Population K-PD Modeling of Plozasiran (ARO-APOC3), a GalNAc-siRNA Conjugate, for the Treatment of Patients with Severe Hypertriglyceridemia

Jack Shi[1], Nathalie H Gosselin[2], Claudia Jomphe[2]
[1] Arrowhead Pharmaceuticals , [2] Certara, Certara Drug Development Solutions

The efficient RNAi mechanism of action results in deep and persistent reductions in serum APOC3 and TG at all doses studied.

The K-PD model estimates a high on-target pharmacological potency with IC50 dose of 3.3 mg in patients with SHTG

Long and persistent PD activity of plozasiran is primarily attributed to its long elimination t1/2 in the liver estimated around 70 days in patients with SHTG, which supports an infrequent (Q3M) dosing regimen for patient convenience

There was no intrinsic or extrinsic factor identified as a statistically significant covariate to influence Plozasiran PD performance

Modeling result supports selecting 25 mg Q3M as the dose for Phase 3 trials in SHTG 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 219 patients with severe hypertriglyceridemia (SHTG; TG > 500 mg/dL), plozasiran doses of 10, 25 and 50 mg administered subcutaneously on day 1 and week 12 during the double-blind period and subsequent Q12W dosing in the extension portion, demonstrated deep, dose-dependent and long-lasting reductions of serum TG with acceptable safety profiles, supporting the initiation of pivotal Phase 3 studies with plozasiran in patients with SHTG.

Methods

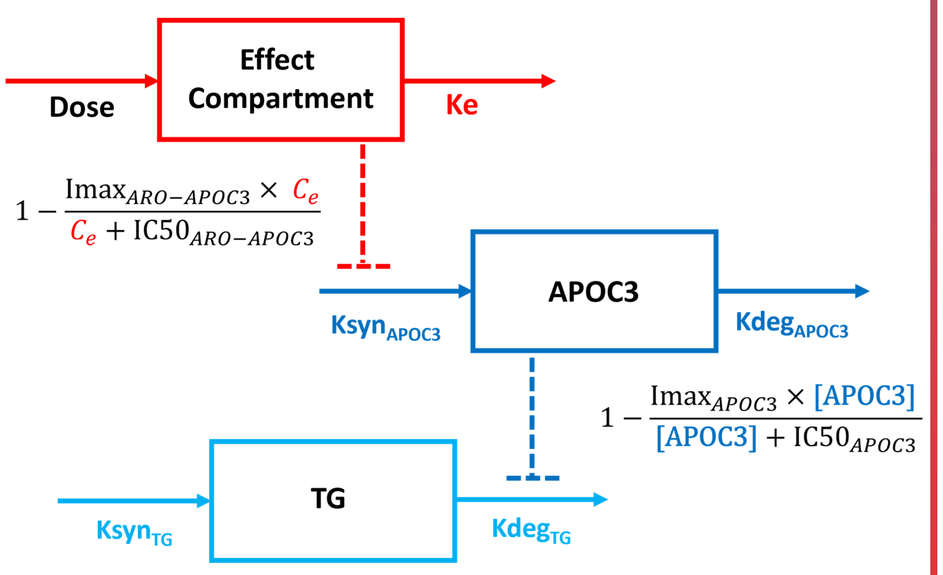
Due to the major disconnect between plozasiran's relatively short plasma exposures and its prolonged pharmacodynamic (PD) effects, its PD effects were best described by a kinetic-pharmacodynamic (K-PD) model. Potential impact of intrinsic and extrinsic factors (i.e., lipid biomarkers, sex, renal and hepatic functions, race [Asian vs Non-Asian], lipid-lowering therapy) was evaluated using standard covariate search techniques involving forward addition and backward elimination adjudicated by pre-specified statistical criteria. Model-based simulations were conducted to support selecting a Phase 3 dose regimen in patients with SHTG by simulating the following dosing regimens:

- Dosing every 120 days (Q120 day) starting on Day 1 at 10 mg, 25 mg and 50 mg
- Dosing every 90 days (Q90 day) starting on Day 1 at 10 mg, 25 mg and 50 mg
- Initial dose on Day 1, a loading dose on Day 30, a 3rd dose on Day 90 and Q90 day dosing afterwards at 10 mg, 25 mg and 50 mg

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 and thereby lowers its level in serum.
- Hepatic plozasiran is eliminated with an estimated $t_{1/2}$ of 70 days in the SHTG patient population, which helps explain its long PD action. The estimated IC_{50} dose of plozasiran was 3.3 mg, 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.
- Simulations projected modest peak-to-trough fluctuations with quarterly (Q3M) dosing with similar time-averaged TG reductions over a dosing cycle between 25 mg (81%) and 50 mg (86%) doses, suggesting that 25 mg Q3M is a near PD saturating dose.
- Monte-Carlo simulations suggest that, at Day 300 (Month 10) or 1 month following the 4th dose of Q90 days administration, ~ 88%, 96% and 99% of SHTG patients would have their fasting serum TG levels reduced below 500 mg/dL for the 10 mg, 25 mg and 50 mg Q90 days dosing regimen, respectively.

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



APOC3 = apolipoprotein C3; Ce= hypothetical concentration of ARO-APOC3 in the effect compartment; $IC_{50ARO-APOC3}$= AROAPOC3 levels to achieve 50% of Imax on APOC3; $IC_{50APOC3}$= APOC3 concentration to achieve 50% of Imax on TG; Imax= inhibitory maximum effect; $Imax_{ARO-APOC3}$= maximum inhibitory effect of ARO-APOC3 on APOC3; $Imax_{APOC3}$ = maximum inhibitory effect of APOC3 on TG; K-PD= kinetic/pharmacodynamic; KdegAPOC3= first-order degradation rate constant of APOC3; KdegTG= first-order degradation rate constant of TG; KE= elimination rate constant from the effect compartment; KsynAPOC3= zero-order synthesis rate constant of APOC3; KsynTG= zero-order synthesis rate constant of TG; TG= triglycerides; SC= subcutaneous

Conclusion

Modeling results support selecting 25 mg Q3M as the dose for the Phase 3 trials in SHTG indication. Dose adjustment is not required for patients with different demographic characteristics, baseline TG levels, or concomitant lipid lowering therapies

Additional Figures

Table 1: Parameter Estimates of the Final Population K-PD Model of APOC3 TG after SC Administration of Plozasiran in Patients with SHTG

Parameters	Estimate	RSE%	95% CI
Typical Values			
Ke (1/day)	0.00990	6.10	0.00872 – 0.0111
Baseline APOC3 (mg/dL)	28.4	2.37	27.0 – 29.7
Ksyn_APOC3 (mg/dL/h)	0.356	5.85	0.315 – 0.397
$Imax_{ARO-APOC3}$ (%)	100 Fixed	n/a	n/a
$IC50_{ARO-APOC3}$ (mg)	3.319	10.5	2.634 – 4.003
Baseline TG (mg/dL)	577	4.29	529 – 626
TG elimination rate constant (Kdeg_TG) (1/h)	0.724 Fixed	n/a	n/a
Imax_APOC3 (%)	100 Fixed	n/a	n/a
$IC50_{APOC3}$ (mg/dL)	2.46	6.45	2.15 – 2.78
Covariate Effects			
Observed Baseline APOC3 on Estimated Baseline APOC3 $\times(BASE/30.5)^{\theta}$	0.781	4.32	0.715 – 0.847
Observed Baseline TG on Estimated Baseline TG $\times(BASE/652)^{\theta}$	1.00	5.17	0.899 – 1.10
Between Subject Variability (Standard Deviation, CV%)			
On Ke	0.648 (72.2%)	6.01	0.571 – 0.724
On Baseline APOC3	0.222 (22.5%)	6.46	0.194 – 0.250
On $IC50_{ARO-APOC3}$	1.14 (163%)	5.82	1.01 – 1.27
On Baseline TG	0.369 (38.2%)	5.34	0.331 – 0.408
Correlation between baseline APOC3 and TG	0.409 (42.7%)	13.6	0.300 – 0.518
Residual Error			
APOC3 Proportional Error	33.2	1.08	32.5 – 33.9
TG Proportional Error	41.2	1.26	40.2 – 42.2

APOC3= apolipoprotein C3; CI = confidence interval; Kdeg_TG= first-order degradation rate of TG; Ke = elimination rate constant from effect compartment; KsynAPOC3 = zero-order production rate constant of APOC3; $IC_{50ARO-APOC3}$= = Effective dose of ARO-APOC3 to achieve 50% of the Imax on APOC3; $IC_{50APOC3}$ = APOC3 levels to achieve 50% of the Imax on TG; $Imax_{ARO-APOC3}$= maximum inhibitory effect of ARO-APOC3 on APOC3; $Imax_{APOC3}$ = maximum inhibitory effect of ARO-APOC3 on TG; NA= not available; RSE = relative standard error; SC= subcutaneous; TG=triglyceride

Figure 2: VPC for Time-Profiles of Relative Change from Baseline of Serum APOC3 and TG in Patients with SHTG

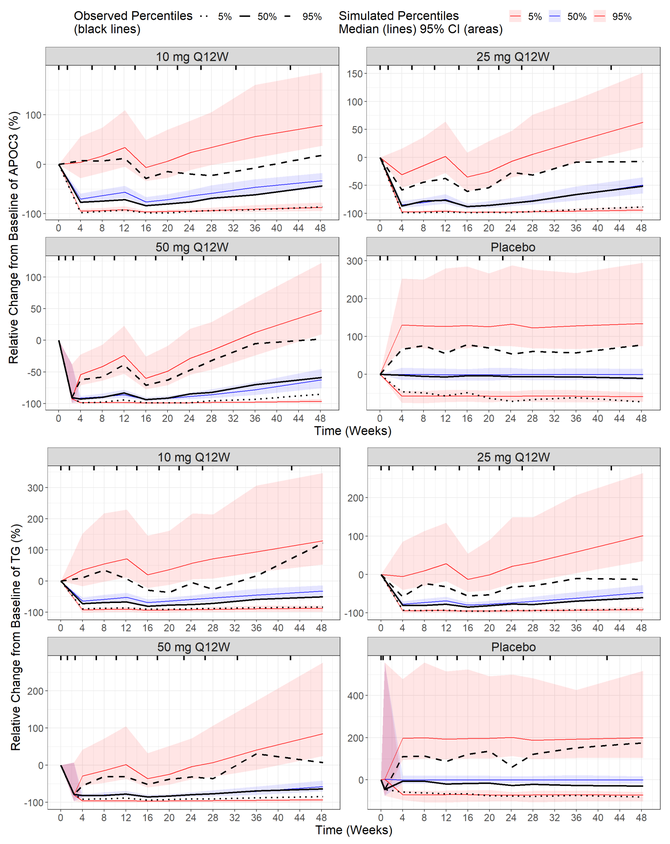
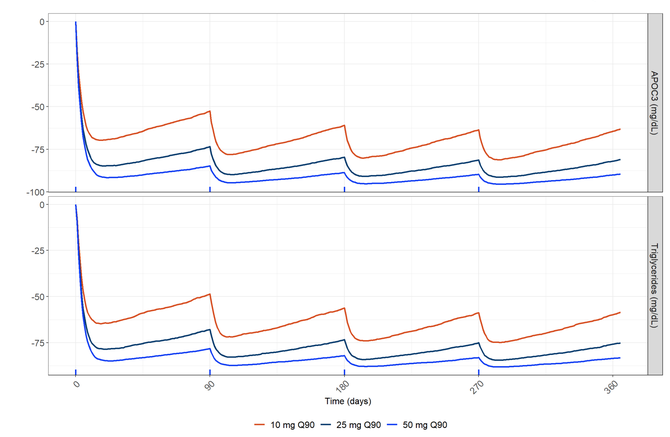


Figure 3: Simulated Relative Change from Baseline of Serum APOC3 and TG in Patients with SHTG – Q90



Want to learn more?
<< Scan Here
Scan me