# Population K-PD Modeling of Plozasiran (ARO-APOC3), a GalNAc-siRNA Conjugate, for the Potential Treatment of Atherosclerotic Cardiovascular Disease (ASCVD) in Patients with Mixed Hyperlipidemia

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**The efficient RNAi mechanism of action results in deep and persistent reductions in serum APOC3 and TG at all doses studied, along with significant decreases in atherogenic lipids such as non-HDL-C and ApoB; the K-PD model estimates a high on-target pharmacological potency with IC50 dose of 54 ug per Kg of body weight in patients with mixed hyperlipidemia**

**Long and persistent PD activity of plozasiran is primarily attributed to its long elimination t1/2 in the liver estimated to be ~ 84 days in patients with mixed hyperlipidemia, and supports an infrequent (Q3M) dosing regimen for patient convenience**

**Weight is a statistically significant covariate to influence APOC3 reductions, but its impact on reducing atherogenic lipids (non-HDL-C and ApoB) is not clinically important. No other intrinsic/extrinsic factors were identified as significant PD covariates**

**Modeling result supports selecting 25 mg Q3M as the dose for Phase 3 trial to treat ASCVD indication**

## Background & Objective

Apolipoprotein C3 (APOC3), a component of triglyceride-rich lipoproteins (TRL), inhibits metabolism of TRLs through both inhibition of lipoprotein lipase (LPL) and reduced liver uptake of TRL remnants. Plozasiran (ARO-APOC3) is a GalNAc-siRNA designed to degrade hepatic APOC3 mRNA transcripts and reduce the production of APOC3 protein with expected reductions in serum triglycerides (TG) and TRL. In a Phase 2b clinical study conducted in 324 patients with mixed dyslipidemia (MD; TG 150-499 mg/dL, LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL), plozasiran doses of 10, 25 and 50 mg administered subcutaneously on Day 1 and Week 12 (1 additional 50 mg cohort on Week 24) during the double-blind period and subsequent Q12/24W dosing in the extension portion demonstrated substantial, dose-dependent and durable reductions in TG and in non-HDL-C and ApoB, two markers of atherogenic lipoproteins, supporting the initiation of a pivotal Phase 3 study with plozasiran in patients with mixed hyperlipidemia to reduce the risks of atherosclerotic cardiovascular disease (ASCVD).

## Methods

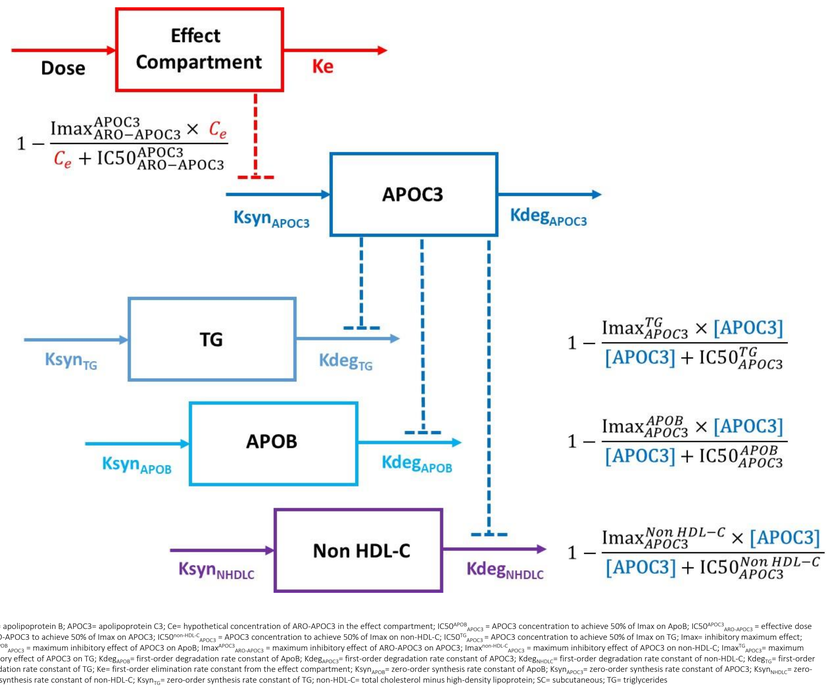
Due to the major disconnect between plozasiran's relatively short plasma exposures and its prolonged pharmacodynamic (PD) effects, its PD effects were best described by a kinetic-pharmacodynamic (K-PD) model. Potential impact of intrinsic and extrinsic factors (i.e., Asian vs non-Asian, White vs non-White, ethnicity, male vs female, liver impairment status (per National Cancer Institute Organ Dysfunction Working Group [NCI-ODWG] criteria), renal impairment status, obese vs. non-obese, tertiles of body weight, preexisting status of diabetic vs. non-diabetic, tertiles of baseline TG and of baseline of non-HDL-C. ) was evaluated using standard covariate search techniques involving forward addition and backward elimination adjudicated by pre-specified statistical criteria. The following dosing scheduled were simulated with dose levels of 10 mg, 25 mg and 50 mg:

- Dose at Day 1 followed by dose every 120 days (Q120)
- Dose at Day 1 followed by dose at Q90
- Dose at Day 1, Day 90 followed by dose every 180 days (Q180)

## Results

- Reductions in APOC3 and TG from the treatment with plozasiran were well described by a two-step, cascading, indirect-response population K-PD model, in which plozasiran, in the effect compartment (liver), inhibits APOC3 biosynthesis, and in turn, increases the rate of elimination of TG, ApoB and non-HDL-C, and thereby lowers their levels in serum.
- Hepatic plozasiran is eliminated with an estimated $t_{1/2}$ of 84 days in the SHTG patient population, which helps explain its long PD action. The estimated $IC_{50}$ dose of plozasiran was 54.1 µg/kg (i.e., 4.80 [2.81, 10.1] mg based on median [minimum, maximum] body weight of the population), suggesting a high on-target pharmacological potency via the efficient RNAi mechanism of action.
- There were no factors either intrinsic (e.g., patient's demographic profiles or baseline values of relevant biomarkers) or extrinsic factors(e.g., concomitant statin use) identified as statistically significant to influence these PD effects of plozasiran, at the exception of baseline levels of TG and ApoB on $IC50^{TG}_{APOC3}$ with higher $IC50^{TG}_{APOC3}$ associated with lower baseline levels of TG but higher baseline levels of ApoB.
- Only minor improvement in non-HDL-C and ApoB reductions was projected for 50 mg vs. 25 mg dose, which are both markedly more superior to 10 mg.
- At the steady-state, 25 mg and 50 mg Q90 day dosing regimens are projected to reduce non-HDL-C by 24% and 26%, respectively, averaged over a dosing cycle. The average reduction in ApoB is predicted to be ~18% and 19% for 25 mg and 50 mg Q90 day dosing, respectively.

Figure 1: Population K-PD Model Scheme for Serum APOC3, Triglyceride, ApoB and Non-HDL-C Levels after SC Administration of Plozasiran




ApoB= apolipoprotein B; APOC3= apolipoprotein C3; Ce= hypothetical concentration of ARO-APOC3 in the effect compartment; $IC50^{APOB}_{APOC3}$ = APOC3 concentration to achieve 50% of Imax on ApoB; $IC50^{APOC3}_{ARO-APOC3}$ = effective dose of ARO-APOC3 to achieve 50% of Imax on APOC3; $IC50^{non-HDL-C}_{APOC3}$ = APOC3 concentration to achieve 50% of Imax on non-HDL-C; $IC50^{TG}_{APOC3}$ = APOC3 concentration to achieve 50% of Imax on TG; Imax= inhibitory maximum effect; $Imax^{APOB}_{APOC3}$ = maximum inhibitory effect of APOC3 on ApoB; $Imax^{APOC3}_{ARO-APOC3}$ = maximum inhibitory effect of ARO-APOC3 on APOC3; $Imax^{non-HDL-C}_{APOC3}$ = maximum inhibitory effect of APOC3 on non-HDL-C; $Imax^{TG}_{APOC3}$= maximum inhibitory effect of APOC3 on TG; $Kdeg_{APOB}$= first-order degradation rate constant of ApoB; $Kdeg_{APOC3}$= first-order degradation rate constant of APOC3; $Kdeg_{NHDLC}$= first-order degradation rate constant of non-HDL-C; $Kdeg_{TG}$= first-order degradation rate constant of TG; Ke= first-order elimination rate constant from the effect compartment; $Ksyn_{APOB}$= zero-order synthesis rate constant of ApoB; $Ksyn_{APOC3}$= zero-order synthesis rate constant of APOC3; $Ksyn_{NHDLC}$= zero-order synthesis rate constant of non-HDL-C; $Ksyn_{TG}$= zero-order synthesis rate constant of TG; non-HDL-C= total cholesterol minus high-density lipoprotein; SC= subcutaneous; TG= triglycerides

## Additional Figures

Table 1: Parameter Estimates of the Final Population K-PD Model after SC Administration of Plozasiran in Patients with Mixed Hyperlipidemia

| Parameters | Estimate |
|---|---|
| **Typical Values** | |
| Elimination rate constant from the effect compartment (Ke) (1/day) | 0.00826 |
| Baseline APOC3 (mg/dL) | 14.0 |
| Synthesis rate of APOC3 ($Ksyn_{APOC3}$) (mg/dL/h) | 0.166 |
| Effective dose of ARO-APOC3 to provide 50% of the Imax on APOC3 ($IC50^{APOC3}_{ARO-APOC3}$) (µg/kg) | 54.1 |
| Baseline TG (mg/dL) | 213 |
| TG elimination rate constant ($Kdeg_{TG}$) (1/h) | 0.724 Fixed |
| Effective concentration of APOC3 to provide 50% of the Imax on TG ($IC50^{TG}_{APOC3}$) (mg/dL) | 4.12 |
| Baseline ApoB (mg/dL) | 99.2 |
| ApoB elimination rate constant ($Kdeg_{ApoB}$) (1/h) | 0.00482 |
| Effective concentration of APOC3 to provide 50% of the Imax on APOB ($IC50^{ApoB}_{APOC3}$) (mg/dL) | 50.0 |
| Baseline Non-HDL-C (mg/dL) | 140 |
| non-HDL-C elimination rate constant ($Kdeg_{non-HDL-C}$) (1/h) | 0.00573 |
| Effective concentration of APOC3 to provide 50% of the Imax on non-HDL-C ($IC50^{nonHDL-C}_{APOC3}$) (mg/dL) | 32.6 |
| **Covariate Effects** | |
| Observed Baseline TG on $IC50^{TG}_{APOC3}$ ×(BASE[mg/dL]/222)$^{\theta}$ | -0.524 |
| Observed Baseline ApoB on $IC50^{TG}_{APOC3}$ ×(BASE[mg/dL]/96.7)$^{\theta}$ | 0.567 |

Note: Imax was fixed to 1
APOC3= apolipoprotein C3; CI = confidence interval; Kdeg_TG= first-order degradation rate of TG; Ke = elimination rate constant from effect compartment; $Ksyn_{APOC3}$ = zero-order production rate constant of APOC3; $IC50^{APOC3}_{ARO-APOC3}$ = Effective dose of ARO-APOC3 to achieve 50% of the Imax on APOC3; $IC50^{TG}_{APOC3}$ = APOC3 levels to achieve 50% of the Imax on TG; $Imax^{APOC3}_{ARO-APOC3}$ = maximum inhibitory effect of ARO-APOC3 on APOC3; $Imax^{TG}_{APOC3}$ = maximum inhibitory effect of ARO-APOC3 on TG; NA= not available; SC= subcutaneous; TG=triglyceride

Figure 2: VPC for Time-Profiles of Relative Change from Baseline of Serum ApoB and non-HDL-C in Patients with Mixed Hyperlipidemia

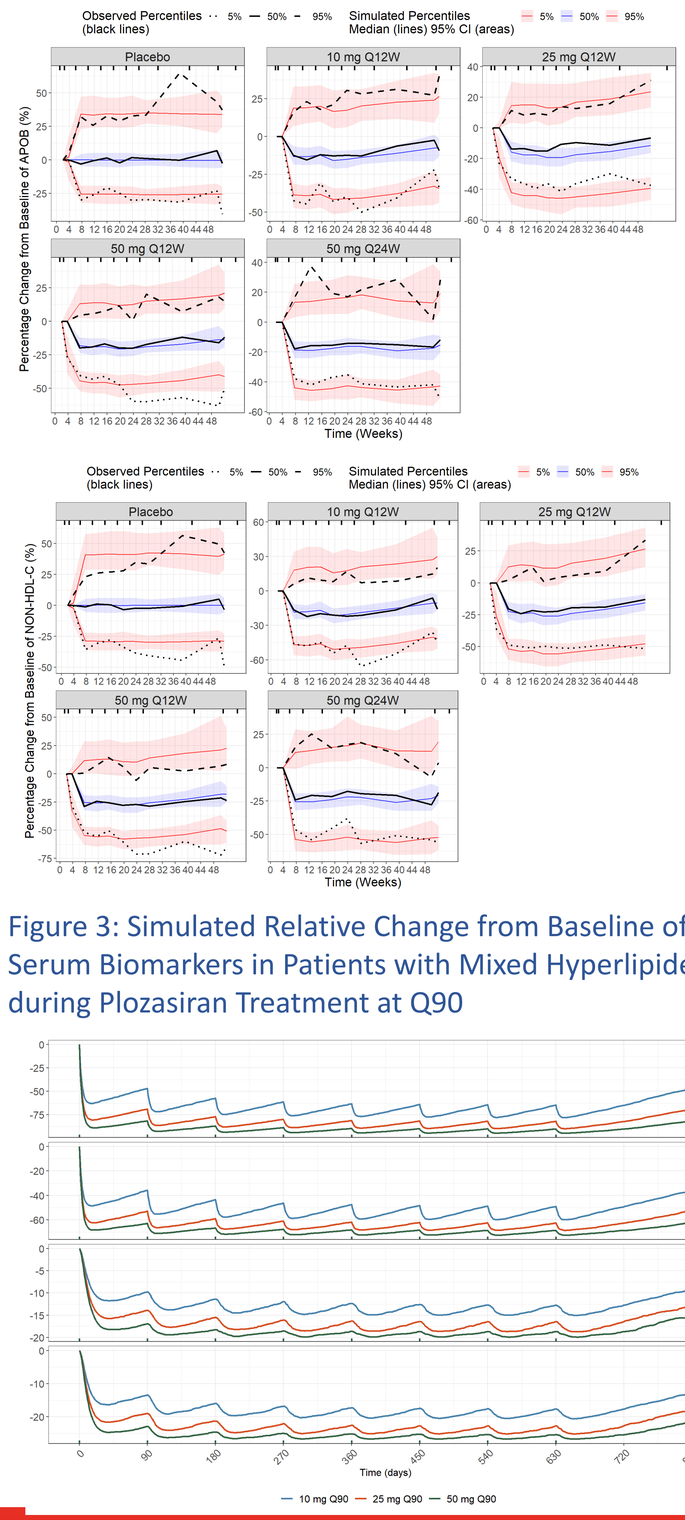



Figure 3: Simulated Relative Change from Baseline of Serum Biomarkers in Patients with Mixed Hyperlipidemia during Plozasiran Treatment at Q90




## Conclusion

The efficient RNAi mechanism of action results in deep and persistent reductions in serum APOC3 and TG at all doses studied, along with significant decreases in atherogenic lipids such as non-HDL-C and ApoB; the K-PD model estimates a high on-target pharmacological potency with IC50 dose of 54 ug per Kg of body weight in patients with mixed hyperlipidemia. Modeling result supports selecting 25 mg Q3M as the dose for Phase 3 trial to treat ASCVD indication. Dose adjustment is not recommended for patients with different demographic characteristics and comorbidities, or background lipid lowering therapies.

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