ARO-DIMER-PA, A DUAL FUNCTION RNA INTERFERENCE THERAPEUTIC TARGETING BOTH PCSK9 AND APOC3 IN ADULTS WITH MIXED HYPERLIPIDEMIA

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#ScientificSessions26

DISCLOSURES

Disclosures: Dr. Laffin serves/served as a consultant or on steering committees for Arrowhead, AstraZeneca, Crispr Therapeutics, Diamedica, Eli Lilly, Kardigan, Madrigal, Medtronic, Mineralys, Novo Nordisk, Novartis, Recor, Retension, Ripple, Viking. He receives royalties from Belvoir Media Group, Elsevier, and Springer Nature

INTRODUCTION

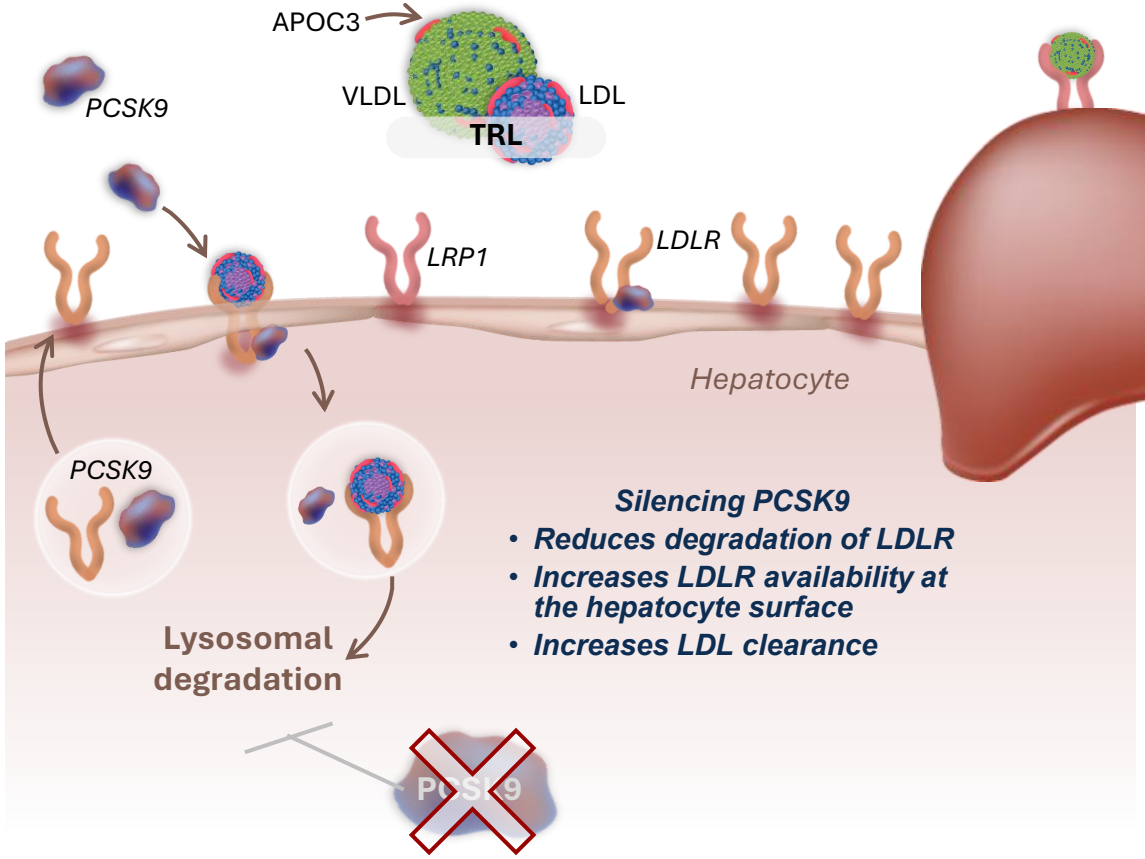
- Mixed hyperlipidemia is characterized by elevated LDL-C and TG-rich lipoproteins, both of which contribute to ASCVD risk.
- Current treatment typically requires multiple therapies to address both lipid pathways
- PCSK9 and APOC3 regulate complementary pathways controlling LDL-C and TRLs, respectively.
- ARO-DIMER-PA is a first-in-class, dual function, liver-targeted, siRNA conjugate designed to *simultaneously* silence both hepatic PCSK9 and APOC3 mRNA expression

APOC3, apolipoprotein C3; **ASCVD**, atherosclerotic cardiovascular disease; **LDL-C**, low-density lipoprotein cholesterol; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **siRNA**, small interfering RNA; **TG,** triglycerides; **TRL**, triglyceride rich lipoprotein.

PCSK9 AND APOC3 IN LIPID METABOLISM AND CLEARANCE

PCSK9

PCSK9 promotes LDLR degradation, reducing LDLR recycling

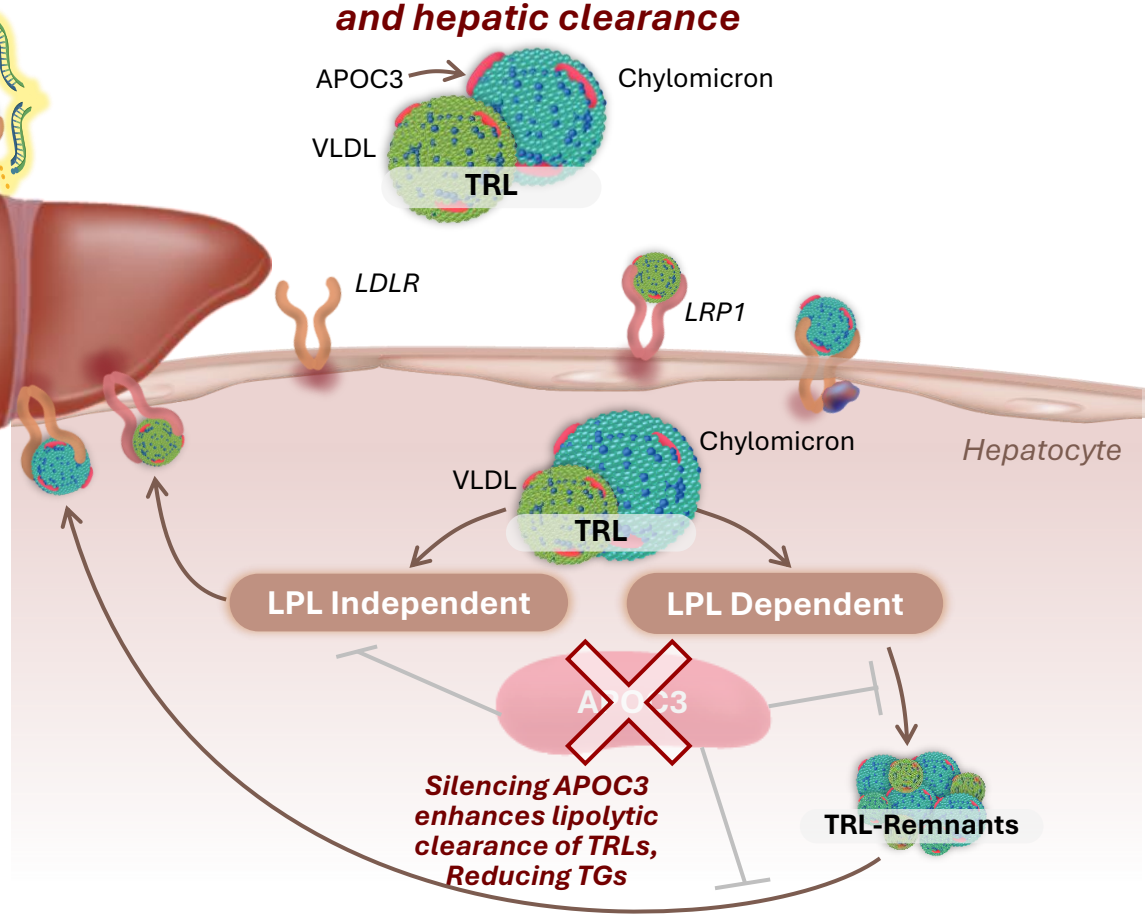


Silencing PCSK9

- ***Reduces degradation of LDLR***
- ***Increases LDLR availability at the hepatocyte surface***
- ***Increases LDL clearance***

APOC3

APOC3 inhibits LPL mediated TRL lipolysis and hepatic clearance



Silencing APOC3 enhances lipolytic clearance of TRLs, Reducing TGs

1. Van Zwol W, et al. *J Clin Med*. 2019; 8:1085. **2.** Ballantyne CM, et al. *New Engl J Med*. 2024; Published online: May 28, 2024.

APOC3, apolipoprotein C3; **LDLR**, low-density lipoprotein receptor; **LPL**, lipoprotein lipase; **LRP1**, low-density lipoprotein receptor-related protein; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **siRNA**, small interfering RNA; **TG,** triglycerides; **TRL**, triglyceride rich lipoproteins; **VLDL**, very low-density lipoprotein.

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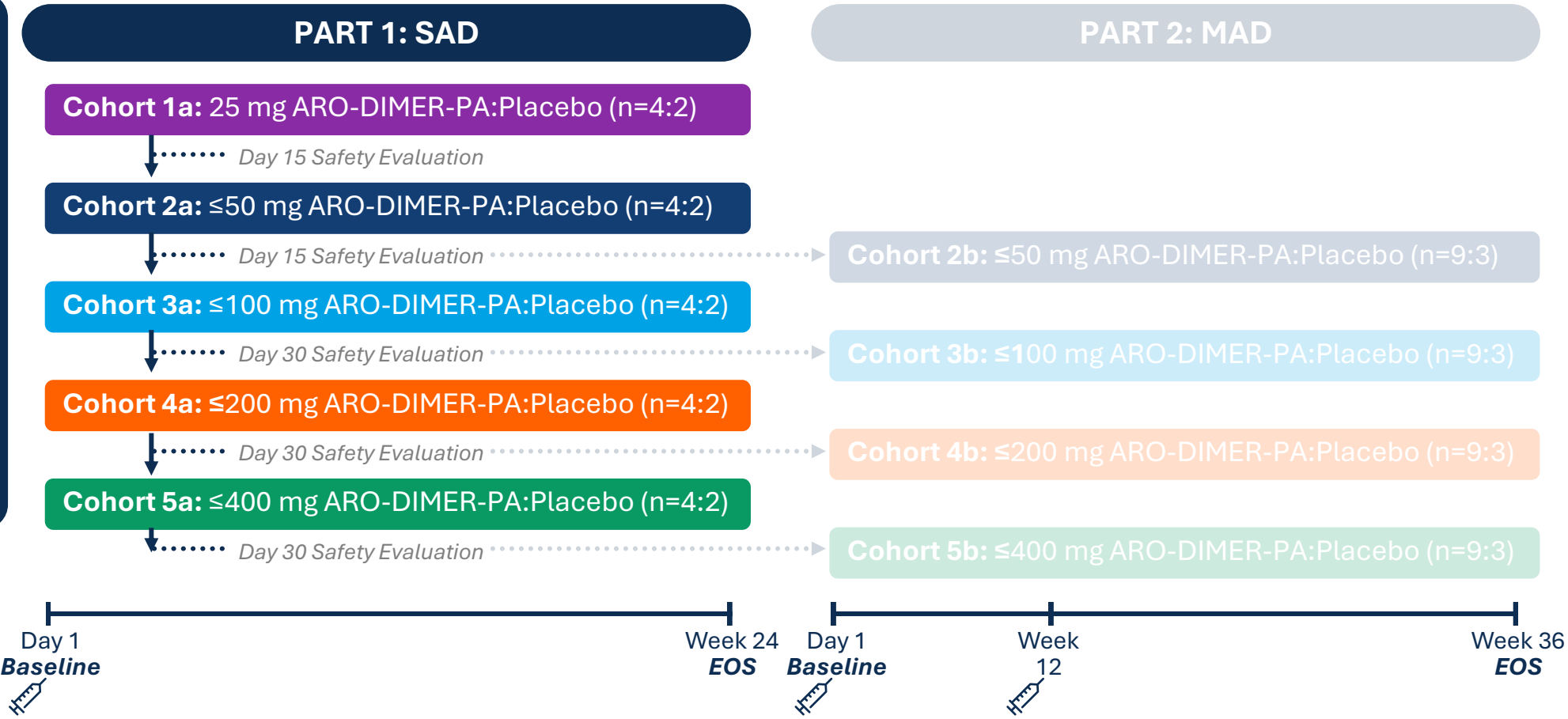
STUDY DESIGN

Subjects with Mixed Hyperlipidemia[a]

1) TGs between ≥150 mg/dL and ≤499 mg/dL

AND

2) non-HDL-C ≥100 mg/dL OR LDL-C ≥70 mg/dL



For Part 1 Cohorts 3a and 4a, all available PD data will be reviewed by the DSC to inform dose escalation to the next SAD cohort (Part 1). To inform initiation of MAD cohorts (3b, 4b, and 5b), all available PD data for the corresponding SAD cohorts will be reviewed by the DSC. [a]If screening TGs ≥100 mg/dL and ≤499 mg/dL , then verifiable historical value of TGs ≥150 mg/dL and ≤499 mg/dL. Screening TG may be repeated if the initial TG level does not meet the criteria. Enrolled participants at 11 sites in Australia, New Zealand, and the country of Georgia.

DSC, Data Safety Committee; **EOS**, end of study; LDL-C, low-density lipoprotein cholesterol; **MAD**, multiple ascending doses; **non-HDL-C**, non-high-density lipoprotein cholesterol; **PD**, pharmacodynamic; **SAD**, single ascending dose; **TG**, triglyceride.

PRIMARY SAFETY ENDPOINT

Incidence, frequency, and severity of treatment-emergent adverse events

SECONDARY EFFICACY ENDPOINTS

Absolute and percent changes from baseline:

- PCSK9
- APOC3
- LDL-C
- Triglycerides

BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS: MIXED HYPERLIPIDEMIA

Characteristic	Placebo (n=10)	25 mg (n=4)	50 mg (n=4)	100 mg (n=4)	200 mg (n=6)	400 mg (n=3)
Mean age — yr	53 ± 13	50 ± 22	34 ± 7.8	50 ± 12	60 ± 14	55 ± 11
Male sex — no. (%)	6 (60)	3 (75)	3 (75)	0 (0)	3 (50)	1 (33)
Body mass index*	33 ± 6.2	30 ± 2.7	30 ± 4.3	35 ± 13	30 ± 5.3	26 ± 2.2
White race† — no. (%)	5 (50)	2 (50)	3 (75)	4 (100)	5 (83)	1 (33)
Diabetes mellitus — no. (%)	1 (10)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)
Background lipid lowering therapy — no. (%)						
Statin	2 (20)	1 (25)	0 (0)	0 (0)	2 (33)	0 (0)
Omega-3 fatty acid or fish oil	2 (20)	0 (0)	1 (25)	0 (0)	1 (17)	0 (0)
PCSK9 — ug/L	290 ± 90	359 ± 114	232 ± 95	303 ± 58	366 ± 150	337 ± 66
APOC3 — mg/dL	12 ± 2.4	12 ± 2.0	12 ± 1.8	13.0 ± 3.7	14 ± 3.1	13 ± 2.5
Cholesterol — mg/dL						
Total cholesterol	219 ± 53	208 ± 38	191 ± 35	244 ± 62	199 ± 68	249 ± 57
HDL cholesterol	39 ± 11	44 ± 2.9	36 ± 6.1	40.5 ± 13	47 ± 16	51 ± 9.5
Direct LDL cholesterol	148 ± 50	126 ± 39	116 ± 29	158 ± 40	108 ± 56	155 ± 47
Non-HDL cholesterol	180 ± 48	164 ± 36	155 ± 36	203 ± 56	151 ± 59	198 ± 57
Median triglycerides‡ (IQR) — mg/dL	163 (133, 227)	177 (173, 197)	202 (154, 246)	207 (160, 246)	143 (135, 195)	166 (139, 220)
Median remnant cholesterol (IQR) — (mg/dL)	29 (22, 40)	35 (30, 46)	42 (33, 45)	40 (30, 62)	41 (32, 60)	38 (36, 54)
Apo B – mg/dL	120 ± 26	105 ± 18	103 ± 21	123 ± 30	95 ± 33	129 ± 37

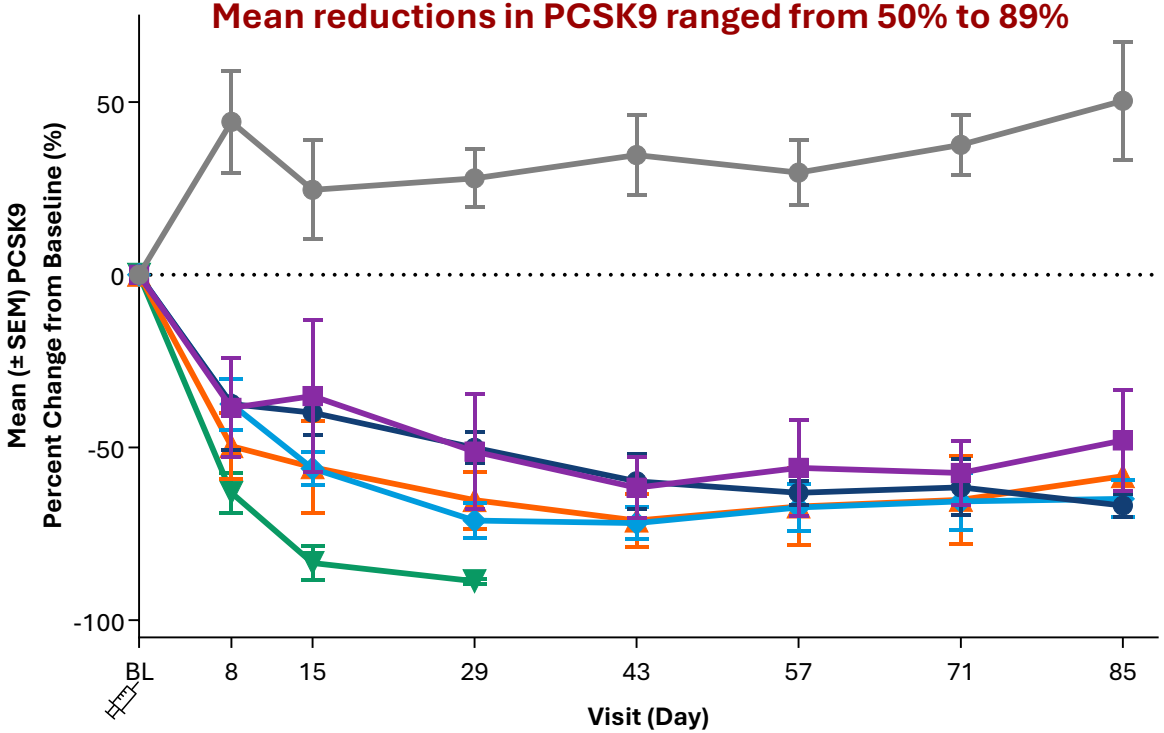
Plus–minus values are means ± SD. Baseline characteristics are shown for all treated participants. Cholesterol conversion to mmol/L, multiply by 0.02586. Triglyceride conversion to mmol/L, multiply by 0.01129. *The body-mass index is the weight in kilograms divided by the square of the height in meters. †Race was self-reported by participants. ‡Baseline triglycerides is defined as the average (ie, geometric mean) of Day 1 predose assessment, and the last valid fasting triglyceride level collected during the screening period.

APOC3, apolipoprotein C3; **HDL**, high-density lipoprotein; **IQR**, interquartile range; **Lp(a)**, lipoprotein (a); **LDL**, low-density lipoprotein; **non-HDL**, non-high-density lipoprotein; **PCSK9**, proprotein convertase subtilisin/kexin type 9.

DURABLE REDUCTIONS IN PCSK9 AND APOC3 OVER TIME WITH ARO-DIMER-PA

PCSK9 Percent Change Over Time

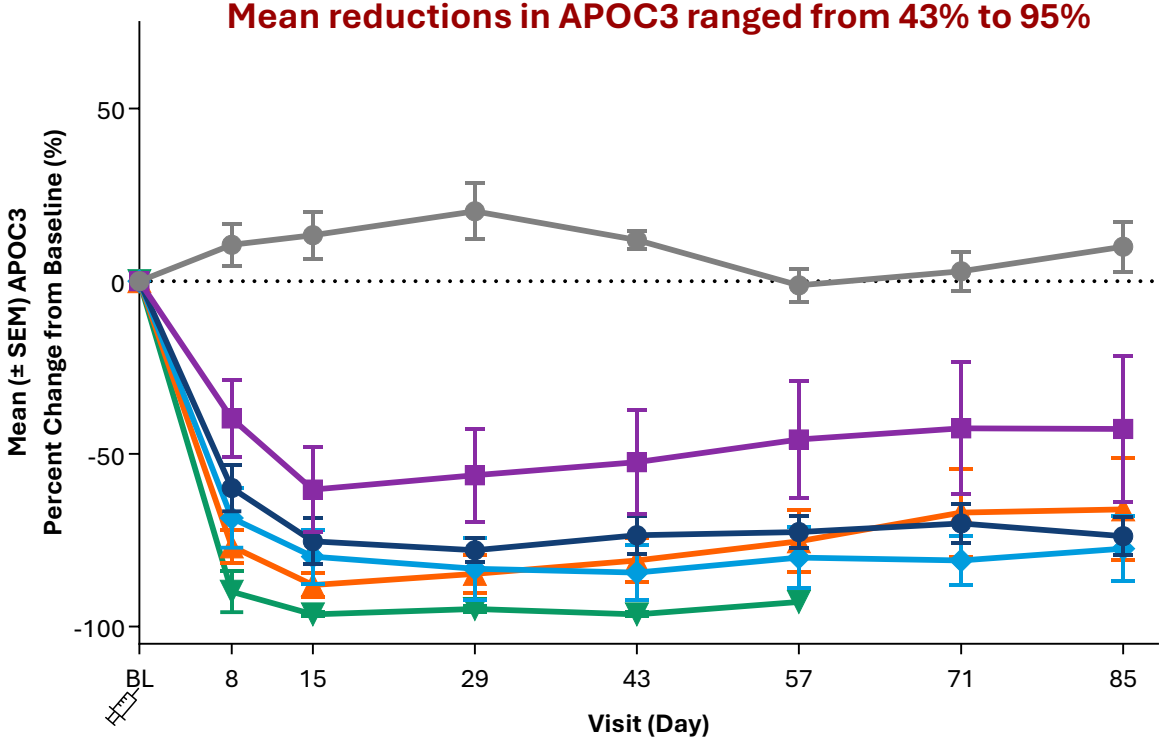
Mean reductions in PCSK9 ranged from 50% to 89%



No. of Participants								
Placebo	10	10	10	10	8	8	7	7
25 mg	4	4	4	4	4	4	4	4
50 mg	4	4	4	4	4	4	4	3
100 mg	4	4	4	4	4	4	4	4
200 mg	6	6	6	6	6	6	6	1
400 mg	3	2	2	2	0	0	0	0

APOC3 Percent Change Over Time

Mean reductions in APOC3 ranged from 43% to 95%



No. of Participants								
Placebo	10	9	10	10	10	9	8	8
25 mg	4	4	4	4	4	4	4	4
50 mg	4	4	4	4	4	4	4	4
100 mg	4	4	4	4	4	4	4	4
200 mg	6	6	6	6	6	6	6	5
400 mg	3	2	2	2	2	1	0	0

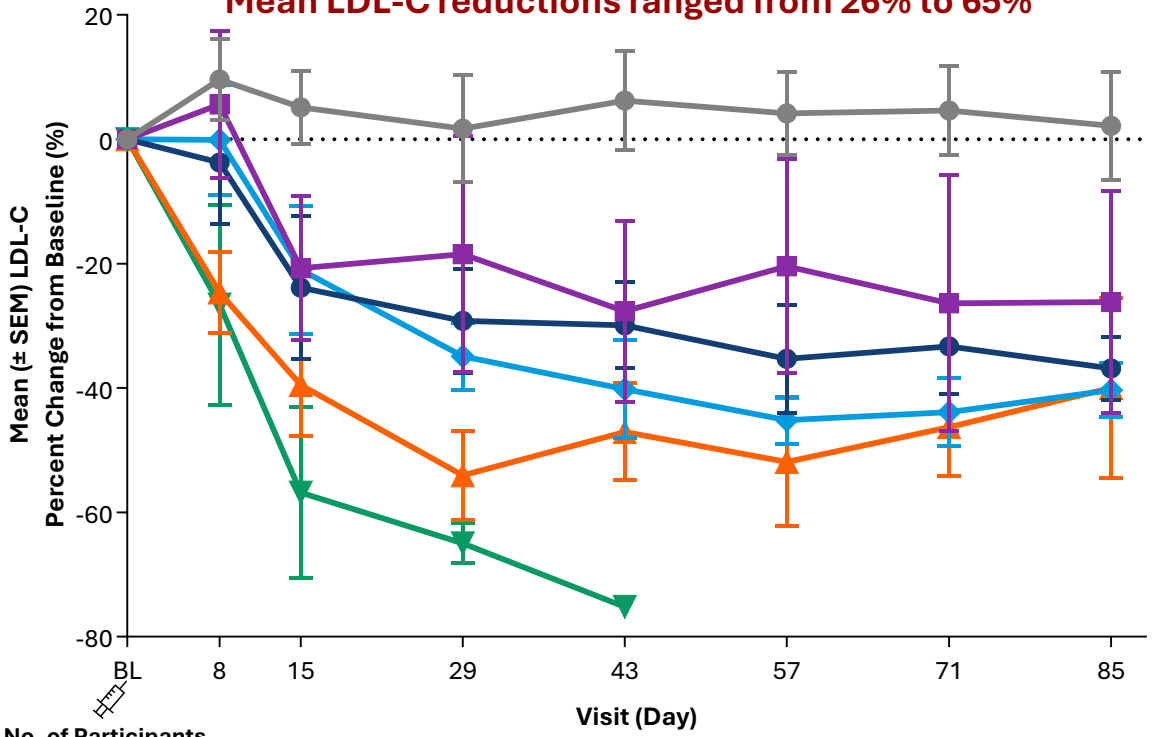
Pooled Placebo | 25 mg | 50 mg | 100 mg | 200 mg | 400 mg

APOC3, apolipoprotein C3; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **SEM**, standard error of the means.

REDUCTIONS IN LDL-C AND TRIGLYCERIDES OVER TIME WITH ARO-DIMER-PA

LDL-C Percent Change Over Time

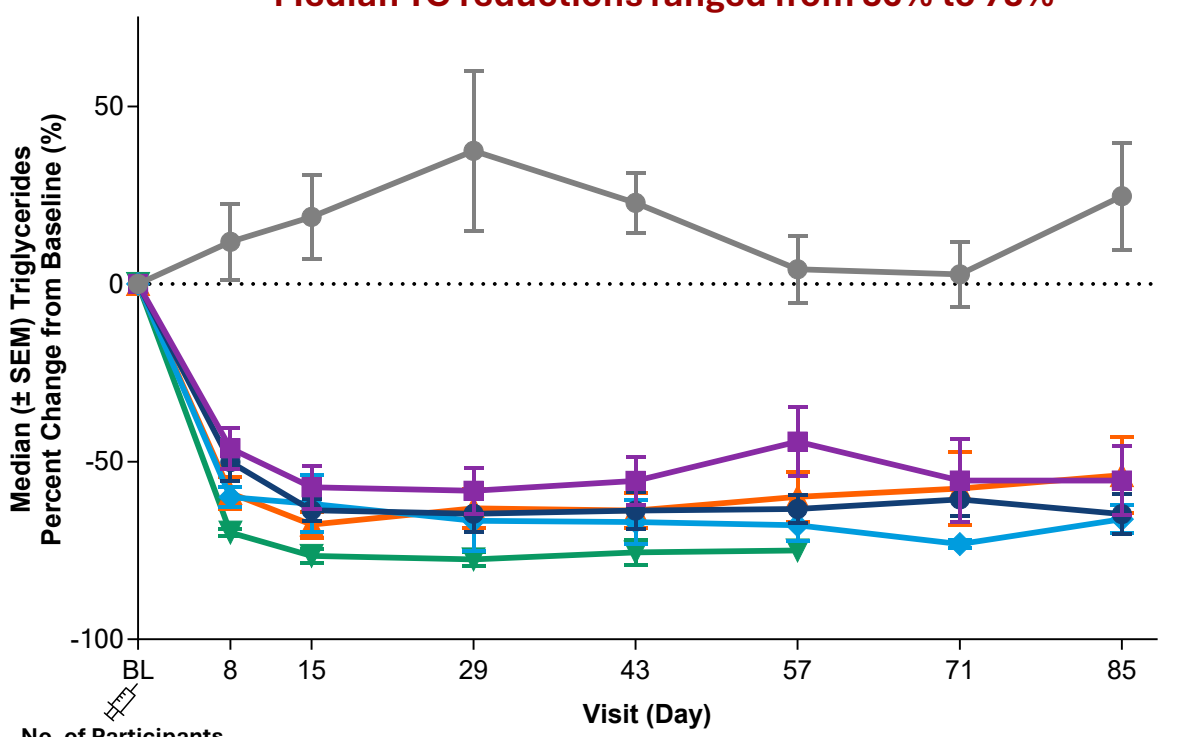
Mean LDL-C reductions ranged from 26% to 65%



No. of Participants								
Placebo	10	9	10	10	10	8	8	8
25 mg	4	4	4	4	4	4	4	4
50 mg	4	4	4	4	4	4	4	4
100 mg	4	4	4	4	4	4	4	4
200 mg	6	6	6	6	6	6	6	5
400 mg	3	2	2	2	1	0	0	0

Triglycerides Percent Change Over Time

Median TG reductions ranged from 56% to 78%



No. of Participants								
Placebo	10	9	10	10	10	9	8	8
25 mg	4	4	4	4	4	4	4	4
50 mg	4	4	4	4	4	4	4	4
100 mg	4	4	4	4	4	4	4	4
200 mg	6	6	6	6	6	6	6	5
400 mg	3	2	2	2	2	1	0	0

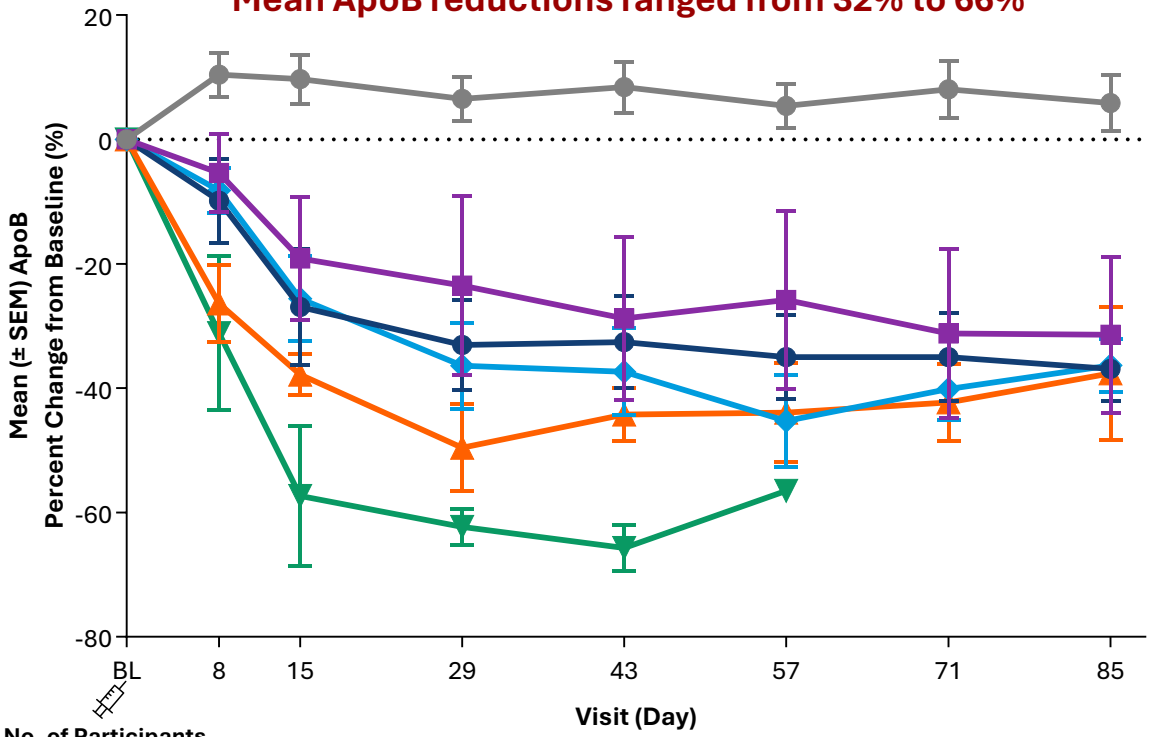
Pooled Placebo | 25 mg | 50 mg | 100 mg | 200 mg | 400 mg

LDL-C, low-density lipoprotein cholesterol; **SEM**, standard error of the means.

REDUCTIONS IN APOB AND REMNANT CHOLESTEROL OVER TIME WITH ARO-DIMER-PA

ApoB Percent Change Over Time

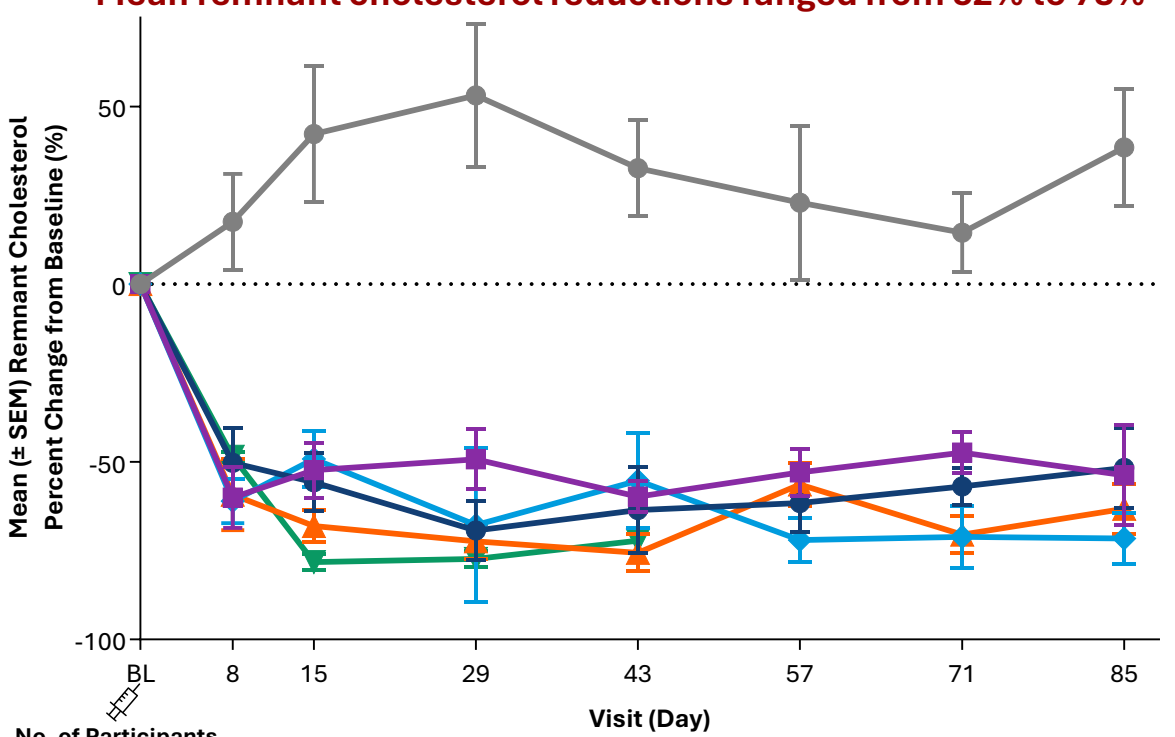
Mean ApoB reductions ranged from 32% to 66%



No. of Participants								
Placebo	10	9	10	10	10	9	8	8
25 mg	4	4	4	4	4	4	4	4
50 mg	4	4	4	4	4	4	4	4
100 mg	4	4	4	4	4	4	4	4
200 mg	6	6	6	6	6	6	6	5
400 mg	3	2	2	2	2	1	0	0

Remnant Cholesterol Percent Change Over Time

Mean remnant cholesterol reductions ranged from 52% to 73%



No. of Participants								
Placebo	10	9	10	10	10	8	8	8
25 mg	4	4	4	4	4	4	4	4
50 mg	4	4	4	4	4	4	4	4
100 mg	4	4	4	4	4	4	4	4
200 mg	6	6	6	6	6	6	6	5
400 mg	3	2	2	2	1	0	0	0

Pooled Placebo | 25 mg | 50 mg | 100 mg | 200 mg | 400 mg

LDL-C, low-density lipoprotein cholesterol; **SEM**, standard error of the means.

SAFETY AND TOLERABILITY OF ARO-DIMER-PA

	Placebo (n=10)	25 mg (n=4)	50 mg (n=4)	100 mg (n=4)	200 mg (n=6)	400 mg (n=3)
Any TEAE, no. (%)*	9 (90)	4 (100)	4 (100)	4 (100)	6 (100)	3 (100)
Grade 1	7 (70)	3 (75)	1 (25)	1 (25)	1 (17)	1 (33)
Grade 2†	2 (20)	1 (25)	3 (75)	3 (75)	5 (83)	1 (33)‡
Grade 3	0	0	0	0	0	1 (33)§
Injection site erythema, no. (%)	0	3 (75)	4 (100)	4 (100)	6 (100)	3 (100)
Pyrexia, no. (%)	0	0	0	2 (50)	4 (67)	1 (33)
Headache, no. (%)	0	0	0	2 (50)	5 (83)	2 (66)
Aminotransferase elevation, no. (%)¶	0	0	0	0	1 (17)	0
Hyperglycemia, no. (%)&	0	0	0	2 (50)	1 (17)	0
HbA1C (%), mean ± SD						
Baseline	5.9 ± 0.4	5.3 ± 0.3	5.2 ± 0.3	5.4 ± 0.4	5.6 ± 0.3	5.5 ± 0.3
Follow-up††	6.0 ± 0.5	5.4 ± 0.2	5.3 ± 0.3	5.5 ± 0.3	5.6 ± 0.2	5.6 ± NA
Absolute change from baseline	0.1 ± 0.2	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	-0.1 ± 0.2	-0.1± NA
Percent change from baseline	0.9 ± 3.9	1.9 ± 1.5	2.0 ± 2.8	2.0 ± 3.0	-0.9 ± 3.7	-1.8 ± NA

- No clear dose-related pattern in overall TEAEs was observed
- No SAEs occurred
- The most common AE was injection site erythema
- No clinically meaningful changes in platelet counts or HbA1c observed
- No clear signs of hepatotoxicity
  - No cases met Hy's law
- Occasional transient hs-CRP elevations around the time of injection**

*Participants were counted once at the highest-grade AE. No Grade 4 or Grade 5 TEAE; No Deaths or SAEs reported across any of the groups. †Grade 2 AE were respiratory and urinary tract infections among placebo-assigned participants; in the 25 mg group of ARO-DIMER-PA 1 had a respiratory infection; in the 50 mg group, 2 had respiratory infections and 1 had injection site erythema; among the 100 mg group, 2 had injection site erythema, and 1 had a limb abscess and headache; among the 200 mg group, 2 had injection site erythema, 1 had abdominal pain and headache, 1 had fever and headache, and 1 had balanoposthitis, depression, headache, and decreased joint range of motion. ‡One participant had a grade 2 event of influenza like illness. §One participant had syncope 6 hours after administration of 400 mg of ARO-DIMER-PA. ¶Investigator reported. **Early post-dose increases in hs-CRP were observed across several cohorts, with the largest mean increase at Day 2 in Cohort 5A; no apparent sustained elevation was observed over time. ††Follow-up measurements are reported at 12 weeks following placebo, ARO-DIMERPA doses of 25, 50, 100, and 200 mg. Follow-up measurements are reported at 8 weeks for 400 mg of ARO-DIMER-PA (n=1).

AE, adverse event; **ALT,** alanine transaminase; **AST,** aspartate aminotransferase; **HbA1c,** glycosylated hemoglobin; **hs-CRP,** high-sensitivity c-reactive protein; **SAE,** serious adverse event; **TEAE,** treatment-emergent adverse event.

CONCLUSIONS

- A single dose of ARO-DIMER-PA achieved simultaneous and sustained suppression of PCSK9 and APOC3, accompanied by substantial reductions in LDL-C and TGs in patients with mixed hyperlipidemia
- These findings provide clinical proof of concept for simultaneously targeting two complementary hepatic pathways with a single dual functional siRNA therapeutic
- Reductions in ApoB and remnant cholesterol suggest broader effects on atherogenic lipoproteins, beyond LDL-C and TGs alone
- ARO-DIMER-PA was generally safe and well-tolerated across the doses evaluated, although tolerability was less favorable at the 400 mg dose.
- These findings support continued evaluation of dual PCSK9/APOC3 inhibition as a potential single-agent strategy for mixed hyperlipidemia; longer term studies are needed to establish optimal dosing, and characterize safety, durability of effect, and potential CV benefit

ApoB,apolipoprotein B; **APOC3**, apolipoprotein C3; **CV**, cardiovascular; **LDL-C**, low-density lipoprotein cholesterol; **PCSK9**, proprotein convertase subtilisin/kexin type 9; **siRNA**, small interfering RNA; **TG,** triglycerides; **TRL**, triglyceride rich lipoprotein.

ARO-DIMER-PA, A DUAL FUNCTION RNA INTERFERENCE THERAPEUTIC TARGETING BOTH PCSK9 AND APOC3 IN ADULTS WITH MIXED HYPERLIPIDEMIA

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