Scientific Sessions 2019

RNA Interference Targeting Hepatic Angiopoietin-Like Protein 3 Results in Prolonged Reductions in Plasma Triglycerides and LDL-C in Human Subjects

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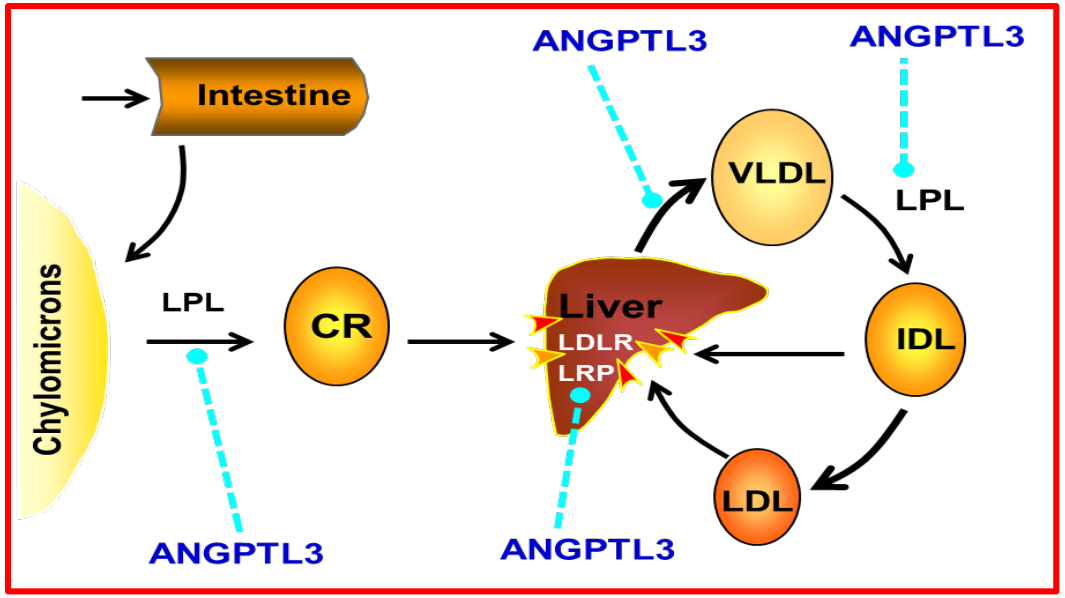
ANGPTL3 as a Target to Treat Dyslipidemia

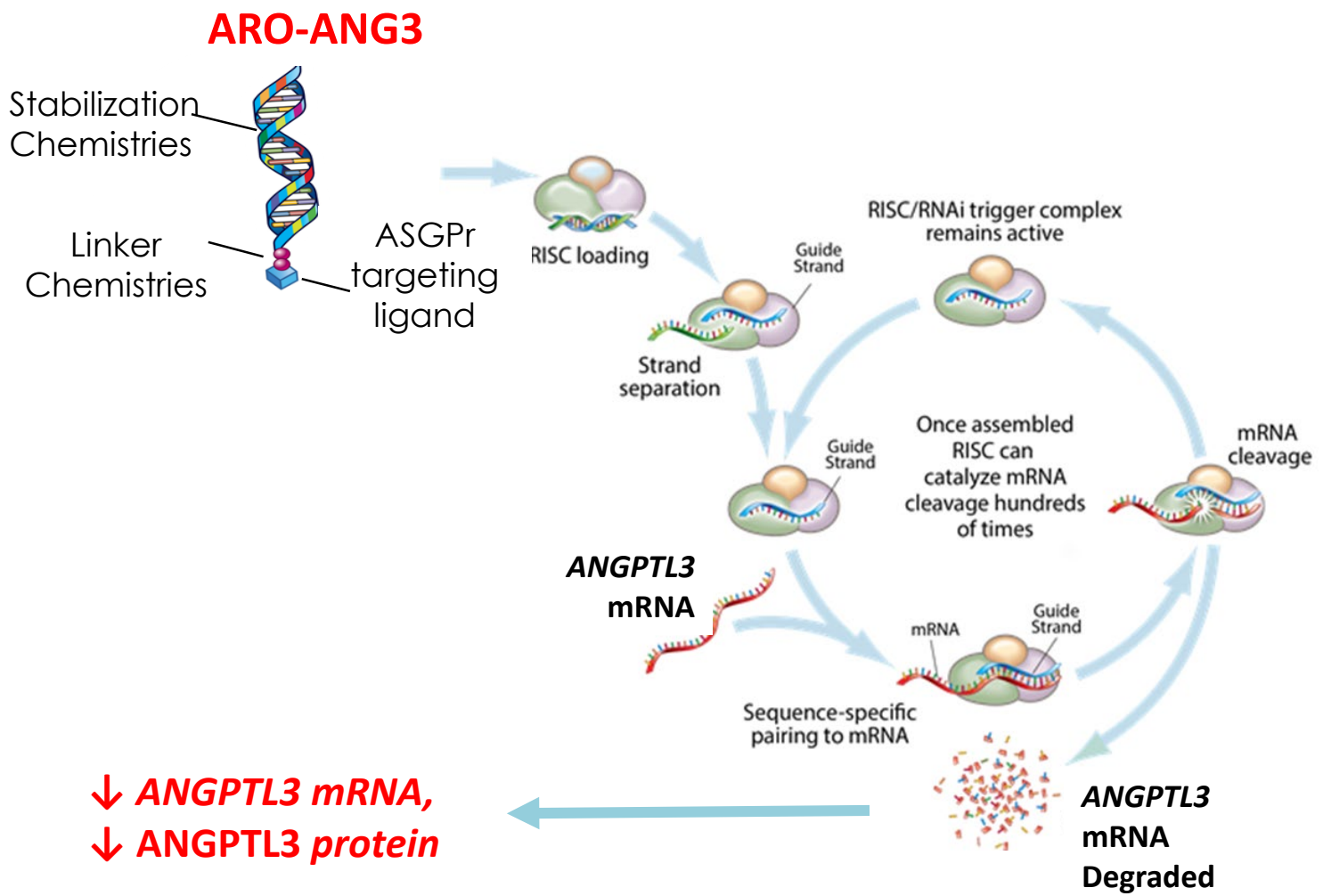
- **Dyslipidemia** is a major risk factor for cardiovascular disease (CVD), and **residual risk of CVD** persists even with current standard of care (including PCKS9 inhibitors)
- **ANGPTL3** is a **key regulator** of **lipid and lipoprotein metabolism** with multiple potential nodes of action
- **Loss-of-function mutations** in *ANGPTL3* lead to low LDL-C, VLDL-C, HDL-C and triglycerides (TG)
  - Reduced risk of CVD based on GWAS
  - No known adverse phenotype associated with genetic deficiency in *ANGPTL3*

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 targeted at the liver**, where it specifically **inhibits and degrades the mRNA for ANGPTL3**
  - This induces deep and durable silencing of the *ANGPTL3* gene while **avoiding off-target effects**



AROANG1001 Study Design: Phase 1/2a Clinical Study

Primary Objective: Safety and Tolerability

Secondary/Exploratory Objectives: PK/PD

- Single & Multiple Dose PK of ARO-ANG3 in healthy volunteers.
- Reduction in fasting serum ANGPTL3 from baseline
- Changes in fasting serum lipids and lipoprotein levels and other metabolic indices

Cohort Descriptions:

Single Dose:

- Cohorts 1-4 : Normal Healthy Volunteers (NHV) with TG >100 mg/dL and LDL-C >70 mg/dL (6 active, 4 placebo (PBO) per cohort)

Multiple Dose (2 monthly doses):

- Cohort 2b-4b: NHV, open label, 4 subjects per cohort
- Cohort 5: NAFLD, (6 active: 3 PBO)
- Cohort 6: LDL-C >70 mg/dL on stable statin regimen, (6 active: 3 PBO)
- Cohort 7, 7b, 7c: HoFH or HeFH, genetically confirmed or Dutch Lipid score of ≥ 8 with LDL-C > 100 mg/dL, (Open label, up to 6 subjects per cohort)
- Cohort 8: Severe hypertriglyceridemia, TG ≥ 500 mg/dL (Open label, up to 6 subjects)

Cohorts 1-4: Baseline Characteristics

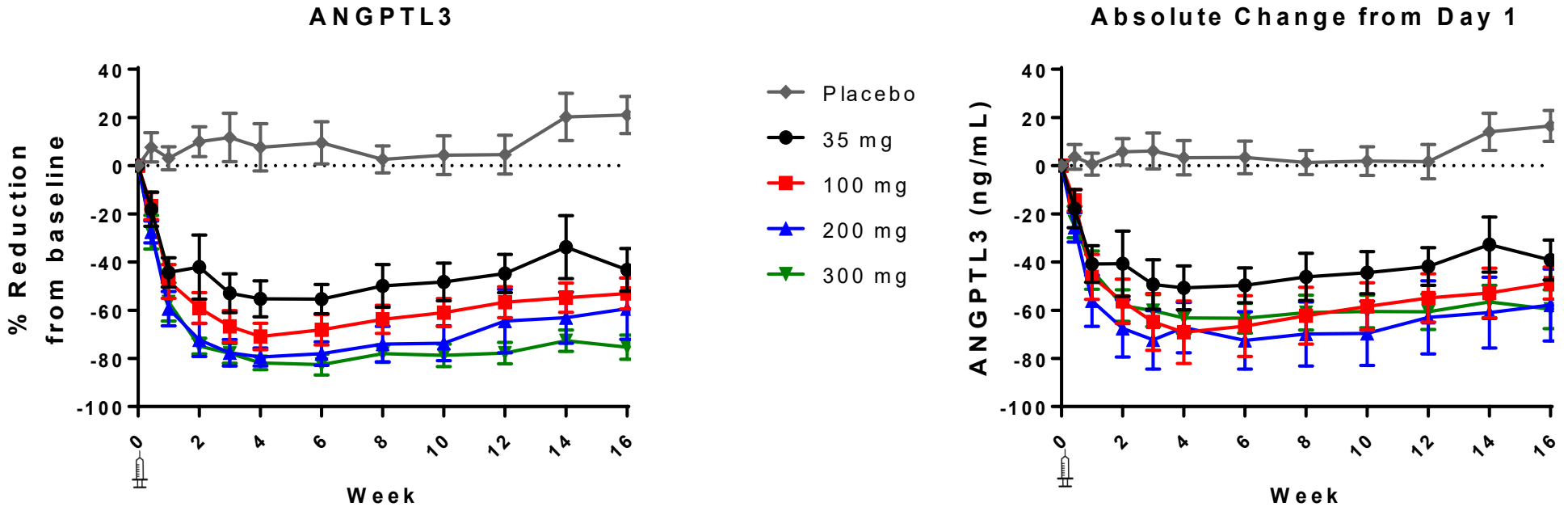
Mean (range) Fasting values	Cohort 1 (35 mg) n = 10 (6 active: 4 PBO)	Cohort 2 (100 mg) n = 10 (6 active: 4 PBO)	Cohort 3 (200 mg) n = 10 (6 active: 4 PBO)	Cohort 4 (300 mg) n = 10 (6 active: 4 PBO)
Age (years)	36.1 (19-58)	47.4 (24-61)	42.2 (32-56)	47.4 (26-64)
% Male	50%	70%	80%	90%
BMI (kg/m^2)	28.1 (22.5 – 33.0)	27.8 (22.6 – 36.6)	31.4 (26.6 – 35.8)	26.7 (23.0 – 32.2)
ANGPTL3 (ng/mL)	76.2 (61-104.1)	75.5 (54.6-130.2)	83.6 (45.5-120.9)	73.1 (47.1-96.7)
Triglycerides (mg/dL)	172 (62-779)	140 (80-310)	202 (115-354)	169 (97-390)
VLDL-C (mg/dL)	20 (12-43)*	28 (15-62)	40 (23-70)	34 (19-77)
LDL-C (mg/dL) (direct assay)	148 (54-220)	168 (101-263)	151 (85-205)	143 (112-217)
HDL-C (mg/dL)	48 (23-58)	49 (35-66)	43 (27-54)	42 (31-66)

* TG too high to calculate VLDL-C in a single subject, not included in mean

Durable, Dose-Dependent Reduction in ANGPTL3

ARO-ANG3 or Placebo given on Day 1

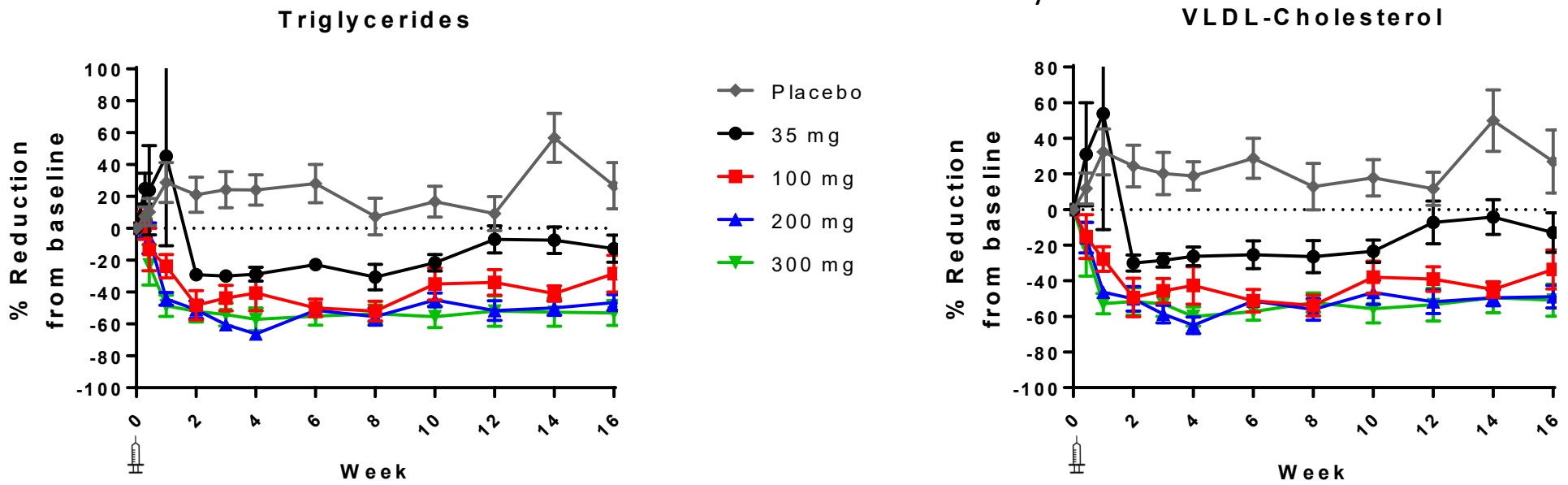
Mean ± SEM



- Mean maximum reduction from baseline in ANGPTL3 (ELISA) ranged from 55% (50 ng/mL) [35 mg] ($p<0.0001$) to 83% (63 ng/mL) [300 mg] ($p<0.0001$)
- Reductions in ANGPTL3 were maintained through end of study, with week 16 mean reductions of 43% (42 ng/mL) [35 mg] to 75% (57 ng/mL) [300 mg]

Dose-Dependent Reductions in Triglycerides and VLDL-C

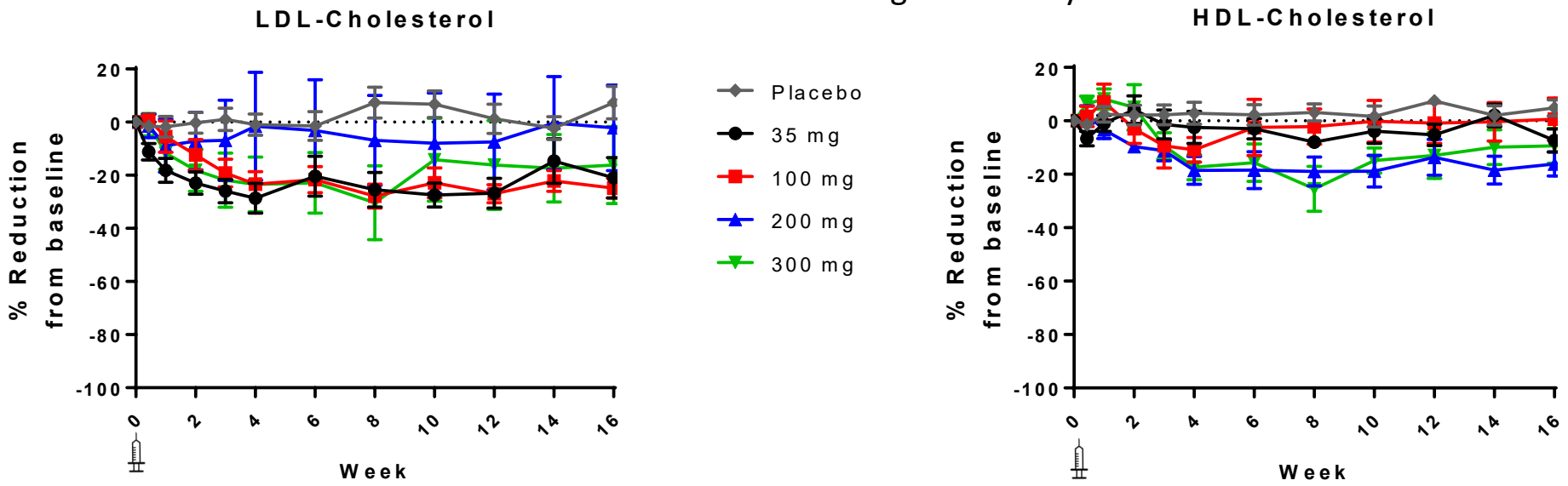
ARO-ANG3 or Placebo on Day 1



- Mean maximum TG reduction from baseline of 31% (38 mg/dL)[35 mg] (p=0.06) to 66% (167 mg/dL) [200 mg] (p=0.0002)
- Mean maximum VLDL-C reduction from baseline of 30% (8 mg/dL)[35 mg] (p=0.006) to 65% (33 mg/dL) [200 mg] (p <0.0001)
- Reduction in TG and VLDL-C maintained through end of study in 200 mg and 300 mg cohorts, with week 16 mean reductions of 47% to 53% for TG, and 49% to 51% for VLDL-C

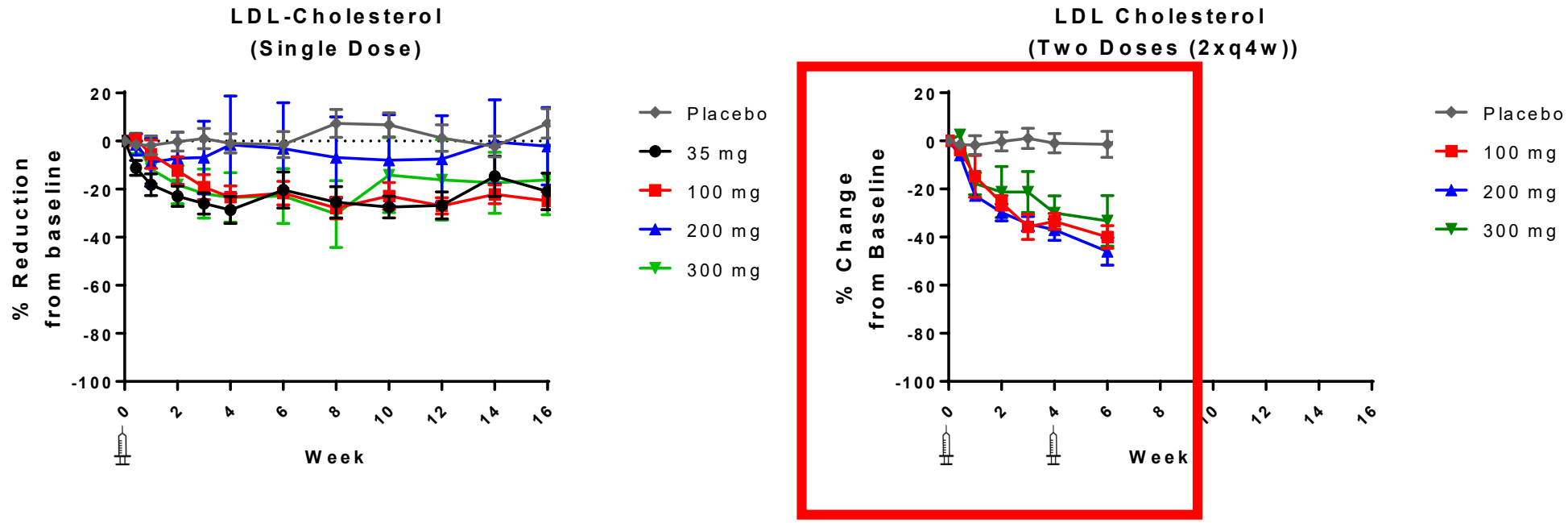
Reductions in LDL-C and HDL-C with ARO-ANG3

ARO-ANG3 or Placebo given on Day 1



- Mean maximum LDL-C reduced by 9% (16 mg/dL) [200 mg] (p=0.40) to 30% (48 mg/dL) [300 mg] (p=0.0004)
- LDL-C mean reductions at week 16 of up to 28% (46 mg/dL) [100 mg] after single dose
- Mean maximum HDL-C reduced by 8% (4 mg/dL) [35 mg] (p=0.02) to 26% (12 mg/dL) [300 mg] (p<0.0001)
- HDL-C mean reductions at week 16 of up to 16% (7 mg/dL) [200 mg]

Reductions in LDL-C with ARO-ANG3 (Single/Multiple Dose)



- Mean maximum reduction in LDL-C with 200 mg single dose blunted by two subjects in this cohort with increasing LDL-C post-dose
  - These two subjects had highest baseline triglycerides in cohort (336 and 354 mg/dL (3.8 and 4.0 mmol/L))
- Multi-dose data with 200 mg demonstrates similar reductions to 100 mg and 300 mg at 6 weeks (33-46% reduction from baseline, $p<0.0001$ for all dose levels)

AROANG1001 Summary Safety Results (NHV cohorts 1-4)

- 40 subjects enrolled received single ascending doses (24 active, 16 placebo)
- **No Serious AEs or drop outs** in subjects on drug
- No significant abnormalities in platelet counts or renal biochemistry
- **Two AEs** of mild transient elevations in ALT (one active, one placebo). No other AEs from lab abnormalities in subjects on drug
  - ALT elevation in one subject on ARO-ANG3 confounded by concomitant ingestion of herbal supplement with known liver toxicity (Peak ALT 192 U/L Day 99, normal by Day 113).
- **1 mild** drug related Local Injection Site Reaction
  - LISR defined based on MedDRA; erythema resolved after 48 hours.

Conclusions

- Loss-of-function mutations in *ANGPTL3* are associated with improved CV outcomes with no adverse clinical phenotype.
  - The lipid phenotype includes reductions in triglycerides, VLDL-C, LDL-C and HDL-C.
- In normal volunteers, this single ascending dose study of **ARO-ANG3, a RNAi therapeutic that specifically silences *ANGPTL3* mRNA in the liver**, has shown:
  - **Dose-dependent reductions in fasting serum ANGPTL3.**
  - **Reductions in fasting TG, VLDL-C, LDL-C and HDL-C, similar to those reported in *ANGPTL3* loss-of-function carriers.**
  - **A favorable safety and tolerability profile.**
- Multi-dose studies in patients with NAFLD, hyperlipidemia on statins , familial hypercholesterolemia, and severe hypertriglyceridemia are underway.
- **ANGPTL3 inhibition is a new mechanism for potentially addressing residual risk of CVD in patients with dyslipidemias.**

Thank you!

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