

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].

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 300 mg and multiple once-daily doses ranging from 18 to 120 mg, Phase 2 study tested multiple once-daily 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 (Phase 3 E-R model). Supportive Phase 2b data (1120 LDL-C records from 379 participants) were included to inform the exposure-relationship at lower exposure levels (Phase 2/3 E-R model).

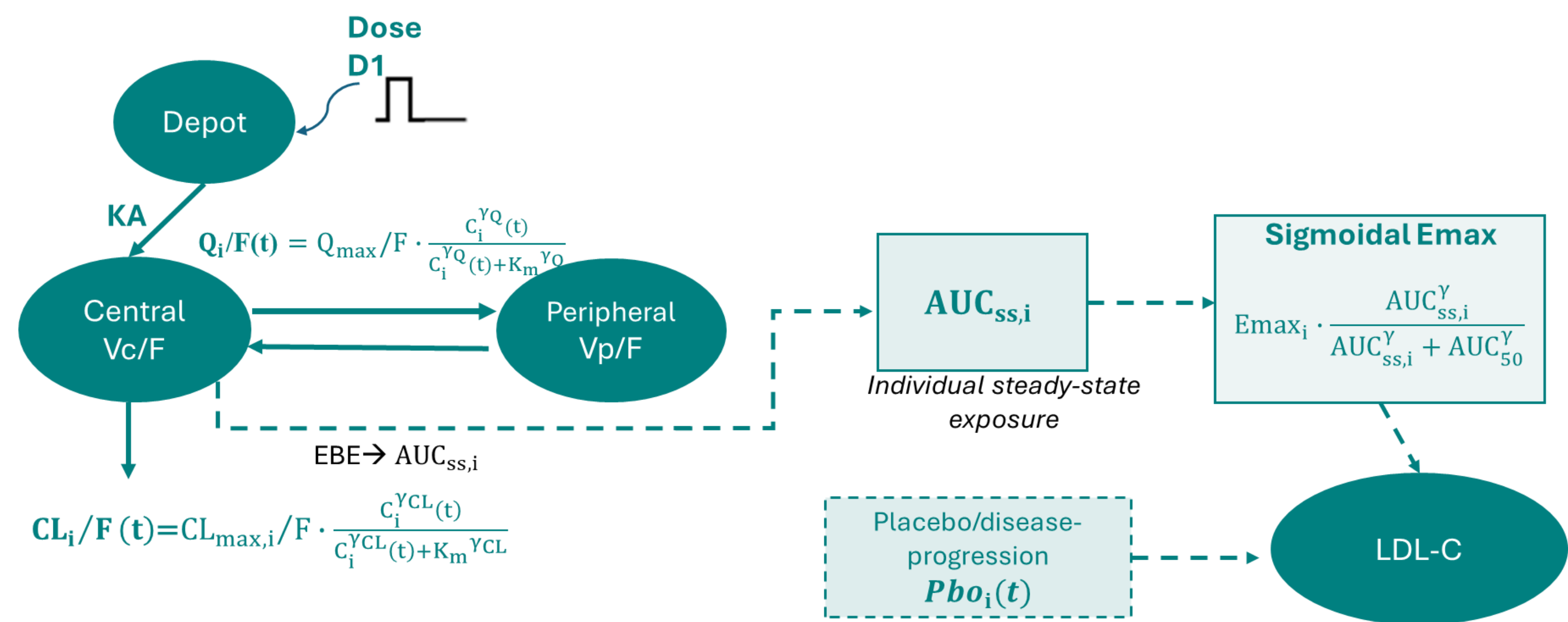
PopPK and E-R Model Development

- 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 **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**), AUC_{ss} corresponding to the half-maximal reduction in LDL-C (**AUC₅₀**), and the Hill coefficient (**γ**), with enlicitide AUC_{ss} 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)**.
- Primary E-R model was developed on pooled Phase 3 data; the resulting structure was then re-estimated on pooled Phase 2/3 data to support inference at lower exposures.
- 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.

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 and assess the impact of intrinsic and extrinsic factors on the exposure-response (E-R) relationship

Figure 1: PopPK and E-R Model Schematic

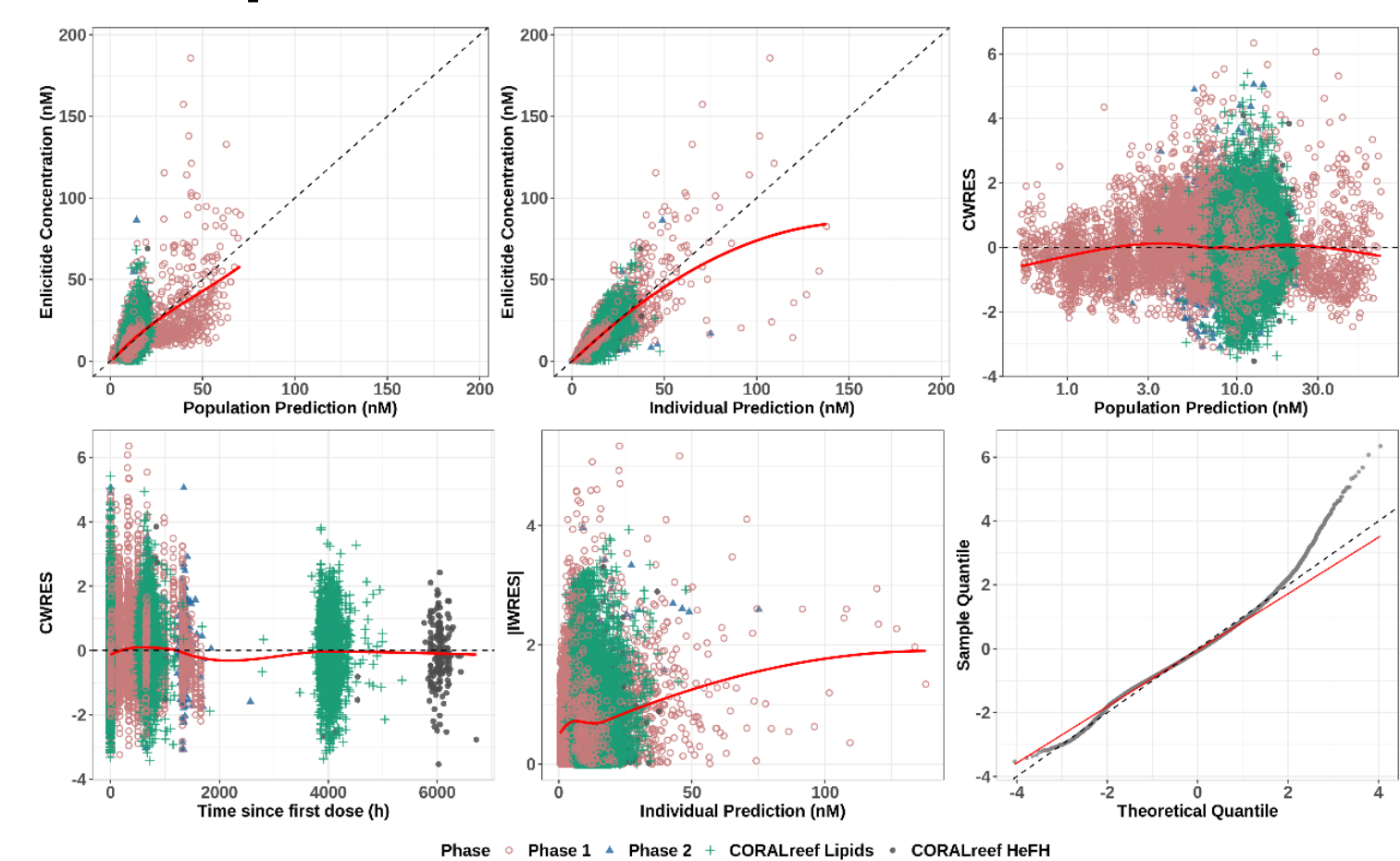


Index “i” is used to describe individual model-predicted parameters CL/F , apparent clearance; EBE empirical Bayes estimate; K_a absorption rate constant; V_c/F apparent central volume of distribution; V_p/F apparent peripheral volume of distribution; Q/F apparent intercompartmental clearance; Solid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

Results

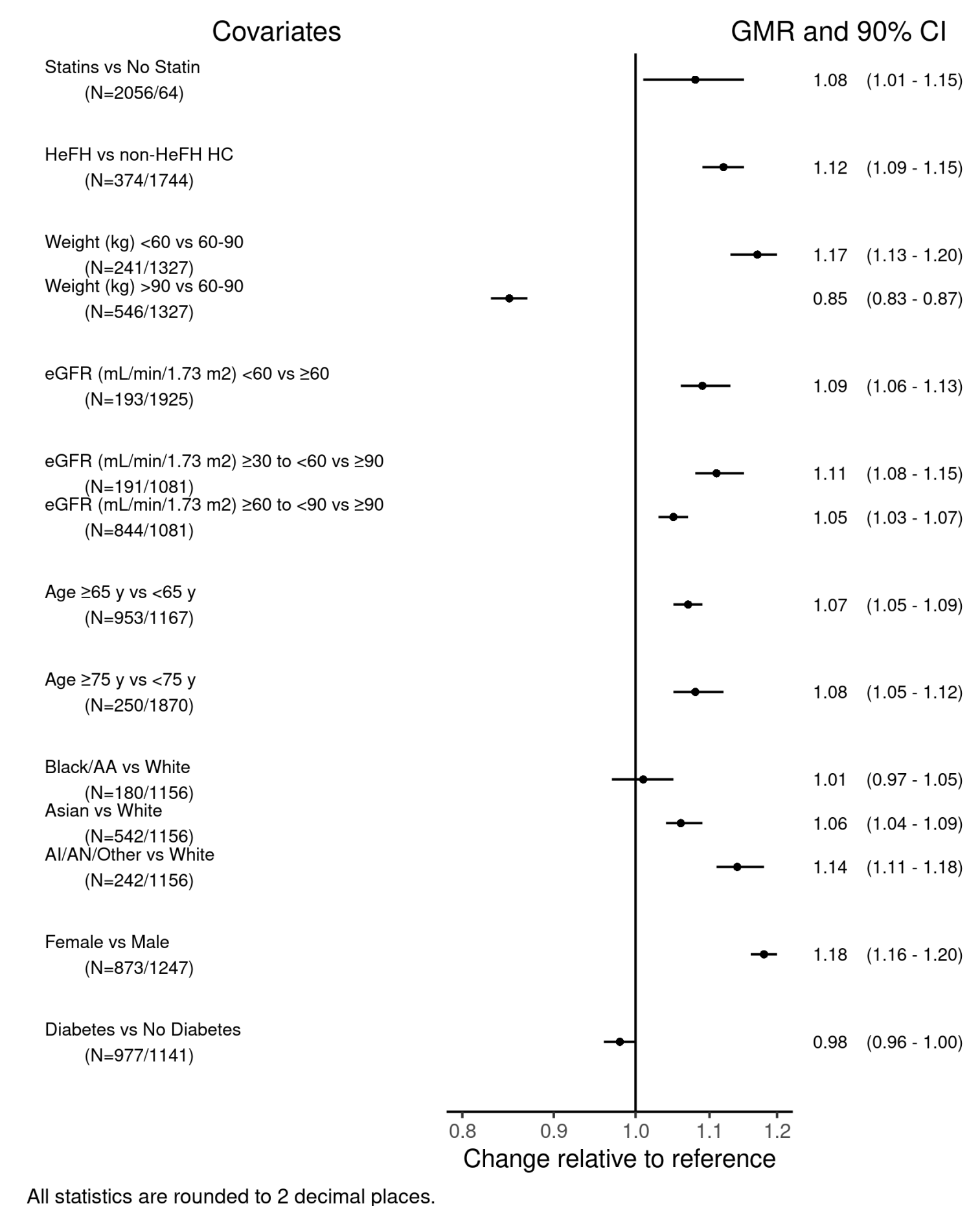
PopPK Modeling and Simulation

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: Simulations from the final PopPK model support no dose adjustment across intrinsic or extrinsic factors in participants with hypercholesterolemia



- 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 CL_{max}/F , body weight on V_c/F , statin use and disease status on CL_{max}/F .
- Forest plot of the relative differences in AUC_{ss} (expressed as Geometric Mean Ratios and 90% Confidence Intervals) of covariate effects on enlicitide exposure at steady state in hypercholesterolemia participants is illustrated in **Figure 3** and supports no dose adjustment for intrinsic or extrinsic factors.

E-R Modeling and Simulation

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

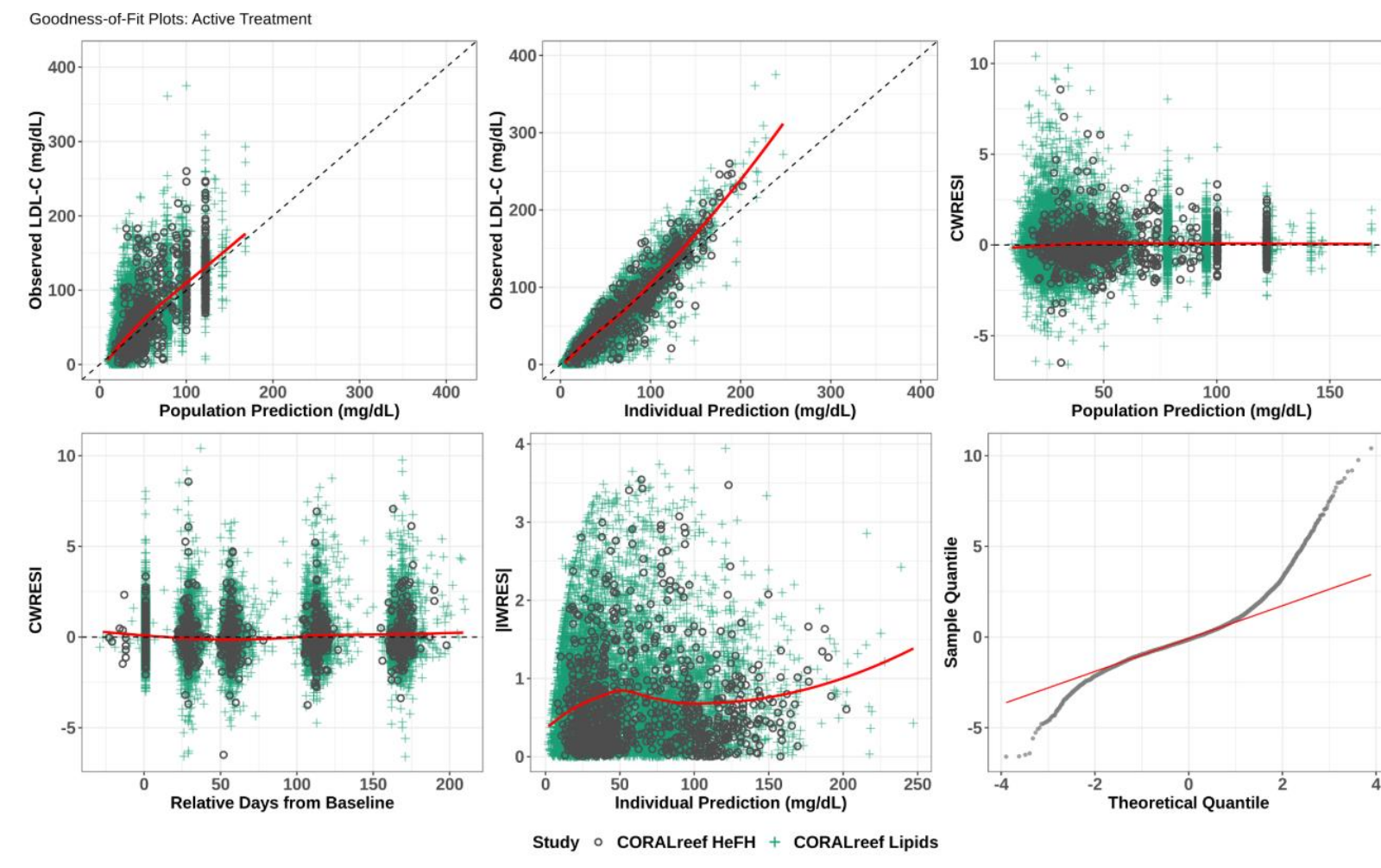
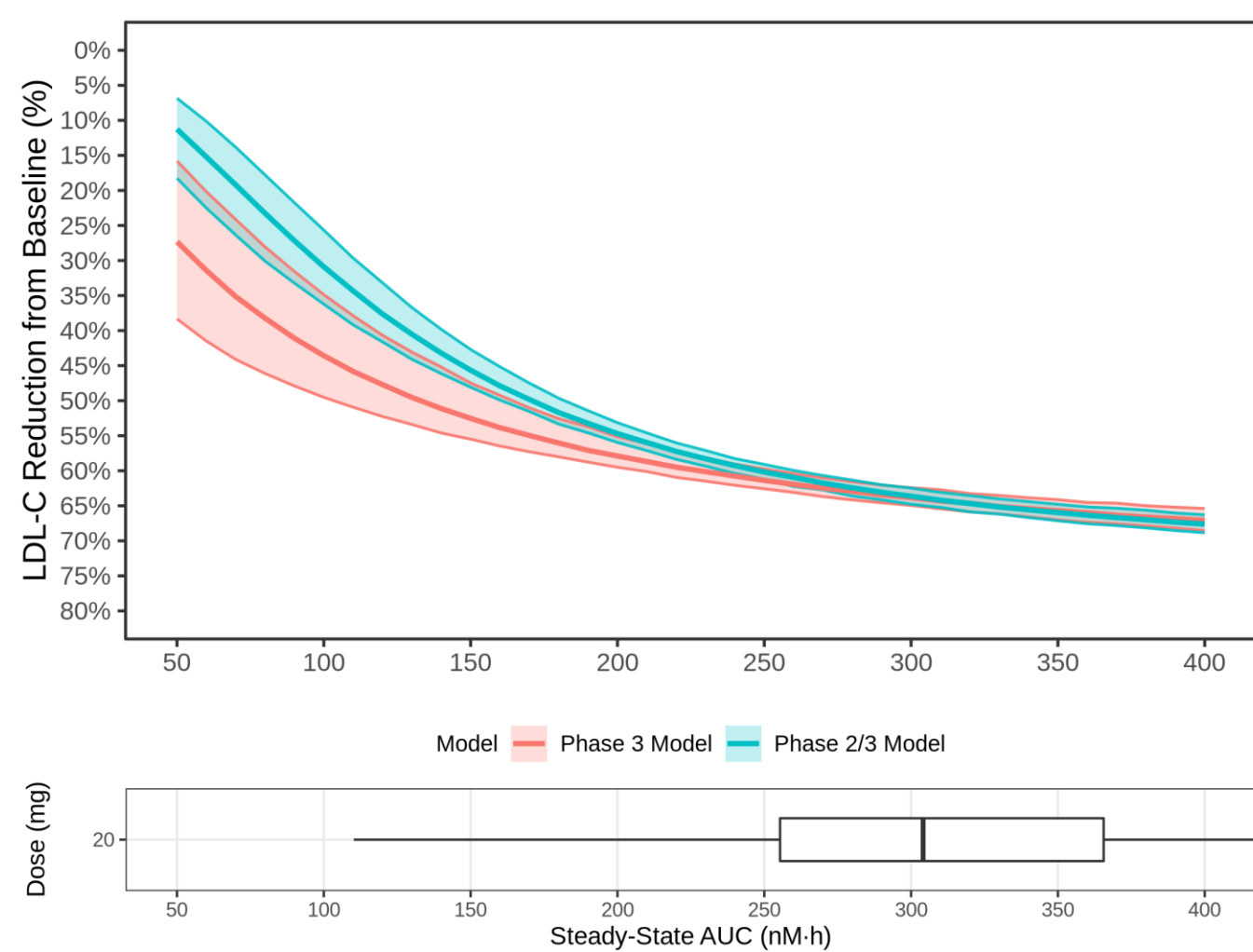


Figure 5: Simulations from the final E-R models indicate that the 20 mg dose is at the plateau of the exposure-response curve



- Simulations from the final E-R models in patients with hypercholesterolemia demonstrated consistent results: a steep increase in LDL-C percent reduction from baseline at Week 24 at lower AUC_{ss} exposures, followed by a gradual plateau at higher exposures (**Figure 5**).
- 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
- Differences between the 2 E-R models were small, with slightly lower LDL-C reduction predicted by Phase 2/3 model at lower exposures, but similar LDL-C reduction within the therapeutic range corresponding to 20 mg.
- Although several covariates including sex and race on $Emax$ were found to be statistically significant, their effects on LDL-C reduction were small (<5–7%) and not clinically meaningful.

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

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- 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.