# ARO-ANG3, an Investigational RNAi Therapeutic, Silences the Expression of ANGPTL3 and Decreases Atherogenic Lipoproteins in Patients With Mixed Dyslipidemia: ARCHES-2 Study Results

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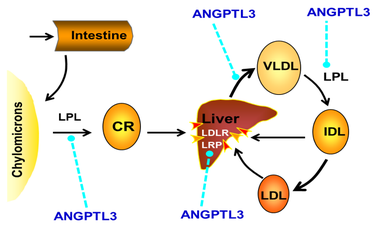
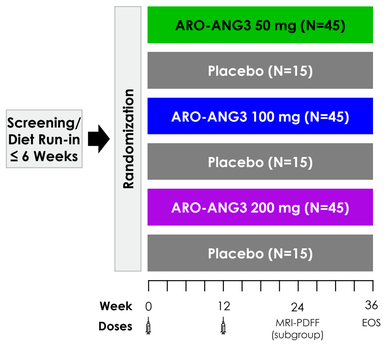
## BACKGROUND

- *ANGPTL3* is a hepatocyte expressed regulator of lipid and lipoprotein metabolism with multiple potential modes of action, including inhibition of lipoprotein lipase (LPL) and endothelial lipase (EL)[1,2]
- *ANGPTL3* loss-of-function variants lead to enhanced LPL and EL activity, resulting in:
  - ▼ TG, LDL-C, VLDL-C/remnant-C, and HDL-C[3-5]
  - ▼ Risk of ASCVD[3,4,6]
- No known adverse phenotype is associated with genetic deficiency in *ANGPTL3*[3,4]

**Potential Modes of ANGPTL3 Action[3-5]**




## STUDY DESIGN AND BASELINE CHARACTERISTICS




*All samples taken after ≥ 10 hour fast.

**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***

- Serum TG at Week 24 **(Primary)**
- ANGPTL3
- Non-HDL-C
- ApoB
- LDL-C
- VLDL-C/Remnant cholesterol
- HDL-C
- Lp(a)
- Liver fat fraction by MRI-PDFF (subgroup)
  - 61 subjects with liver fat fraction ≥ 8% at baseline were evaluated again at Week 24
- Safety

**End of Study (1 year results)**

- All subjects reached Week 36
- (Data cutoff 22 May 2023)

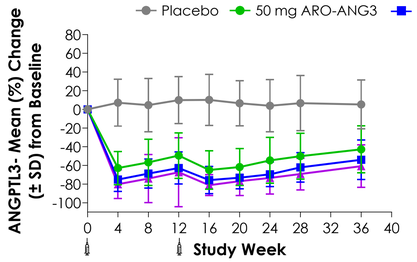
### Baseline Characteristics

| | Placebo (N=51) | ARO-ANG3 50 mg (N=51) | ARO-ANG3 100 mg (N=51) | ARO-ANG3 200 mg (N=51) |
|---|---|---|---|---|
| Mean (SD) age, years | 60.2 (11.3) | 60.4 (12.7) | 60.0 (9.9) | 61.5 (12.5) |
| Female, n (%) | 24 (47) | 25 (49) | 22 (43) | 24 (47) |
| White, n (%) | 48 (94) | 49 (96) | 49 (96) | 49 (96) |
| Mean (SD) BMI, kg/m² | 33.0 (6.8) | 33.3 (4.7) | 32.5 (5.5) | 31.6 (5.5) |
| Mean (SD) ANGPTL3, μg/L | 93.2 (29.0) | 98.6 (35.7) | 93.2 (27.4) | 101.2 (36.2) |
| Median (Q1, Q3) TG, mg/dL | 219.9 (181.2, 266.8) | 223.3 (178.6, 303.3) | 228.4 (190.5, 265.4) | 234.1 (183.5, 329.1) |
| Mean (SD) LDL-C (UC), mg/dL | 93.7 (31.2) | 102.8 (29.4) | 101.2 (45.3) | 92.1 (34.1) |
| Mean (SD) non-HDL-C, mg/dL | 138.6 (41.6) | 151.3 (36.2) | 149.8 (47.2) | 143.3 (39.6) |
| Mean (SD) ApoB, mg/dL | 95.6 (24.4) | 105.0 (24.1) | 100.1 (25.8) | 94.1 (25.0) |
| Mean (SD) remnant cholesterol[a], mg/dL | 44.9 (34.3) | 48.5 (19.2) | 48.6 (31.4) | 51.2 (27.5) |
| Mean (SD) HDL-C, mg/dL | 41.6 (11.9) | 43.1 (13.2) | 39.8 (10.5) | 42.3 (13.6) |

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

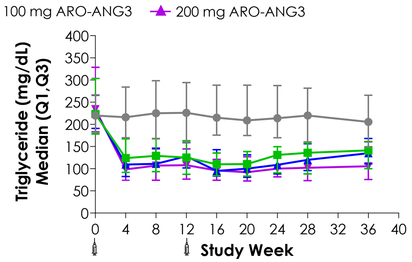
## RESULTS

**ANGPTL3**




| ANGPTL3 Difference vs Placebo (%) at Week 24 | | | |
|---|---|---|---|
| Placebo (N=51 ) | 50 mg (N=51) | 100 mg (N=51) | 200 mg (N=51) |
| --- | -54.3** | -69.8** | -73.7** |

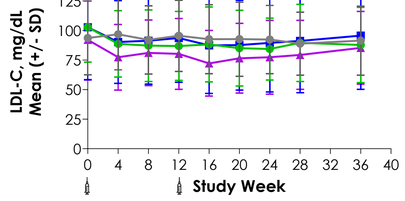
**Triglycerides**




| Triglyceride Difference vs Placebo (%) at Week 24 | | | |
|---|---|---|---|
| Placebo (N=51 ) | 50 mg (N=51) | 100 mg (N=51) | 200 mg (N=51) |
| --- | -51.2** | -56.6** | -63.1** |

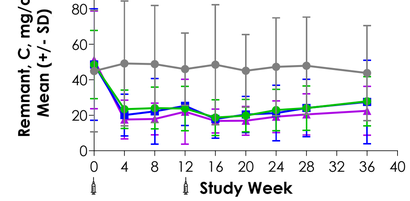
Least Square Mean Difference vs Placebo (%) *p<0.05; **p<0.0001.

**LDL-C (Ultracentrifugation)[a]**




| LDL-C (UC)[b] Difference vs Placebo (%) at Week 24 | | | |
|---|---|---|---|
| Placebo (N=51 ) | 50 mg (N=51) | 100 mg (N=51) | 200 mg (N=51) |
| --- | -15.8* | -13.6* | -19.9* |

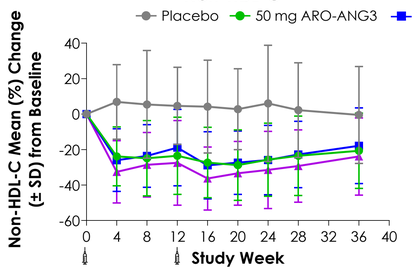
**Remnant Cholesterol[b]**




| Remnant Cholesterol Difference vs Placebo (%) at Week 24 | | | |
|---|---|---|---|
| Placebo (N=51 ) | 50 mg (N=51) | 100 mg (N=51) | 200 mg (N=51) |
| --- | -72.6** | -75.9** | -82.0** |

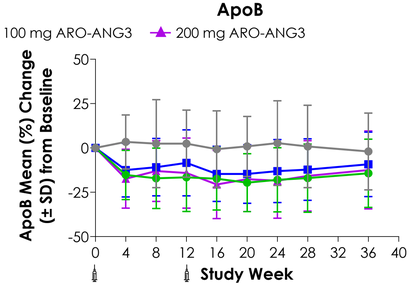
Least Square Mean Difference vs Placebo (%). [a]One patient with baseline value at 17 mg/dL was removed from the analysis; *p<0.05; **p<0.0001. [b]Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C (Ultracentrifugation [UC])).

**Non-HDL-C**




| Non-HDL-C Difference vs Placebo (%) at Week 24 | | | |
|---|---|---|---|
| Placebo (N=51 ) | 50 mg (N=51) | 100 mg (N=51) | 200 mg (N=51) |
| --- | -29.2** | -28.7** | -36.4** |

**ApoB**




| ApoB Difference vs Placebo (%) at Week 24 | | | |
|---|---|---|---|
| Placebo (N=51 ) | 50 mg (N=51) | 100 mg (N=51) | 200 mg (N=51) |
| --- | -18.7** | -15.2* | -21.9** |

Least Square Mean Difference vs Placebo (%): *p<0.05; **p<0.0001.

### Lipoprotein(a), HDL-C and Liver Fat

- Lipoprotein(a), least square mean difference vs placebo (%) at Study Week 24 is -7.3, -20.0 and -17.1 for 50mg, 100mg and 200mg ARO-ANG3 treatment, respectively
- HDL-C least square mean difference vs placebo (%) at Study Week 24 is -12.0, -21.6 and -24.5 for 50mg, 100mg and 200mg ARO-ANG3 treatment, respectively
- Liver fat median percent decrease from baseline to Week 24 measured by MRI-PDFF in a subset of patients with baseline >8% (N=58, completing Week 24) is -18.9% (placebo) and -16.0%, -21.3% and -28.6% (50mg, 100mg and 200mg, ARO-ANG3 treatment, respectively)

### TEAEs Occurring > 5% in the Trial

| | N (%) | | | |
|---|---|---|---|---|
| | Placebo | ARO-ANG 50 mg | ARO-ANG 100 mg | ARO-ANG 200 mg |
| **TEAEs** | | | | |
| Covid-19 | 9 (18%) | 10 (20%) | 12 (24%) | 11 (21%) |
| Upper respiratory tract infection | 4 (8%) | 5 (10%) | 1 (2%) | 5 (10%) |
| Headache | 2 (4%) | 5 (10%) | 2 (4%) | 7 (14%) |
| Urinary tract infection | 2 (4%) | 3 (6%) | 3 (6%) | 6 (12%) |
| Diabetes (Diabetes mellitus, TII DM) | 2 (4%) | 2 (4%) | 2 (4%) | 7 (14%) |
| Injection site pain | 0 (0%) | 5 (10%) | 4 (8%) | 2 (4%) |
| Nausea | 2 (4%) | 3 (6%) | 3 (6%) | 3 (6%) |
| Back pain | 0 (0%) | 3 (6%) | 2 (4%) | 6 (12%) |
| Dizziness | 3 (6%) | 2 (4%) | 4 (8%) | 1 (2%) |
| Treatment-Related AEs | 9 (18%) | 13 (26%) | 9 (18%) | 13 (25%) |
| SAEs | 4 (8%) | 5 (10%) | 0 (0%) | 1 (2%) |
| TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal | 1 (2%) | 0 (0%) | 1 (2%) | 0 (0%) |
| TEAEs associated with death | 1 (2%) | 0 (0%) | 0 (0%) | 0 (0%) |

- TEAEs reported to date are consistent with events in this patient population and with their underlying pathologies and comorbidities
- All SAEs were recovered/resolved (except 1 SAE with an outcome of death in the placebo group)
- Overall favorable safety profile. All TEAEs were manageable, none led to treatment discontinuation, interruption or study withdrawal in the treatment groups (50, 100mg, or 200mg of ARO-ANG3)

Cumulative data to 25 May 2023.

## CONCLUSIONS

- ARCHES-2 data demonstrate ARO-ANG3 significantly lowers TGs, ANGPTL3 and atherogenic triglyceride-rich lipoproteins (TRLs), LDL, and total apoB in patients with mixed dyslipidemia.
- ARCHES-2 data further demonstrate a favorable safety profile for ARO-ANG3 in patients with mixed dyslipidemia.
- The reductions in serum lipids and lipoproteins and favorable safety profile seen in ARCHES-2 support the potential of ARO-ANG3 to treat residual ASCVD risk in patients with elevated TRLs not at LDL-C goal.

## DISCLOSURES

**RS Rosenson** reports grant/research support from (all paid to institution, not individual): Amgen, Arrowhead, Novartis, Eli Lilly, Regeneron; consulting fees from Amgen, Arrowhead, CRISPR Therapeutics, Eli Lilly, Lipigon, Novartis, Precision Biosciences, Regeneron, UltraGenyx, Verve; non-promotional speaking fee from Amgen and Kowa; other support from MediMergent, LLC (significant); and is an UpToDate, Inc. stock shareholder (significant). **GF Watts** reports grants and/or honoraria from Amgen, Novartis, Arrowhead, Esperion, Astrazeneca, Pfizer, Novo Nordisk, Silence Therapeutics, CSL Seqirus, and Sanofi-Regeneron. **D Gaudet** reports grants and/or honoraria from Alnylam, Amgen, Arrowhead, AstraZeneca, Boehringer-Ingelheim, CRISPR Therapeutics, Dalcor Pharma, Eli Lilly, Esperion, Ionis, Kowa, Novartis, Pfizer, Regeneron, Sanofi, Ultragenyx and Verve Therapeutics. **RA Hegele** has served on advisory boards for Acasti, Akcea-Ionis, Amgen, Arrowhead, HLS Therapeutics, Novartis, Pfizer, Sanofi and Regeneron, and has received honoraria for continuing medical education talks from Amgen, HLS Therapeutics and Novartis. **CM Ballantyne** reports grants and/or honoraria from Abbott Diagnostic, Akcea, Allthera, Amarin, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Esperion, Gementech, Gilead, Illumina, Ionis, Matinas BioPharma Inc, Merck, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche Diagnostic, and Sanofi-Synthelabo. **SJ Nicholls** reports grants and/or honoraria from Akcea, Amarin, Amgen, Anthera, Arrowhead Pharmaceuticals Inc, AstraZeneca, Boehringer Ingelheim, Cerenis, CSL Behring, Eli Lilly, Esperion, InfraReDx, LipoScience, The Medicines Company, Merck, New Amsterdam Pharma, Novartis, Omthera, Resverlogix, Roche, Sanofi-Regeneron, and Takeda. **T Chang, K Modesto, S Melquist, R Fu,** and **J San Martin** are all current employees of Arrowhead Pharmaceuticals. **D Altamirano** has no disclosures.

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