Integrated Population Pharmacokinetic and Exposure-Response Modeling of Enlicitide in Hypercholesterolemia Patients Supports Clinical Dose Recommendation Across Patient Subgroups

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Background

Despite the well-established cardiovascular benefit of low-density lipoprotein cholesterol (LDL-C) lowering, real-world use of PCSK9-targeted therapies remains limited, in part due to reliance on injectable formulations.

Enlicitide decanoate is a novel, oral macrocyclic peptide proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor developed as a once-daily oral LDL-C-lowering therapy to enable robust LDL-C reduction and reduction of cardiovascular risk, offering potential for improved accessibility and adherence [1].

Objectives

- To characterize the population pharmacokinetics (PopPK) of enlicitide across Phase 1, Phase 2 and Phase 3 studies, and evaluate intrinsic and extrinsic factor effects.
- To characterize the relationship between enlicitide exposure and LDL-C reduction in participants with hypercholesterolemia, assess the impact of intrinsic and extrinsic factors on the exposure–response (E-R) relationship, assess whether exposure differences translate into clinically meaningful effect on LDL-C reduction and whether the same dose can be recommended across all subgroups

Methods

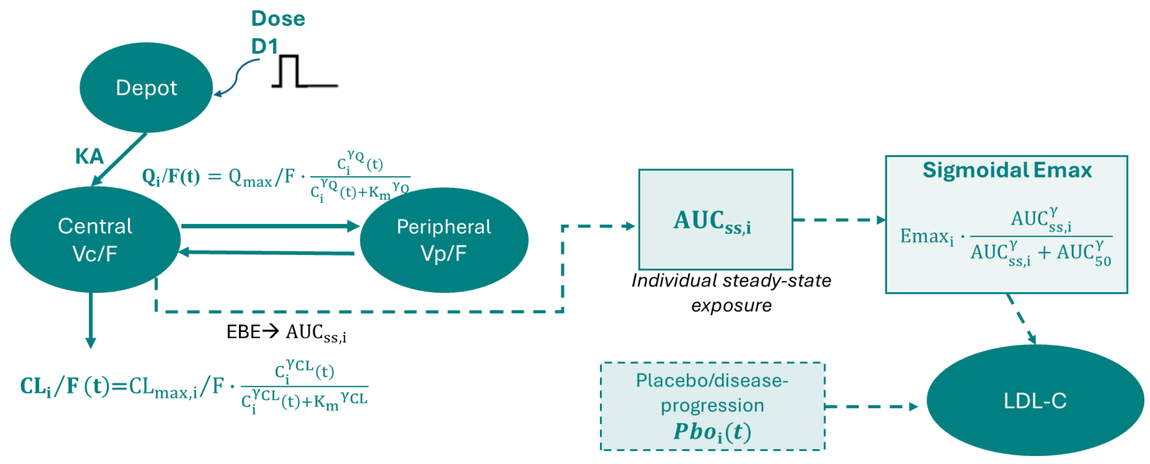
Data

- Plasma concentration data from 11 clinical studies (eight Phase 1, one Phase 2, and two Phase 3) of enlicitide were pooled, comprising 19,158 observations from 2713 participants, including healthy volunteers and hypercholesterolemia patients (including heterozygous familial hypercholesterolemia (HeFH)).
- Rich PK sampling was available from Phase 1 studies and sparse sampling from Phase 2/3 trials, enabling robust characterization of enlicitide PK across a broad exposure range.
- Phase 1 studies included single doses ranging from 18 to 90 mg and multiple once-daily doses ranging from 20 to 300 mg, Phase 2 study tested multiple doses of 6, 12, 18 and 30 mg and placebo; Phase 3 studies evaluated 20 mg dose and placebo.
- Data from Phase 3 studies (**CORALreef Lipids** and **CORALreef HeFH**) included 15338 LDL-C records from 3183 participants and were pooled for primary analysis.

PopPK and E-R Model Development

- PopPK analysis evaluated one- and two-compartment models with zeroth-order infusion into the depot compartment (**D1**), first-order absorption (**KA**) and both linear and concentration-dependent elimination to account for PCSK9-mediated clearance [2].
- Individual steady- state AUC_{0-24}, denoted as $\mathbf{AUC_{ss,i}}$ was simulated from the final PopPK model and used to drive E-R model
- LDL-C reduction over time was parameterized in terms of model-estimated baseline LDL-C (**LDLC-BL**), maximal fractional reduction in LDL-C (**Emax**), AUCss corresponding to the half-maximal reduction in LDL-C ($\mathbf{AUC_{50}}$), and the Hill coefficient ($\boldsymbol{\gamma}$), with enlicitide AUCss describing a percentage reduction in LDL-C from baseline.
- A time-dependent change in LDL-C concentrations in both placebo and active-treated participants was added to the model, accounting for drug-free disease progression, **Pbo(t).**
- Candidate covariates explored in PopPK and E-R models were evaluated using a stepwise procedure, and included body weight, estimated glomerular filtration rate (eGFR), concomitant statin use, hypercholesterolemia disease status, demographics, and diabetes mellitus status.

Figure 1: PopPK and E-R Model Schematic

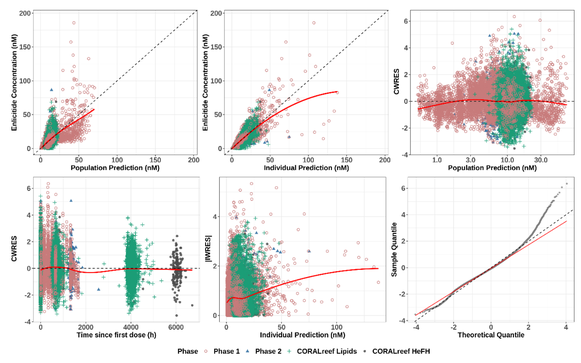


Index "i" is used to describe individual model-predicted parameters CL/F, apparent clearance; EBE empirical Bayes estimate; Ka absorption rate constant; Vc/F apparent central volume of distribution; Vp/F apparent peripheral volume of distribution; Q/F apparent intercompartmental clearance; Solid arrows: mass transfer

Results

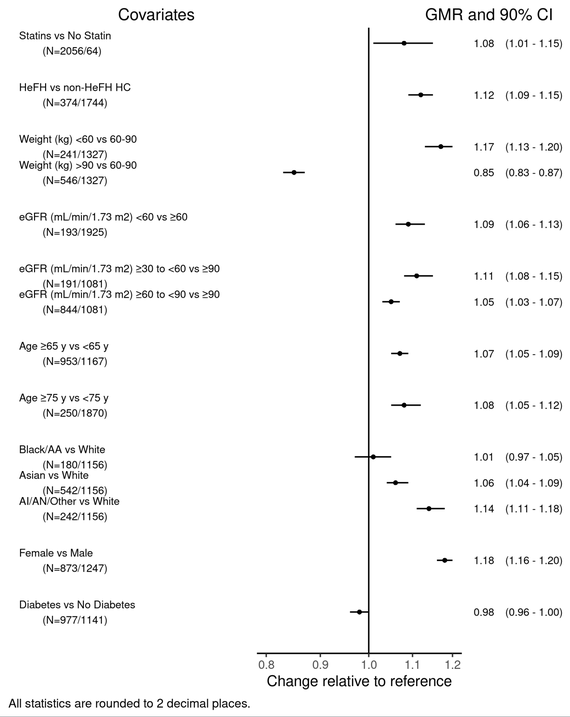
PopPK Modeling and Simulation

Figure 2: Goodness-of-fit plots for enlicitide final PopPK model



- The final PopPK model was a two-compartment model **(Figure 1)** with apparent clearance (**CL/F**), and apparent intercompartmental clearance (**Q/F**) parameterized as Hill functions in which clearance decreases with decreasing concentrations
- Diagnostic plots demonstrated good agreement across studies, dose levels, and populations **(Figure 2)**

Figure 3: Forest Plot of the Relative Differences in AUCss (Expressed as Geometric Mean Ratios and 90% Confidence Intervals) of Covariate Effects on MK-0616 Exposure at Steady State in Hypercholesterolemia Participants



All statistics are rounded to 2 decimal places.

- Inter-individual variability in exposure was moderate (<30% coefficient of variation, CV) in the Phase 3 population.
- Covariate effects in PopPK model: body weight and eGFR on CLmax/F, body weight on Vc/F, statin use and disease status on CLmax/F
- No dose adjustment is required for intrinsic or extrinsic factors **(Figure 3)**

E-R Modeling and Simulation

Figure 4: Goodness-of-fit plots for the final Exposure-LDL-C model

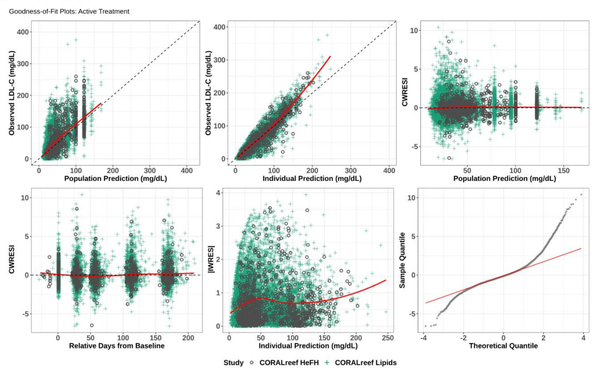


Figure 5: LDL-C Change From Baseline at Week 24 vs. AUCss in Hypercholesterolemia Patients

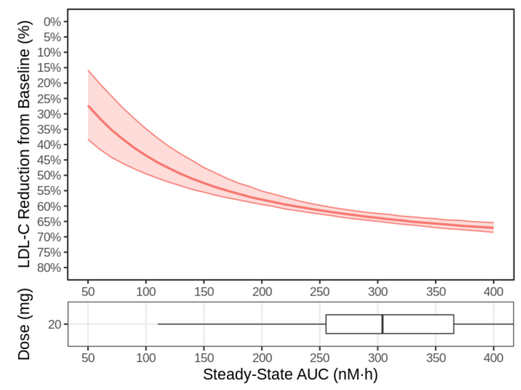
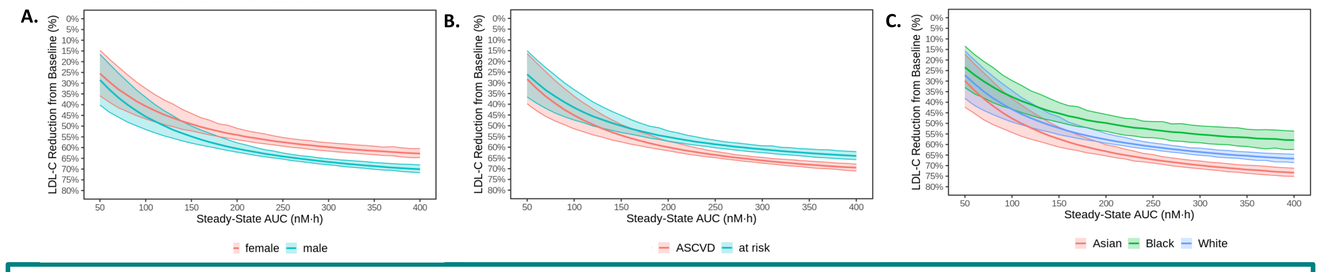


Figure 6: LDL-C Change From Baseline at Week 24 vs. AUCss, in Hypercholesterolemia Participants, stratified by (A) sex; (B) presence of ASCVD; (C) race



The 20-mg once-daily dose resulted in exposures associated with near maximal effect (~64% LDL-C reduction from baseline) with minimal incremental benefit predicted at higher exposures **(Figure 5)**

Although several covariates were statistically significant, their effects on LDL-C reduction were small (<5–7%) and not clinically meaningful **(Figure 6)**

Conclusions

- An integrated modeling framework translated pharmacokinetic variability into clinical response and demonstrated that therapeutic exposures are near maximal efficacy.
- These results support a 20-mg once-daily oral dosing of enlicitide without adjustment for specific patient subgroups and highlight the value of end-to-end model-informed drug development.

References

[1] Navar, A.M., Mikhailova, E., Catapano, A.L., et al. A placebo-controlled trial of the oral PCSK9 inhibitor enlicitide. New England Journal of Medicine (2026) 394:529-539.

[2] Gibiansky, L., Gibiansky, E., Kakkar, T., Ma, P. Approximations of the target-mediated drug disposition model and identifiability of model parameters. J Pharmacokinet Pharmacodyn (2008) 35(5): 573–591.

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