Population Kinetic-Pharmacodynamic (K-PD) Modeling of Multiple Lipid Biomarker Responses to Zodasiran in Patients with Mixed Dyslipidemia

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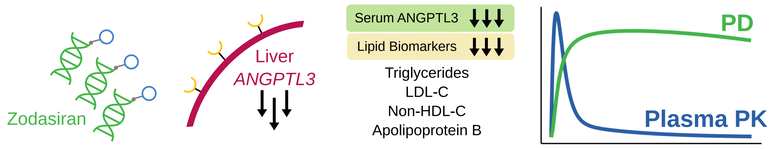
Background

Zodasiran is a small interfering RNA (siRNA)-based therapeutic targeting hepatic angiopoietin-like protein 3 (ANGPTL3) in development for cardiometabolic indications. Subcutaneously (SC) administered zodasiran undergoes plasma elimination within days,[1] but the beneficial pharmacodynamic (PD) effects on lipid biomarkers, including reductions in triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B (ApoB), persist for months after one dose.

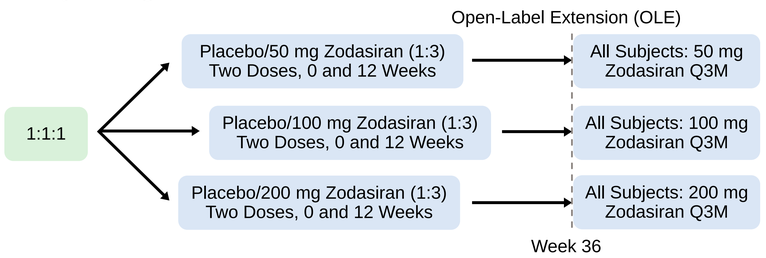


Here, we develop a population kinetic-pharmacodynamic (K-PD) model to describe the dose-dependent PD responses to zodasiran in mixed dyslipidemia (MD). Model-based simulations are used to inform dose regimen selection in the MD population for a Phase 3 trial for prevention of atherosclerotic cardiovascular disease (ASCVD).

Methods

Dosing records, lipid measurements, and covariate data from a Phase 2b study in patients (N=204) with MD (ARCHES-2, NCT04832971) administered either 50, 100, or 200 mg SC zodasiran were used for model development.

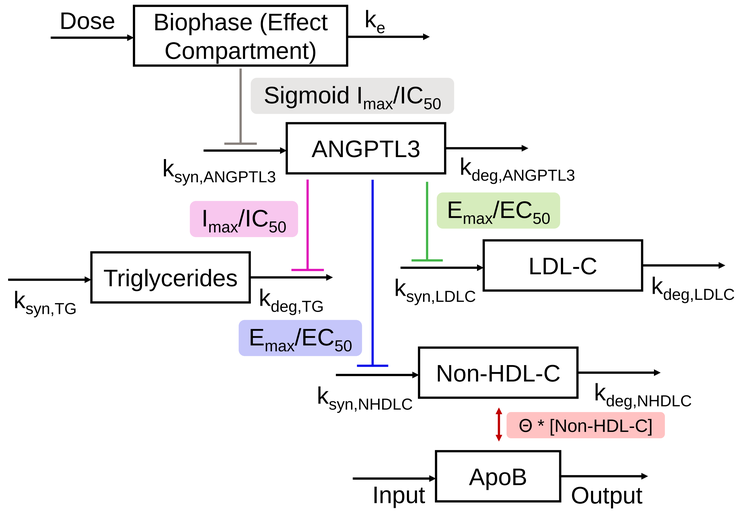
Study Design



A nonlinear mixed-effects modeling (NONMEM v7.5.1) approach was taken. Model selection was based on the zodasiran mechanism of action and guided by objective function value (OFV), model stability, and evaluation of diagnostic plots. Covariate inclusion was based on the statistical strength of covariate-parameter relationships and resulting improvement in OFV.[2] Power models were used for continuous covariates. Parameter uncertainty was explored with sampling-importance-resampling (SIR) and the predictive ability of the model was verified via visual predictive check (VPC). Simulations of zodasiran dose regimens were conducted in R (v4.3.2) with the mrgsolve package (v1.3.0).

Results and Simulations

Structural Model

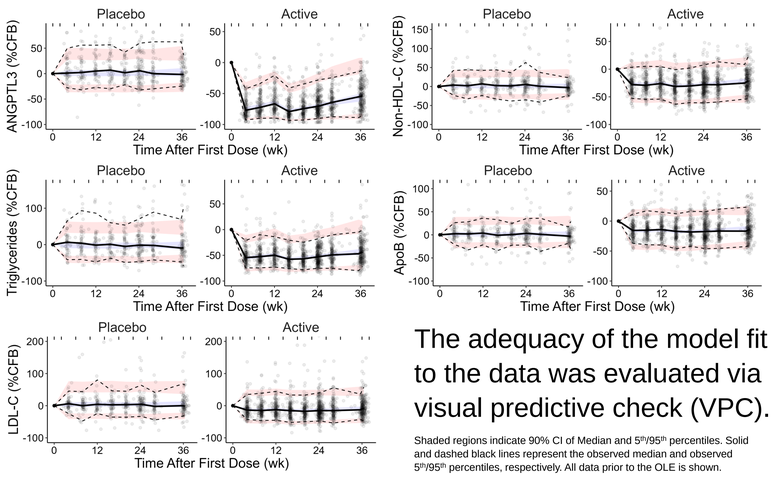


Key Parameter Estimates

Parameter	Estimate	95% CI
k_e (day^{-1})	**0.0113**	[0.0102, 0.0127]
$IC_{50,zod}^{ANGPTL3}$ (mg)	**13.3**	[10.8, 15.9]
Covariate Effect of Baseline TG on $E_{max,ANGPTL3}^{NHDLC}$	**0.68**	[0.29, 1.06]

The k_e estimate of 0.0113 day^{-1} indicates the biophase half-life of zodasiran is ~61 days, far longer than the plasma PK elimination half-life of ~4-5 hours. The $IC_{50,zod}^{ANGPTL3}$, or the dose of zodasiran to reduce ANGPTL3 synthesis by half, is 13.3 mg, providing insight into the strong ANGPTL3 reductions observed at all dose levels. Baseline TG was a positive covariate with $E_{max,ANGPTL3}^{NHDLC}$, indicating that the non-HDL-C response to zodasiran may be stronger in MD patients with higher baseline TG levels.

Goodness-of-Fit

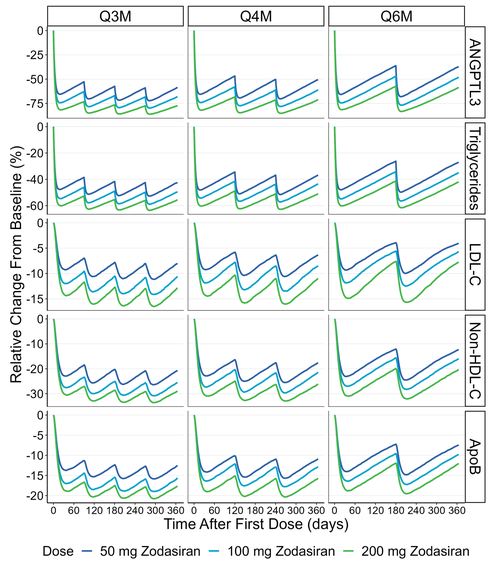


The adequacy of the model fit to the data was evaluated via visual predictive check (VPC).

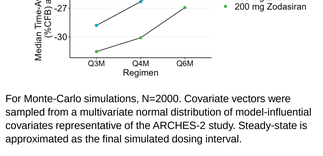
Shaded regions indicate 90% CI of Median and 5th/95th percentiles. Solid and dashed black lines represent the observed median and observed 5th/95th percentiles, respectively. All data prior to the OLE is shown.

Simulations

Dosing regimens of 50, 100, or 200 mg SC zodasiran administered every three, four, or six months (Q3M/Q4M/Q6M) were simulated. Summary parameters of the time-averaged, nadir, and trough biomarker responses at steady-state were quantified.

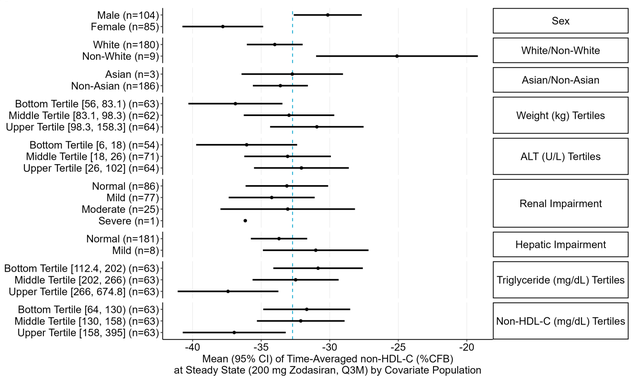


Parameter	Regimen	Dose (mg)	% Change From Baseline at Steady State (Median)		
			LDL-C	Non-HDL-C	ApoB
Average	Q3M	50	-9.9	-24.1	-14.7
		100	-12.9	-28.8	-17.8
		200	-15.2	-31.5	-19.5
	Q4M	50	-8.7	-22.1	-13.6
		100	-11.4	-26.3	-15.8
		200	-14	-30.1	-18.4
Nadir	Q3M	50	-11.1	-26.4	-15.8
		100	-14.2	-30.8	-19
		200	-16.5	-33.6	-20.8
	Q4M	50	-10.6	-25.5	-15.7
		100	-13.5	-29.7	-17.8
		200	-16	-32.9	-20.3
Trough	Q3M	50	-8.2	-21.1	-12.8
		100	-10.9	-25.9	-16.1
		200	-13.2	-29.4	-17.9
	Q4M	50	-6.5	-18	-11.2
		100	-8.7	-22	-13.1
		200	-11.3	-26.6	-16



For Monte-Carlo simulations, N=2000. Covariate vectors were sampled from a multivariate normal distribution of model-influential covariates representative of the ARCHES-2 study. Steady-state is approximated as the final simulated dosing interval.

Posterior simulations of steady-state time-averaged biomarker responses (Q3M, 200 mg) projected greater percentage reductions of non-HDL-C in subjects with higher baseline triglyceride/non-HDL-C levels.



For posterior simulations, N=189. Subjects that did not receive drug and therefore have unevaluable posterior parameters are omitted from analysis. The dashed blue line represents the typical subject, with parameters set to their population estimates and with model influential covariates set to the median of the K-PD analysis population.

Conclusions

We present a K-PD model which adequately characterizes lipid biomarker dynamics after multiple doses of zodasiran in MD patients. Simulations support a dosing regimen of Q3M/Q4M zodasiran at 200 mg in a Phase 3 trial for prevention of ASCVD. We identify intrinsic patient factors, including hyperlipidemia severity, that may associate with treatment benefit.

[1]Watts *et al.* RNA interference targeting ANGPTL3 for triglycerides and cholesterol lowering: phase 1 basket trial cohorts. *Nature Medicine*. (2023)
[2]Ayral *et al.* A novel method based on unbiased correlations tests for covariate selection in nonlinear mixed effects models: The COSSAC approach. *CPT: Pharmacometrics and Systems Pharmacology*. (2021)