Supplementary materials

Bioequivalence test visualization

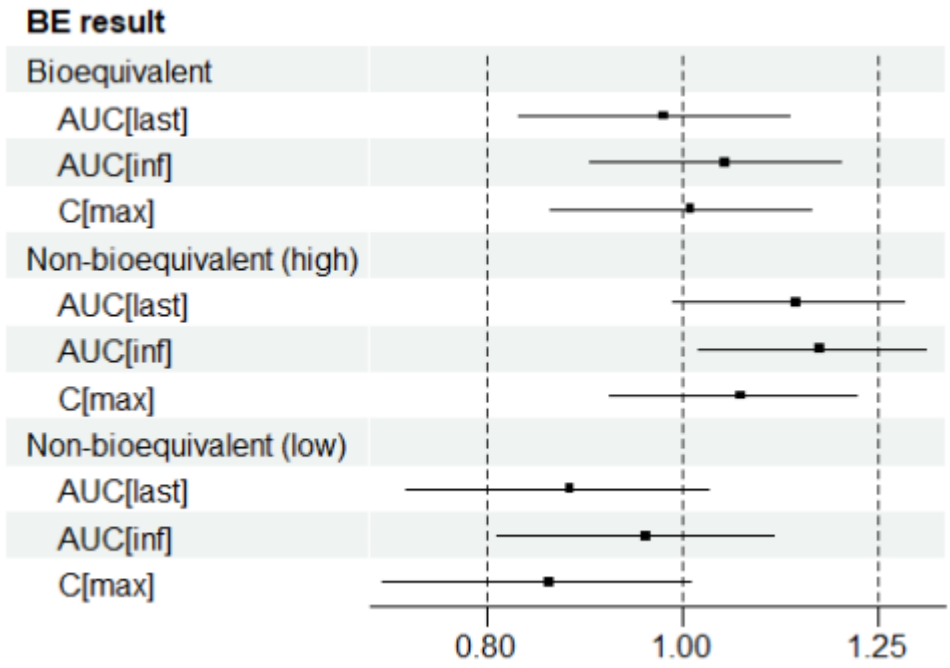

Figure S1. Examples of two one-sided tests used to determine bioequivalence. The intervals on the right are 90% confidence intervals of test-to-reference ratios of bioequivalence metrics (AUC, C_{max}) for three different formulations. For the test formulation to pass the two one-sided tests, the lower limit of the confidence interval (5^{th} percentile) must be above 80%, and the upper limit (95^{th} percentile) must be lower than 125%. This is fulfilled in the top example, but not in the middle and bottom examples.

Settings

NONMEM code for the bootstrap method used in the bootstrap model selection procedure

$SIM (20181215) BOOTSTRAP=-1 NSUB=1000 STRAT=GROUP
$ESTIMATION PRINT=1 MAXEVAL=9999 METHOD=1 INTER NOABORT SADDLE_RESET=1

The above is performed for each model in the model pool. Stratification on the GROUP variable maintains the same proportions of treatments, treatment sequences, sampling schedules in all bootstrapped datasets.

SIR setting used in the weight-based model averaging procedure

$COV SIRSAMPLE=2000 SIRNITER=6 SIRDF=n IACCEPT=0.4 FILE=sir.ext

The SIRDF setting was set to the number of subjects of each scenario.

COV setting in weight-based model averaging using the covariance matrix output for parameter uncertainty

$COV UNCONDITIONAL

Density plot of geometric mean ratio and CI percentiles

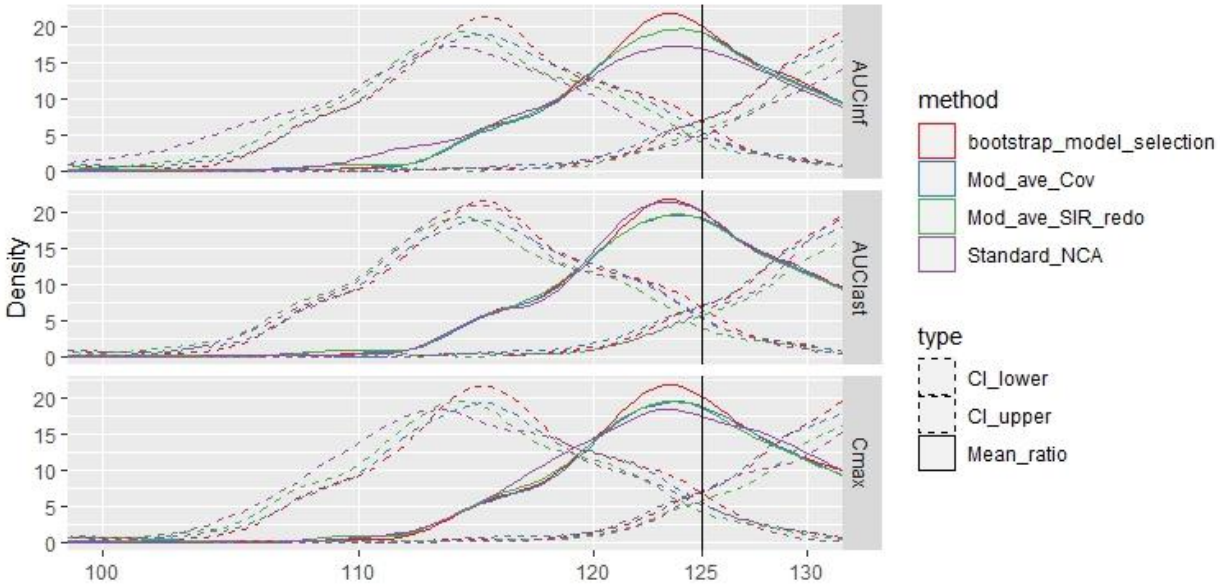

Figure S2. Density plot of the geometric mean ratio (GMR, solid lines) and its 5th and 95th percentiles (dashed lines to the left and right of the mean) for AUCinf, AUClast, and Cmax in the oral formulation rich crossover scenario. The type I error is the area under the 95th percentile curve to the left of the 125% upper limit of the bioequivalence region.