EPB174

Impact of Intrinsic and Extrinsic Factors on the Pharmacokinetics of Long-Acting Lenacapavir for Treatment of HIV

Naveed Shaik,[1] Francesco Bellanti,[2] Craig Comisar,[2] Sandhya Girish,[1] Martin Rhee,[1] Renu Singh,[1] Ramesh Palaparthy[1]

[1]Gilead Sciences, Inc., Foster City, California, USA; [2]Certara, Princeton, New Jersey, USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Introduction

- Lenacapavir (LEN) is a novel, first-in-class, selective inhibitor of HIV-1 capsid function, which has potent antiviral activity, low clearance (CL), and physicochemical properties well suited for a long-acting injectable or oral formulation
- LEN is currently being developed for treatment and prevention of HIV-1 infection
- In ongoing Phase 2/3 studies (CAPELLA[1] and CALIBRATE[2]), LEN in combination with other antiretroviral agents led to high rates of virologic suppression and was well tolerated; in these studies, people with HIV-1 (PWH) received 2 weeks of oral LEN loading (600 mg on Days 1 and 2, and 300 mg on Day 8) prior to starting subcutaneous (SC) injection dose on Day 15 in an every 6 months regimen (Q6M)

Objectives

- To evaluate the population pharmacokinetics (PopPK) of LEN in healthy volunteers (HVs) and PWH using data collected across 7 studies
- To estimate typical values and interindividual variability (IIV) of PK parameters
- To evaluate the effects of demographic and physiologic covariates

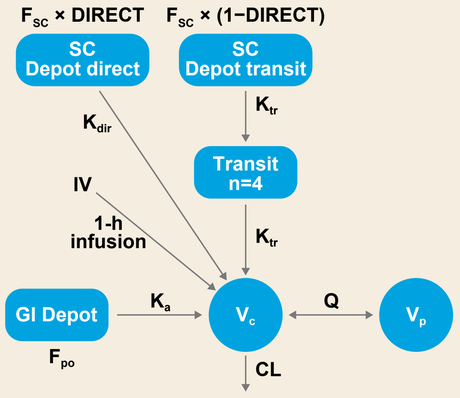
Methods

- PK data were pooled from 7 studies (5 Phase 1 studies [n=48], 1 Phase 2 study [n=148], and 1 Phase 2/3 study [n=62]) in HVs and PWH who received intravenous (IV)/oral/SC LEN
  - Multiple samples were collected: intensive PK on Day 1, predose and postdose on Days 8 and 15, and multiple time points during SC maintenance
- PopPK analysis was performed using nonlinear mixed-effects modeling (NONMEM® [ICON plc, Dublin, Ireland]) software
- Several intrinsic and extrinsic factors/covariates including pharmacoenhancers/boosters (cobicistat or ritonavir), body weight, age, sex, race, ethnicity, dose, disease status (treatment naïve [TN] and heavily treatment-experienced [HTE]), food, formulation, and creatinine CL were evaluated
- LEN exposures were simulated using Bayesian post-hoc PK parameters and presented across applicable covariates
- First-order conditional estimation with interaction was the primary method used for PK model parameter estimation
- Sensitivity analyses using all available data were performed to determine the impact of relevant covariates on the following LEN exposure parameters during both the oral loading (Days 1–15) and SC maintenance period (Day 15–Week 26)
  - Area under curve over dosing interval (AUC_{tau})
  - Maximal concentration (C_{max})
  - Concentration at end of dosing interval (C_{trough})

Results

- The PopPK analysis dataset included 7053 samples from 384 participants with ≥1 measurable concentration; 198 samples were below the limit of quantitation and were, therefore, excluded from the analysis; thus, 6855 LEN concentrations from 384 participants were used in the PopPK analysis
- The final LEN model was described by a 2-compartment model with first-order absorption after oral administration, parallel-direct (first-order) and transit-compartment absorption after SC administration, and first-order elimination
- The effects of weight on CL, V_c, V_p, and Q were included using fixed allometric exponents of 0.75 and 1 for CL and volume of distribution, respectively; dose was found to affect F_{po}, and age, sex, and dose were found to affect CL

LEN Structural PK Model



F_{po}, oral bioavailability; F_{sc}, SC bioavailability; GI, gastrointestinal; K_a, absorption rate constant; K_{dir}, direct absorption rate constant; K_{tr}, transit absorption rate constant; Q, intercompartmental CL; V_c, volume of central compartment; V_p, volume of peripheral compartment.

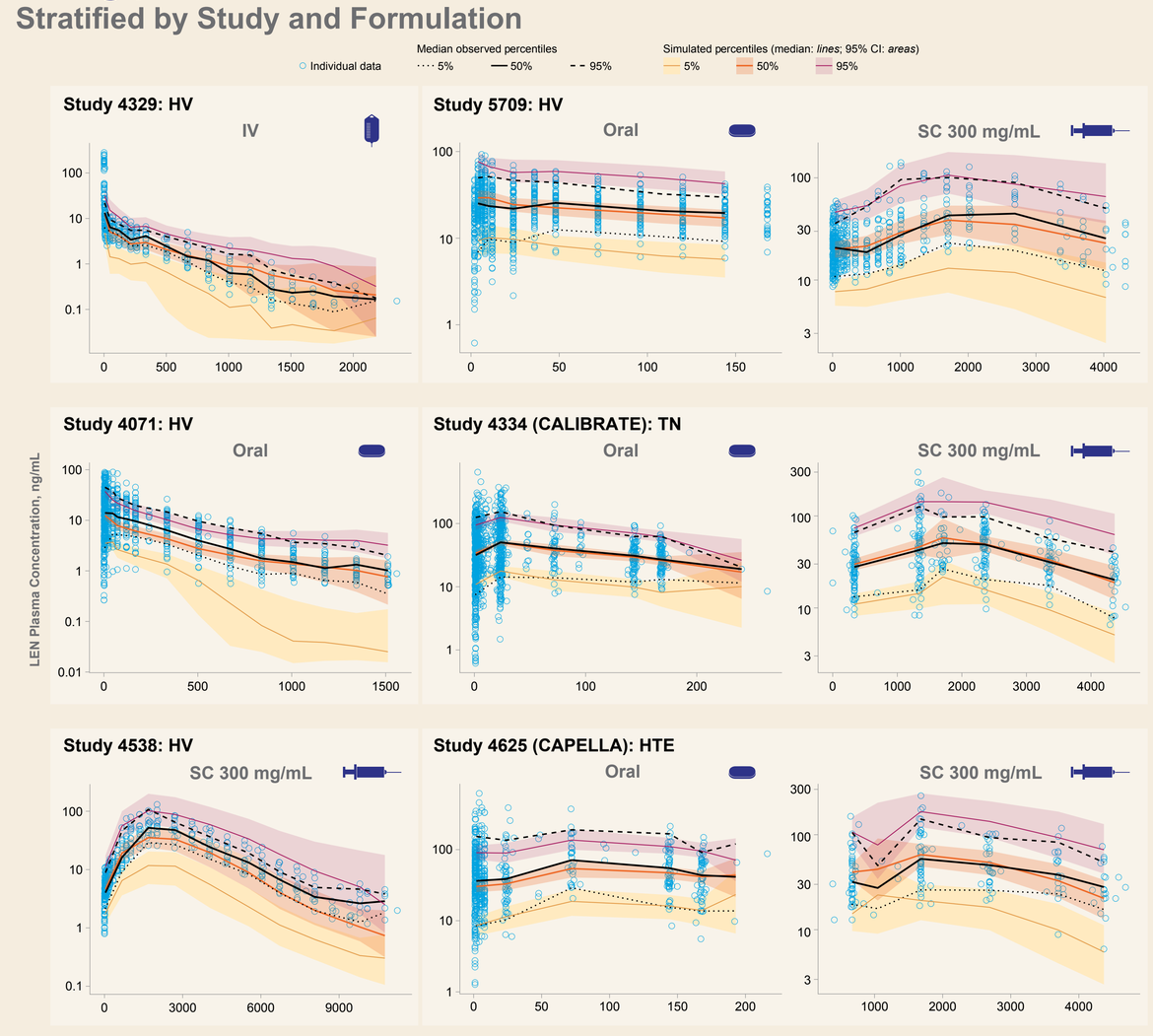
Summary of Final Model PK Parameters for LEN

Parameter	HTE
θ_1: CL, L/h	3.62 (9.9%)
θ_2: V_c, L	67.9 (6%)
θ_3: PO K_a, 1/h	0.0286 (8.2%)
θ_4: V_p, L	908 (10.1%)
θ_5: Q, L/h	41.2 (5.3%)
θ_6: SC K_{tr}, 1/h	0.00202 (3.1%)
θ_7: SC K_{dir}, 1/h	0.00038 (7.9%)
θ_8: SC fraction for direct absorption	0.421 (5.6%)
θ_9: F_{po} relative to IV	0.0627 (9.1%)
θ_{10}: F_{sc} relative to IV	1.02 (8.1%)
θ_{11}: dose effect on F_{po}	-0.414 (11.5%)
θ_{12}: dose effect on CL	0.0887 (33.7%)
θ_{13}: HV effect on CL	0.462 (26.6%)
θ_{14}: weight effect on CL and Q	0.75
θ_{15}: weight effect on V_c and V_p	1
θ_{16}: HV effect on V_p	1.35 (15.9%)
θ_{17}: age effect on CL	-0.165 (64.8%)
θ_{18}: female effect on CL	-0.193 (25.4%)
θ_{19}: pharmacoenhancer/booster effect on F_{po}	0.534 (35%)
θ_{20}: SC 150 mg/mL effect on V_p	-0.795 (5.8%)
θ_{21}: SC 150 mg/mL effect on K_{tr}	0.433 (26.3%)
θ_{22}: CL effect on TN	0.161 (64.6%)
ω_{11}: IIV on CL, %CV	43.2% (4.6%)
ω_{22}: IIV on V_c, %CV	0%
ω_{33}: IIV on V_p, %CV	85.4% (5.5%)
ω_{44}: IIV on K_{tr}, %CV	32.4% (8.9%)
ω_{55}: IIV on K_a, %CV	78.4% (4.5%)
ω_{66}: IIV on K_{dir}, %CV	0%
ω_{77}: IIV on F_{sc}, %CV	38.9% (9.6%)
σ_1: residual proportional variability, %CV	27.3% (2%)
σ_2: residual additive, ng/mL	0.05

CV, coefficient of variation.

Comparison of Observed and Predicted LEN Concentrations Using pcVPCs

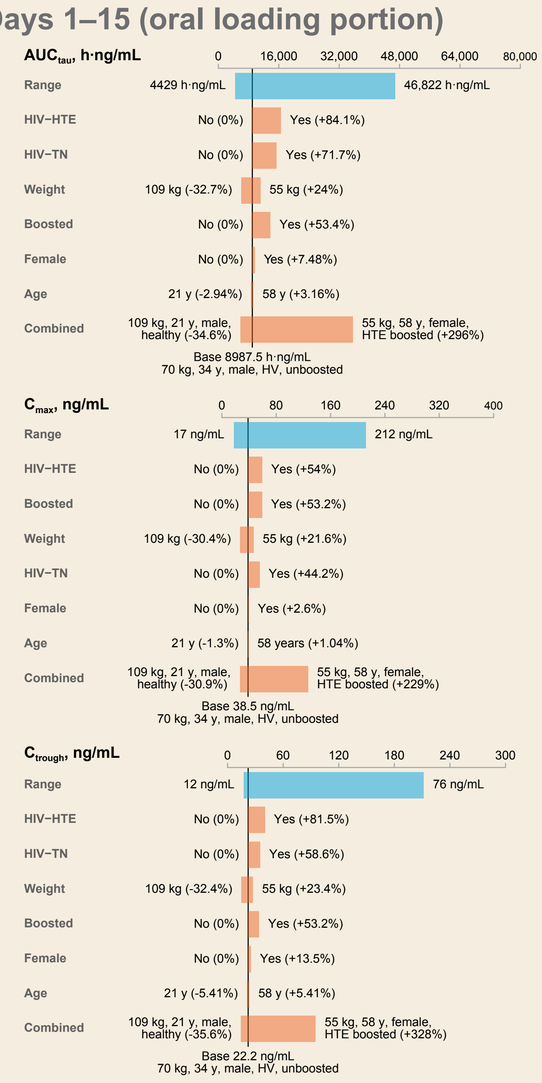
Stratified by Study and Formulation



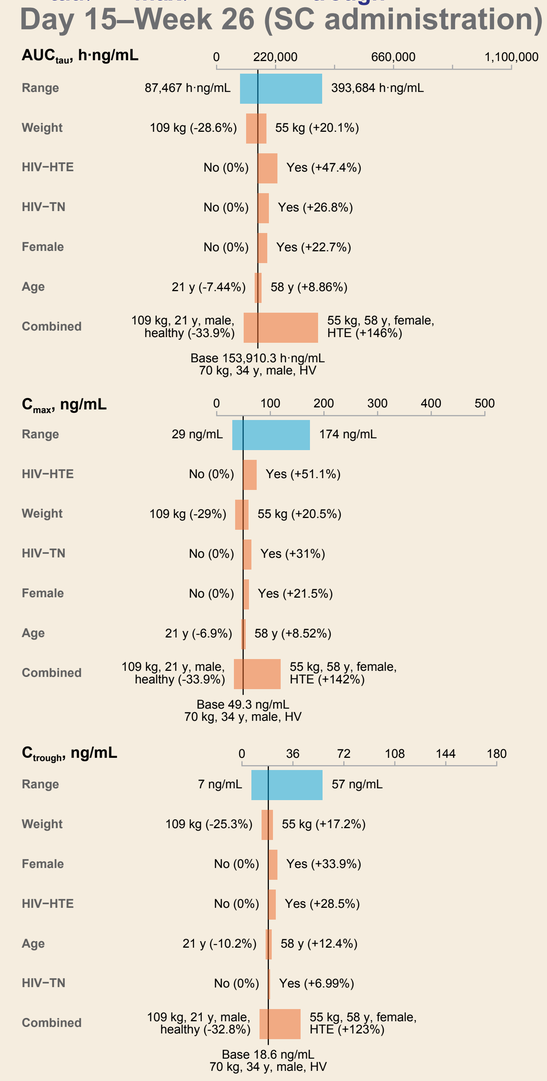
CI, confidence interval; pcVPCs, prediction-corrected visual predictive checks.

Effects of Covariates on LEN AUC_{tau}, C_{max}, and C_{trough}*

Days 1–15 (oral loading portion)



Day 15–Week 26 (SC administration)



*Base refers to median post hoc AUC_{tau}, C_{max}, and C_{trough}; *blue shading* represents 5th to 95th percentile exposure range across entire analyzed population; *orange shading* represents influence of single or combined covariates on steady-state exposure; upper and lower values for each covariate capture 90% of plausible range in population; %s represent % changes of exposures from base; covariates sorted by descending influence.

- HVs had 46.2% higher CL as compared to HTE participants; TN participants had 16.1% higher CL as compared to HTE participants; pharmacoenhancers/boosters (cobicistat or ritonavir) were found to increase LEN F_{po} by 58.7%
- LEN exposures (AUC_{tau}, C_{max} and C_{trough}) were inversely correlated with weight, with % changes ranging from −32.4% to +23.4% (relative to median exposures) for participants with extreme covariate values (ie, 5th and 95th weight percentiles)

Conclusions

- Plasma concentrations of LEN were well described by a 2-compartment model with first-order absorption after oral administration, parallel-direct (first-order) and transit-compartment absorption after SC administration, and first-order elimination
- Body weight and pharmacoenhancers/boosters were identified as significant covariates impacting LEN exposure; however, the changes in exposure were not clinically meaningful
- Higher LEN exposures were observed in HTE participants compared with participants without HIV, potentially due to unaccounted for and complex disease-related confounders (eg, enzyme and transporter expression may change with HIV status[3]); LEN exposures in TN participants were higher than participants without HIV, but lower than HTE participants
- No dose adjustment for LEN is needed for the intrinsic and extrinsic factors evaluated in this analysis

References: **1.** Segal-Maurer S, et al. N Engl J Med 2022;386:1793-803; **2.** Gupta SK, et al. CROI 2022, abstr 138; **3.** Andrade A, Flexner C. AIDS Clin Care 2000;12:91-5. **Acknowledgments:** We extend our thanks to the participants and their families. These studies were funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, New York, New York, USA, funded by Gilead.

© 2022 Gilead Sciences, Inc. All rights reserved.