#AHA22

ARO-ANG3, an Investigational RNAi Therapeutic, Decreases Serum Angiopoietin-like Protein 3, Triglycerides, and Cholesterol in Patients With Mixed Dyslipidemia

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On behalf of the ARCHES-2 Study Team

American Heart Association.

Financial Disclosure

Presenter

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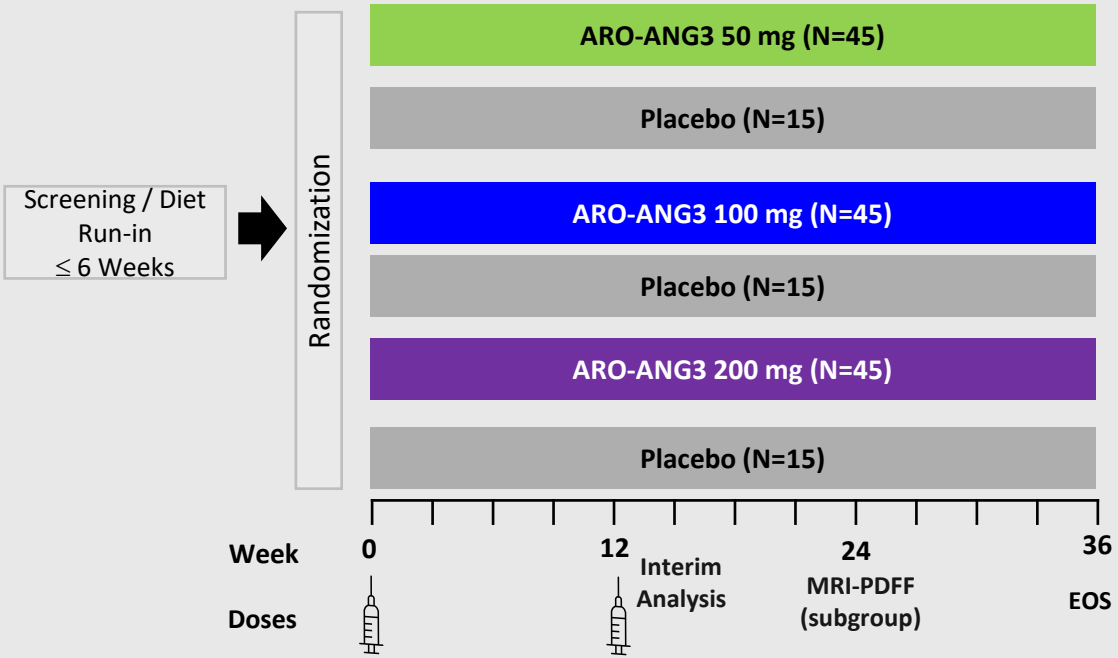
Angiopoietin-like Protein 3 (ANGPTL3) as a Target to Treat Dyslipidemia

- Dyslipidemia is a major risk factor for cardiovascular disease (CVD). The residual lipoprotein 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 modes of action, including inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL)
- Loss of function mutations in *ANGPTL3* lead to enhanced LPL and EL activity, resulting in:
  - Low Triglycerides (TG), LDL-C, VLDL-C, and HDL-C
  - Reduced risk of coronary artery disease[a,b]
  - No known adverse phenotype associated with genetic deficiency in *ANGPTL3*
- ARO-ANG3 is an investigational, hepatocyte-targeted RNA interference (RNAi) therapeutic designed to specifically silence *ANGPTL3* mRNA expression and mimic ANGPTL3 deficiency

ARCHES-2 : Data cutoff 06 Jul 2022

[a]Dewey FE et al. 2017 NEJM 377: 211-221, [b]Stitziel NO et al. 2017 JACC 69:2054-2063

ARCHES-2: Ongoing Double-blind, Placebo-controlled, Dose Ranging Study of ARO-ANG3 In Subjects With Mixed Dyslipidemia



Study Population:

- fasting TG between 150-499 mg/dL and either
  - LDL-C ≥ 70 mg/dL or
  - Non-HDL-C ≥ 100 mg/dL
- Stable optimal statin therapy

Key Endpoints[a]

- Serum TG
- ANGPTL3
- Non-HDL-C
- ApoB
- LDL-C
- Remnant cholesterol
- HDL-C
- Liver fat fraction by MRI-PDFF (subgroup)
  - 35 subjects with liver fat fraction ≥ 8% at baseline were evaluated again at Week 24

Interim Analysis

- conducted when all subjects reached Week 12 (Data cutoff July 6, 2022), Week 16 data reported

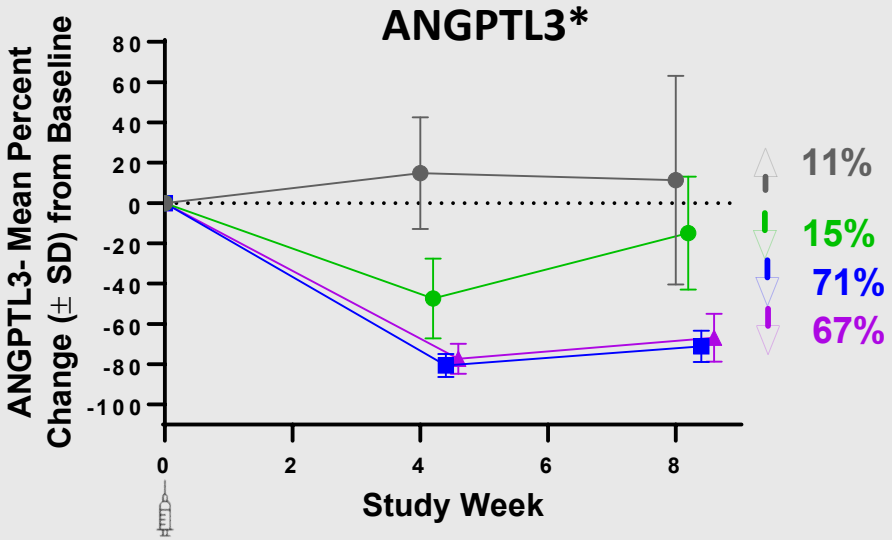
[a] All samples taken after ≥ 10 hour fast

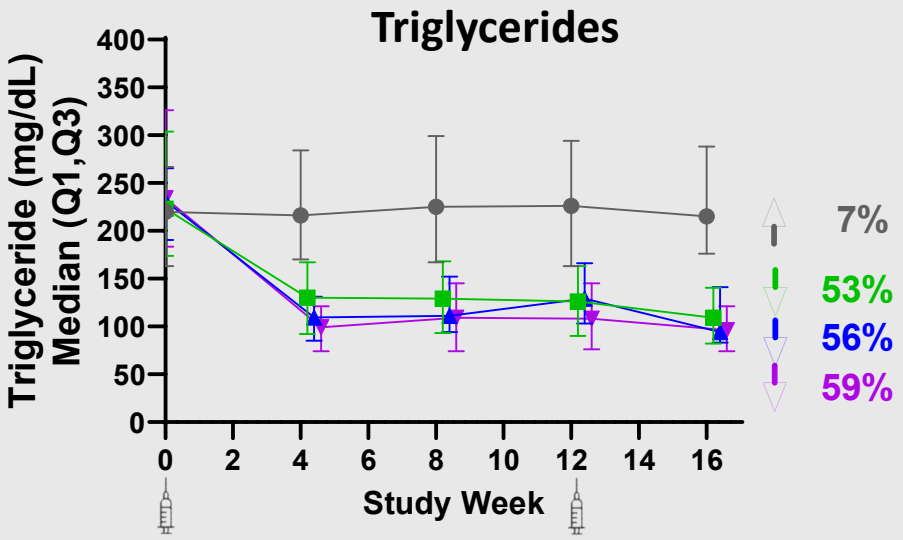
Baseline Characteristics

	Pooled Placebo	ARO-ANG3		
	(N=51)	50 mg (N=51)	100 mg (N=50)	200 mg (N=51)
Mean (SD) age, years	60.2 (11.3)	60.4 (12.7)	60.1 (10.0)	61.5 (12.5)
Female, n (%)	24 (47)	25 (49)	21 (42)	24 (47)
White, n (%)	48 (94)	49 (96)	49 (98)	49 (96)
Mean (SD) BMI, kg/m^2	33.0 (6.8)	33.3 (4.7)	32.6 (5.5)	31.6 (5.5)
Mean (SD) ANGPTL3,[a] µg/L	84.8 (27.7) n=11	74.1 (34.2) n=7	68.9 (10.6) n=5	84.7 (18.1) n=9
Median (Q1, Q3) TG, mg/dL	219.9 (163.2, 266.8)	223.3 (173.8, 303.3)	231.2 (190.5, 265.4)	234.1 (183.5, 326.2)
Mean (SD) LDL-C (Martin Hopkins), mg/dL	102.5 (30.6)	112.8 (29.7)	108.7 (44.8)	105.6 (33.7)
Mean (SD) non-HDL-C, mg/dL	138.6 (41.6)	151.5 (36.0)	149.3 (47.5)	143.3 (39.6)
Mean (SD) ApoB, mg/dL	95.7 (24.1)	106.8 (23.4)	99.6 (26.2)	94.9 (25.0)
Mean (SD) remnant cholesterol,[b] mg/dL	36.1 (31.6)	38.7 (12.1)	40.6 (30.8)	37.6 (14.9)
Mean (SD) HDL-C, mg/dL	41.6 (11.9)	43.2 (13.3)	39.9 (10.6)	42.3 (13.6)

[a] Limited ANGPTL3 results available at the data cutoff date (06 Jul 2022)
[b] Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C (Martin-Hopkins))

ARO-ANG3 Decreases Serum ANGPTL3 and Triglycerides

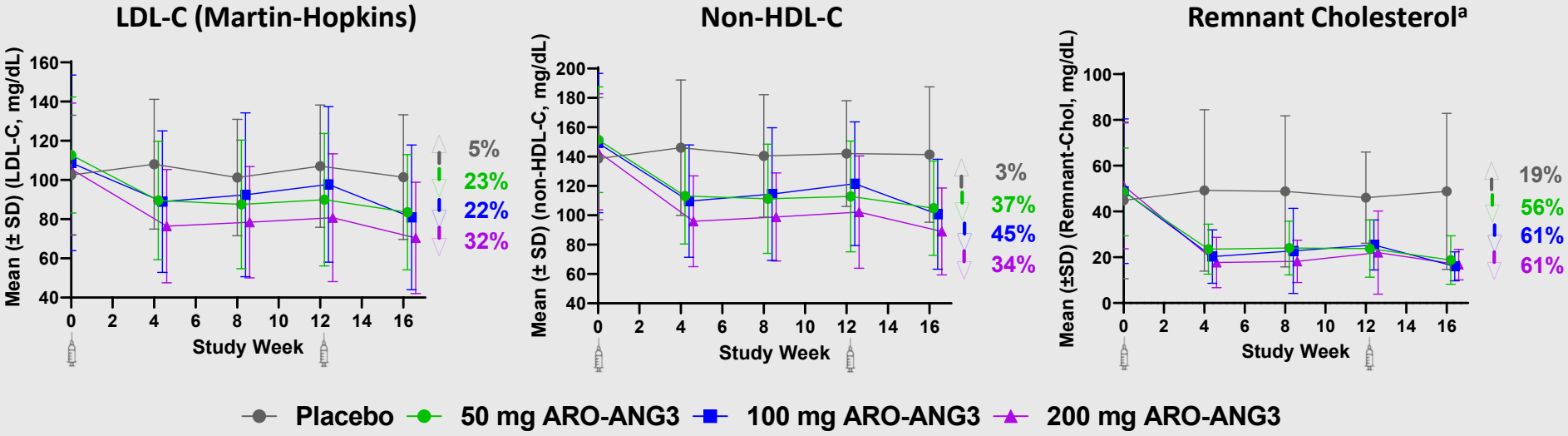




Placebo | 50 mg ARO-ANG3 | 100 mg ARO-ANG3 | 200 mg ARO-ANG3

*Limited ANGPTL3 results available at the data cutoff date (06 Jul 2022)

ARO-ANG3 Decreases Serum LDL-C, Non-HDL-C And Remnant Cholesterol

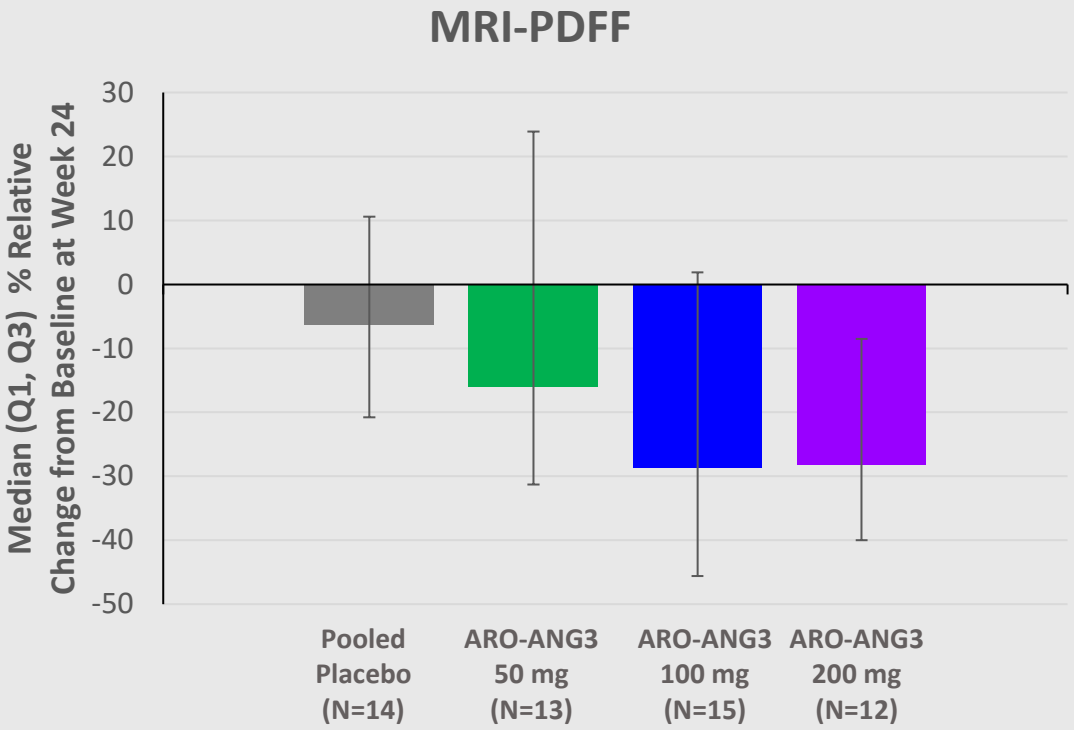


- ARO-ANG3 also reduced ApoB and HDL-C
  - Mean ApoB decreased by 13.2% to 21.8% at Week 16, compared with 0.0% for placebo
  - Mean HDL-C decreased by 17.3% to 30.6% at Week 16, compared with 2.1 % increase for placebo

ARCHES-2 : Data cutoff 06 Jul 2022

[a] Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C (Martin-Hopkins))

Data To Date Suggest ARO-ANG3 is Associated with Reduced Liver Fat Fraction



- Subgroup of 35 Subjects with liver fat fraction of >8% at baseline were selected for additional MRI-PDFF at Week 24
- To date, no AEs related to changes in liver function tests (LFTs)
- One subject (<1%) had a transient elevation of ALT (>3x upper limit of normal (no elevated total bilirubin))

Aggregated Summary of Adverse Events

# of Subjects Reporting ≥ 1 Treatment Emergent Adverse Event[a] (TEAE) N (%)	131/203 (65%)
TEAEs occurring in ≥ 5 subjects	N (%)
COVID-19	22 (11%)
Urinary tract infection	16 (8%)
Upper respiratory infection	13 (6%)
Headache	12 (6%)
Injection site pain	11 (5%)
Diabetes (Diabetes mellitus, Type 2 diabetes mellitus, glycosylated hemoglobin increase)	9 (4%)
Nausea	8 (4%)
Back pain	7 (3%)
Diarrhea	5 (2%)
Dizziness	5 (2%)
Hypertension	5 (2%)
Injection site erythema	5 (2%)
Osteoarthritis	5 (2%)
Treatment-related TEAEs	39 (19%)
Serious TEAEs	9 (4%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	1 (<1%)
TEAEs causing deaths	1 (<1%)

- TEAEs reported to date are consistent with those expected in this patient population and with associated underlying comorbidities
- Mean change from baseline in HbA1c at Week 16 across cohorts was 0.16% to 0.25% in subjects receiving ARO-ANG3 and -0.05% in subjects receiving placebo, driven by patients with baseline diabetes
- 1 death due to myocardial infarction in subject with multiple recent history of cardiovascular events (eg, CAD, STEMI, PCI, PAD, CHF)
  - Event occurred ~10 weeks after dosing of blinded investigational product and was considered unrelated to study drug.

[a]To maintain data blind, all TEAEs were pooled regardless of treatment assignment

Interim Analysis of ARCHES-2 Study of ARO-ANG3 Suggests Favorable Changes in Lipoproteins in Subjects With Mixed Dyslipidemia

- In subjects with mixed dyslipidemia who had baseline median TGs of 220 mg/dL to 234 mg/dL, treatment with ARO-ANG3 at doses of 50 mg, 100 mg or 200 mg ARO-ANG3 resulted in substantial reductions of:
  - ANGPTL3 up to 71% at Week 8
  - TGs up to 59 % at Week 16
  - LDL-C up to 32% at Week 16
- ARO-ANG3 is associated with relative reduction in liver fat fraction at Week 24, with no AEs related to LFT changes reported to date
- TEAEs reported to date are consistent with those expected in this patient population and with associated underlying comorbidities
- The favorable changes in serum lipids and lipoproteins support the potential value of ARO-ANG3 for the treatment of mixed dyslipidemia in patients at risk of atherosclerotic cardiovascular disease

THANK YOU

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Scientific Sessions

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