

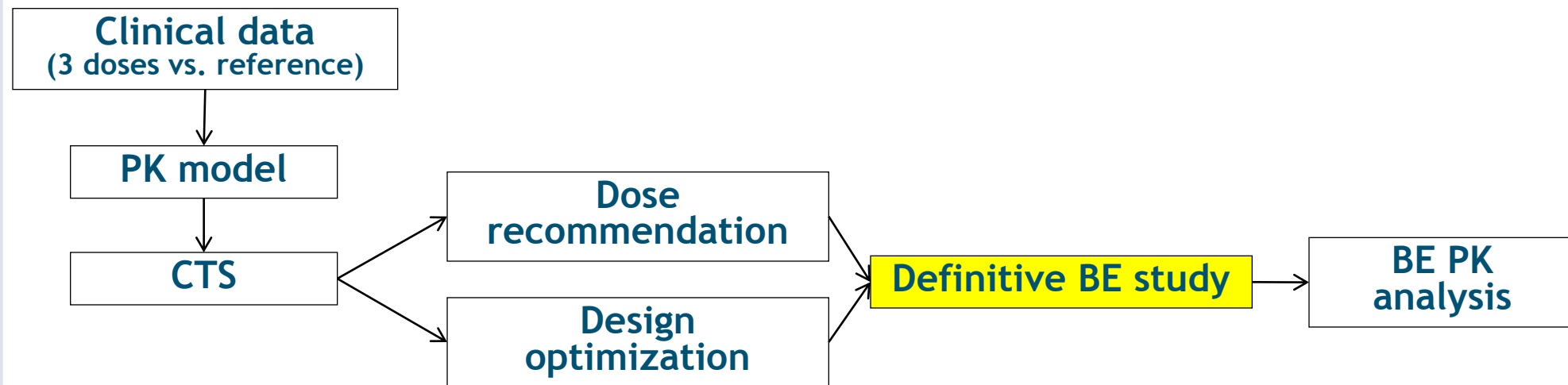
Modeling and simulation to predict the outcome of a definitive bioequivalence study for a compound with non-linear absorption

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OBJECTIVE

The objective was to perform population pharmacokinetic (PK) modeling and clinical trial simulations (CTS) to inform the study design of a future bioequivalence (BE) study comparing a reference, marketed, drug product with an innovative supra-bioavailable formulation of the same active moiety, exhibiting non-linear absorption characteristics.



Why do we need the modeling and simulation to select the dose for the bioequivalence study?

- The compound exhibits non-linear absorption
- Three doses of the test formulation in the pilot study were investigated in order to well describe the non-linear PK using Population PK modeling
- M&S was proposed to
 - describe the non-linear absorption
 - simulate definitive BE study
 - compare concurrent candidate designs (dose and sample size)
 - select the best design

Based on M&S, the definitive BE study will be designed and conducted.

METHODS

A pilot clinical bioavailability study comparing three doses of the novel formulation (equivalent to 25%, 51% and 102% of the reference dose) was performed in 16 healthy subjects. A population PK model was developed using NONMEM based on combined drug concentrations resulting from the administration of both formulations (novel and reference).

Following successful qualification of the population PK model, CTS were performed using various sources of variability including uncertainty on fixed effect parameters.

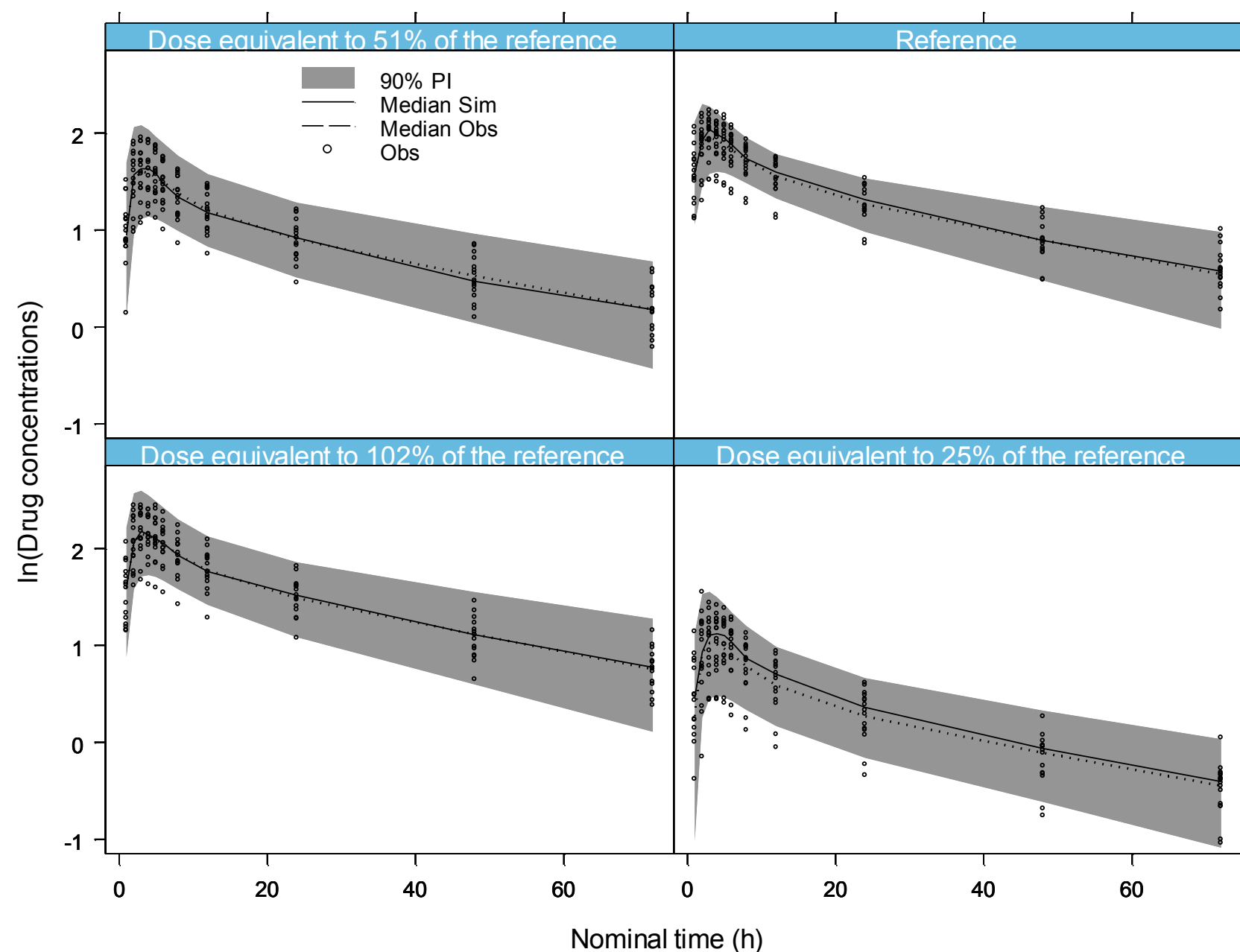
The design selected to simulate a definitive bioequivalence study was a 2 x 2 Latin square comparing the 2 formulations after single dose, complete washout between periods. Three dose levels of the novel formulation (equivalent to 70%, 76% and 82% of the reference, expressed as the active moiety) were selected. To determine the sample size, a target statistical power of 90% was selected. AUC and C_{max} were derived on each simulated profile for each simulated trial. An ANOVA model was used to derive 90% CI for AUC and C_{max} for each simulated trial. 1000 trials were simulated for each sample size.

RESULTS

In the PK model, drug concentrations were analyzed simultaneously with different absorption models and a common disposition model for both formulations. The bioavailability of the novel formulation relative to the reference was adequately described by a power model with a population estimate of -0.339 for the exponent.

$$F_{rel} = 1.82 \times DOSE^{-0.339}$$

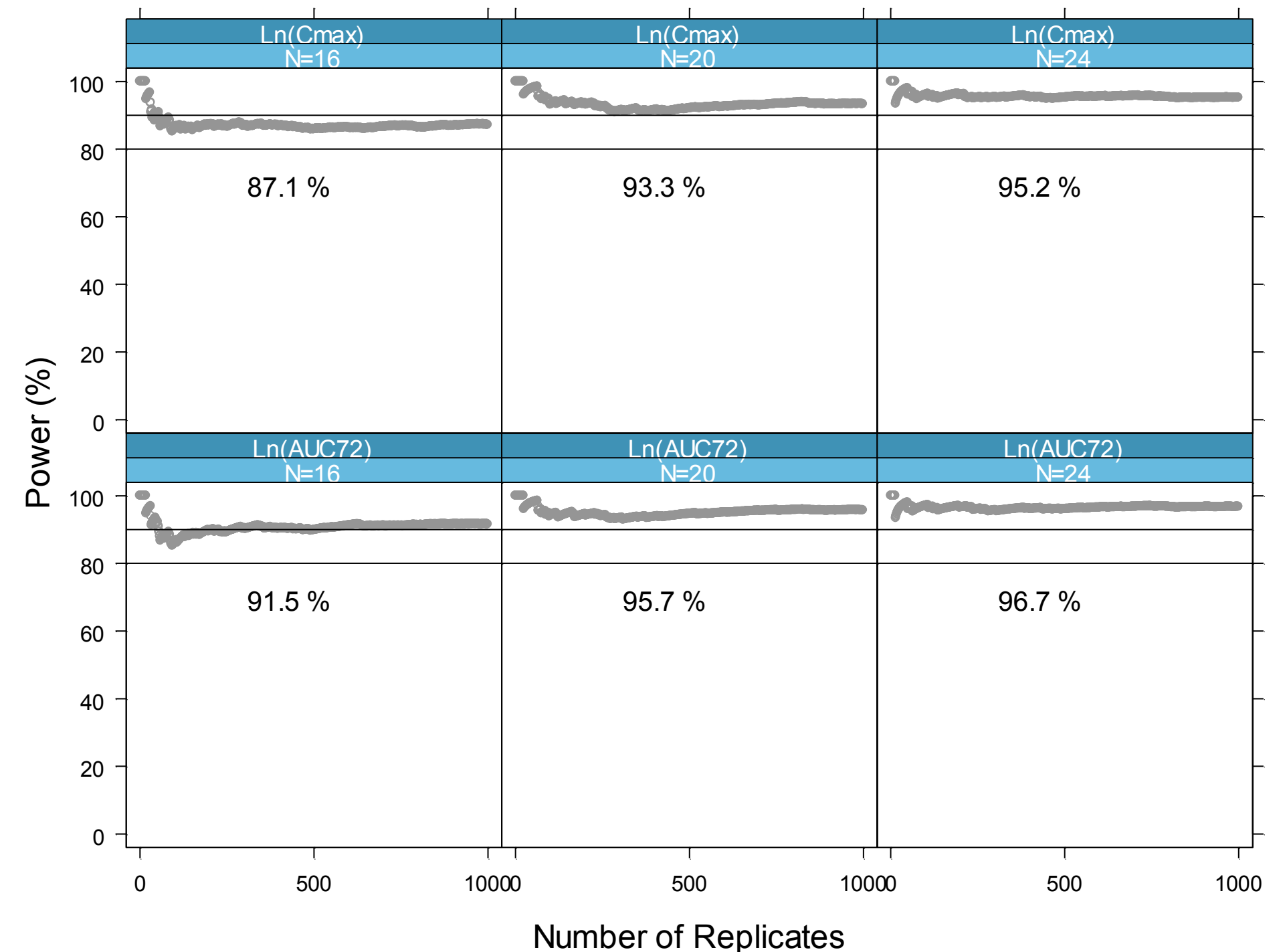
Figure 1 Visual predictive checks - Final - ln(data) on y-axis



The design selected was 2 x 2 Latin square (2 sequences, 2 periods) comparing the 2 formulations after single dose, with completed wash-out period. 1000 replications of the trial were performed.

RESULTS

Figure 2 - Statistical power versus number of replicates by scenario following administration of the reference and doses equivalent to 76% of the reference



Thanks to the supra-bioavailability, a dose containing 76% of the reference dose is likely to demonstrate bioequivalence with the reference. Moreover, 20 subjects would be sufficient to demonstrate bioequivalence with the reference on both C_{max} and AUC, with a statistical power in excess of 90%. Figure 2 also illustrates that power calculations reach a « plateau » after approximately 500 replicates.

Figure 3 Ratio test/reference and 90% CI for the 1000 replicates of CTS following administration of the reference and a dose containing 76% of the reference dose

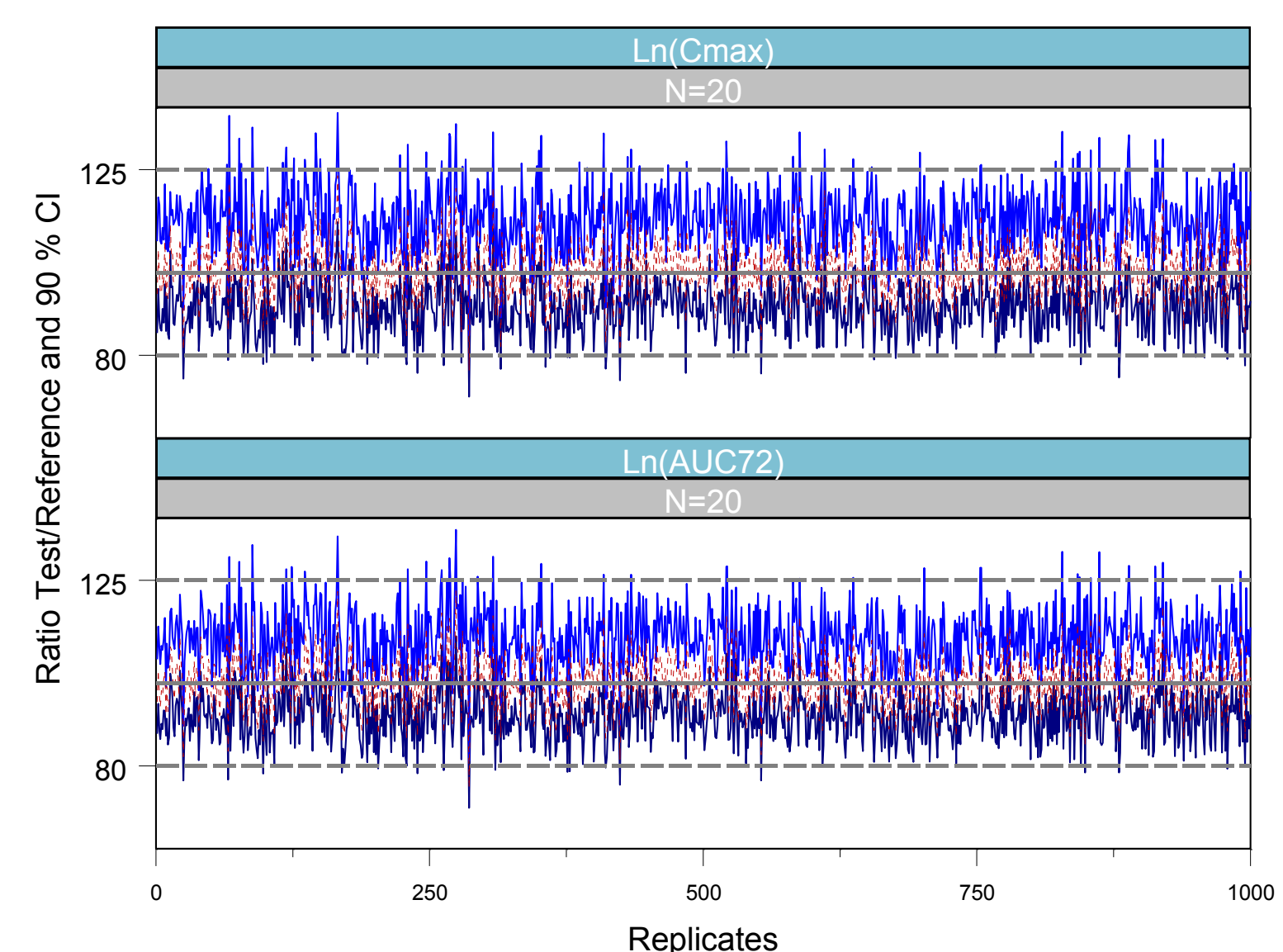


Table 1 - Statistical power results of CTS - 1000 replicates by scenario following administration of the reference and doses equivalent to 70%, 76% and 82% of the reference

Dose 70% of the reference vs. reference		
Scenarios	Power for AUC ₇₂ (%)	Power for C _{max} (%)
Base design (N=16)	85.8	80.8
Subjects_20 (N=20)	89.0	85.5
Subjects_24 (N=24)	91.6	89.3
Dose 76% of the reference vs. reference		
Scenarios	Power for AUC ₇₂ (%)	Power for C _{max} (%)
Base design (N=16)	91.5	87.1
Subjects_20 (N=20)	95.7	93.3
Subjects_24 (N=24)	96.7	95.2
Dose 82% of the reference vs. reference		
Scenarios	Power for AUC ₇₂ (%)	Power for C _{max} (%)
Base design (N=16)	83.5	75.2
Subjects_20 (N=20)	86.7	80.3
Subjects_24 (N=24)	90.4	85.2

Alternative doses appeared to be less ideal, as they would require more than 24 subjects to demonstrate bioequivalence.

CONCLUSIONS

The modeling and simulation approach supported the design (i.e. optimal dose and sample size) of a definitive bioequivalence study between a novel formulation and the reference one.

The definitive bioequivalence was conducted based on CTS recommendations.

The statistical analysis of a confirmatory BE study performed and the results showed a close agreement with the CTS-based predictions (not presented).