Pharmacodynamic effect of ARO-ANG3, an investigational RNA interference therapeutic targeting hepatic angiopoietin-like protein 3, in patients with dyslipidemia

GF Watts[1], C Schwabe[2], R Scott[3], P Gladding[4], D Sullivan[5], J Baker[6], P Clifton[7], J Hamilton[8], B Given[8], J San Martin[8], S Melquist[8], T Chang[8], N Rajicic[8], I Goldberg[9], D Gaudet[10], JW Knowles[11], RA Hegele[12], C Ballantyne[13] on behalf of the AROANG1001 Study Investigators

[1]University of Western Australia, Perth, Australia; [2]Auckland Clinical Studies, Auckland, New Zealand; [3]Lipid and Diabetes Research, Christchurch Hospital, Christchurch 8011, New Zealand; [4]Waitemata District Health Board, Auckland, New Zealand; [5]Royal Prince Alfred Hospital, Sydney, Australia; [6]Middlemore Hospital, Auckland, New Zealand; [7]Royal Adelaide Hospital, Adelaide, Australia; [8]Arrowhead Pharmaceuticals, Inc., Pasadena, United States; [9]NYU School of Medicine, NYU Langone Health, New York City, United States; [10]Department of Medicine, Université de Montréal and ECOGENE-21 Clinical Research Center, Chicoutimi,Canada;[11]Stanford Division of Cardiovascular Medicine and Cardiovascular Institute, School of Medicine, Stanford, United States; [12]University of Western Ontario, London, Canada; [13]Baylor College of Medicine, Houston, United States

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Co-authors:

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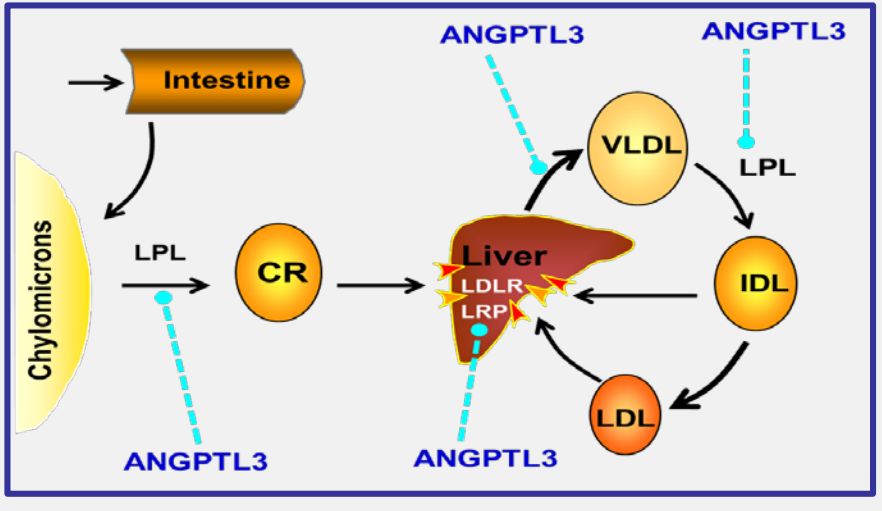
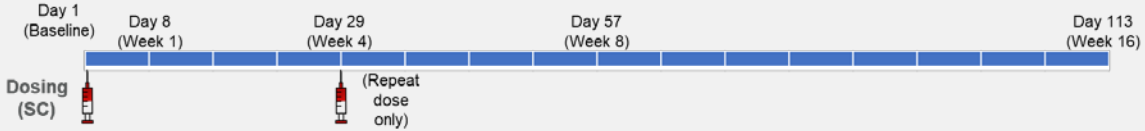
ANGPTL3 as a target to treat dyslipidemia

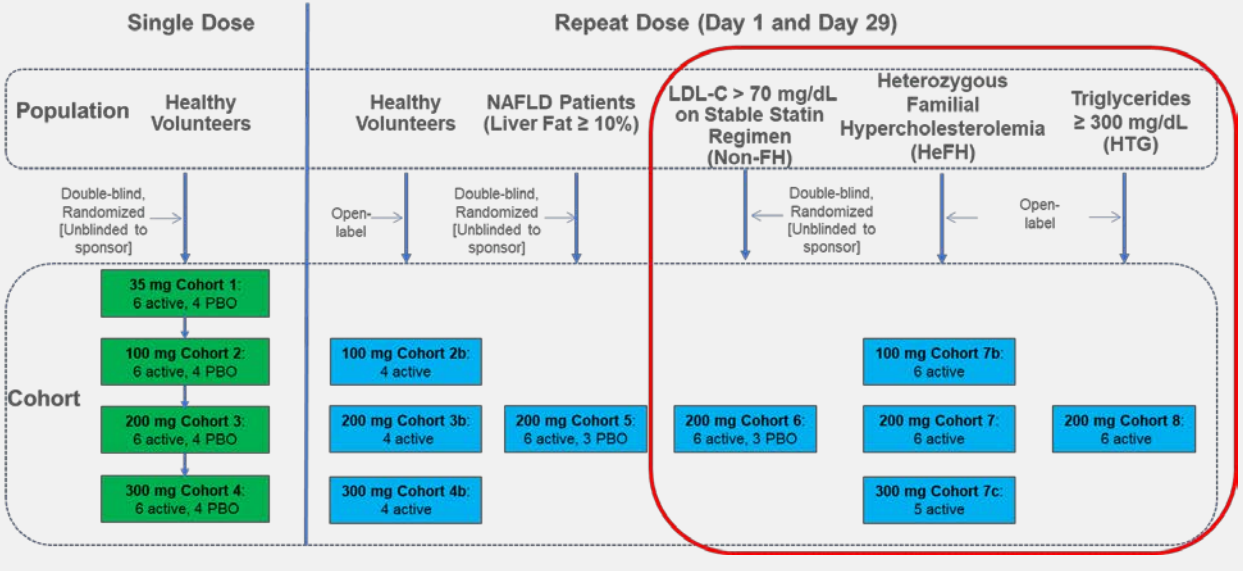
- **Dyslipidemia** is a major risk factor for cardiovascular disease (CVD), and **residual risk of CVD persists** even with current standard of care (including PCSK9 inhibitors)
- **ANGPTL3** is a **key regulator of lipid and lipoprotein metabolism** with multiple potential nodes of action, including 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 TG, LDL-C, VLDL-C, and HDL-C
  - Reduced risk of CVD, and
  - No known adverse phenotype associated with genetic deficiency in *ANGPTL3*
- **ARO-ANG3** is an investigational synthetic, double-stranded, hepatocyte-targeted RNA interference (RNAi) trigger designed to specifically silence *ANGPTL3* mRNA expression in the liver

Potential Regulatory Nodes of Action of ANGPTL3



Phase 1 Study to evaluate the effect of ARO-ANG3 in dyslipidemic patients





Study Endpoints

Safety (Primary):

- Incidence and frequency of adverse events

Key Pharmacodynamic and Lipid Parameters:

- Change from baseline over time in ANGPTL3
- Change from baseline over time in the following parameters: fasting Triglycerides, LDL-C, non-HDL-C, and HDL-C

Patient Populations

- **HeFH** - Heterozygous Familial Hypercholesterolemia (HeFH) patients – genetically confirmed or Dutch lipid clinic network score ≥ 6
- **Non-FH** – Patients on stable statin regimen that are not at LDL-C goal (LDL-C > 70 mg/dL)
- **HTG** - Hypertriglyceridemia patients with TG >300 mg/dL at screening

Data cutoff: 30 Apr 2020

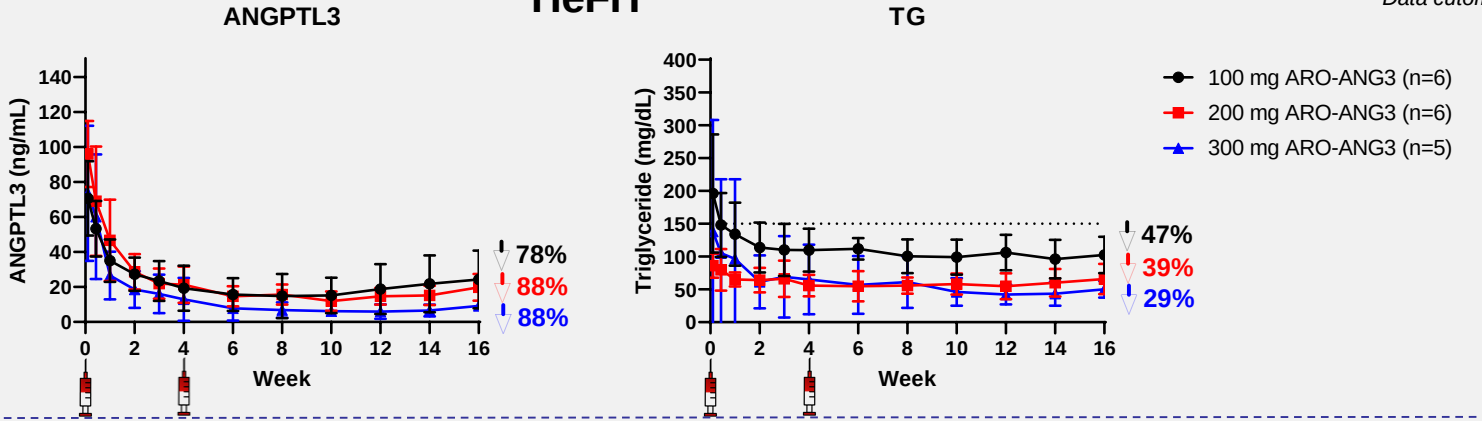
Baseline characteristics of HeFH, Non-FH and HTG patient cohorts

	HeFH Patients			Non-FH Patients		HTG Patients
Mean (range) Fasting values	100 mg ARO-ANG3 (n=6)	200 mg ARO-ANG3 (n=6)	300 mg ARO-ANG3 (n = 5)	Placebo (n=3)	200 mg ARO-ANG3 (n=6)	200 mg ARO-ANG3 (n=6)
Age (years)	43.5 (19-61)	49.3 (25-65)	45.2 (20-70)	58.7 (51-63)	51.7 (31-62)	62.8 (51-69)
Male (%)	50	50	60	67	83	67
BMI (kg/m^2)	29.9 (25.1-35.0)	28.0 (21.0-36.9)	25.6 (19.4-29.8)	28.8 (28.0-29.5)	26.8 (21.5-36.4)	31.2 (27.8-36.9)
ANGPTL3 (ng/mL)	71 (45-91)	96 (76-127)	74 (36-134)	91 (69-131)	87 (59-112)	107 (68-161)
Triglycerides (mg/dL)	196 (94-360)	86 (66-118)	138 (38-441)	198 (121-271)	87 (68-130)	973 (189-2743)
LDL-C (mg/dL) (direct assay)	129 (95-191)	146 (91-171)	126 (96-174)	98 (56-132)	96 (68-198)	79 (13-179)
Non-HDL-C (mg/dL)	171 (121-229)	168 (109-207)	163 (105-230)	131 (83-180)	112 (84-217)	236 (141-385)
HDL-C (mg/dL)	45 (32-59)	60 (46-86)	44 (30-57)	57 (54-61)	43 (34-53)	37 (10-75)
ApoB (mg/dL)	132 (88-202)	106 (73-138)	100 (75-135)	87 (60-124)	78 (64-133)	106 (71-149)

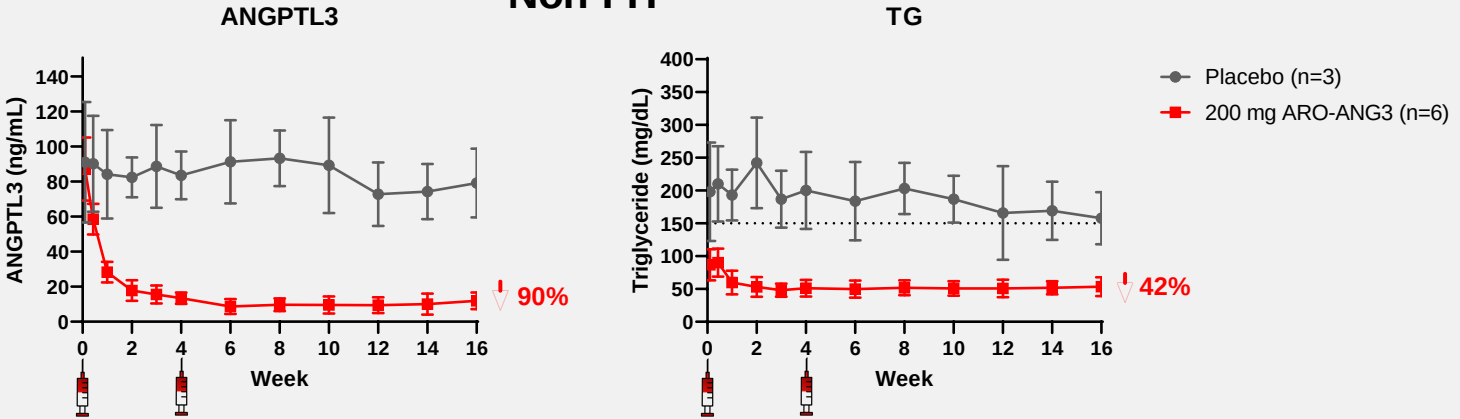
ARO-ANG3 substantially reduces ANGPTL3 and TG in HeFH and non-FH patients

Data cutoff: 30 Apr 2020

HeFH



Non-FH

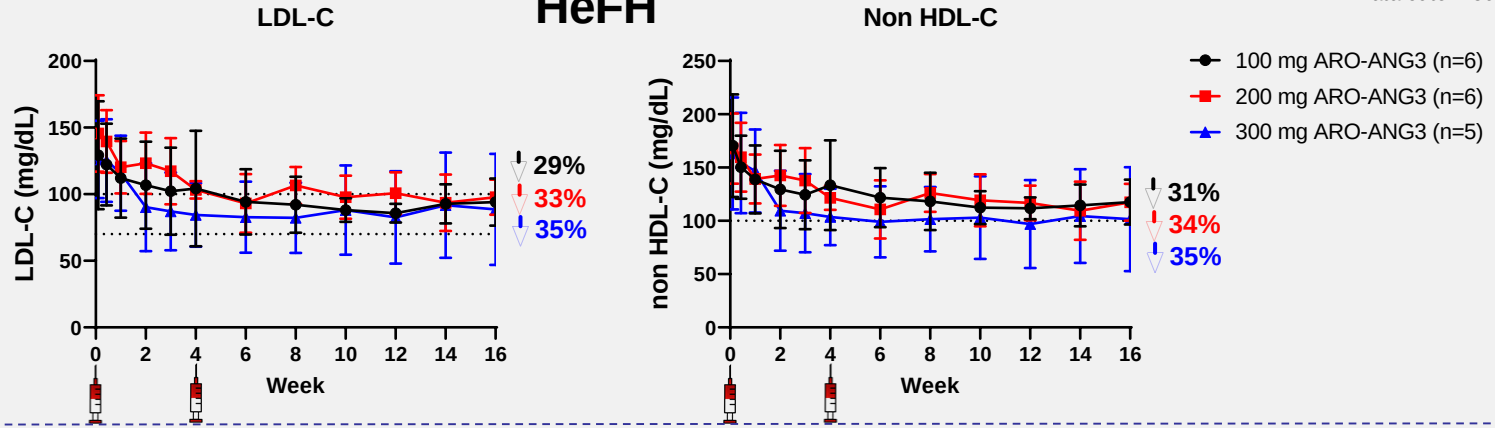


Mean values +/- SD are plotted for each cohort ;% values are maximum mean reductions for each cohort (n>1 subject at a visit date)

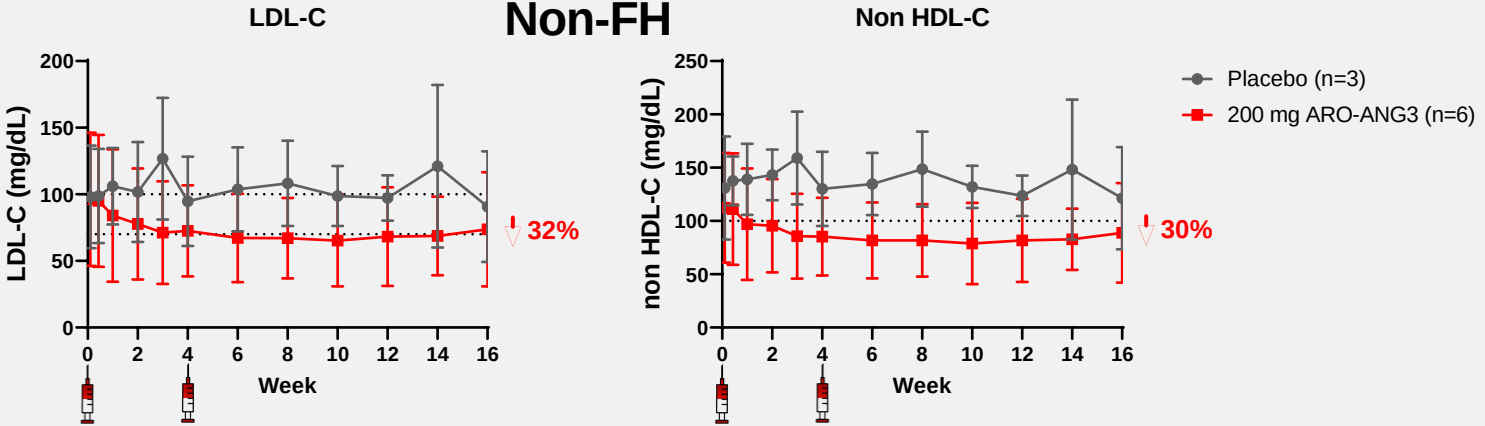
ARO-ANG3 substantially reduces LDL-C and non-HDL-C in HeFH and non-FH patients

Data cutoff: 30 Apr 2020

HeFH



Non-FH

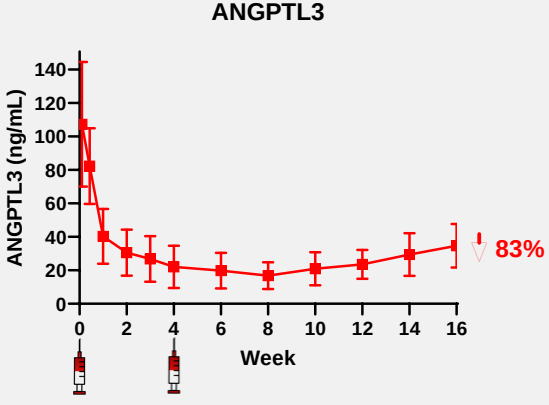


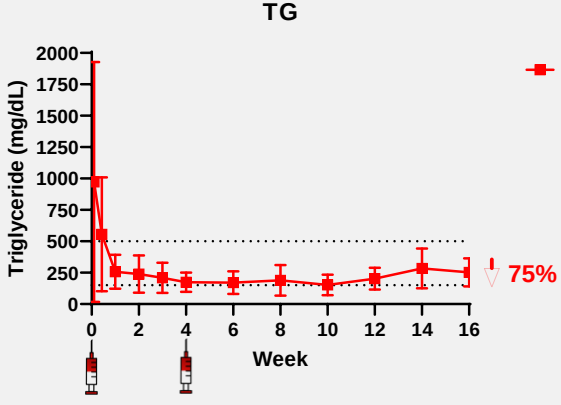
Mean values +/- SD are plotted for each cohort ;% values are maximum mean reductions for each cohort (n>1 subject at a visit date)

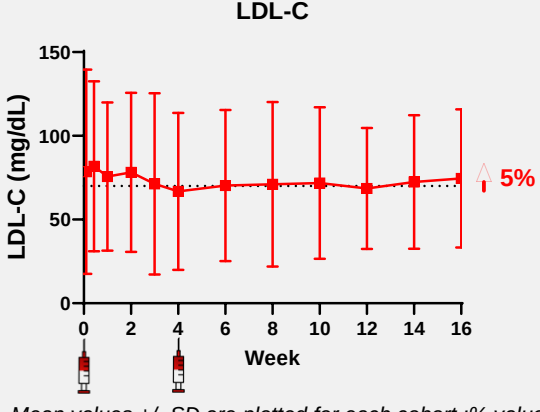
ARO-ANG3 substantially reduces ANGPTL3, TG and non-HDL-C in HTG patients

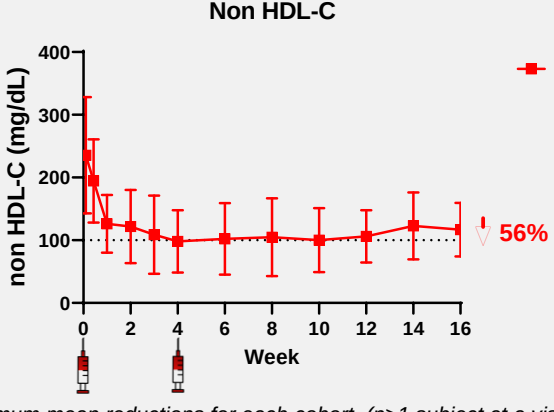
Data cutoff: 30 Apr 2020

HTG









Mean values +/- SD are plotted for each cohort ;% values are maximum mean reductions for each cohort (n>1 subject at a visit date)

Summary of interim safety data

	HeFH	HTG	Non-FH		
TEAEs Reported in > 2 subjects, AE Term (MedDRA Preferred Term)	**HeFH All Doses n = 17**	**200 mg n=6**	**200 mg Active n=6**	**Placebo n=3**	**Total Active n = 29**
Headache	4 (23.5%)	1 (17%)	0	1 (33%)	5 (17%)
Contusion	4 (23.5%)	0	0	0	4 (14%)
Oropharyngeal pain	3 (18%)	1 (17%)	0	0	4 (14%)
Vascular access site bruising/hematoma	2 (12%)	1 (17%)	1 (17%)	0	4 (14%)
Injection site erythema, bruising, pain, swelling	3 (18%)	0	0	1 (33%)	3 (10%)
Dizziness	2 (12%)	0	1 (17%)	1 (33%)	3 (10%)
Muscle spasm	1 (6%)	2 (33%)	0	0	3 (10%)
Presyncope, Syncope	3 (18%)	0	0	0	3 (10%)
Upper respiratory tract infection, Respiratory tract infection	1 (6%)	0	2 (33%)	1 (33%)	3 (10%)

- Two subjects reported SAEs (1 case of ketosis related to dapaglifozin and dehydration, 1 case of syncope with fibula fracture), both cases not related to ARO-ANG3.
- Two AEs of ALT elevation were reported. One case was asymptomatic (baseline 34 U/L, peak 91 U/L). The other (baseline 30 U/L, peak 238 U/L Day 29, 68 U/L Day 43 and 34 U/L at Day 113/EOS) was transient and associated with gastroenteritis. Neither associated with clinically significant elevations in total bilirubin.
- No clinically significant adverse changes in platelets
- No drug discontinuations
- Contusion AEs (n=4)
  - 2 events related to mechanical fall
  - 1 event related to NSAID treatment

Safety Data cut-off 11Sept 2020

ARO-ANG3, an investigational RNAi therapeutic targeting *ANGPTL3* mRNA transcripts results in sustained favorable lipid changes

- In **HeFH and Non-FH patients**,100 mg, 200 mg or 300 mg ARO-ANG3 SC resulted in mean reductions of:
  - -78% to -90% for ANGPTL3
  - -29% to -47% for TG
  - -29% to -35% for LDL-C
  - -31% to -35% for non-HDL-C
- In **HTG patients**, 200 mg of ARO-ANG3 SC resulted in mean reductions of:
  - -83% for ANGPTL3
  - -75% for TG
  - +5% for LDL-C
  - -56% for non-HDL-C
- ARO-ANG3 maintained reductions in these lipid parameters for **>12 weeks post second dose**, regardless of patient population
- ARO-ANG3 had a **favorable safety and tolerability** profile

ARO-ANG3 produces a substantial and prolonged reduction of LDL-C, non-HDL-C and TGs, and may prove useful as a therapeutic option in patients with dyslipidemia