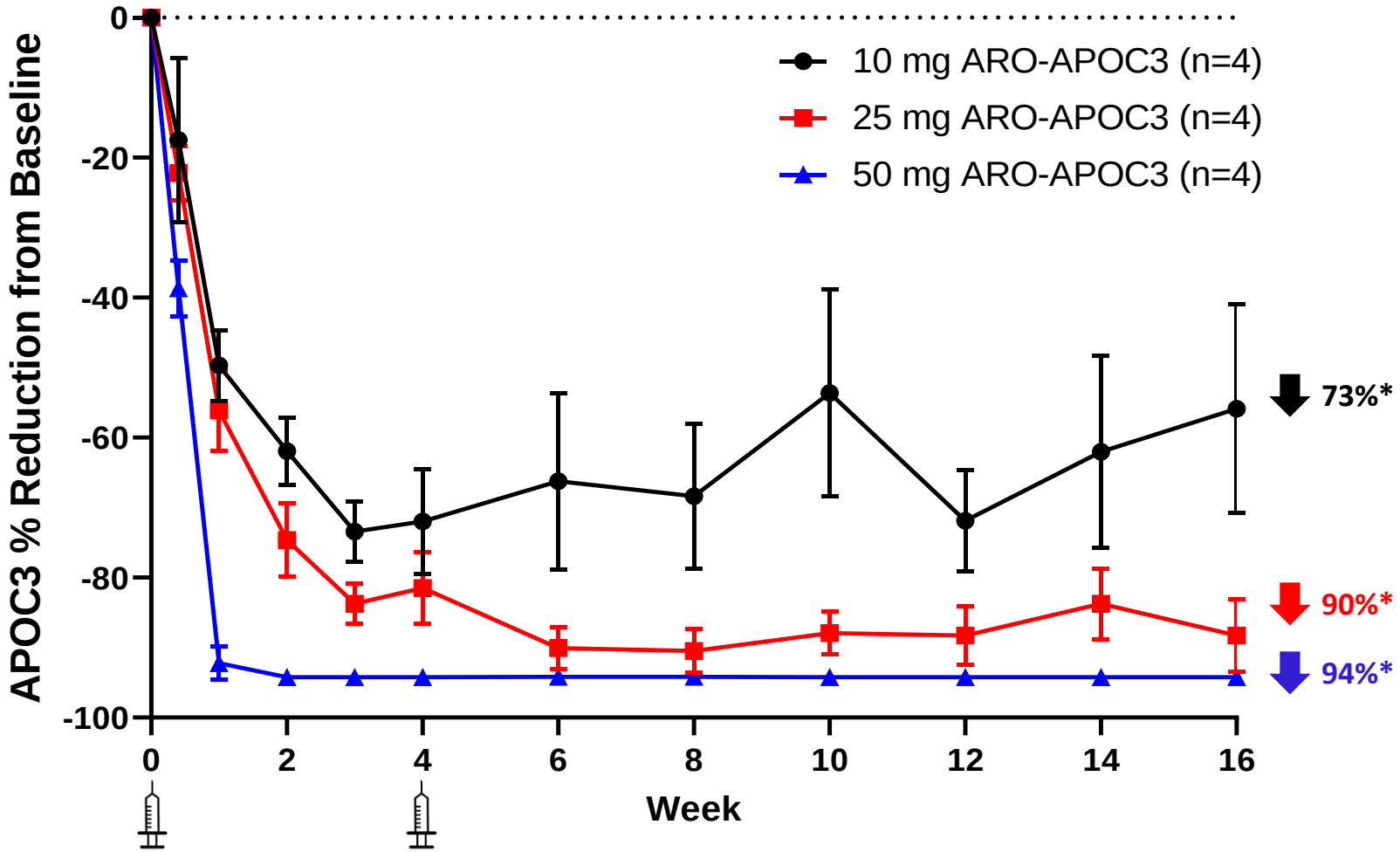
Study Objectives	
Primary Objective	• Evaluate incidence of adverse events as a measure of safety and tolerability
Secondary Objectives	• Evaluate pharmacokinetics • Determine change from baseline in serum APOC3
Exploratory Objectives	• Evaluate fasting lipids (Triglycerides, LDL-C, ApoB, HDL-C, ApoA1) • Evaluate fasting and 2-hour postprandial triglycerides at weeks 0 and 12

Baseline Characteristics of Repeat Dose Healthy Volunteers*

	Repeat Dose		
Mean (Range)	10 mg Cohort 6 n = 4 (all active)	25 mg Cohort 7 n = 4 (all active)	50 mg Cohort 8 n = 4 (all active)
Age (years)	50.0 (41-57)	50.5 (46-55)	50.0 (37-61)
% Male	75%	50%	75%
BMI (kg/m^2) at screening	27.9 (21.8-32.8)	32.2 (25.1-34.1)	30.0 (25.6-36.2)
APOC3 (g/L)	**0.11 (0.09 – 0.13)**	**0.10 (0.08 – 0.12)**	**0.08 (0.07 – 0.10)**
Triglycerides (mmol/L)	**1.65 (1.14 – 2.20)**	**1.64 (1.14 – 2.11)**	**1.59 (1.14 - 2.24)**
LDL-C (mmol/L) (direct assay)	3.71 (2.95 – 4.38)	5.17 (4.43 – 7.12)	3.00 (2.20 – 3.70)
HDL-C (mmol/L)	1.21 (1.01 - 1.40)	1.25 (1.06 – 1.61)	1.08 (0.93 – 1.19)
TC (mmol/L)	5.68 (4.77 – 6.42)	7.23 (6.27 - 9.17)	4.86 (4.22 - 5.59)
Non-HDL-C (mmol/L)	4.47 (3.37 – 5.41)	5.98 (5.21 – 7.98)	3.78 (3.06 - 4.56)
ApoA1 (g/L)	1.50 (1.47 - 1.58)	1.59 (1.45 - 1.82)	1.27 (1.14 - 1.43)
ApoB (g/L)	1.14 (0.85 - 1.37)	1.45 (1.23 - 1.89)	0.90 (0.74 - 1.06)

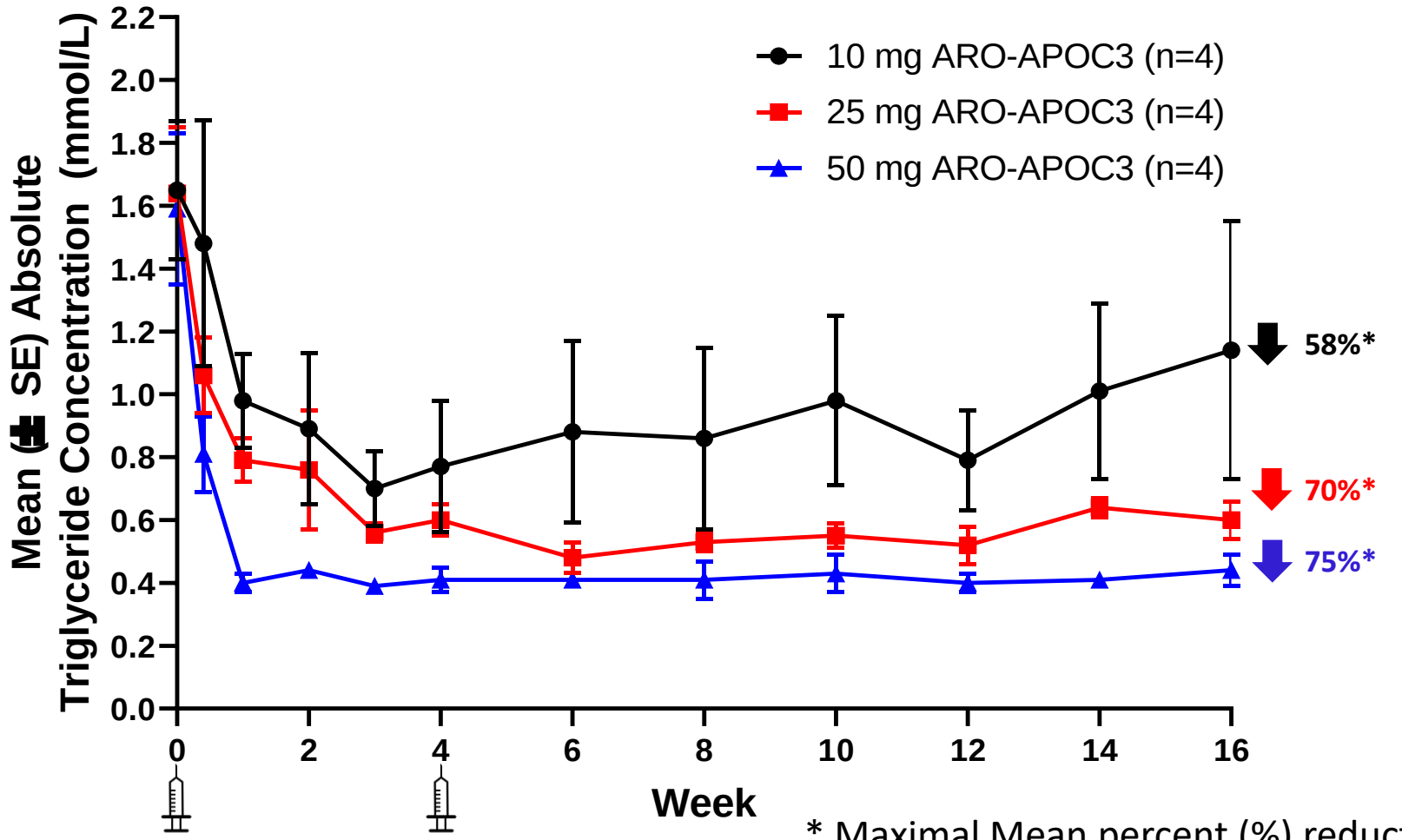
*Inclusion criteria: TG > 0.903 mmol/L, not on statins or other lipid-lowering medications

Repeat Dose ARO-APOC3 Demonstrated Substantial and Durable Reductions in APOC3 in Healthy Volunteers Over 16 Weeks



* Maximal Mean percent (%) reductions from baseline

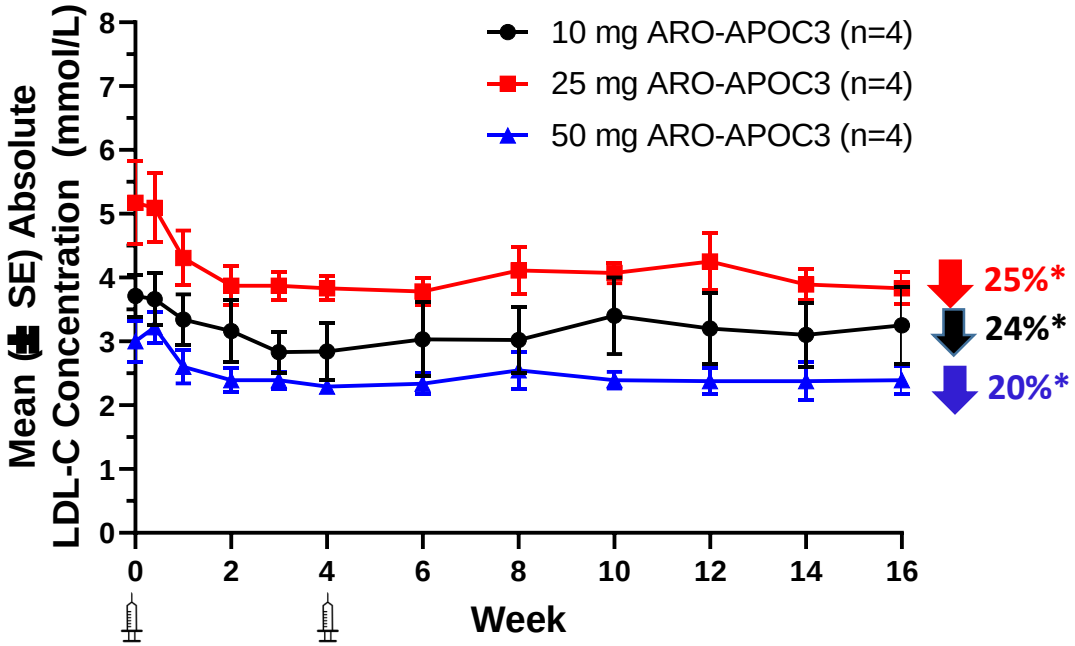
Repeat Dose ARO-APOC3 Demonstrated Substantial and Durable Reductions in TG in Healthy Volunteers Over 16 Weeks



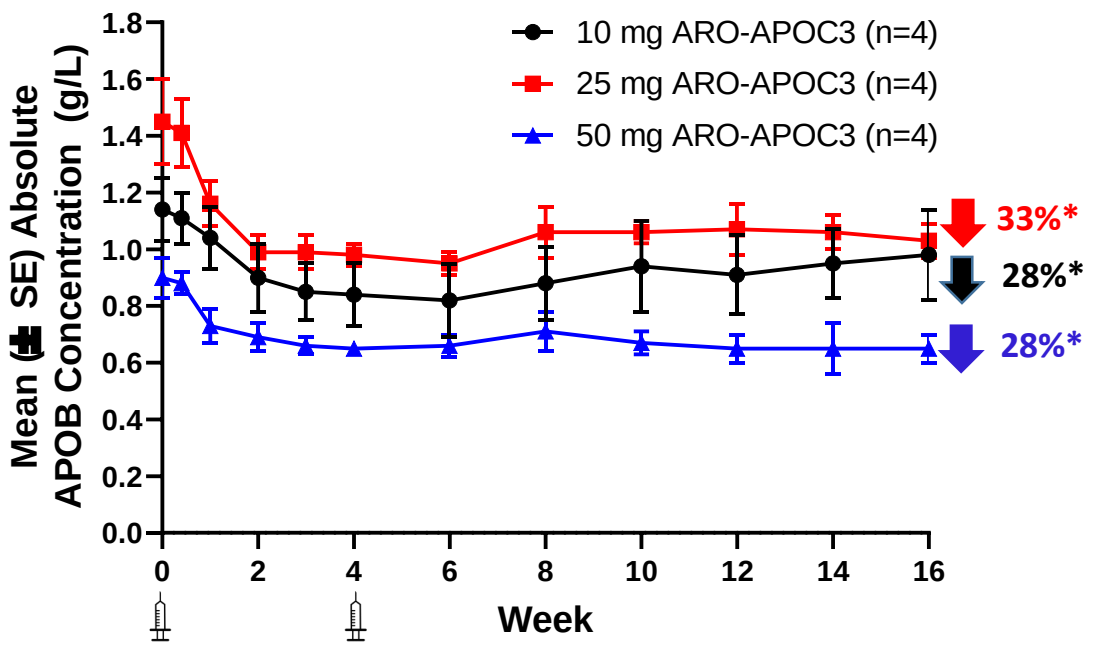
* Maximal Mean percent (%) reductions from baseline

Repeat Dose ARO-APOC3 Demonstrated Reductions in LDL-C and ApoB in Healthy Volunteers Over 16 Weeks

LDL-C

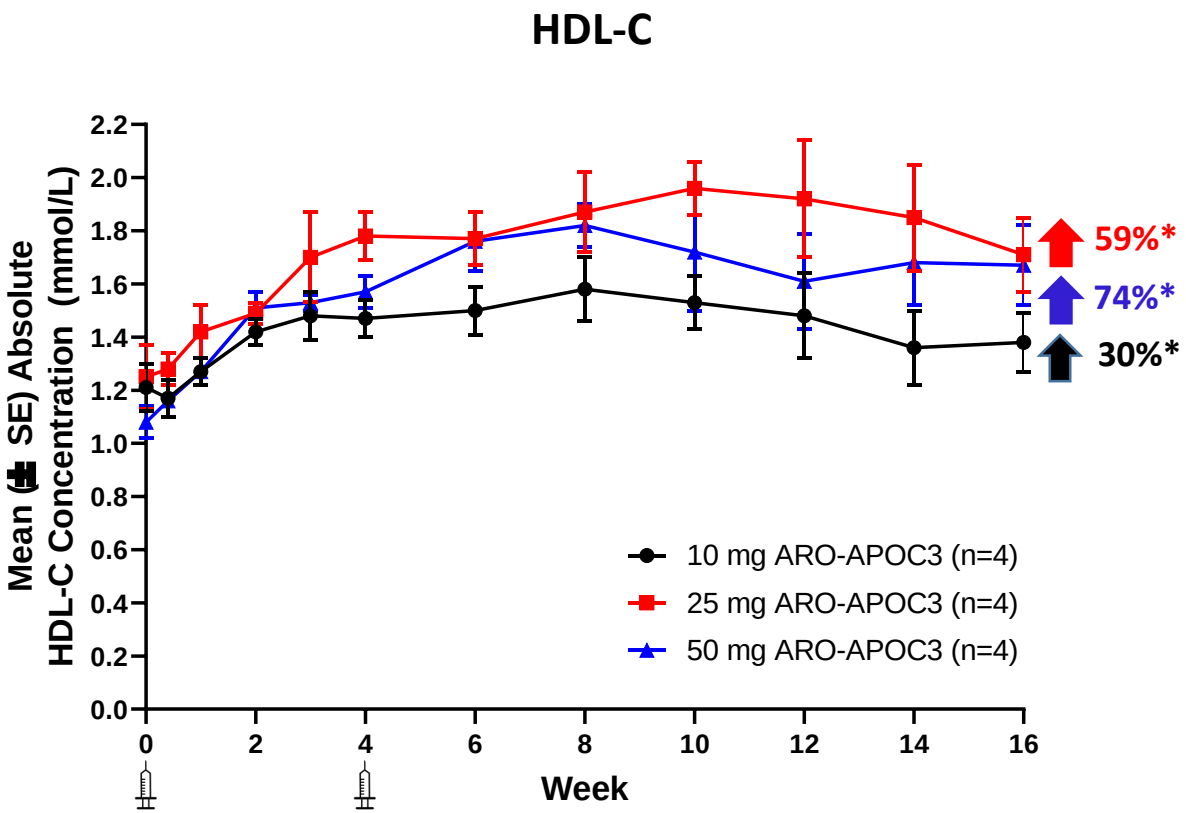


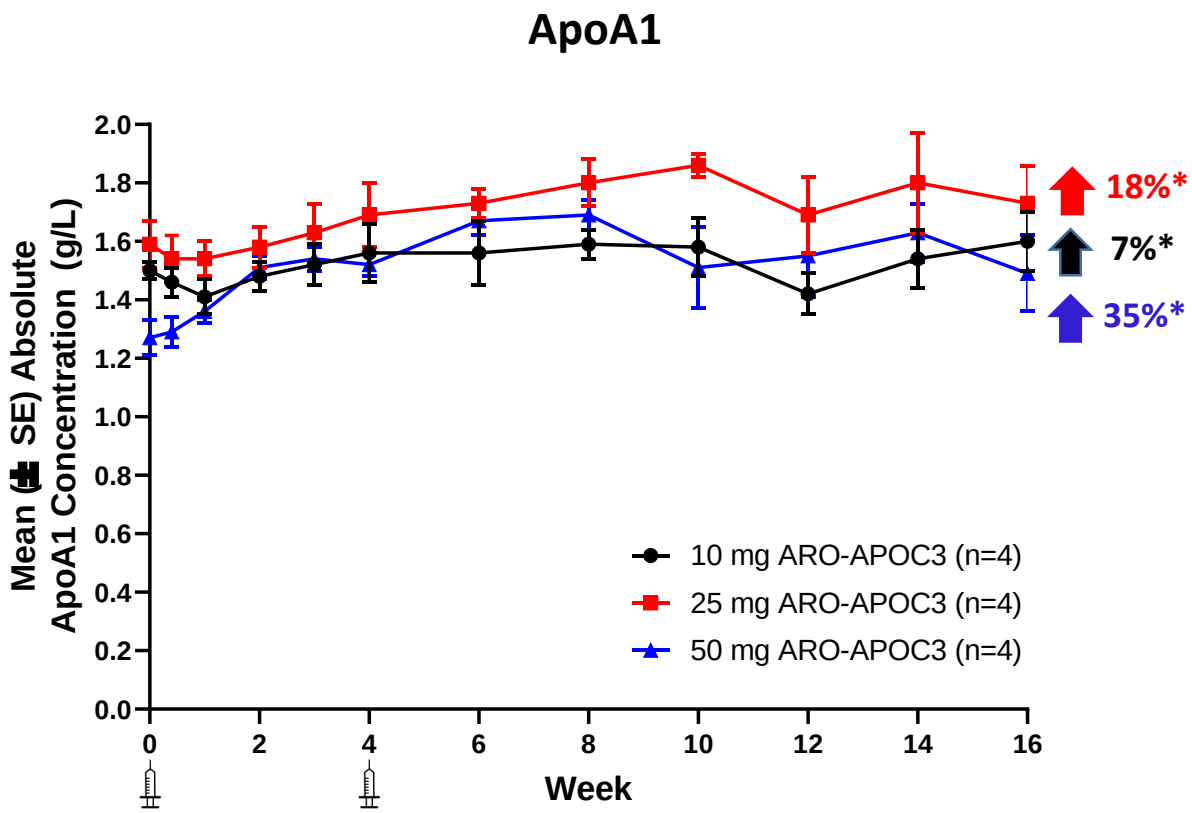
ApoB



* Maximal Mean percent (%) reductions from baseline

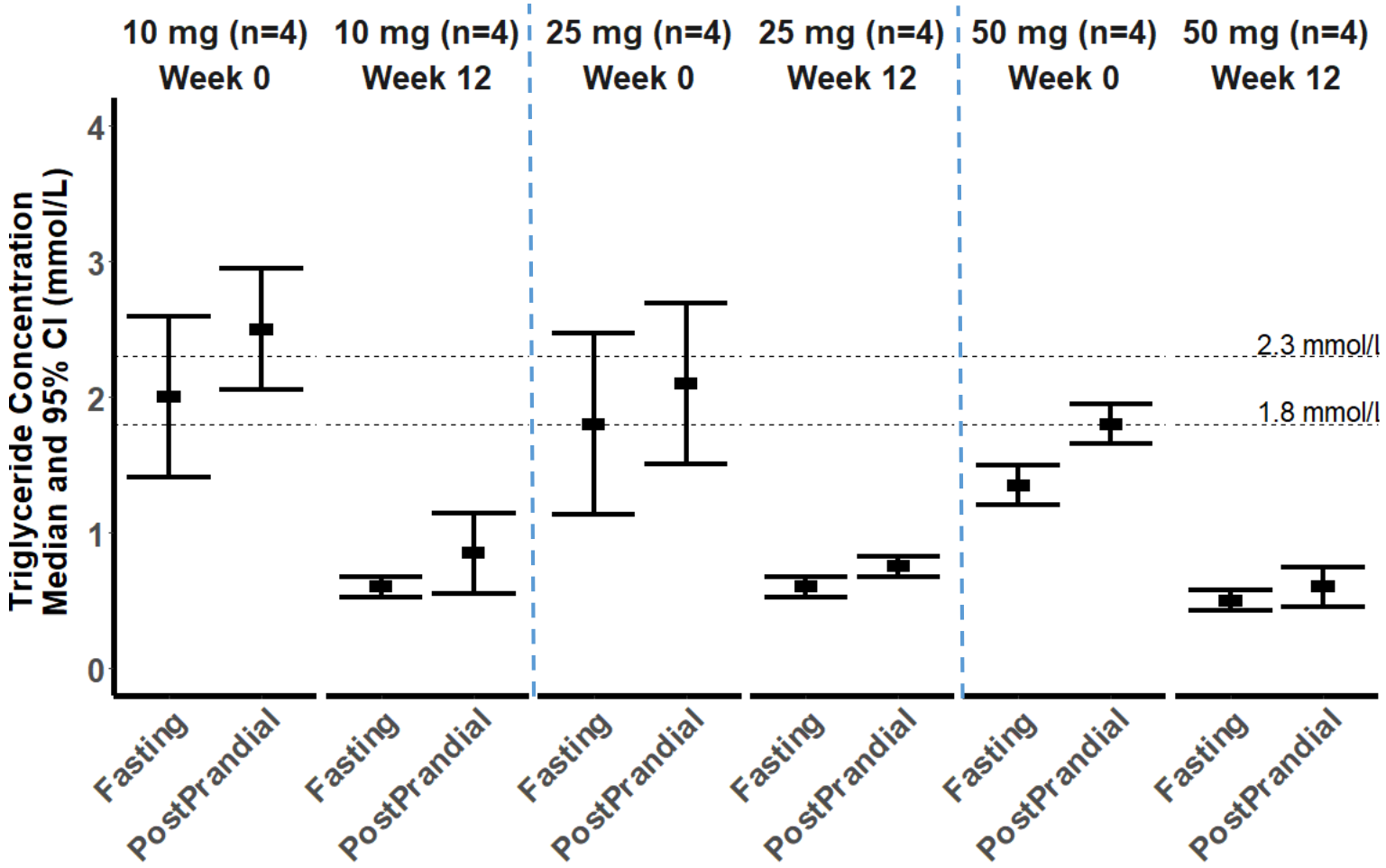
Repeat Dose ARO-APOC3 Demonstrated Increases in HDL-C and ApoA1 in Healthy Volunteers Over 16 Weeks





* Maximal Mean percent (%) increase from baseline

Reduced fasting and postprandial TG increase at Week 12 versus Week 0 in healthy volunteers receiving ARO-APOC3 *



*Standardized high fat meal consumed followed by 2-hour post-prandial TG measurement.

Summary of Safety: Repeat Dose Healthy Volunteer Cohorts*

All AEs Reported in >1 Subject (MedDRA Preferred Terms)	10 mg Cohort 6 n = 4 (all active)	25 mg Cohort 7 n = 4 (all active)	50 mg Cohort 8 n = 4 (all active)	Total n = 12
Any AE at injection site (e.g. injection site reaction, erythema, bruising)	0 (0)	3 (75%)	4 (100%)	7 (58%)
Diarrhea	2 (50%)	1 (25%)	1 (25%)	4 (33%)
Vascular access site bruising	0 (0)	1 (25%)	2 (50%)	3 (25%)
Headache	0 (0)	2 (50%)	1 (25%)	3 (25%)
Upper respiratory tract infection	0 (0)	1 (25%)	1 (25)	2 (17%)
Dermatitis contact	0 (0)	1 (25%)	1 (25%)	2 (17%)

* Safety data through Week 16 (end of study)
**Defined per protocol based on specific preferred terms with duration of at least 48 hours

- AEs generally mild
- All injection site AEs were mild
  - 17% of subjects (2 of 12) experienced Local Injection Site Reactions**
  - Most injection site AEs resolve in <48 hours
- No reported SAEs
- No clinically significant adverse changes in platelets, total bilirubin, creatinine, transaminases

Summary and Conclusions

- In normal volunteers, repeat doses of ARO-APOC3, an investigational RNAi therapeutic that silences *APOC3* mRNA, resulted in:
  - Reduction in APOC3
  - Maximal mean fasting lipid, lipoprotein, and apolipoprotein changes of:
    - -75% for TG
    - -25% for LDL-C
    - -33% for ApoB
    - +75% for HDL-C
- ARO-APOC3 had a favorable safety and tolerability profile
- APOC3 inhibition produced expected favorable lipid changes, with reduced TG and LDL-C and increased HDL-C