Supplementary Material 2

Comparison between typical values and geometric means for metrics and metric ratios

Aims

To compare typical values and geometric means for metrics and metric ratios in the context of a bioequivalence study

Methods

Simulations were carried out for a series of scenarios to compare typical values and geometric means in metrics (C_{max}, AUC_{last}, AUC_{inf}) and their ratios between reference and generic drug products. Specifically, the model used for simulations here was similar to the true model used for the simulation experiment in the main text, which is a one-compartmental PK model with first-order absorption and first-order elimination. The typical values of pharmacokinetic parameters for reference product were 40.36 mL/h for clearance (CL), 480 mL for volume of distribution (V), 1.48 h^{-1} for rate of absorption (ka). A series of scenarios were generated regarding the different factors (Table S2-1): (1) treatment effect: FTRT=1.25, KATRT=0.3, and KATRT=3; (2) random effect model, i.e., different combinations of PK parameters with between-subject variation (BSV) and between-occasion variation (BOV); (3) magnitude of variation in the random effect model.

Table S2-1: The model parameters set for the random effect in different scenarios. For each model and variance level, simulation was performed for FTRT=1.25, KATRT=0.3, and KATRT=3, respectively.

Model	Variance	CL		V		KA		F	
		BSV	BOV	BSV	BOV	BSV	BOV	BSV	BOV
BOV on all	High	0.25	0.0225	0.25	0.0225	0.25	0.0225	-	-
	Low	0.04	0.01	0.01	0.0025	0.04	0.01	-	-
BOV on CL	High	-	0.25	0.25	-	0.25	-	0.25	-
	Low	-	0.04	0.01	-	0.04	-	0.04	-
BOV on F	High	0.25	-	0.25	-	0.25	-	-	0.0225
	Low	0.04	-	0.01	-	0.04	-	-	0.01
BOV on KA	High	0.25	-	0.25	-	-	0.25	0.25	-
	Low	0.04	-	0.01	-	-	0.04	0.04	-

For each scenario, PK data were simulated for 50,000 subjects with a 2-formulation and 2-period crossover design. For each period, a bolus dose of 4 mg was given with a complete washout and the last sampling time of 24 hr. In this simulation study, the individual metric values were calculated based on analytical solutions instead of the NCA method to remove the variation due to the study design (i.e., the limited sampling times). Specifically, the individual metrics were calculated using individual PK parameters and thus residual errors were ignored. The equations used to calculate the typical metrics (by using typical values of PK parameters) and individual metrics (using individual PK parameters) are as follows:

$$k = \frac{CL}{V} \qquad \text{Equation S2-1}$$

$$C_{max} = \frac{FDka}{V(ka-k)}\left(e^{-k\frac{ln(ka)-ln(k)}{ka-k}} - e^{-ka\frac{ln(ka)-ln(k)}{ka-k}}\right)$$ Equation S2-2

$$AUC_{last} = \frac{FDka}{V(ka-k)}\left(\frac{1}{k}(1 - e^{-kt_{last}}) - \frac{1}{ka}(1 - e^{-kat_{last}})\right)$$ Equation S2-3

$$AUC = \frac{FD}{CL}$$ Equation S2-4

For the test-to-reference ratio, typical ratio and individual ratio were calculated based on typical metrics and individual metrics, respectively. The geometric mean ratio (GMR) was calculated based on all 50,000 subjects for each simulation.

To investigate the difference between typical ratios and GMR in a wider range of KATRT, simulations were performed for KATRT ranging 0.1 to 10 with a step size of 0.02 based on the model of IOV on F. For each value of KATRT, PK profiles reference and test products for a total of 40 subjects were simulated.

Results:

Figure S2-1 shows the comparison between GMR and typical values when FTRT=1.25 and KATRT=1. It is seen that the geometric means were different from typical values for AUC_{last} and C_{max} for all the models. The GMRs were not significantly different from typical ratios.

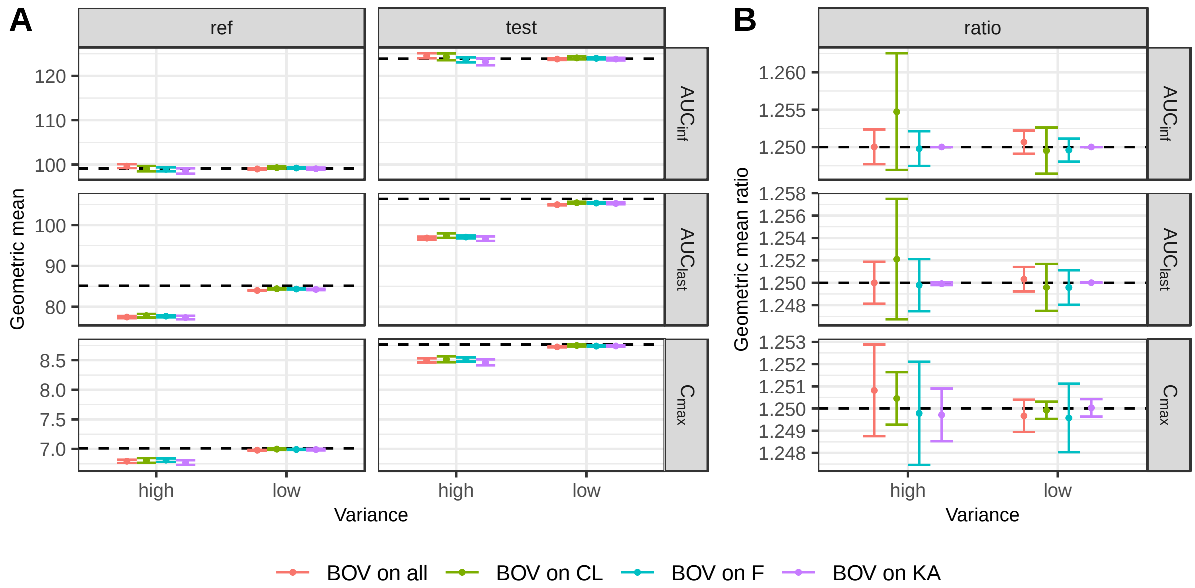

Figure S2-1: The comparison between the geometric means and typical values (horizontal black dashed lines) for metrics (A) and reference-to-test ratios (B) from a simulation of 50,000 subjects in the scenario of FTRT=1.25 and KATRT=1. The error bars represent 95% confidence interval for the means based on normal distribution.

Figure S2-2 shows the comparison between GMR and typical values when FTRT=1 and KATRT=0.3. It is seen that the geometric means were different from typical values for AUC_{last} and C_{max} but not AUC_{inf} for all the models. The GMRs were smaller than typical ratios for AUC_{last} and C_{max}.

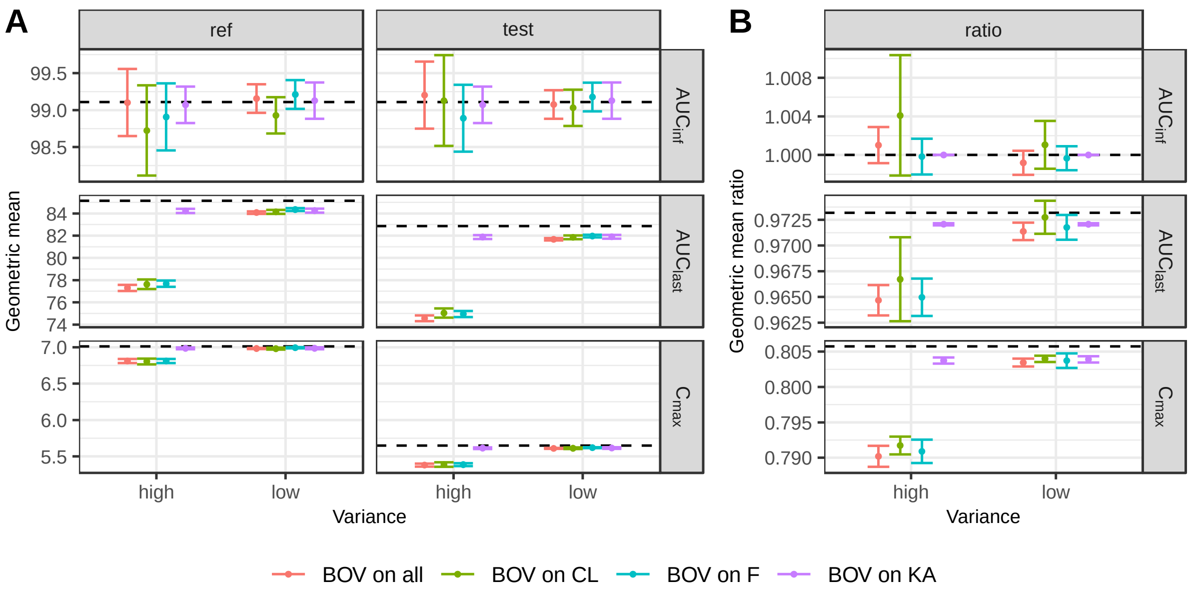

Figure S2-2: The comparison between the geometric means and typical values (horizontal black dashed lines) for metrics (A) and reference-to-test ratios (B) from a simulation of 50,000 subjects in the scenario of FTRT=1 and KATRT=0.3. The error bars represent 95% confidence interval for the means based on normal distribution.

Figure S2-3 shows the comparison between GMR and typical values when FTRT=1 and KATRT=3. It is seen that the geometric means were different from typical values for AUC_{last} and C_{max} but not AUC_{inf} for all the models. The GMRs were larger than typical ratios for C_{max}.

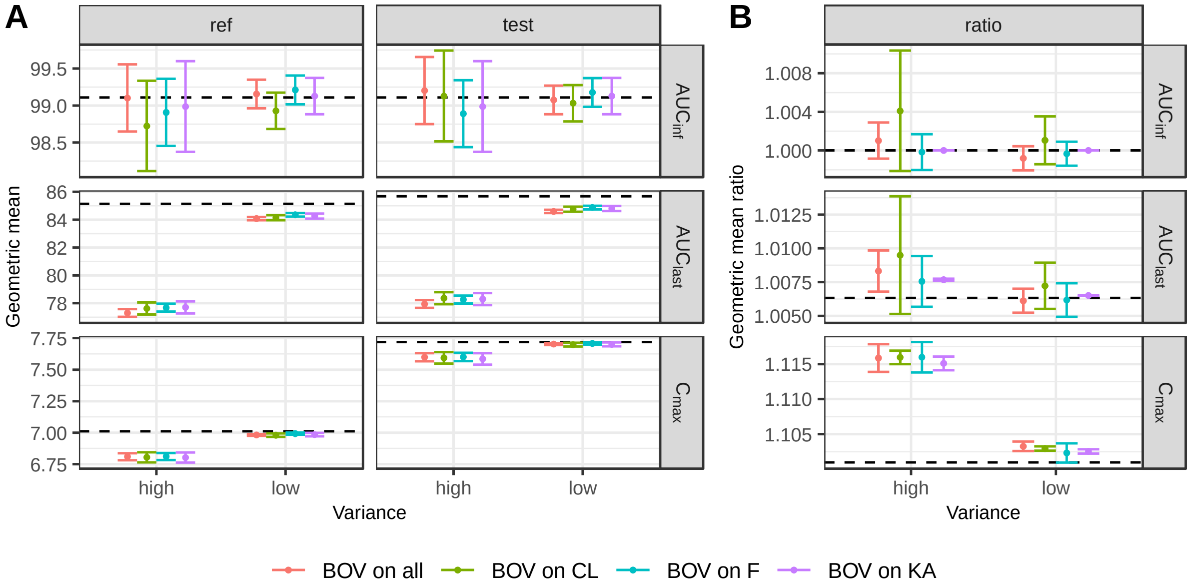

Figure S2-3: The comparison between the geometric means and typical values (horizontal black dashed lines) for metrics (A) and reference-to-test ratios (B) from a simulation of 50,000 subjects in the scenario of FTRT=1 and KATRT=3. The error bars represent 95% confidence interval for the means based on normal distribution.

Figure S2-4 shows the GMR and typical ratios for different values of KATRT. KATRT did not affect GMR or typical ratios of AUC_{inf}, which was 1 for the whole range of KATRT. The impact of KATRT is similar on AUC_{last}, except when KATRT is smaller. The impact of KATRT is mainly on C_{max}, whose reference-to-test ratio ranged approximately from 0.6 to 1.15. The GMR and typical ratios are different.

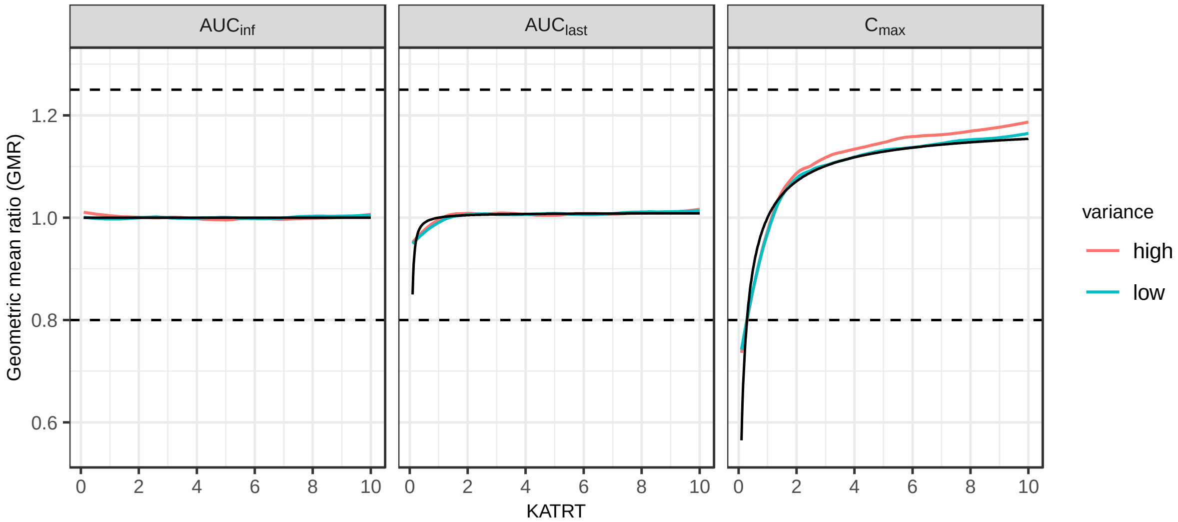

Figure S2-4: The reference-to-test ratios for KATRT ranging from 0.1 to 10 with a step size =0.02 based on the model with IOV only on F. The black curves represent typical ratios. The thin red fluctuated lines represent the geometric mean ratios when the model has a high variation level and the corresponding smooth curves are represented by the thick red curves. The thin blue fluctuated lines represent the geometric mean ratios when the model has a low variation level and the corresponding smooth curves are represented by the thick blue curves. The horizontal black dashed lines indicate 0.8 and 1.25.