POPULATION PHARMACOKINETIC ANALYSIS OF CENOBAMATE

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PURPOSE

- Cenobamate, a small-molecule drug developed by SK Life Science, Inc., is approved and marketed for focal (partial-onset) seizures in adults in several countries under the brand names of XCOPRI® or ONTOZRY®.[1,2]
- The purpose of this population pharmacokinetic (PopPK) analysis was to describe cenobamate PK and identify clinically meaningful effects of covariates on its drug disposition.

METHODS

- The analysis included pooled cenobamate data from eight phase 1 studies, two phase 2 trials, and one phase 3 trial.
  - Phase 1 studies included healthy, elderly, renally impaired, and hepatically impaired subjects, while the phase 2 and 3 trials included patients with treatment-resistant focal seizures (**Table 1**).
- The analysis dataset included 8,700 observations from 960 subjects who had taken oral doses ranging from 5 to 750 mg (single dose) and 50 to 600 mg/day administered once daily (multiple doses).
  - Most of the cenobamate data were derived from multiple dosing at 100 mg/day (14.2% of subjects), 200 mg/day (67.5%), and 400 mg/day (9.3%).

Table 1. Summary of Participant Demographics

Characteristic	All Subjects, N=960
Age (years)	
Mean (SD)	40.6 (13)
Median (range)	39 (18-77)
Male, n (%)	548 (57)
Female, n (%)	412 (43)
Body weight (kg)	
Mean (SD)	79.1 (18)
Median (range)	77 (31.6-167)
BMI (kg/m^2)	
Mean (SD)	27.1 (5.4)
Median (range)	26.4 (15.3-52.0)
Study site, n (%)	
Asia	131 (13.6)
Europe	276 (28.8)
North America	529 (55.1)
Pacific rim	24 (2.5)
Race, n (%)	
Asian	90 (9.4)
African American	123 (12.8)
Caucasian	657 (68.4)
Hispanic	27 (2.8)
Other	63 (6.6)
Total bilirubin (µmol/L)	
Mean (SD)	6.73 (4.7)
Median (range)	5.13 (1.71-58.3)
Creatinine clearance (mL/min)	
Mean (SD)	133 (48)
Median (range)	125 (15.3-416)
BSA (m^2)	
Mean (SD)	1.9 (0.24)
Median (range)	1.9 (1.09-2.76)
Seizure status, n (%)	
Without focal seizures[a]	244 (25.4)
With focal seizures	716 (74.6)

[a]The population of patients without focal seizures included subjects with renal and/or hepatic impairment. BMI, body mass index; BSA, body surface area.

- Non-linear mixed effects methods were implemented in NONMEM (version 7.3.0) to describe plasma PK of cenobamate, as well as the data variability between subjects, or inter-individual variability (IIV), as a function of time, dose, disease status, and other subject characteristics.
- The final best-fit model was qualified by standard numerical and graphical goodness-of-fit (GOF) checks, including visual predictive check (VPC).

RESULTS

- Cenobamate plasma PK was well described by a two-compartment model with a first-order, absorption lag, and dose-dependent elimination parameter that accounted for non-linearity in drug exposures below 200 mg, or the maintenance therapeutic daily dose.
- The estimated CL/F was 0.533 L/h, V_1/F was 42.4 liters, and V_2/F was 7.27 liters (**Table 2**).

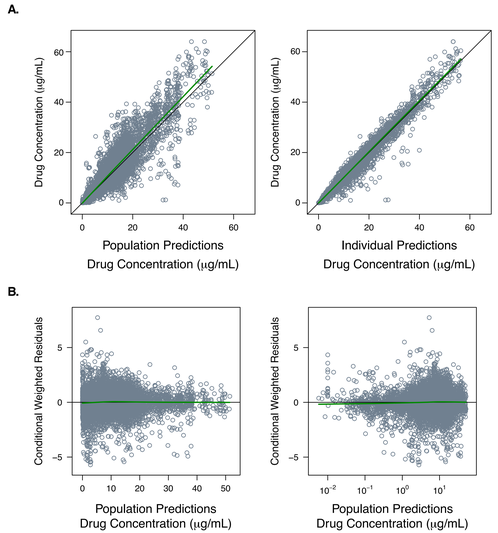
Table 2. Parameter Estimates for the Final Population Pharmacokinetic Model

Parameter	Alias	Estimate	RSE (%)	95% CI
θ_1	k_a (h^{-1})	2.74	6.61	(2.38-3.09)
θ_2	CL/F (L/h)	0.533	1.38	(0.518-0.547)
θ_3	V_1/F (L)	42.4	1.79	(40.9-43.9)
θ_4	Lag time (h)	0.240	0.893	(0.236-0.244)
θ_5	Q/F (L/h)	1.84	9.74	(1.49-2.20)
θ_6	V_2/F (L)	7.27	7.78	(6.16-8.37)
θ_7	Exponential dose effect on CL/F	-0.0280	13.0	(-0.0352 to -0.0209)
θ_8	Linear effect of BSA on CL/F (m^{-2})	0.611	7.09	(0.526 - 0.696)
θ_9	Effect of clobazam on CL/F	-0.190	19.8	(-0.264 to -0.116)
θ_{10}	Linear effect of bilirubin on CL/F (IU)	-0.0119	-9.69	(-0.0141 to -0.00961)
θ_{11}	Linear effect of body weight on V_1/F (kg^{-1})	0.0120	6.14	(0.0106-0.0135)
θ_{12}	Effect of carbamazepine on CL/F	0.150	28.1	(0.0674-0.232)
θ_{13}	Change in CL/F among African Americans	-0.147	16.5	(-0.195 to -0.0998)
θ_{14}	Change in V_1/F among African Americans	-0.0935	19.4	(-0.129 to -0.0579)
θ_{15}	Change in CL/F among Hispanics	-0.133	18.3	(-0.181 to -0.0856)
$\omega_{1,1}$	ω^2_{ka}	1.10	14.1	(0.793-1.40)
$\omega_{2,2}$	ω^2_{CL}	0.106	6.45	(0.0927-0.120)
$\omega_{3,3}$	ω^2_{V2}	0.0138	22.2	(0.00779-0.0198)
$\sigma_{1,1}$	$\sigma^2_{proportional}$	0.0177	5.31	(0.0158-0.0195)
$\sigma_{2,2}$	$\sigma^2_{additive}$	0.00147	38	(0.000374-0.00256)

Parameter values for the structural PopPK model. ω^2x, variance of the IIV for parameter X.
CL/F, apparent systemic clearance; k_a, absorption rate; Q/F, apparent intercompartment clearance; V_1/F, apparent central volume of distribution; V_2/F, apparent peripheral volume of distribution. IIV, inter-individual variability. IIV is derived from variance according to $\sqrt{\omega^2}$x.

- **Figure 1** shows the goodness-of-fit plots, which reflect that the final model demonstrated appropriate agreement between predicted and observed data values.

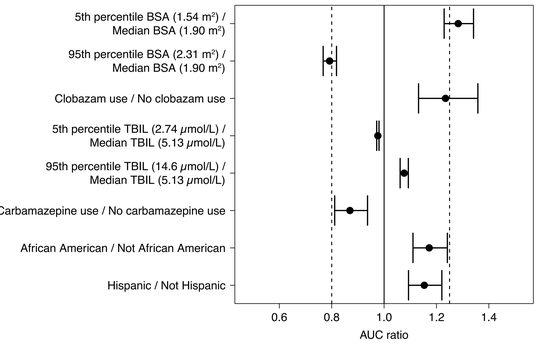
Figure 1. Cenobamate Goodness-of-Fit Plots: A) Observations vs Population and Individual Predictions for Final Model; B) Conditional Weighted Residuals vs Predictions for Final Model



Circles represent observed data, individual predictions, population predictions, and individual weighted residuals. Black line represents line of identity and green line (LOESS smooth) represents data trend line. LOESS, locally estimated scatterplot smoothing.

- Race/ethnicity was associated with changes in both CL/F and V_1/F, with African American subjects having a higher median area under the concentration-time curve (AUC) by 17.2% compared with non-African American subjects (**Figure 2**).

Figure 2. Impact of Covariates on AUC for Final Model



NOTE: 90% confidence intervals in AUC ratio relative to typical AUC (median and 90% confidence interval illustrated as dot with whiskers). For continuous covariates, the plot indicates the ratio between the AUCs at a covariate value at the 5th and 95th percentile and AUC at the median value of the covariate in the population, respectively. For categorical covariates, the plot indicates the ratio of the AUC at the less common covariate value over AUC at the more common value. Dashed lines indicate ratios of 0.8 and 1.25.
AUC, area under the concentration-time curve; BSA, body surface area; TBIL, total bilirubin.

- Hispanic ethnicity, carbamazepine intake, and clobazam intake were associated with a change in cenobamate CL/F of 13% decrease, 15% increase, and 19% decrease, respectively.
- Although race/ethnicity was identified as a statistically significant covariate, past clinical studies indicate that it may not be clinically meaningful to modify the cenobamate dosing regimen for these populations. This is also supported by the AUC ratios in **Figure 2**, which do not indicate clinical significance.
- In addition, a linear effect was seen on the CL/F of cenobamate with total bilirubin concentrations and body weight (that is collinear to BSA).
- No significant PK differences were observed between healthy subjects and patients with focal seizures.
- No statistically significant effects on CL/F were seen with the concomitant use of lacosamide, lamotrigine, levetiracetam, oxcarbazepine, topiramate, or valproate with cenobamate.

CONCLUSIONS

- The PopPK model described cenobamate PK well.
- This PopPK model is suitable for predicting individual plasma cenobamate exposures for use in subsequent exposure-response analyses.

REFERENCES

1. XCOPRI® (cenobamate tablets), for oral use, CV [prescribing information]. Paramus, NJ: SK Life Science, Inc.; April 2024.
2. Ontozry [summary of product characteristics]. Rome, Italy: Angelini Pharma S.p.A; June 2023.

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DISCLOSURES

FJ: Employee, qPharmetra LLC. qPharmetra was contracted by SK Life Science, Inc., to perform this study.
JK, VV: Employees, SK Life Science, Inc.

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