RNAi Inhibition of Angiopoietin-like Protein 3 (ANGPTL3) with ARO-ANG3 Mimics the Lipid and Lipoprotein Profile of Familial Combined Hypolipidemia

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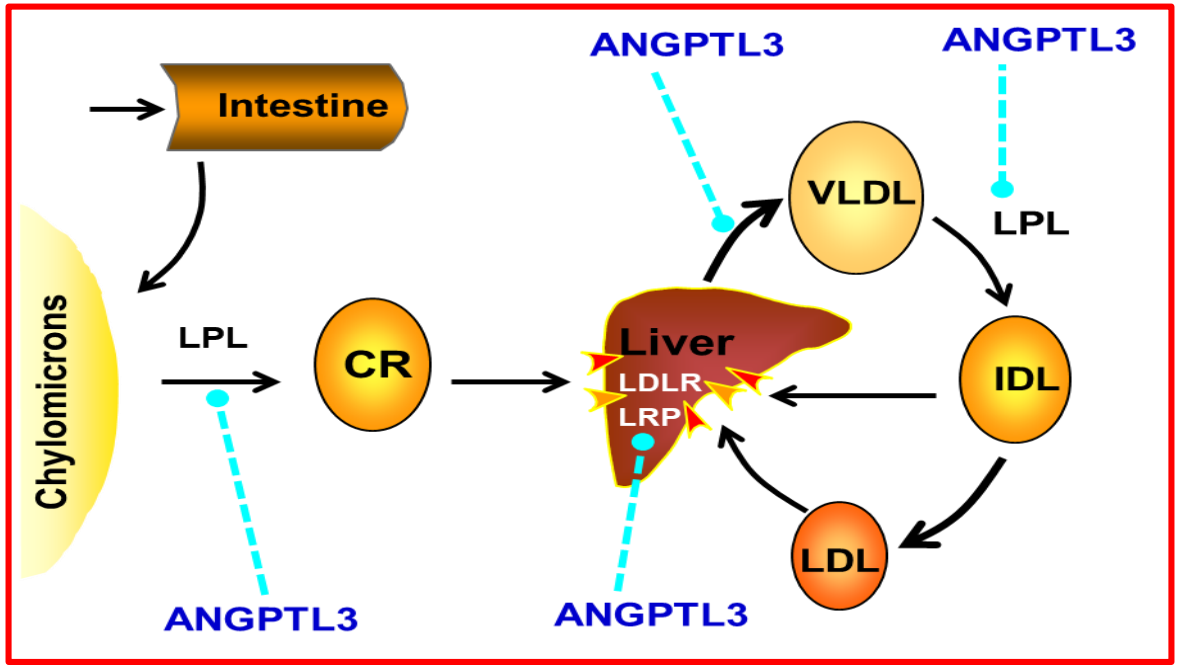
ANGPTL3 as a Target to Treat Dyslipidemia

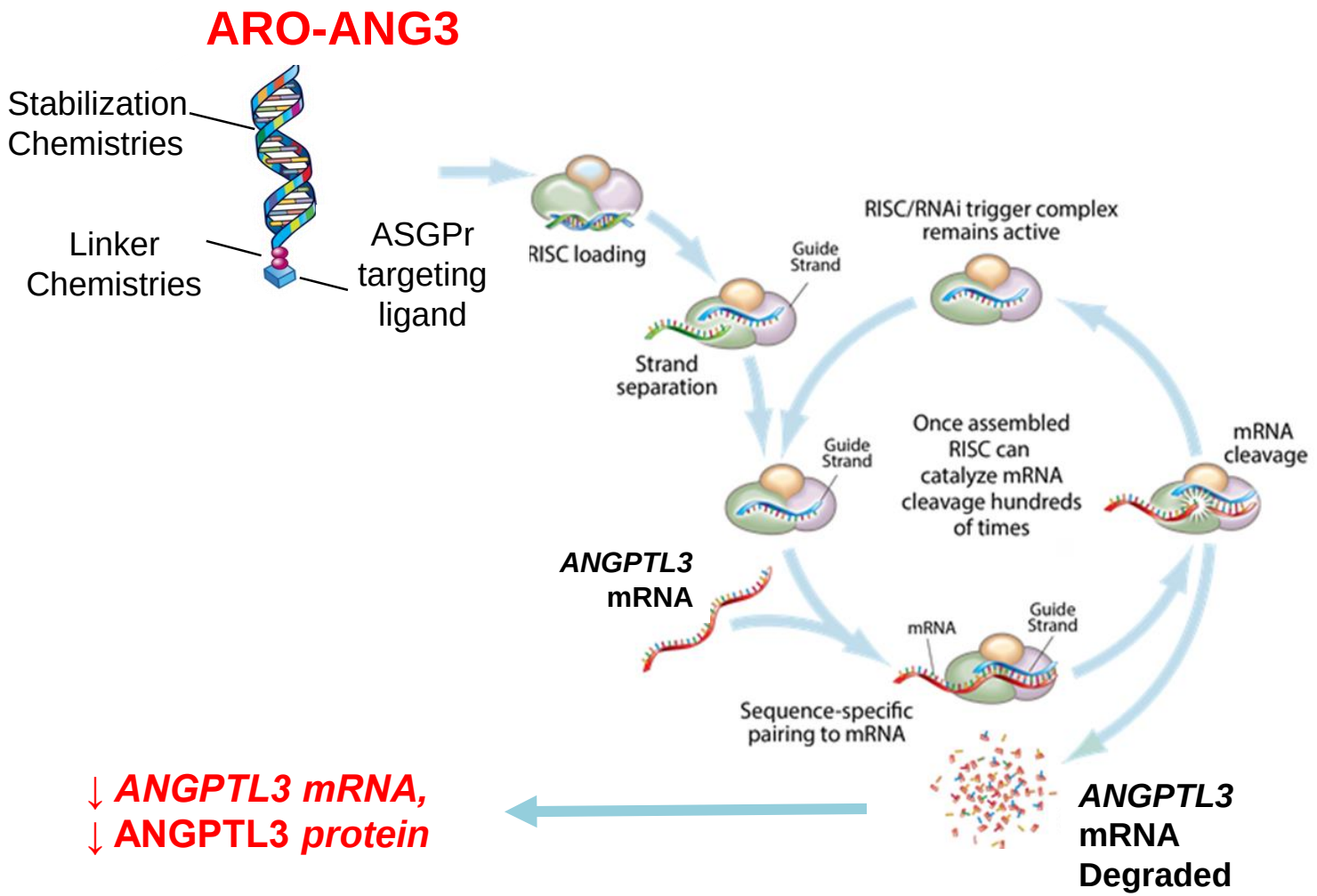
- **Dyslipidemia** is a major risk factor for cardiovascular disease (CVD), and **residual risk of CVD** persists even with current standard of care (including PCSK9 inhibitors)
- **ANGPTL3** is a **key regulator** of **lipid and lipoprotein metabolism** with multiple potential nodes of action
- **Loss-of-function mutations** in *ANGPTL3* lead to low LDL-C, VLDL-C, HDL-C, and triglycerides (TG)
  - Reduced risk of CVD based on genetic studies
  - No known adverse phenotype associated with genetic deficiency in *ANGPTL3*
  - Homozygotes have familial combined hypolipidemia

Potential Regulatory Nodes of Action of ANGPTL3

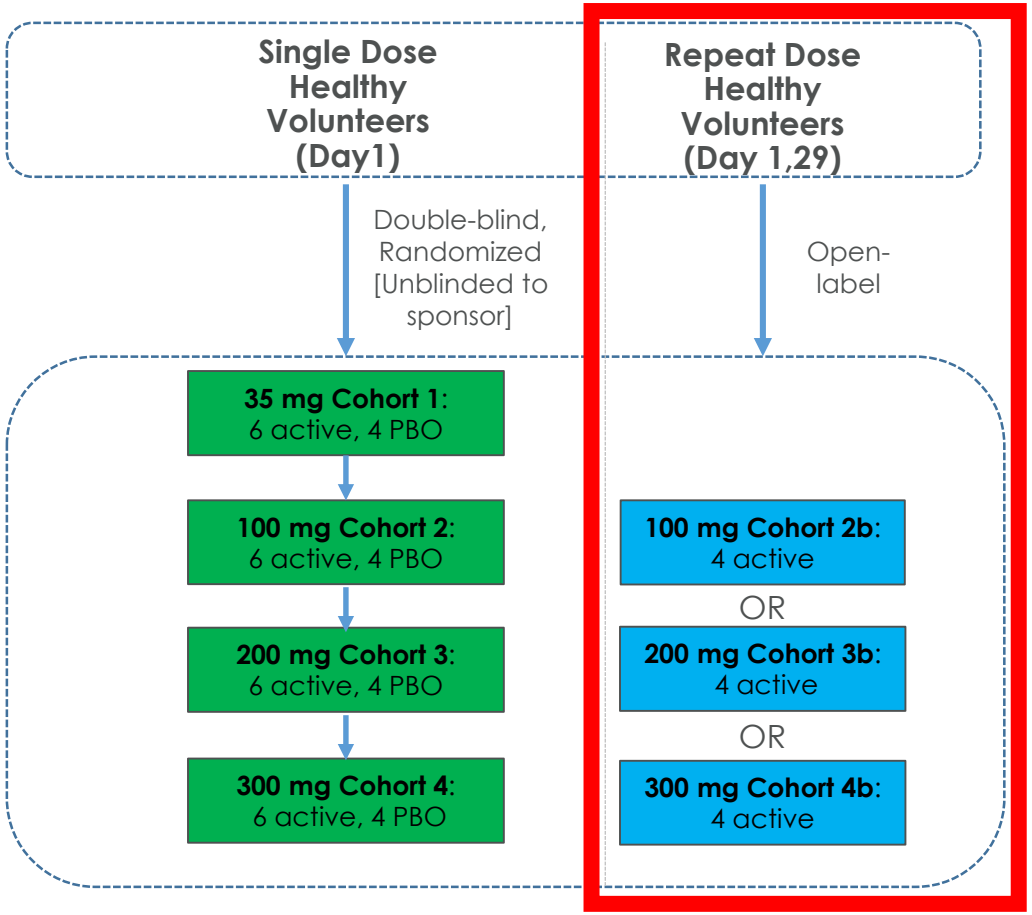


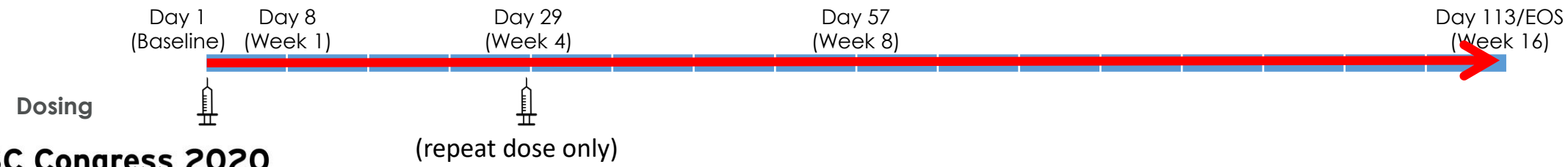
Silencing *ANGPTL3* with ARO-ANG3 by RNA interference

- **ANGPTL3** is primarily synthesized in **hepatocytes**
- Ideal target for **gene silencing therapy with a specific siRNA** derived from Arrowhead's TRiM™ platform
  - **ARO-ANG3** is a SC administered **siRNA directed to hepatocytes**, where it specifically **degrades the mRNA for ANGPTL3**
  - This induces deep and durable silencing of the *ANGPTL3* gene while **avoiding off-target effects**



AROANG1001 First-in-Human Study Design – Healthy Volunteers





- Results from single dose cohorts presented at AHA 2019
- **Subcutaneous doses of ARO-ANG3 on days 1 and 29 for repeat dose healthy volunteer cohorts**
- Repeat dose patient cohorts are fully enrolled and results will be discussed in the future

Phase 1 study evaluating the safety, pharmacokinetic and pharmacodynamic effects of ARO-ANG3: STUDY OBJECTIVES

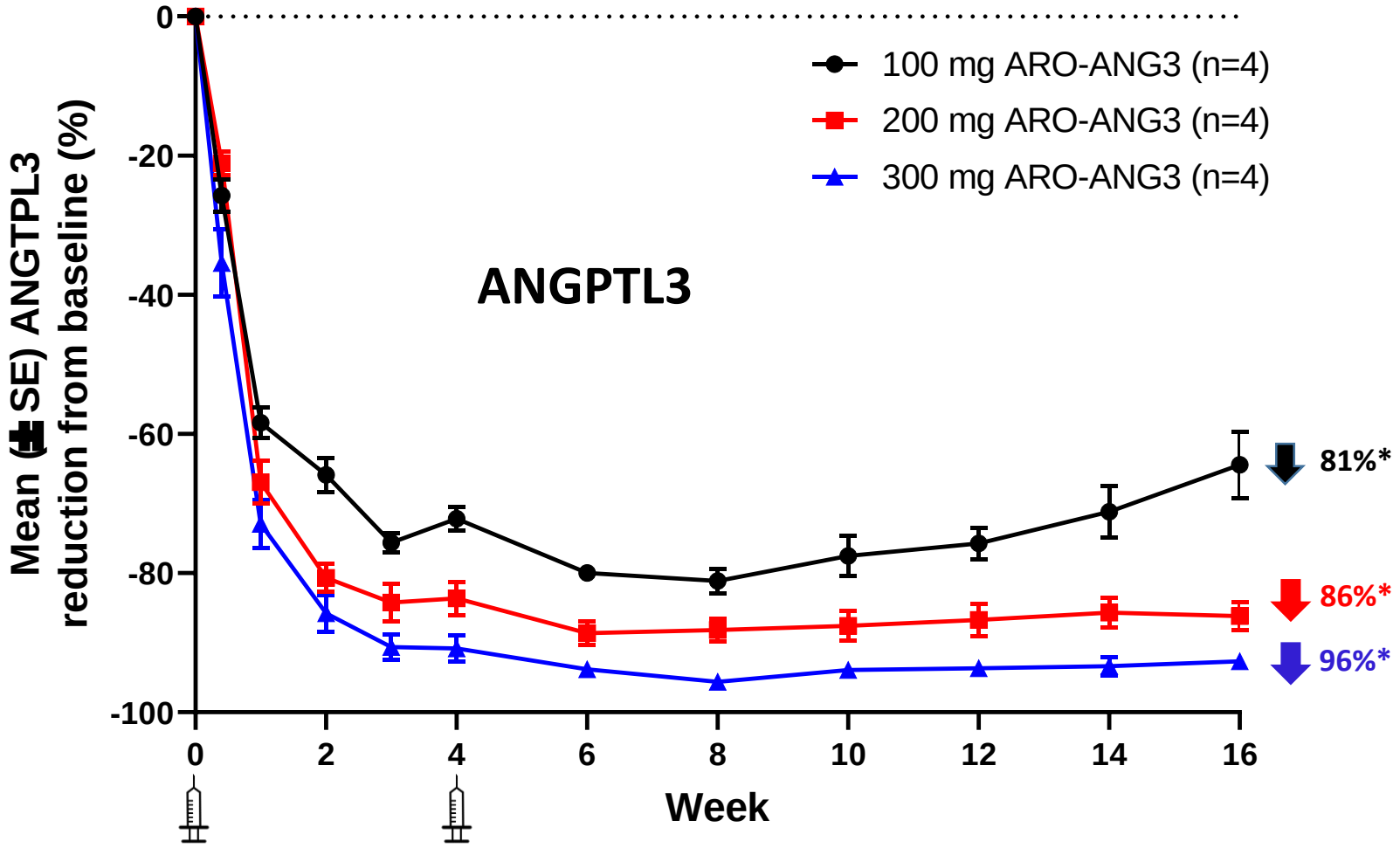
	Specific Objectives
Primary Objective	• Evaluate incidence of adverse events as a measure of safety and tolerability
Secondary Objectives	• Evaluate pharmacokinetics • Determine change from baseline serum ANGPTL3
Exploratory Objectives	• Evaluate fasting lipids and lipoproteins (including TG, LDL-C, Non-HDL-C, HDL-C, ApoB) • Evaluate fasting and 2-hour postprandial TGs

Baseline Characteristics of Repeat Dose Healthy Volunteers*

	Repeat Dose		
Mean (Range)	100 mg Cohort 2b n = 4 (all active)	200 mg Cohort 3b n = 4 (all active)	300 mg Cohort 4b n = 4 (all active)
Age (years)	47.0 (20 – 62)	43.3 (29-55)	30.8 (22-42)
% Male	50%	100%	50%
BMI (kg/m^2)	25.1 (21.7 – 28.0)	25.3 (22.4 – 28.4)	32.0 (25.6 – 39.9)
ANGPTL3 (ng/mL)	**98 (92 - 112)**	**107 (90 - 119)**	**91 (69 - 107)**
TG (mmol/L)	**1.67 (0.81 – 2.31)**	**1.59 (1.27 – 1.85)**	**1.83 (0.64 - 3.66)**
VLDL-C (mmol/L)	0.76 (0.36 – 1.06)	0.73 (0.57 – 0.85)	0.83 (0.28 – 1.68)
LDL-C (mmol/L) (direct assay)	4.09 (3.29 – 5.00)	3.22 (2.75 – 3.96)	2.88 (2.28 – 3.68)
HDL-C (mmol/L)	1.30 (0.98 - 1.97)	1.02 (0.93 – 1.14)	0.95 (0.67 – 1.42)
TC (mmol/L)	6.39 (5.34 - 7.30)	5.26 (4.90 - 5.88)	4.87 (3.91 - 5.80)
Non-HDL-C (mmol/L)	5.10 (3.94 - 6.11)	4.24(3.76 - 4.90)	3.92 (3.11 - 5.13)
ApoB (mmol/L)	1.16 (0.86 - 1.43)	0.96 (0.81 - 1.09)	0.91 (0.75 - 1.21)

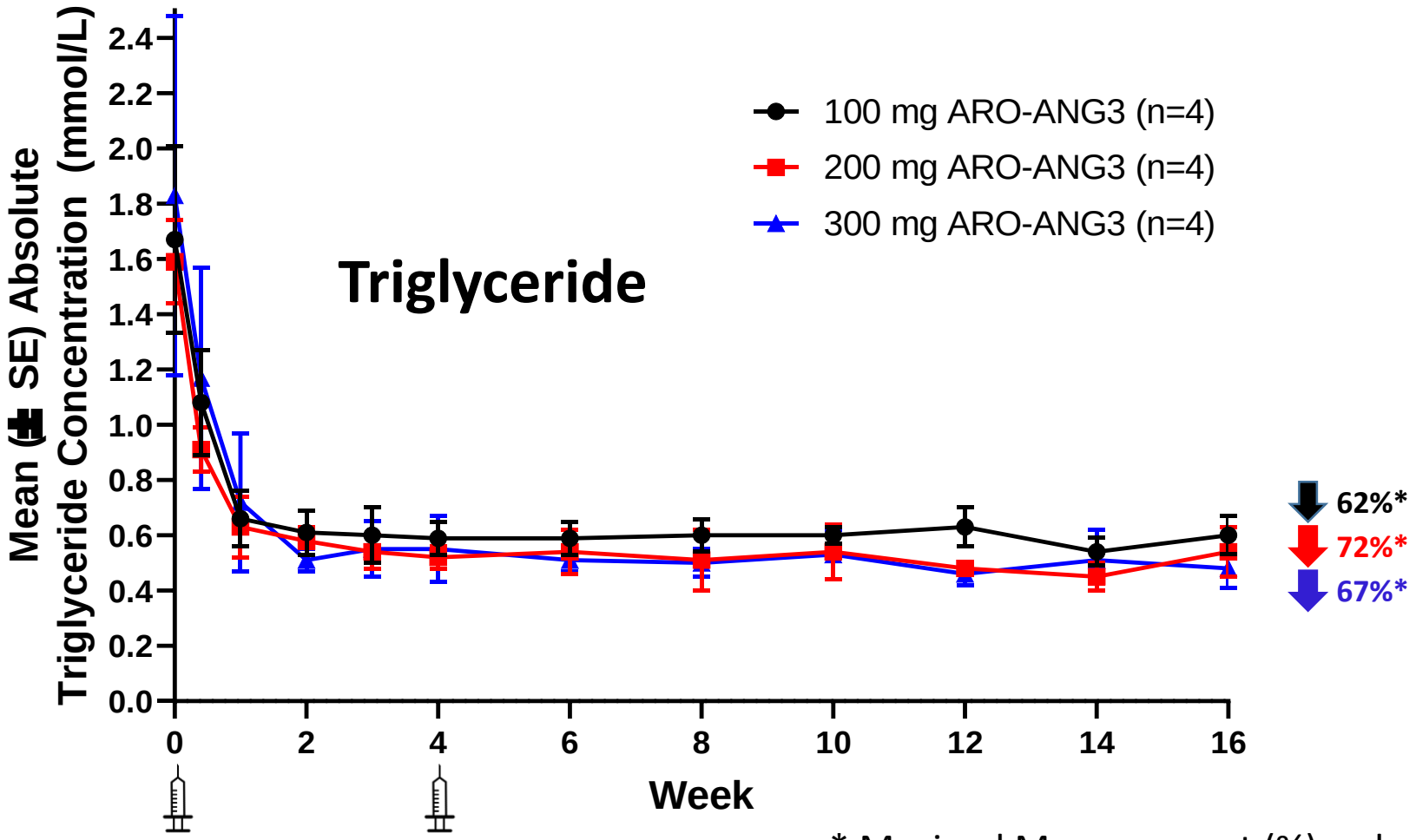
*Inclusion criteria: TG > 1.13 mmol/L and LDL-C >1.81 mmol/L, not on statins or other lipid-lowering medications

Repeat Dose ARO-ANG3 Demonstrated Substantial and Durable Reductions in ANGPTL3 in Healthy Volunteers Over 16 Weeks



* Maximal Mean percent (%) reductions from baseline

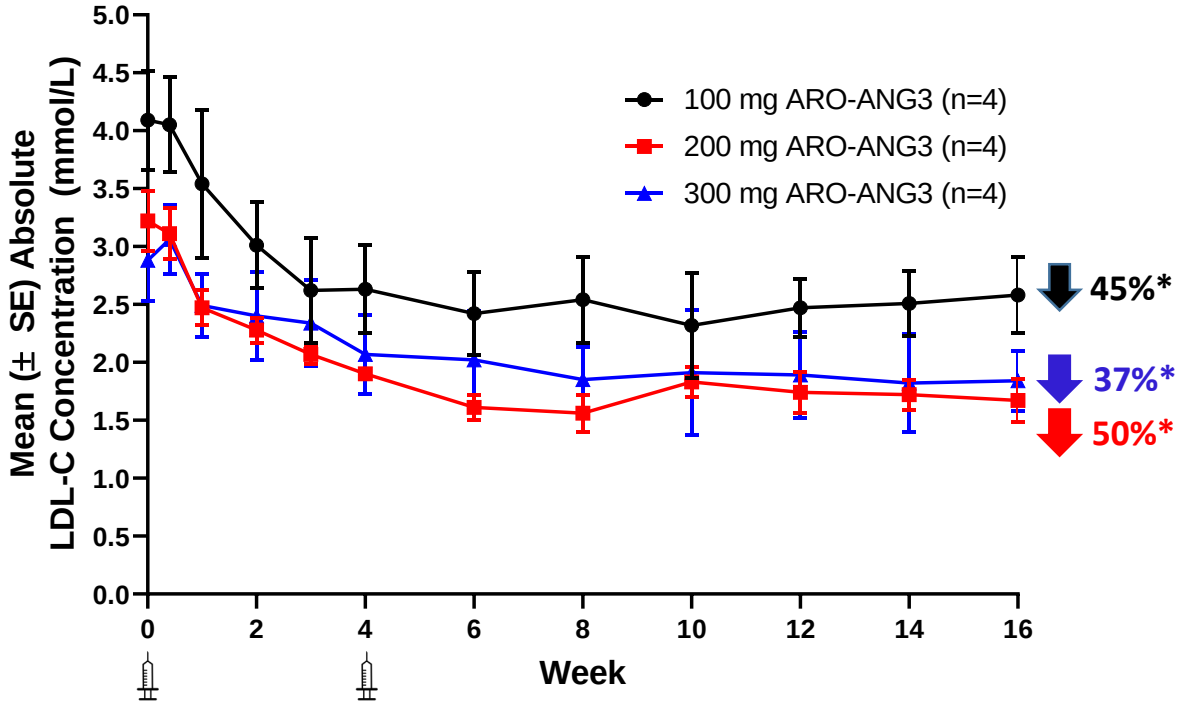
Repeat Dose ARO-ANG3 Demonstrated Substantial and Durable Reductions in TG in Healthy Volunteers Over 16 Weeks



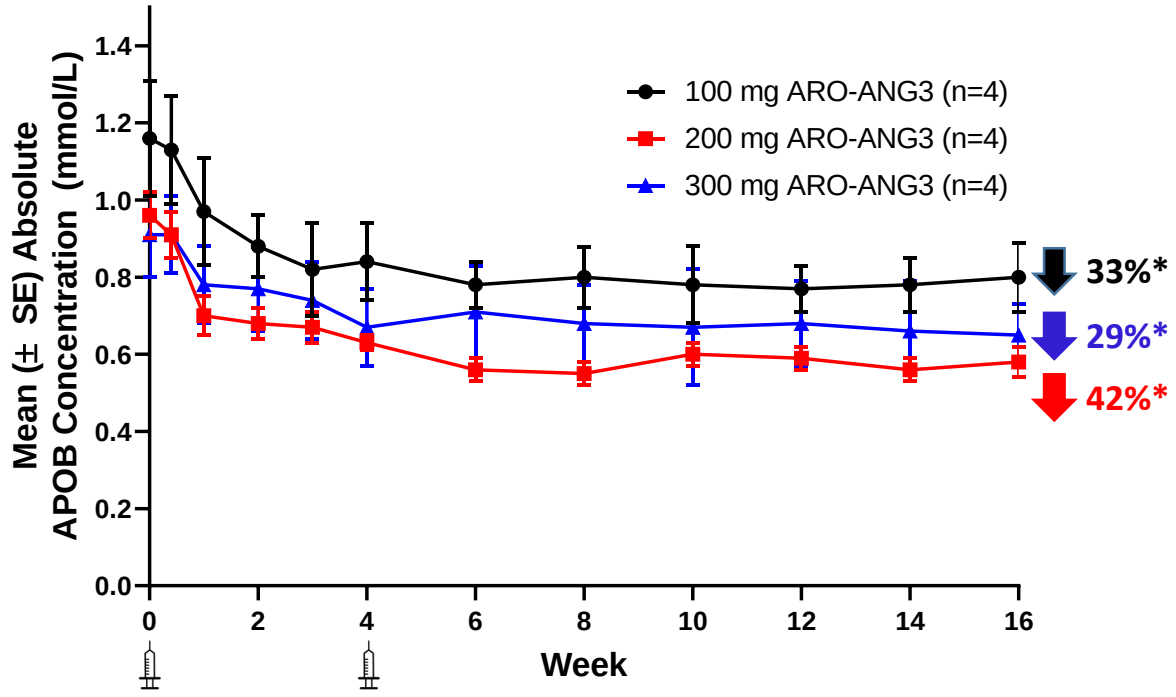
* Maximal Mean percent (%) reductions from baseline

Repeat Dose ARO-ANG3 Demonstrated Reductions in LDL-C and APOB in Healthy Volunteers Over 16 Weeks

LDL-C



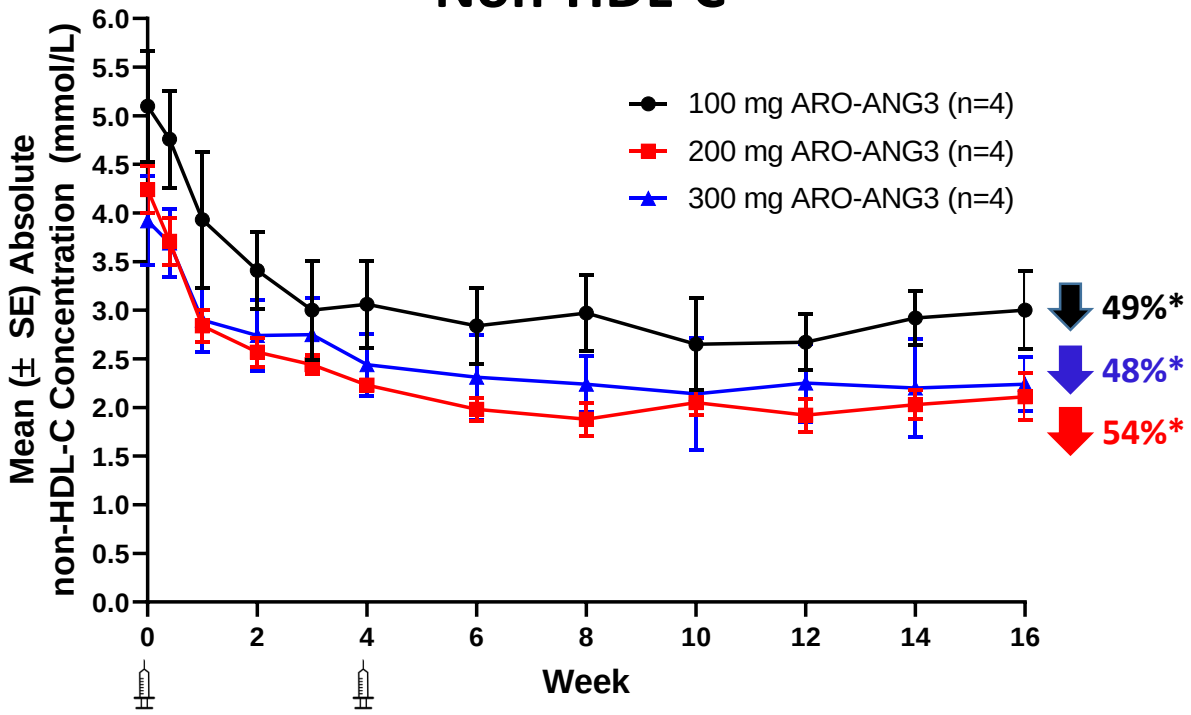
ApoB



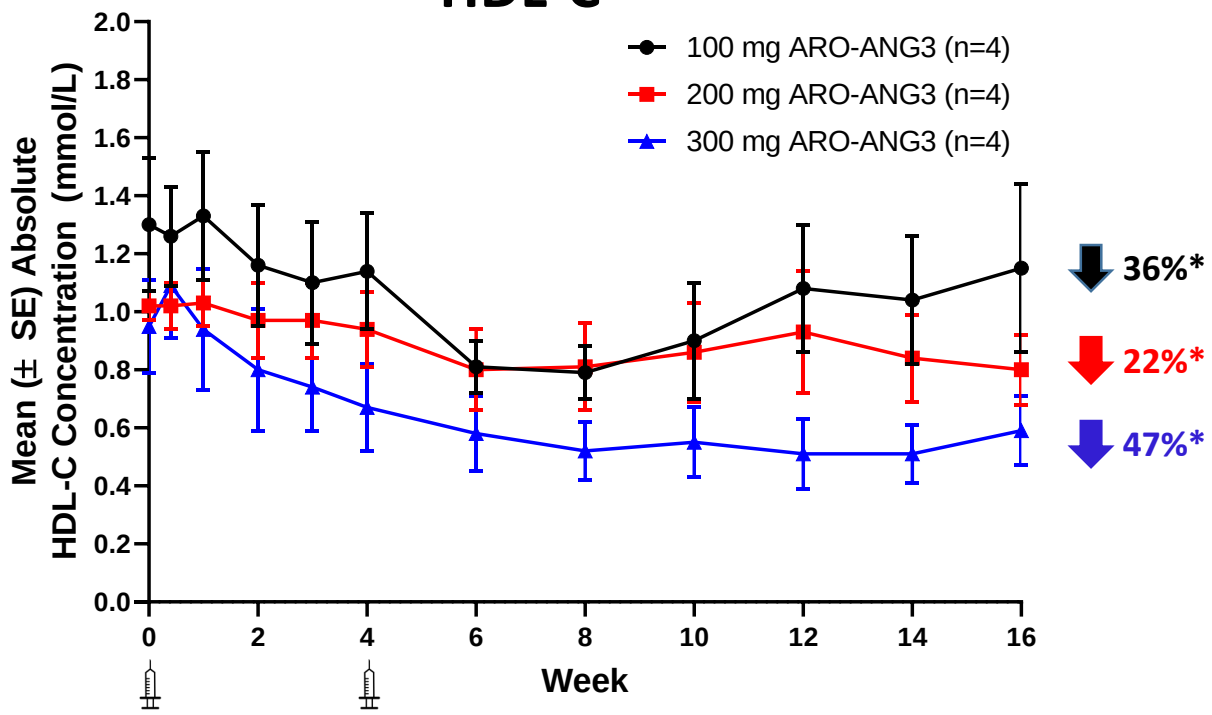
* Maximal Mean percent (%) reductions from baseline

Repeat Dose ARO-ANG3 Demonstrated Reductions in non-HDL-C and HDL-C in Healthy Volunteers Over 16 Weeks

Non-HDL-C

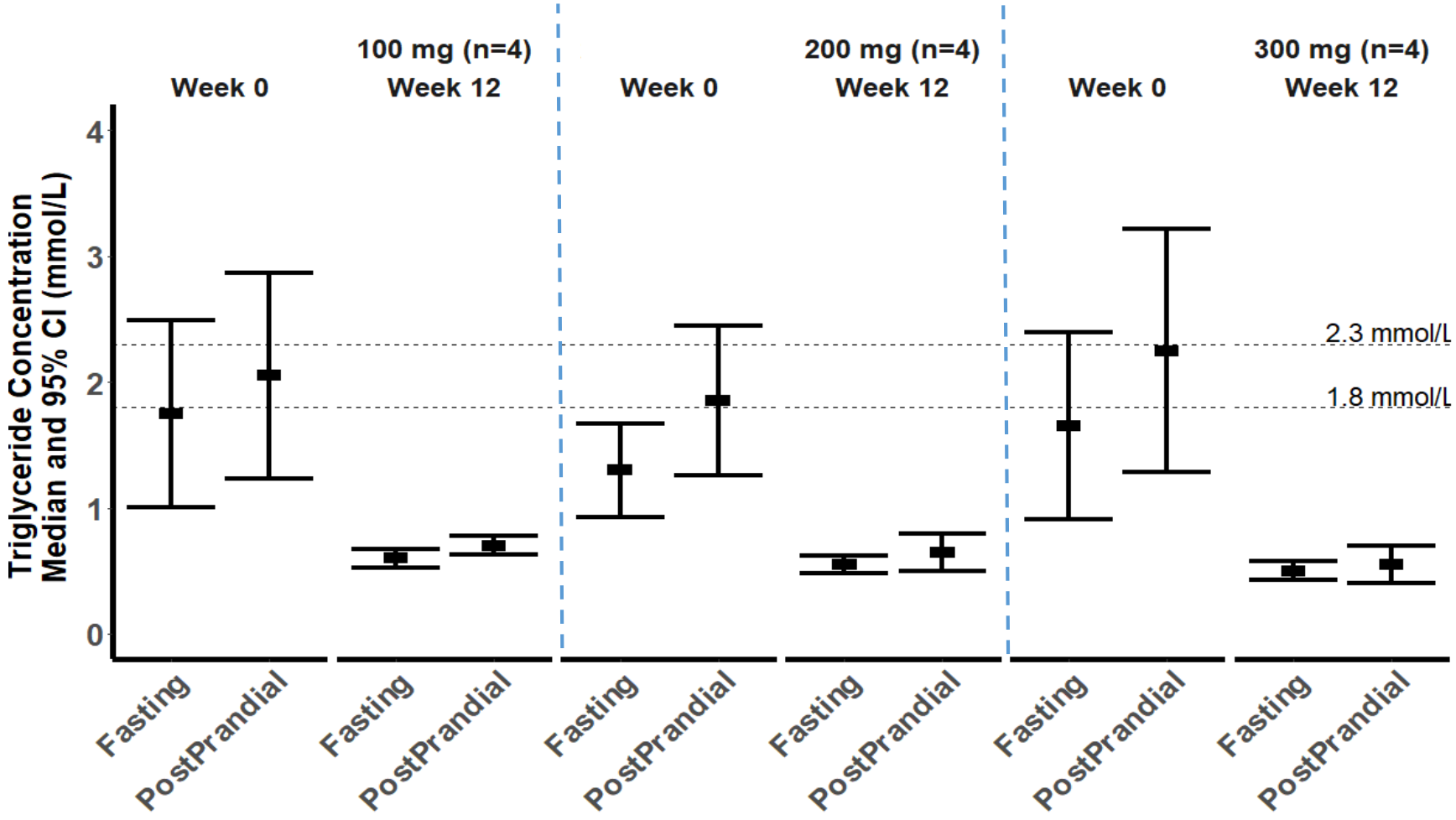


HDL-C



* Maximal Mean percent (%) reductions from baseline

Reduction in fasting and postprandial TG in healthy volunteers receiving ARO-ANG3, Week 12



POST-PRANDIAL STUDY

Standardized oral fat load followed by 2-hour TG measurement.

Safety Summary: Repeat Dose Healthy Volunteer Cohorts *

AEs Reported in > 1 subject AE Term (MedDRA Preferred Term)	100 mg Cohort 2b n = 4 (all active)	200 mg Cohort 3b n = 4 (all active)	300 mg Cohort 4b n = 4 (all active)	Total n = 12
Headache	1 (25%)	1 (25%)	3 (75%)	5 (42%)
Upper respiratory tract infection	1 (25%)	1 (25%)	2 (50%)	4 (33%)
Vascular access site bruising, Vascular access site swelling	1 (25%)	0 (0)	3 (75%)	4 (33%)
Ligament sprain, Muscle strain, Tendon injury	2 (50%)	0 (0)	1 (25%)	3 (25%)
Diarrhea	0 (0)	0 (0)	2 (50%)	2 (17%)
Injection site bruising, injection site discoloration	0 (0)	0 (0)	2 (50%)	2 (17%)
Lethargy	1 (25%)	1 (25%)	0 (0)	2 (17%)
Abdominal pain, Abdominal pain lower	1 (25%)	0 (0)	1 (25%)	2 (17%)

- No reported SAEs
- No discontinuation of dosing
- No clinically significant adverse changes in platelets, total bilirubin, creatinine, transaminases
- Headache (all mild, all considered “not related” to drug) was most common AE

*Safety data through 16 weeks (end of study)

Summary and Conclusions

- In normal volunteers, repeat doses of ARO-ANG3, an investigational RNAi therapeutic that silences *ANGPTL3* mRNA, demonstrated:
  - Dose-dependent reduction in fasting ANGPTL3
  - Maximal mean reductions in fasting lipid, lipoprotein, and apolipoprotein concentrations of:
    - -71% in TG
    - -50% in LDL-C
    - -42% in ApoB
    - -34% in non-HDL-C
    - -47% in HDL-C
  - Lipid, lipoprotein, and apolipoprotein reductions sustained to week 16
- ARO-ANG3 had a favorable safety and tolerability profile
- ANGPTL3 inhibition has the potential to effectively correct combined hyperlipidemia and decrease residual risk in patients with CVD on guideline-recommended standard of care