EAS

92nd Congress

26-29 May 2024 | Lyon, France

MUIR Study Results
Plozasiran, an Investigational RNAi Therapeutic, Silences Apolipoprotein C3, and Reduces Atherosclerosis Associated Lipoproteins in Patients with Mixed Hyperlipidemia

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Disclosure

	No, nothing to disclose
X	**Yes, please specify:**

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership / Equity Position	Employee	Other (please specify)
Abbott Diagnostic	x							Grants
Akcea	x							Grants
Althera	x							Grants
Amarin	x							Grants
Amgen	x							Grants
Arrowhead	x							Grants
AstraZeneca	x							Grants
Denka Seiken	x							Grants
Esperion	x							Grants
Genentech	x							Grants
Gilead	x							Grants

Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership / Equity Position	Employee	Other (please specify)
Illumina	x							Grants
Ionis	x							Grants
Matina BioPharma	x							Grants
Merck	x							Grants
New Amsterdam	x							Grants
Novartis	x							Grants
Novo Nordisk	x							Grants
Pfizer	x							Grants
Regeneron	x							Grants
Roche Diagnostic	x							Grants
Sanofi-Synthelabo	x							Grants

Triglyceride Rich Lipoproteins (TRL) Are A Genetically Validated Target Associated With Increased Atherosclerotic Cardiovascular Disease (ASCVD) Risk

- Numerous epidemiologic studies have shown an association between higher TRL and an increased risk of ASCVD[1-2]

- A growing number of genome-wide association and Mendelian randomization studies support a causal role for TRL in ASCVD[3-7]

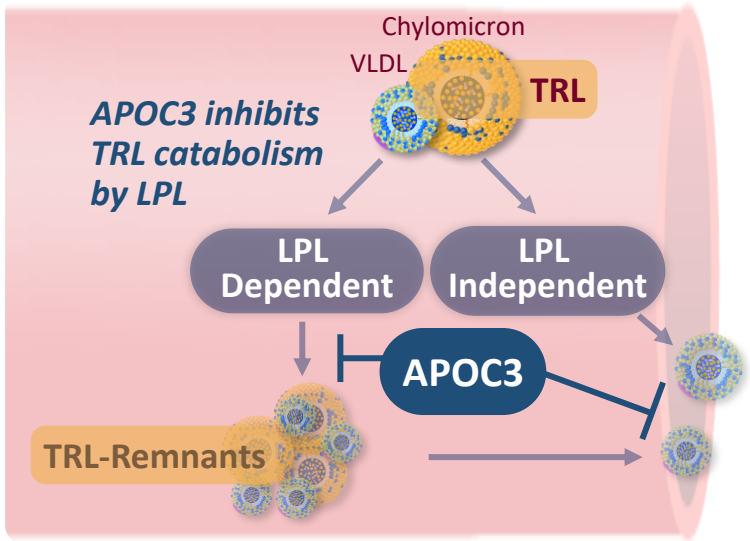
- Despite potent LDL-C-lowering therapies, residual ASCVD risk persists due to high levels of atherogenic TRL[8-11]

1. Bharadiya VM. *Curr Cardiovasc Risk Rep*. 2022;16:131–144. **2.** Baratta, F. et al. *Int J Mol Sci*. 2023;24:4268. **3.** Bjornson E, et al. *Eur Heart J.* 2023;44:4186-4195. **4.** Nordestgaard BG. *Circ Res*. 2016;118:547-563. **5.** Virani SS, et al. *J Am Coll Cardiol.* 2021;78(9):960-993. **6.** Hussain A, et al. *Curr Atheroscler Rep*. 2020;22:25. **7.** Park JE and Miller M. *Curr Cardiovasc Risk Rep*. 2019;13:6. **8.** Gugliucci A. *J Clin Med.* 2023;12:4399. **9.** Silverman MG, et al. *JAMA*. 2016;316(12):1289-1297. **10.** Langsted A, et al. *J Int Med*. 2020;288:116–127. **11.** Fu L, et al. *Diabetes Care.* 2022;45(9):2136-2143.
ASCVD, atherosclerotic cardiovascular disease; **CVD**, coronary vascular disease; **LDL-C**, low density lipoprotein cholesterol; **TRL**, triglyceride rich lipoprotein.

Plozasiran (ARO-APOC3) is an Investigational RNAi Therapeutic That Inhibits APOC3 Production and Thus Substantially Reduces TRL in Patients With Mixed Hyperlipidemia

APOC3[1]

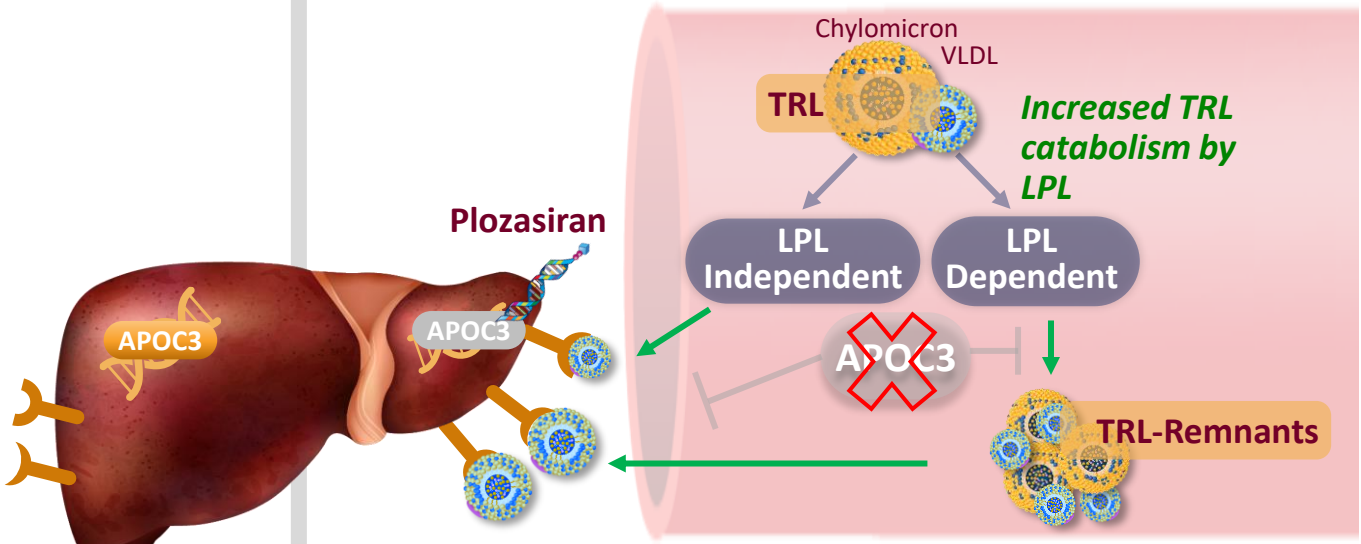
APOC3 Inhibits TRL Catabolism and Hepatic Clearance Leading to Increased TGs



APOC3 inhibits TRL clearance by inhibiting uptake by liver receptors

Plozasiran

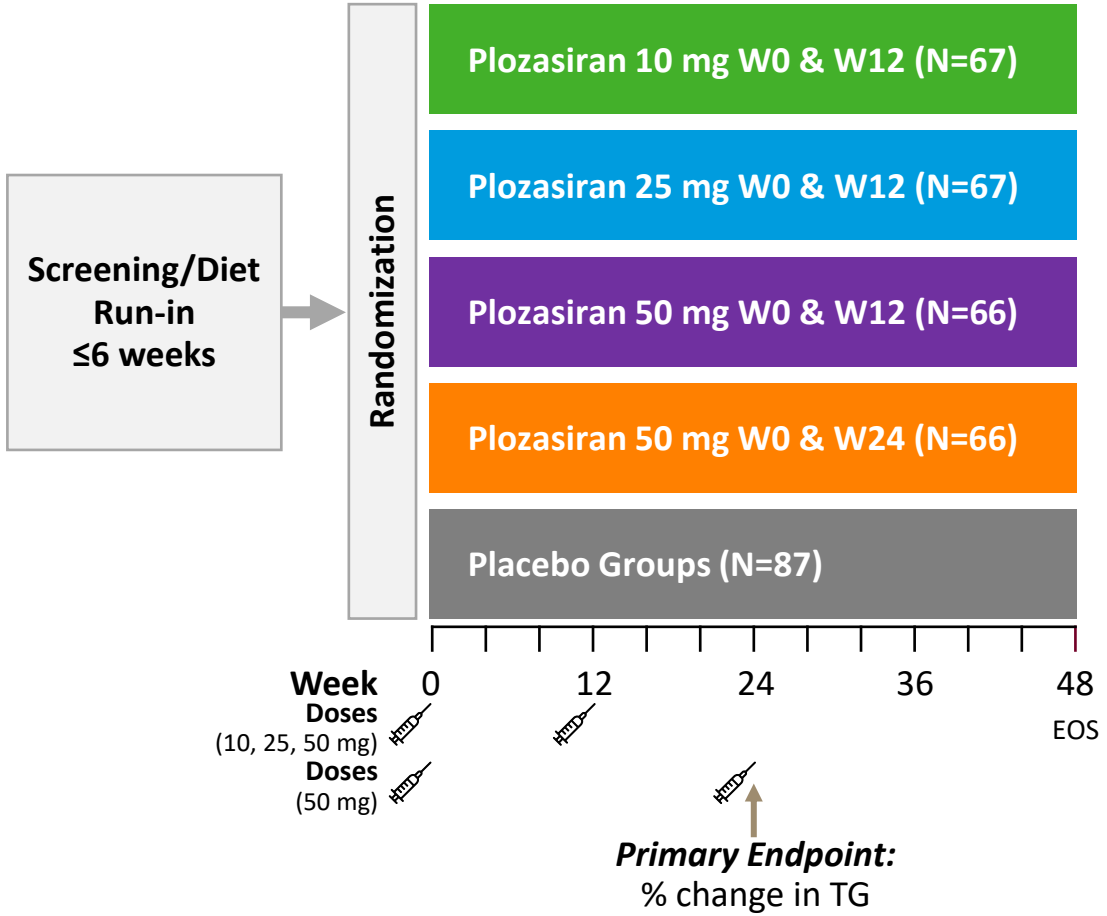
Silencing of APOC3 Enables TRL Catabolism and Hepatic Clearance Leading to Reduced TGs



Increased TRL clearance

1. Van Zwol W, et al. *J Clin Med*. 2019;8:1085. **TRL-remnants** are very atherogenic lipoproteins composed primarily of VLDL and IDL and represents the amount of cholesterol in remnant lipoproteins. **APOC3**, apolipoprotein C3; **IDL**, intermediate-density lipoprotein; **LPL**, lipoprotein lipase; **RNAi**, ribonucleic acid interference; **TG**, triglycerides; **TRL**, triglyceride rich lipoproteins; **VLDL**, very low density lipoprotein.

MUIR: A Randomized Double-Blind, Phase 2b Placebo-Controlled, Dose Ranging Study of Plozasiran in Patients With Mixed Hyperlipidemia



- **Study Objectives:** To evaluate safety and efficacy for lowering TG and atherogenic lipoproteins in patients with Mixed Hyperlipidemia, and to explore optimal dosing
- **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*:** % change from baseline and over time in:
  - Primary endpoint: TG
  - Key secondary and exploratory parameters: APOC3, non-HDL-C, LDL-C, HDL-C, ApoB, remnant cholesterol
  - Safety
- **OLE:** All patients were eligible to enroll in the OLE at the end of the study

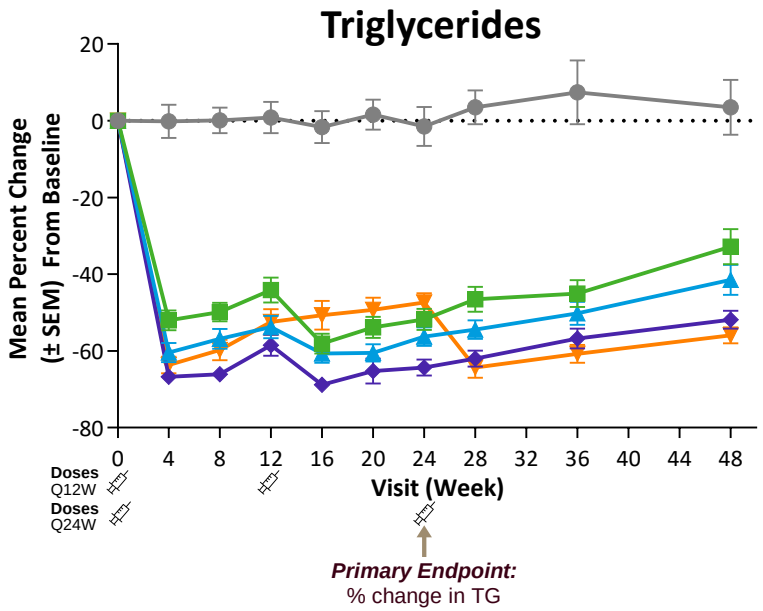
*All samples taken after ≥10 hour fast. **ApoB**, apolipoprotein B; **APOC3**, apolipoprotein C3; **EOS**, end of study; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **LP**, lipoprotein; **Non-HDL-C**, non high density lipoprotein cholesterol; **OLE**, open label extension; **TG**, triglyceride; **VLDL-C**, very low density lipoprotein cholesterol; **W**, week.

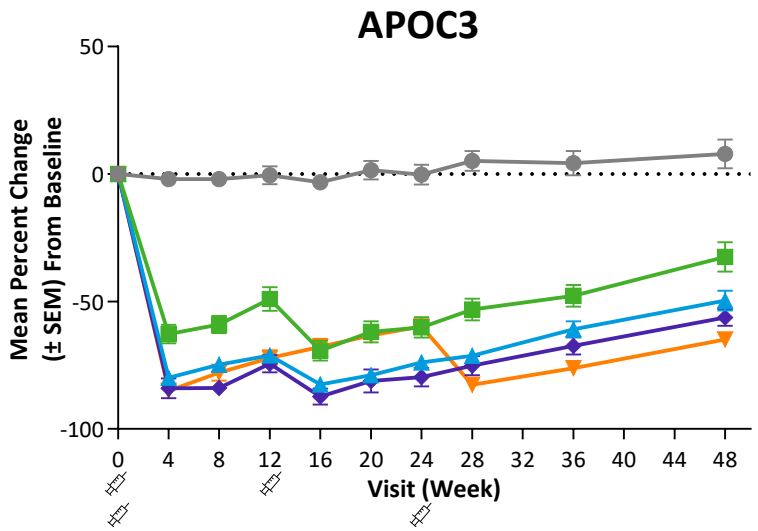
Baseline Characteristics

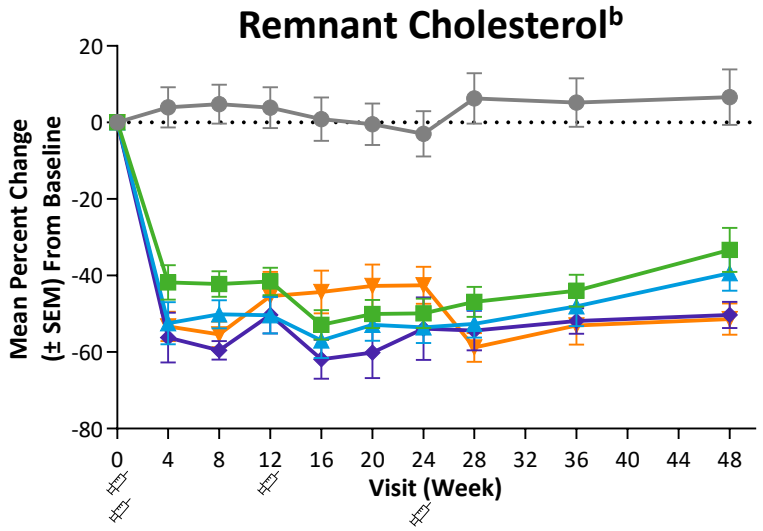
	Pooled Placebo (N=87)	Plozasiran 10 mg Q12W (N=67)	Plozasiran 25 mg Q12W (N=67)	Plozasiran 50 mg Q12W (N=66)	Plozasiran 50 mg Q24W (N=66)
Mean (SD) Age, years	58.9 (9.7)	60.2 (11.7)	61.3 (11.3)	62.6 (10.5)	61.3 (11.8)
Female, n (%)	41 (47.1)	31 (46.3)	30 (44.8)	29 (43.9)	23 (34.8)
White, n (%)	79 (90.8)	62 (92.5)	60 (89.6)	63 (95.5)	62 (93.9)
Mean (SD) BMI, kg/m^2	31.2 (5.4)	30.5 (5.7)	32.4 (6.7)	32.6 (6.5)	32.0 (5.6)
Mean (SD) APOC3,[a] mg/L	14.6 (4.7)	15.5 (5.5)	15.6 (5.5)	15.0 (5.7)	15.0 (5.5)
Mean (SD) Remnant cholesterol,[b] mg/dL	45.0 (18.9)	48.3 (20.5)	46.1 (20.3)	48.8 (27.2)	47.4 (23.1)
Mean (SD) Triglyceride, mg/dL	237.2 (76.2)	253.2 (81.4)	234.1 (72.7)	250.3 (81.3)	248.0 (80.6)
Median (Q1, Q3) Triglyceride, mg/dL	217.2 (182.7, 275.9)	222.9 (192.4, 323.1)	213.9 (180.2, 275.0)	228.9 (187.3, 296.4)	232.7 (182.1, 298.7)
Mean (SD) Non-HDL-C, mg/dL	148.3 (43.4)	153.5 (42.0)	147.7 (48.4)	151.8 (49.3)	153.0 (42.7)
Mean (SD) ApoB, mg/dL	102.3 (29.6)	102.6 (23.0)	100.9 (27.2)	100.6 (27.6)	104.5 (24.2)
Mean (SD) HDL-C, mg/dL	42.1 (11.1)	42.2 (11.1)	44.7 (13.6)	42.7 (11.7)	40.8 (12.6)
Mean (SD) LDL-C (UC), mg/dL	101.6 (38.7)	105.1 (37.0)	101.6 (43.4)	103.0 (39.7)	105.6 (31.8)

[a]Analysis that removed n=3 participants with baseline values of BLOQ (ad hoc); [b]Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C, ultracentrifugation). **ApoB**, apolipoprotein B; **APOC3**, apoliprotein C3; **BLOQ**, below limits of quantification; **BMI**, body mass index; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **N**, number; **Q**, quartile; **Q12W**, two doses given on Day 1 and Week 12; **Q24W**, two doses given on Day 1 and Week 24; **SD**, standard deviation; **UC**, ultracentrifuge; **W**, week.

Plozasiran Demonstrated Substantial and Durable Decreases in APOC3 and Consequently in TG and TRL







LS Mean*[a] % Change from Baseline					
24 Weeks	-2	-52 p<0.0001	-58 p<0.0001	-64 p<0.0001	-46 p<0.0001
48 Weeks	+2	-33	-43	-50	-55

LS Mean* % Change from Baseline					
24 Weeks	-2	-59 p<0.0001	-74 p<0.0001	-80 p<0.0001	-58 p<0.0001
48 Weeks	+6	-31	-49	-54	-65

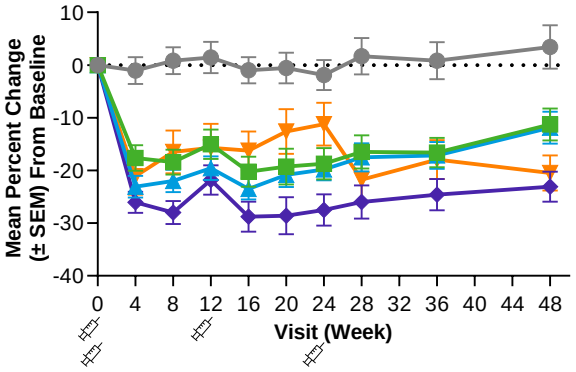
LS Mean* % Change from Baseline					
24 Weeks	-5	-48 p<0.0001	-54 p<0.0001	-53 p<0.0001	-42 p<0.0001
48 Weeks	+3	-33	-38	-44	-51

Placebo
Plozasiran 10 mg Q12W
Plozasiran 25 mg Q12W
Plozasiran 50 mg Q12W
Plozasiran 50 mg Q24W

[a]Three patients with BLOQ values at baseline were removed from the analysis; [b]Based on calculation: remnant cholesterol = (total cholesterol) – (HDL-C) – (LDL-C, ultracentrifugation). *Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling. **APOC3**, apolipoprotein C3; **BLOQ**, below the limit of quantification; **LS**, least squares; **Q**, quartile; **Q12W**, two doses given on Day 1 and Week 12; **Q24W**, two doses given on Day 1 and Week 24; **SE**, standard error; **SEM**, standard error of the mean.

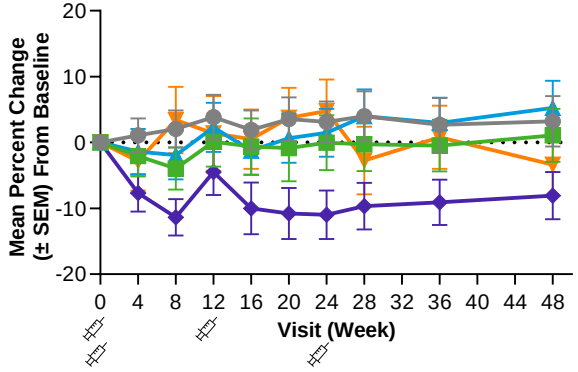
Plozasiran Demonstrated Robust Decreases in Atherogenic Lipoproteins and Increases in HDL-C

Non-HDL-C



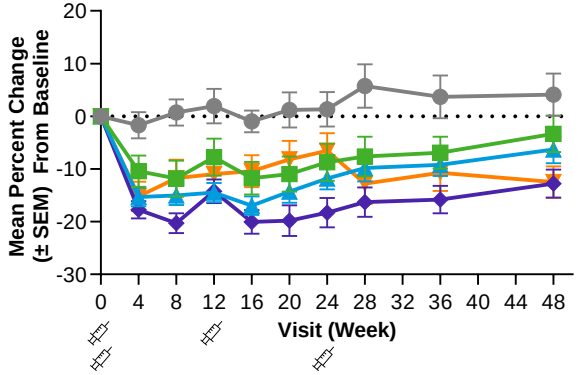
LS Mean % Change from Baseline					
24 Weeks	-3	-19	-20	-27	-10
48 Weeks	2	-12	-12	-22	-20

LDL-C



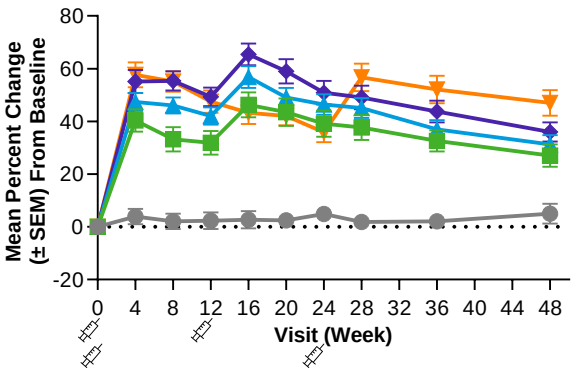
LS Mean % Change from Baseline					
24 Weeks	3	-1	1	-10	6
48 Weeks	3	0	4	-8	-2

ApoB



LS Mean % Change from Baseline					
24 Weeks	1	-10	-12	-18	-6
48 Weeks	3	-5	-6	-12	-12

HDL-C



LS Mean % Change from Baseline					
24 Weeks	5	38	47	51	33
48 Weeks	5	25	31	34	45

Placebo
Plozasiran 10 mg Q12W
Plozasiran 25 mg Q12W
Plozasiran 50 mg Q12W
Plozasiran 50 mg Q24W

Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling **ApoB**, apolipoprotein B; **HDL-C**, high density lipoprotein cholesterol; **LDL-C**, low density lipoprotein cholesterol; **LS**, least squares; **n**, number; **Non-HDL-C**, non high density lipoprotein cholesterol; **Q12W**, two doses given on Day 1 and Week 12; **Q24W**, two doses given on Day 1 and Week 24; **SD**, standard deviation; **SE**, standard error; **W**, week.

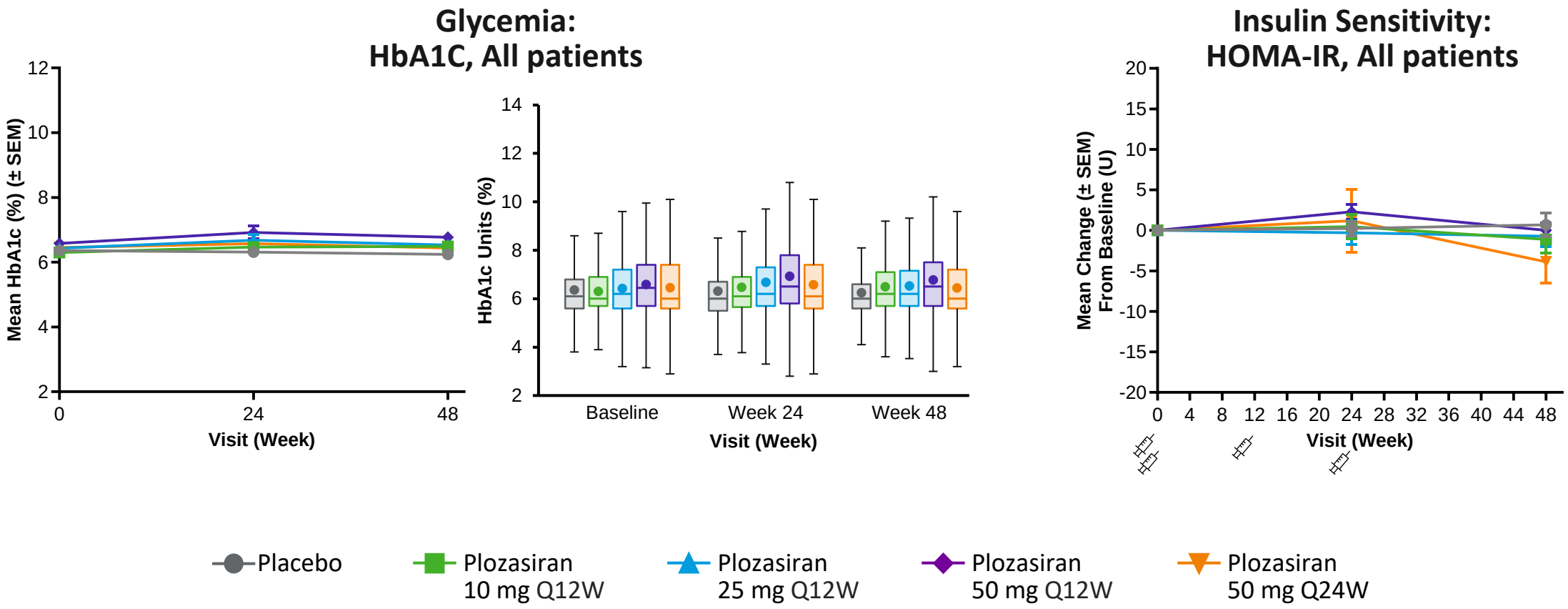
Summary of Adverse Events

	Pooled Placebo (N=87)	Plozasiran 10 mg Q12W (N=67)	Plozasiran 25 mg Q12W (N=67)	Plozasiran 50 mg Q12W (N=66)	Plozasiran 50 mg Q24W (N=66)
TEAEs	55 (63)	46 (69)	45 (67)	47 (71)	49 (74)
Covid 19	11 (13)	7 (10)	10 (15)	8 (12)	5 (8)
Upper respiratory tract infection	7 (8)	3 (4)	7 (10)	1 (2)	9 (14)
Headache	3 (3)	1 (1)	2 (3)	4 (6)	5 (8)
Urinary tract infection	6 (7)	3 (4)	4 (6)	4 (6)	0
Worsening glycemic control[a]	9 (10)	8 (12)	5 (7)	13 (20)	14 (21)
Bronchitis	1(1)	4 (6)	2 (3)	2 (3)	5 (8)
Serious TEAEs	5 (6)	2 (3)	5 (7)	7 (11)	5 (8)
TEAEs leading to drug discontinuation, dose interruptions, or study withdrawal	2 (2)	0	0	1 (2)	2 (3)
Deaths[b]	0	0	1 (1)	2 (3)	1 (2)
Platelets					
Baseline, mean (SD), (10^9/L)	254.4 (63.6)	250.7 (68.4)	244.0 (65.7)	245.8 (58.5)	241.3 (68.5)
Mean (SD) change from baseline at Week 24	9.8 (43.7)	4.1 (51.3)	6.4 (41.1)	10.2 (38.0)	12.0 (53.0)
Mean (SD) change from baseline at Week 48	2.9 (33.2)	-2.6 (38.0)	13.8 (52.2)	9.6 (35.6)	9.7 (37.8)

- TEAEs reflect comorbidities and underlying conditions of the study population
- Platelets unchanged
- Worsened glycemic control reported at 50 mg
- Data includes exposure out to 48 weeks

[a]Worsening glycemic control defined by multiple glycemic control parameters including but not limited to hemoglobin A1c, new onset diabetes mellitus, type 2 diabetes mellitus, diabetes mellitus, hyperglycemia, insulin resistance; worsening glycemic control was observed in patients with uncontrolled diabetes. [b]There were 4 SAEs with the outcome of death reported, one death was due to pneumonia in a participant in the 25-mg quarterly group, one death was due to septic shock in a participants in the 50-mg-quarterly group, one death by suicide was due to a psychiatric disorder in a participant in the 50-mg-quarterly group, and one death from aortic aneurysm rupture was due to a vascular disorder in a participant in the 50-mg-half-yearly group. All deaths were determined to be not related to plozasiran or placebo. **SD**, standard deviation; **TEAEs**, treatment emergent adverse events; **W**, week.

Minimal Change in Mean HbA1C or HOMA-IR



HbA1C, hemoglobin A1C; **HOMA-IR**, homeostatic model assessment for insulin resistance; **SEM**, standard error of mean; **W**, week.

Plozasiran Demonstrated Potent and Durable Reductions of Atherogenic Lipoproteins in Mixed Hyperlipidemia

- By silencing APOC3, plozasiran significantly reduced TGs and atherogenic triglyceride rich lipoproteins and increased HDL, across all dose levels at Week 24 in patients with mixed hyperlipidemia
  - APOC3 ↓ to -80%
  - TG ↓ to -64%
  - Remnant cholesterol ↓ to -54%
  - ApoB ↓ to -18%
  - Non-HDL-C ↓ to -27%
  - HDL-C ↑ up to +51%
- Plozasiran had a favorable safety profile in this study
- Plozasiran is the first RNAi investigational molecule that has demonstrated substantial reductions in triglyceride rich lipoproteins in this mixed hyperlipidemia population
- Plozasiran is a promising potential treatment for patients with increased risk for ASCVD due to elevated triglyceride rich lipoproteins and these data support further development of plozasiran in Phase 3 programs including a clinical outcomes trial

We would like to thank the patients and caregivers who participated in this study

ASCVD, atherosclerotic cardiovascular disease; **ApoB**, apolipoprotein B; **APOC3**, apolipoprotein C3; **ASCVD**, atherosclerotic cardiovascular disease **HDL-C**, high density lipoprotein cholesterol; **Non-HDL-C**, non high density lipoprotein cholesterol; **RNAi**, ribonucleic acid interference; **TG**, triglyceride; **TGs**, triglycerides.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Plozasiran, an RNA Interference Agent Targeting APOC3, for Mixed Hyperlipidemia

Christie M. Ballantyne, M.D., Szilard Vasas, M.D., Masoud Azizad, M.D., Peter Clifton, M.B., B.S., Ph.D., Robert S. Rosenson, M.D., Ting Chang, Ph.D., Stacey Melquist, Ph.D., Rong Zhou, Ph.D., Ma'an Mushin, M.D., Nicholas J. Leeper, M.D., Jennifer Hellawell, M.D., and Daniel Gaudet, M.D., Ph.D.