ARO-ANG3, an Investigational RNAi Therapeutic, Decreases Serum LDL-Cholesterol, Apolipoprotein B, and Angiopoietin-like Protein 3 in Patients with Homozygous Familial Hypercholesterolaemia

Frederick Raal[a], Jean Bergeron[b], Gerald F. Watts[c], Daniel Gaudet[d], David Sullivan[e], Traci Turner[f], Robert A. Hegele[g], Christie M. Ballantyne[h], Joshua W. Knowles[i], Ira Goldberg[j], Ran Fu[k], Sudar Alagarsamy[k], James Hamilton[k], Robert S. Rosenson[l]

[a]University of the Witwatersrand, Johannesburg, South Africa; [b]Université Laval, Québec, QC, Canada; [c]University of Western Australia, Perth, Australia and Department of Cardiology, Royal Perth Hospital; [d]Université de Montréal, Montréal, Québec, Canada; [e]Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia; [f]Metabolic and Atherosclerosis Research Center, Medpace, Cincinnati, OH, USA; [g]Robarts Research Institute, London, Ontario, Canada; [h]Baylor College of Medicine, Houston, TX, USA; [i]Stanford University, Stanford, CA, USA; [j]NYU Langone Health, NY, NY, USA; [k]Arrowhead Pharmaceuticals, Pasadena, CA, USA; [l]Icahn School of Medicine at Mt Sinai, Mount Sinai, NY, USA

Background: Angiopoietin-like protein 3 (*ANGPTL3*) regulates lipoprotein metabolism by inhibiting lipoprotein and endothelial lipases. *ANGPTL3* loss-of-function variants have decreased circulating LDL-C. ARO-ANG3 is a liver-targeted RNAi therapeutic that inhibits *ANGPTL3* expression and decreases atherogenic lipoproteins through non-LDL receptor mediated mechanisms which may reduce LDL-C in patients with LDL receptor deficiency such as homozygous familial hypercholesterolaemia (HoFH).

Methods: In this open-label Phase 2 study, 18 HoFH patients with a mean fasting baseline LDL-C of 10.0 mmol/L (range: 2.3 to 21.6 mmol/L) on lipid-lowering standard of care (including apheresis), were randomized to receive subcutaneous injections of 200 mg or 300 mg ARO-ANG3 on Day 1 and Week 12. The primary endpoint was fasting LDL-C percent change from baseline to Week 24. The lipid cut-off date for this interim analysis was 17 April 2023 and includes data from 17 subjects who have completed Week 20.

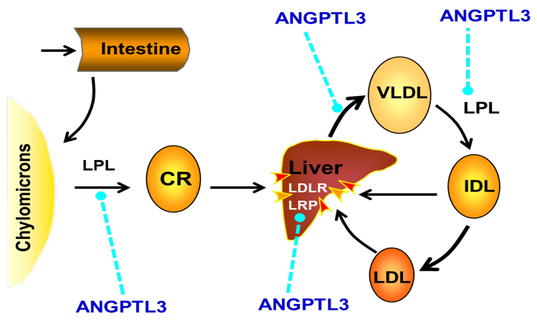
Results: At Week 20, 200 mg and 300 mg doses of ARO-ANG3 achieved mean reductions from Baseline (and mean percent change) in LDL-C (Martin Hopkins) of -4.4 mmol/L, -5.0 mmol/L (-48.1%, -44.0%), Apolipoprotein B of -0.97 g/L, -0.89 g/L (-39.2%, -34.5%), and *ANGPTL3* of -54.6 ng/mL, -87.9 ng/mL (-82.7%, -80.1%), respectively. No drug discontinuations, drug-related SAEs or AEs related to elevated ALTs were reported. The most frequent AEs were injection site pain and erythema (11.1%), and nasopharyngitis (11.1%).

Conclusions: These interim data suggest that HoFH patients on lipid-lowering standard care who received ARO-ANG3 achieved additional reductions in LDL-C, similar to *ANGPTL3*-targeted monoclonal antibodies. This supports further investigation of ARO-ANG3 in HoFH patients.

ANGPTL3 Regulates Lipid and Lipoprotein Metabolism

- *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)
- *ANGPTL3* loss-of-function variants lead to enhanced LPL and EL activity, resulting in:
  - ▼ TG, LDL-C, VLDL-C, and HDL-C
  - ▼ Risk of ASCVD
- No known adverse phenotype is associated with genetic deficiency in *ANGPTL3*

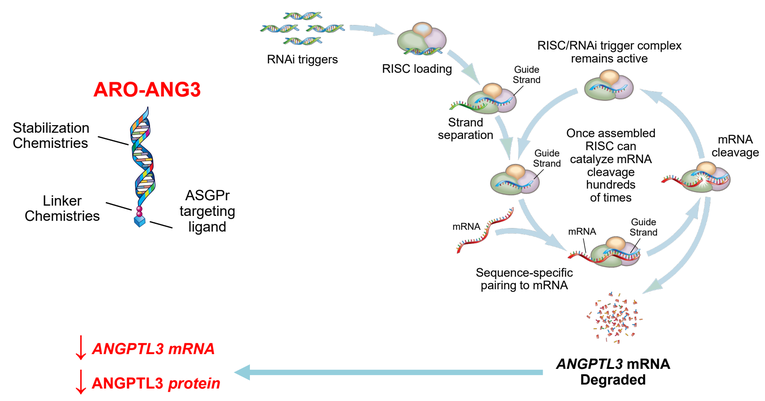
Potential Modes of ANGPTL3 Action[1]



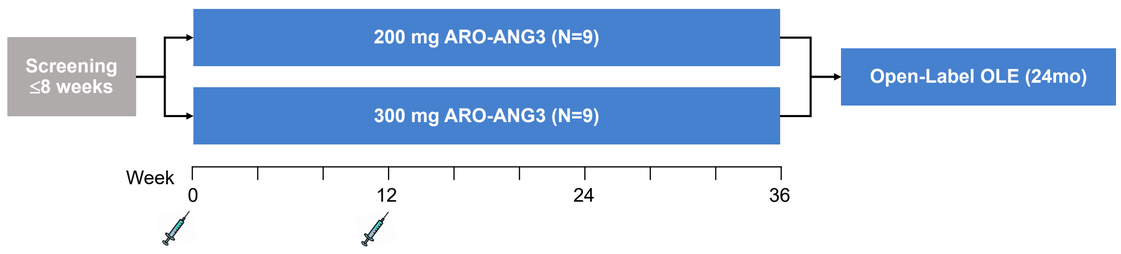
ARO-ANG3 is a siRNA Therapeutic Designed to Silence ANGPTL3 and Reduce LDL-C

ANGPTL3 is an ideal target for **ARO-ANG3, a hepatocyte targeted siRNA** designed to silence *ANGPTL3* gene expression

- **ARO-ANG3** is a subcutaneously administered **siRNA targeted at the hepatocyte**, where it specifically **inhibits and degrades the *ANGPTL3* mRNA**
- **ARO-ANG3** induces deep and durable silencing of the *ANGPTL3* gene while **avoiding off-target effects**



GATEWAY Study Design



Primary Endpoint

- Percent change from baseline to Week 24 in fasting LDL-C

Key Secondary Pharmacodynamic Endpoints

- Percent and absolute change from baseline in LDL-C, *ANGPTL3*, Total ApoB, HDL-C, TGs and Non-HDL-C at each scheduled assessment (fasting)

Key Inclusion Criteria

- HoFH confirmed by genetic testing or clinical diagnosis
- Fasting LDL-C >2.6 mmol/L at Screening
- Fasting TG <3.39 mmol/L at Screening
- Stable low-fat diet and standard of care medications, including apheresis, statins, ezetimibe and PCSK9 inhibitors

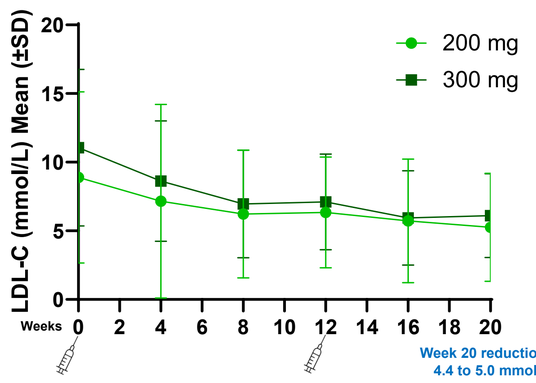
GATEWAY Patient Baseline Characteristics

	ARO-ANG3	
	200 mg (N=9)	300 mg (N=9)
Mean (SD) age, years	49.6 (19.5)	36.3 (17.9)
Female, n (%)	7 (77.8)	6 (66.7)
White, n (%)	6 (66.7)	8 (88.9)
Mean (SD) BMI, kg/m^2	25.8 (5.8)	28.0 (6.1)
Mean (SD) LDL-C (Martin Hopkins), mmol/L	8.9 (6.2)	11.1 (5.7)
Mean (SD) ANGPTL3, ng/mL*	69.9 (32.5)	104.3 (66.8)
Mean (SD) ApoB, g/L	2.3 (1.4)	2.6 (1.0)
Mean (SD) TG, mmol/L	1.5 (1.0)	1.2 (0.5)
Mean (SD) non-HDL-C, mmol/L	9.7 (6.6)	11.7 (5.7)
Mean (SD) VLDL-C (Calculated), mmol/L	0.8 (0.6)	0.6 (0.3)
Mean (SD) HDL-C, mmol/L	1.2 (0.4)	1.1 (0.5)

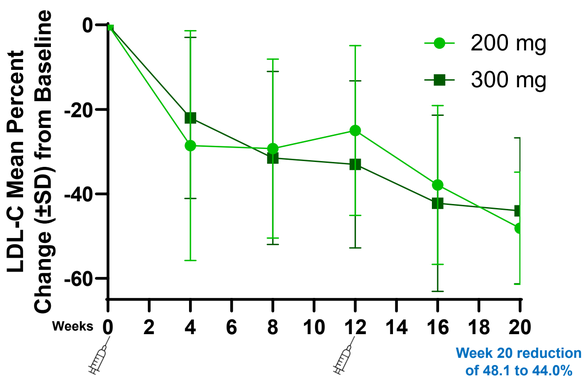
*N=8 patients for each ARO-ANG3 200 mg and 300 mg dose group

ARO-ANG3 Reduces LDL-C, ANGPTL3 and ApoB

Absolute LDL-C Change

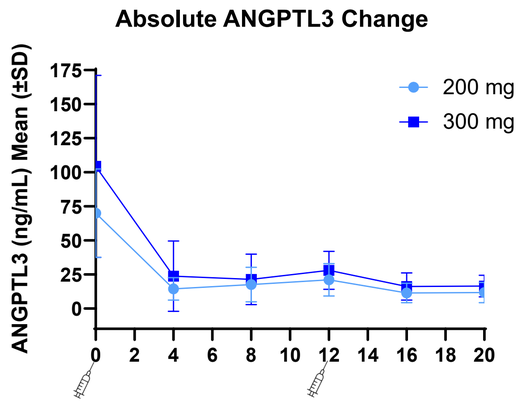


Percent LDL-C Change from Baseline

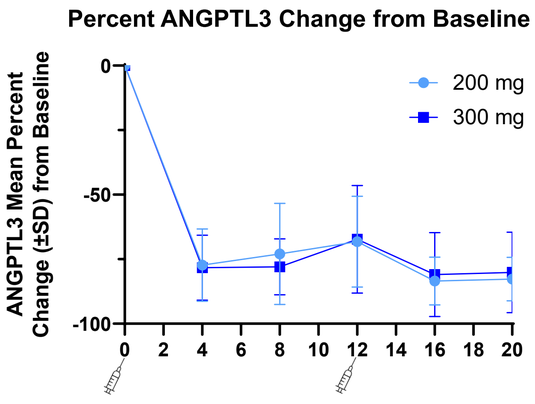


- **Week 20 LDL-C (Martin-Hopkins) reductions of 4.4 to 5.0 mmol/L and 48.1% to 44.0% at 200 mg, 300 mg dose respectively**

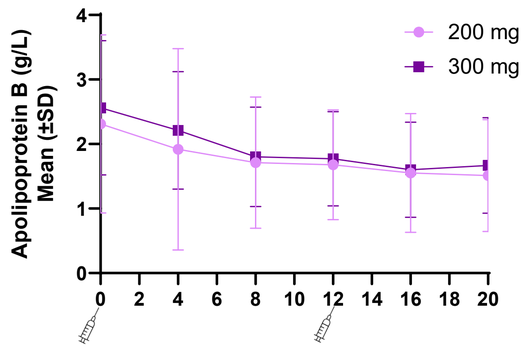
Absolute ANGPTL3 Change



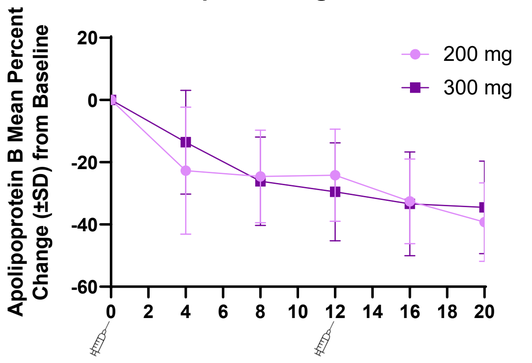
Percent ANGPTL3 Change from Baseline



Absolute ApoB Change



Percent ApoB Change from Baseline



- **Week 20 ApoB reductions of 0.97 to 0.89 g/L and 39.2% to 34.5% at 200 mg, 300 mg dose, respectively**
- **Week 20 ANGPTL3 reductions of 82.7% to 80.1% at 200 mg, 300 mg dose, respectively**

	200 mg (n=8)			300 mg (n=9)		
	Baseline (mmol/L)	Wk 20 (mmol/L)	% Change from Baseline	Baseline (mmol/L)	Wk 20 (mmol/L)	% Change from Baseline
HDL-C (mean ± SD)	1.29 ± 0.35	0.86 ± 0.34	-29.2 ± 28.7	1.09 ± 0.51	0.75 ± 0.44	-32.7 ± 16.2
non-HDL-C (mean ± SD)	10.45 ± 6.52	5.70 ± 3.97	-47.0 ± 12.4	11.69 ± 5.70	6.54 ± 3.10	-43.0 ± 16.1
TG (mean ± SD)	1.58 ± 1.03	0.77 ± 0.27	-38.8 ± 29.5	1.17 ± 0.48	0.76 ± 0.18	-28.3 ± 24.0

- **Consistent with human genetic data, ANGPTL3 inhibition reduces HDL-C, non-HDL-C, and TGs**

# of Subjects (>1) Reporting Treatment Emergent Adverse Event (TEAE) n (%)	Total N=18
Dizziness	2 (11%)
Injection site pain	2 (11%)
Nasopharyngitis	2 (11%)
Treatment-related TEAEs	8 (44%)
Serious TEAEs	1 (5.6%)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	0 (0%)
TEAEs causing deaths	0 (0%)

- Single SAE of 2nd degree AV block requiring pacemaker placement in a patient with extensive ASCVD history. Considered not related to ARO-ANG3
- No AEs related to elevations in transaminases

SUMMARY

- In HoFH patients, ARO-ANG3 reduced serum ANGPTL3 by up to 82.7% resulting in LDL-C reductions of 44% to 48%
- Reductions achieved on top of continued standard of care including statins, ezetimibe, PCSK9 inhibitors and apheresis
- Safety profile favorable without any newly identified pattern of AEs in an HoFH population
- HoFH Phase 3 planning is ongoing

Adam, et al., *J Lipid Res.* 2020;61(9):1271-86.
Ballantyne, Saunders/Elsevier; 2015.
Dewey, et al., *N Engl J Med.* 2017;377(3):211-21.
Minicocci et al., *Lipid Res.* 2013;54(12):3481-90.
Musunuru, et al., *N Engl J Med.* 2010;363(23):2220-7.
Ridker et al., *N Engl J Med.* 1997;336(14):973-9.
Stitziel, et al., *J Am Coll Cardiol* 2017;69(16):2054-63.
Watts, et al, AHA 2020 Abstract: 15751.

arrowhead pharmaceuticals