# Plozasiran (ARO-APOC3), an Investigational RNAi, Demonstrates Robust and Durable Triglyceride Reductions in Patients With Mixed Dyslipidemia, MUIR Final Results

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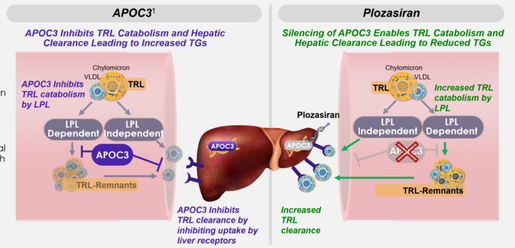
## INTRODUCTION

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

- Numerous epidemiologic studies have shown an association between higher TRL and an increased risk of atherosclerotic cardiovascular disease (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 low density lipoprotein cholesterol (LDL-C)-lowering therapies, residual ASCVD risk persists due to high levels of atherogenic TRL[8-11]
- In Phase 2 studies, plozasiran has shown to be a highly specific RNAi molecule with deep and durable gene silencing

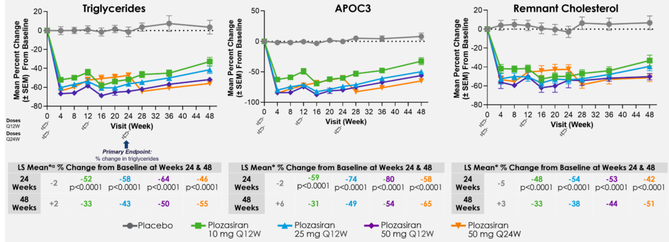
*Plozasiran is an investigational RNAi therapeutic that substantially reduces TRLs in patients with SHTG*






## RESULTS

**Plozasiran Demonstrates Substantial and Durable Decreases in APOC3 and Consequently in Triglycerides and Triglyceride Rich Lipoproteins**




| LS Mean*[a] % Change from Baseline at Weeks 24 & 48 | Placebo | Plozasiran 10 mg Q12W | Plozasiran 25 mg Q12W | Plozasiran 50 mg Q12W | Plozasiran 50 mg Q24W |
|---|---|---|---|---|---|
| 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 at Weeks 24 & 48 | Placebo | Plozasiran 10 mg Q12W | Plozasiran 25 mg Q12W | Plozasiran 50 mg Q12W | Plozasiran 50 mg Q24W |
|---|---|---|---|---|---|
| 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 at Weeks 24 & 48 | Placebo | Plozasiran 10 mg Q12W | Plozasiran 25 mg Q12W | Plozasiran 50 mg Q12W | Plozasiran 50 mg Q24W |
|---|---|---|---|---|---|
| 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 |

*Three patients with BLOQ values at baseline were removed from the analysis; [a]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.

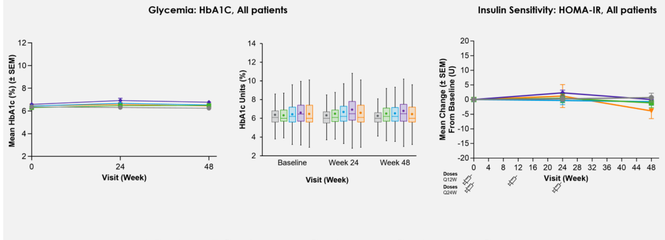


**APOC3**, apolipoprotein C3; **BLOQ**, below the limit of quantification; **LS**, least squares; **Q**, quartile; **Q12W**, two doses given on Day 1 and Week 12; **Q24W**, two doses given on Day 1 and Week 24; **SE**, standard error; **SEM**, standard error of the mean.



## RESULTS

**Measurements of Glycemia and Insulin Sensitivity**






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

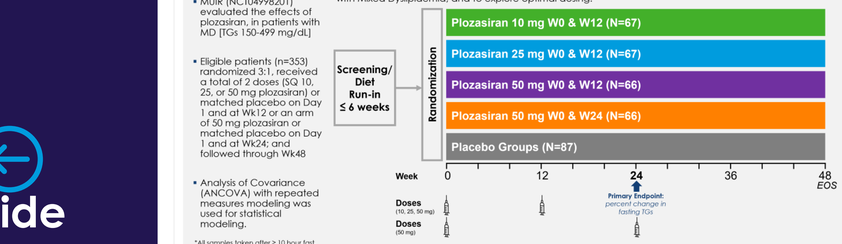


## METHODS

**MUIR: A Randomized Double-Blind, Phase 2b Placebo-Controlled, Dose Ranging Study of Plozasiran (ARO-APOC3) In Patients With Mixed Dyslipidemia**

- MUIR (NCT04998201) evaluated the effects of plozasiran, in patients with MD [TGs 150-499 mg/dL]
- Eligible patients (n=353) randomized 3:1, received a total of 2 doses (SQ 10, 25, or 50 mg plozasiran) or matched placebo on Day 1 and at Wk12 or an arm of 50 mg plozasiran or matched placebo on Day 1 and at Wk24; and followed through Wk48
- Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling.

**Study Objectives:** To evaluate safety and efficacy for lowering TG and atherogenic lipoproteins in patients with Mixed Dyslipidemia, and to explore optimal dosing.




*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; **OLE**, open-label extension; **TG**, triglycerides; **VLDL-C**, very low density lipoprotein cholesterol; **W**, week.



## RESULTS

**Plozasiran Showed a Favorable Safety Profile with Balanced Rates of TEAEs Leading to Discontinuation vs Placebo**

**Table 3. Summary Of Adverse Events**

| | Pooled Placebo (N=87) | Plozasiran (Q12W) 10 mg (N=67) | Plozasiran (Q12W) 25 mg (N=67) | Plozasiran (Q12W) 50 mg (N=66) | Plozasiran 50 mg Q24W (N=66) |
|---|---|---|---|---|---|
| **Treatment-emergent adverse events (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 reported to date reflect comorbidities and underlying conditions of the study population
- Platelets Unchanged
- Worsened glycemic control reported with 50 mg dose
- Data includes exposure out to 48 weeks

*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; n (%); worsening glycemic control was observed in patients with uncontrolled diabetes. bThere 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 participant 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.



**TEAEs**, treatment emergent adverse events; **W**, week



## CONCLUSIONS

- By silencing APOC3, plozasiran significantly reduced TGs and atherogenic triglyceride rich lipoproteins, across all dose levels at Week 24 in patients with mixed dyslipidemia
  - APOC3 ↓ to -80%
  - TG ↓ to -64%
  - Remnant cholesterol ↓ to -54%
  - ApoB ↓ to -18%
  - Non-HDL-C ↓ to -27%
  - HDL-C ↑ up to +51%
- Plozasiran has 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 dyslipidemia 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



## RESULTS

**Table 1. Baseline Characteristics**

| | Pooled Placebo (N=87) | Plozasiran (Q12W) 10 mg (N=67) | Plozasiran (Q12W) 25 mg (N=67) | Plozasiran (Q12W) 50 mg (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/m²** | 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) |
| **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) |

*Analysis that removed n=3 participants with baseline values below limits of quantification, BLOQ (ad hoc); [a]Based on calculation: remnant cholesterol = (total cholesterol) - (HDL-C) - (LDL-C, ultracentrifugation).



**Apo8**, apolipoprotein B; **APOC3**, apolipoprotein 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.



## RESULTS

**Plozasiran Affects Multiple Lipid Parameters Demonstrating Robust Decreases In Atherogenic Lipoproteins And Increases In HDL-C**

- Plozasiran produced LS mean reductions in APOC3 of -80% and TGs of –64% at Wk24, representing trough effect with quarterly dosing (p<0.0001)
- This effect of plozasiran was durable with reductions in APOC3 and TGs of –65% and –55% respectively at Wk48 (p<0.0001)
- Durable and significant reductions in other atherogenic lipoprotein (LP) parameters were also observed with LS mean changes at 24 and 48-weeks respectively, RC to -54% and -51%, non-HDL-C to -27% and -22% and ApoB to -18% and -12%
- HDL-C substantially increased

**Table 2. Percent Change From Baseline in Serum Lipid and Lipoprotein Concentrations at Week 24**

| | Pooled Placebo (N=87) | Plozasiran (Q12W) 10 mg (N=67) | Plozasiran (Q12W) 25 mg (N=67) | Plozasiran (Q12W) 50 mg (N=66) | Plozasiran 50 mg Q24W (N=66) |
|---|---|---|---|---|---|
| **LDL-C (Ultracentrifugation)** | | | | | |
| Baseline mean, mg/dL (SD) | 101.6 (38.7) | 105.1 (37.0) | 101.6 (43.4) | 103.0 (39.7) | 105.6 (31.8) |
| **LS mean (SE) % change at Week 24** | **3.2 (3.3)** | **-0.9 (3.8)** | **0.5 (3.7)** | **-10.4 (3.7)** | **6.0 (3.7)** |
| LS mean (SE) % change at Week 48 | 2.9 (3.5) | 0.2 (4.0) | 4.2 (3.9) | -7.8 (4.0) | -2.3 (4.0) |
| **Non-HDL-C** | | | | | |
| Baseline mean, mg/dL (SD) | 148.3 (43.4) | 153.5 (42.0) | 147.7 (48.4) | 151.8 (49.3) | 153.0 (42.7) |
| **LS mean (SE) % change at Week 24** | **-2.7 (2.6)** | **-19.3 (2.9)** | **-20.1 (2.9)** | **-26.9 (2.9)** | **-10.3 (2.9)** |
| LS mean (SE) % change at Week 48 | 1.7 (3.0) | -12.1 (3.4) | -12.1 (3.3) | -21.8 (3.4) | -20.0 (3.4) |
| **ApoB** | | | | | |
| Baseline mean, mg/dL (SD) | 102.3 (29.6) | 102.6 (23.0) | 100.9 (27.2) | 100.6 (27.6) | 104.5 (24.2) |
| **LS mean (SE) % change at Week 24** | **0.8 (2.6)** | **-9.5 (2.9)** | **-12.2 (2.9)** | **-18.3 (2.9)** | **-5.7 (2.9)** |
| LS mean (SE) % change at Week 48 | 3.3 (2.8) | -4.7 (3.1) | -6.4 (3.1) | -12.2 (3.1) | -11.9 (3.1) |
| **HDL-C** | | | | | |
| Baseline mean, mg/dL (SD) | 42.1 (11.1) | 42.2 (11.1) | 44.7 (13.6) | 42.7 (11.7) | 40.8 (12.6) |
| **LS mean (SE) % change at Week 24** | **4.7 (3.3)** | **37.9 (3.8)** | **46.8 (3.8)** | **50.5 (3.8)** | **32.8 (3.8)** |
| LS mean (SE) % change at Week 48 | 4.5 (3.5) | 25.4 (4.0) | 30.5 (4.0) | 34.3 (4.0) | 44.5 (4.0) |

Analysis of Covariance (ANCOVA) with repeated measures modeling was used for statistical modeling.



**Apo8**, apolipoprotein B; **HDL-C**, high-density lipoprotein cholesterol; **LDL-C**, low-density lipoprotein cholesterol; **LS**, least-squares; **n**, number; **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.



## REFERENCES & ACKNOWLEDGEMENTS

**ACKNOWLEDGEMENTS**

- Arrowhead Pharmaceuticals and the authors would like to thank the patients and caregivers who participated in this study; Jack Shi of Arrowhead for contributions to the understanding of the pharmacology of the project, Nick Leeper of Stanford Medicine for critical review, Nathalie Kertesz of Arrowhead for contributions to writing and review. Susanna Mac provided medical writing support on behalf of Arrowhead and Heather Hartley-Thorne of Sephirus Communications Inc. for graphical support and Poster Design on behalf of Arrowhead.

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**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. **12.** Van Zwol W, et al. *J Clin Med*. 2019;8:1085.

# INTRODUCTION

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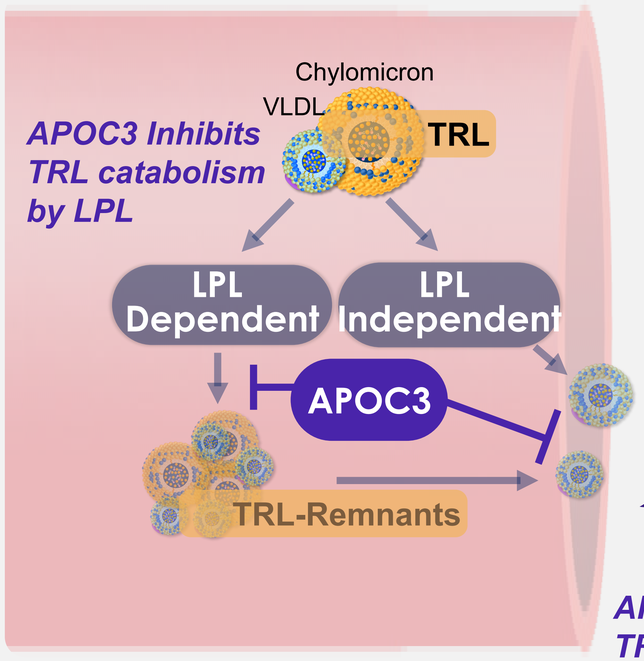
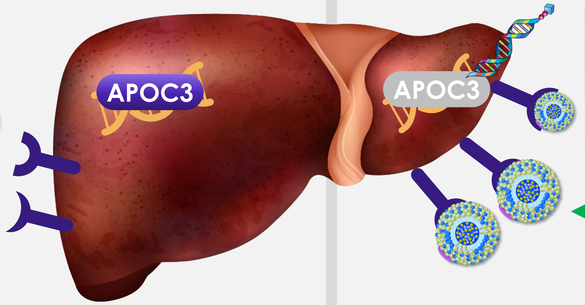
- In Phase 2 studies, plozasiran has shown to be a highly specific RNAi molecule with deep and durable gene silencing

***Plozasiran is an investigational RNAi therapeutic that substantially reduces TRLs in patients with SHTG***

### *APOC3*[1]

***APOC3 Inhibits TRL Catabolism and Hepatic Clearance Leading to Increased TGs***

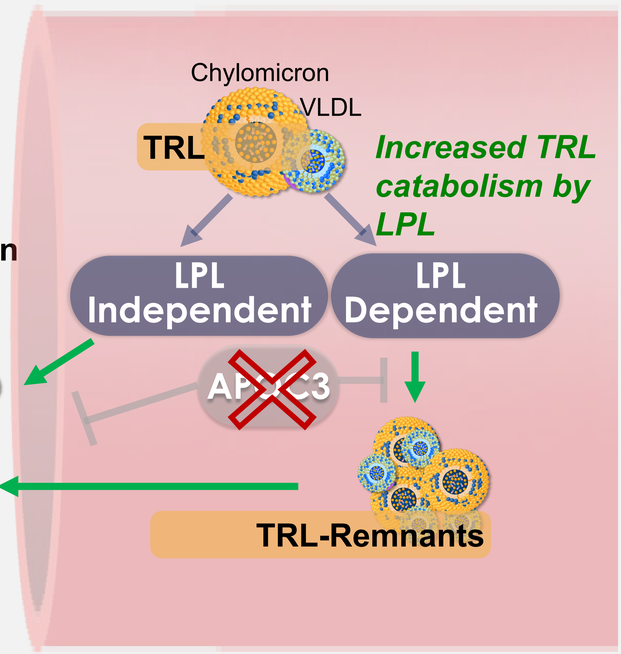



***APOC3 Inhibits TRL clearance by inhibiting uptake by liver receptors***

### *Plozasiran*

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




***Increased TRL clearance***

# METHODS

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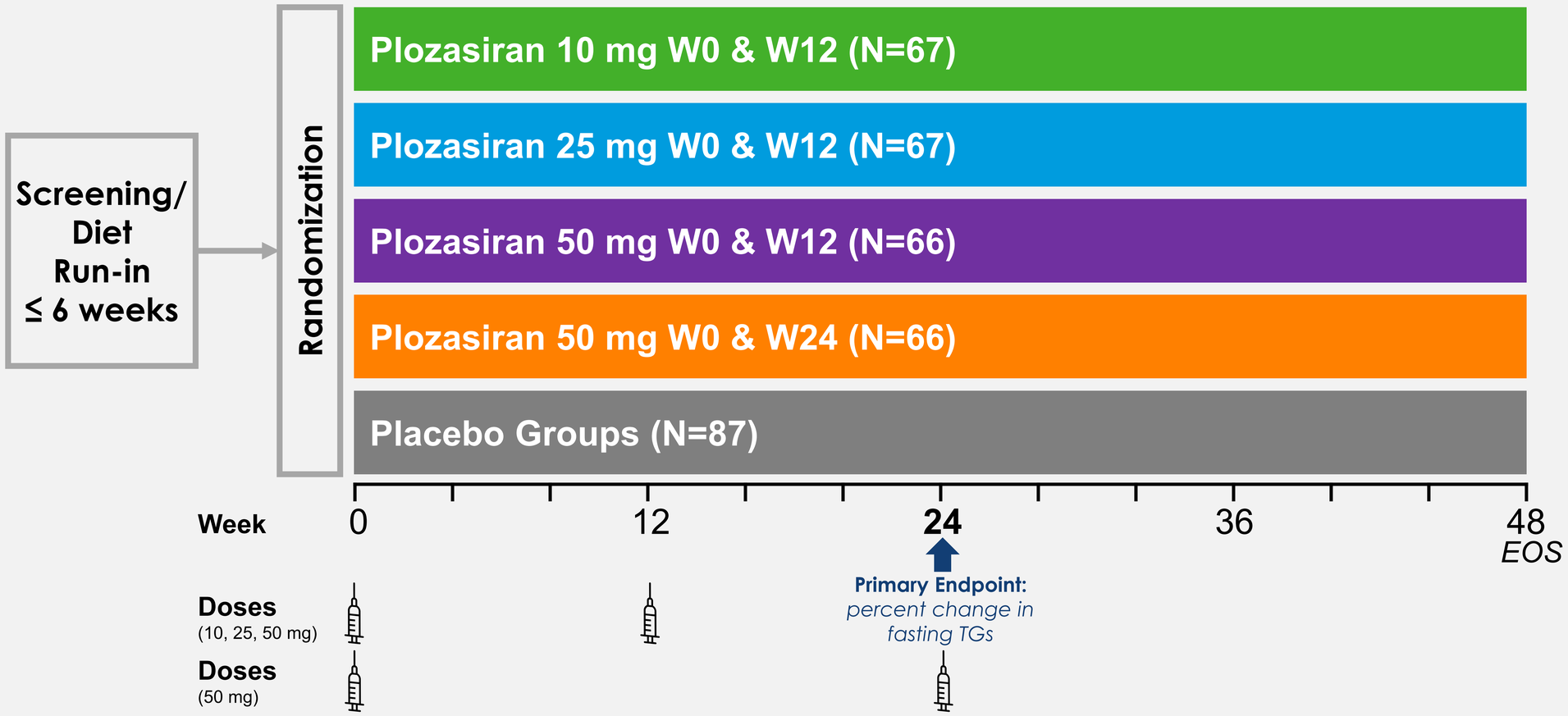

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[a]Analysis that removed n=3 participants with baseline values below limits of quantitation, BLOQ (ad hoc);
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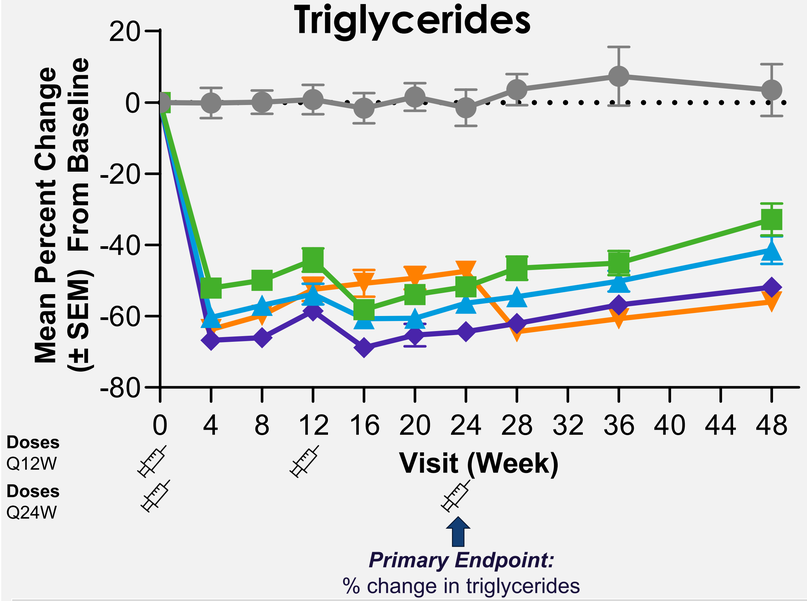
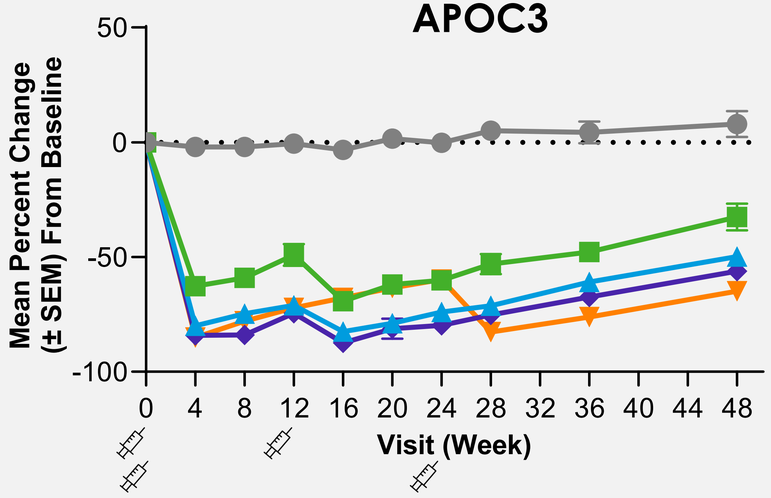
## Plozasiran Demonstrates Substantial and Durable Decreases in APOC3 and Consequently in Triglycerides and Triglyceride Rich Lipoproteins

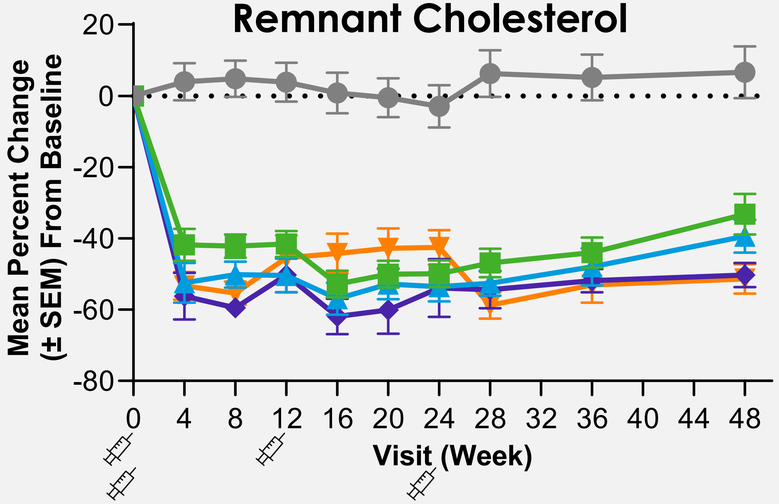
### Triglycerides




### APOC3




### Remnant Cholesterol




| LS Mean*[a] % Change from Baseline at Weeks 24 & 48 | | | | | |
|---|---|---|---|---|---|
| 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 at Weeks 24 & 48 | | | | | |
|---|---|---|---|---|---|
| 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 at Weeks 24 & 48 | | | | | |
|---|---|---|---|---|---|
| 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.

# RESULTS

## Plozasiran Affects Multiple Lipid Parameters Demonstrating Robust Decreases In Atherogenic Lipoproteins And Increases In HDL-C

- Plozasiran produced LS mean reductions in APOC3 of -80% and TGs of –64% at Wk24, representing trough effect with quarterly dosing ($p<0.0001$)
- This effect of plozasiran was durable with reductions in APOC3 and TGs of -65% and –55% respectively at Wk48 ($p<0.0001$)
- Durable and significant reductions in other atherogenic lipoprotein (LP) parameters were also observed with LS mean changes at 24 and 48-weeks respectively, RC to -54% and -51%, non-HDL-C to -27% and -22% and ApoB to -18% and -12%
- HDL-C substantially increased

**Table 2. Percent Change From Baseline in Serum Lipid and Lipoprotein Concentrations at Week 24**

| | Pooled Placebo (N=87) | Plozasiran (Q12W) 10 mg (N=67) | Plozasiran (Q12W) 25 mg (N=67) | Plozasiran (Q12W) 50 mg (N=66) | Plozasiran 50 mg Q24W (N=66) |
|---|---|---|---|---|---|
| **LDL-C (Ultracentrifugation)** | | | | | |
| Baseline mean, mg/dL (SD) | 101.6 (38.7) | 105.1 (37.0) | 101.6 (43.4) | 103.0 (39.7) | 105.6 (31.8) |
| **LS mean (SE) % change at Week 24** | **3.2 (3.3)** | **-0.9 (3.8)** | **0.5 (3.7)** | **-10.4 (3.7)** | **6.0 (3.7)** |
| LS mean (SE) % change at Week 48 | 2.9 (3.5) | 0.2 (4.0) | 4.2 (3.9) | -7.8 (4.0) | -2.3 (4.0) |
| **Non-HDL-C** | | | | | |
| Baseline mean, mg/dL (SD) | 148.3 (43.4) | 153.5 (42.0) | 147.7 (48.4) | 151.8 (49.3) | 153.0 (42.7) |
| **LS mean (SE) % change at Week 24** | **-2.7 (2.6)** | **-19.3 (2.9)** | **-20.1 (2.9)** | **-26.9 (2.9)** | **-10.3 (2.9)** |
| LS mean (SE) % change at Week 48 | 1.7 (3.0) | -12.1 (3.4) | -12.1 (3.3) | -21.8 (3.4) | -20.0 (3.4) |
| **ApoB** | | | | | |
| Baseline mean, mg/dL (SD) | 102.3 (29.6) | 102.6 (23.0) | 100.9 (27.2) | 100.6 (27.6) | 104.5 (24.2) |
| **LS mean (SE) % change at Week 24** | **0.8 (2.6)** | **-9.5 (2.9)** | **-12.2 (2.9)** | **-18.3 (2.9)** | **-5.7 (2.9)** |
| LS mean (SE) % change at Week 48 | 3.3 (2.8) | -4.7 (3.1) | -6.4 (3.1) | -12.2 (3.1) | -11.9 (3.1) |
| **HDL-C** | | | | | |
| Baseline mean, mg/dL (SD) | 42.1 (11.1) | 42.2 (11.1) | 44.7 (13.6) | 42.7 (11.7) | 40.8 (12.6) |
| **LS mean (SE) % change at Week 24** | **4.7 (3.3)** | **37.9 (3.8)** | **46.8 (3.8)** | **50.5 (3.8)** | **32.8 (3.8)** |
| LS mean (SE) % change at Week 48 | 4.5 (3.5) | 25.4 (4.0) | 30.5 (4.0) | 34.3 (4.0) | 44.5 (4.0) |

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; **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.

# RESULTS

## Plozasiran Showed a Favorable Safety Profile with Balanced Rates of TEAEs Leading to Discontinuation vs Placebo

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

### Table 3. Summary Of Adverse Events

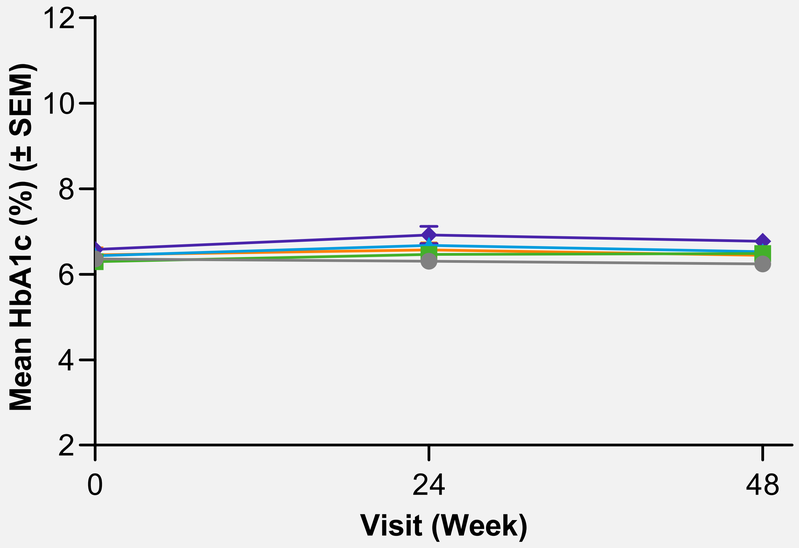
| | Pooled Placebo (N=87) | Plozasiran (Q12W) 10 mg (N=67) | Plozasiran (Q12W) 25 mg (N=67) | Plozasiran (Q12W) 50 mg (N=66) | Plozasiran 50 mg Q24W (N=66) |
|---|---|---|---|---|---|
| **Treatment-emergent adverse events (TEAEs)** | 55 (63) | 46 (69) | 45 (67) | 47 (71) | 49 (74) |
| **Covid 19** | 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) |

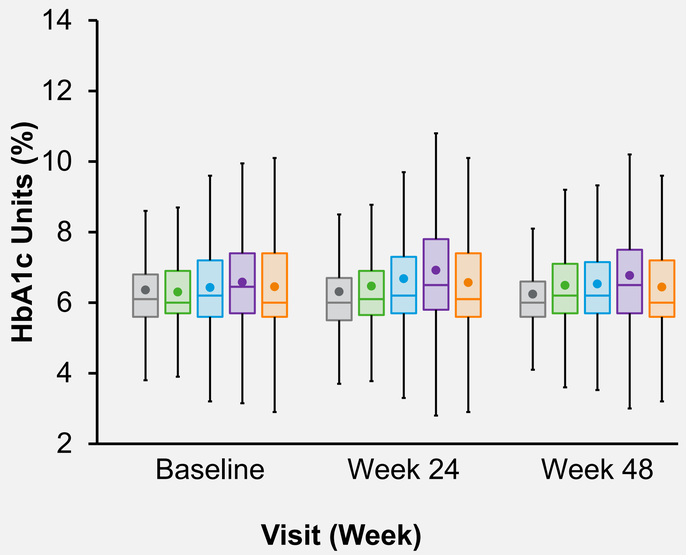
*Worsening glycemic control defined by multiple glycemic control parameters including but not limited to hemoglobin A1c, new onset diabetes mellitus, type 2 diabetes mellitus, diabetes mellitus, hyperglycemia, insulin resistance; n (%); worsening glycemic control was observed in patients with uncontrolled diabetes. bThere 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.

# RESULTS

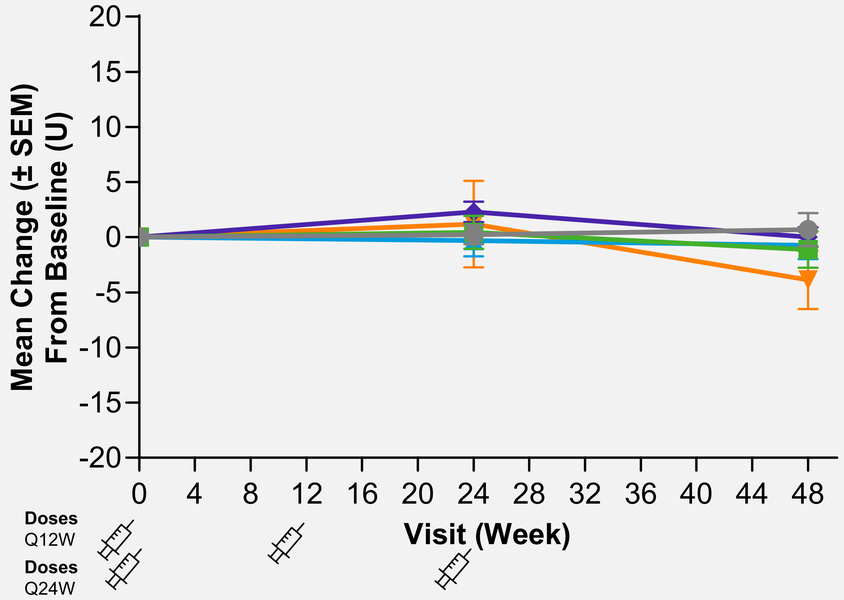
## Measurements of Glycemia and Insulin Sensitivity

### Glycemia: HbA1C, All patients




### Insulin Sensitivity: HOMA-IR, All patients




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



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

# CONCLUSIONS

- By silencing APOC3, plozasiran significantly reduced TGs and atherogenic triglyceride rich lipoproteins, across all dose levels at Week 24 in patients with mixed dyslipidemia
  - APOC3 ↓ to -80%
  - TG ↓ to -64%
  - Remnant cholesterol ↓ to -54%
  - ApoB ↓ to -18%
  - Non-HDL-C ↓ to -27%
  - HDL-C ↑ up to +51%
- Plozasiran has 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 dyslipidemia 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

# REFERENCES & ACKNOWLEDGEMENTS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