Model-based testing to assess C_{max} bioequivalence in highly variable drugs

Antoine Croxo [1 2] Florence Loingeville [2] Julie Bertrand [1]

[1] *Université Paris Cité, Inserm, IAME, UMR 1137 - MOCLID, F-75018 Paris, France*

[2] *University of Lille, CHU Lille, ULR 2694 - METRICS : Evaluation of Health Technologies and Medical Practices, F-59000, Lille, France*

BACKGROUND

- **Bioequivalence** (BE) studies performed to compare **pharmacokinetics** (PK) of reference R and test T drug formulations
  - Linear mixed-effects model (LMEM) on AUC and C_{max} obtained by non-compartmental analysis (NCA)
    - → $\beta^{Tr}, \beta^{S}, \beta^{P}$ treatment, sequence and period effects
    - → Geometric mean ratio (GMR) $= e^{\beta^{Tr}}$
  - Two one-sided tests (TOST) on β^{Tr} with $\delta = log(1.25)$ the BE threshold

  ⇒ Average Bioequivalence testing (**ABE**)
- NCA-based BE assessment cannot handle sparse sampling schemes

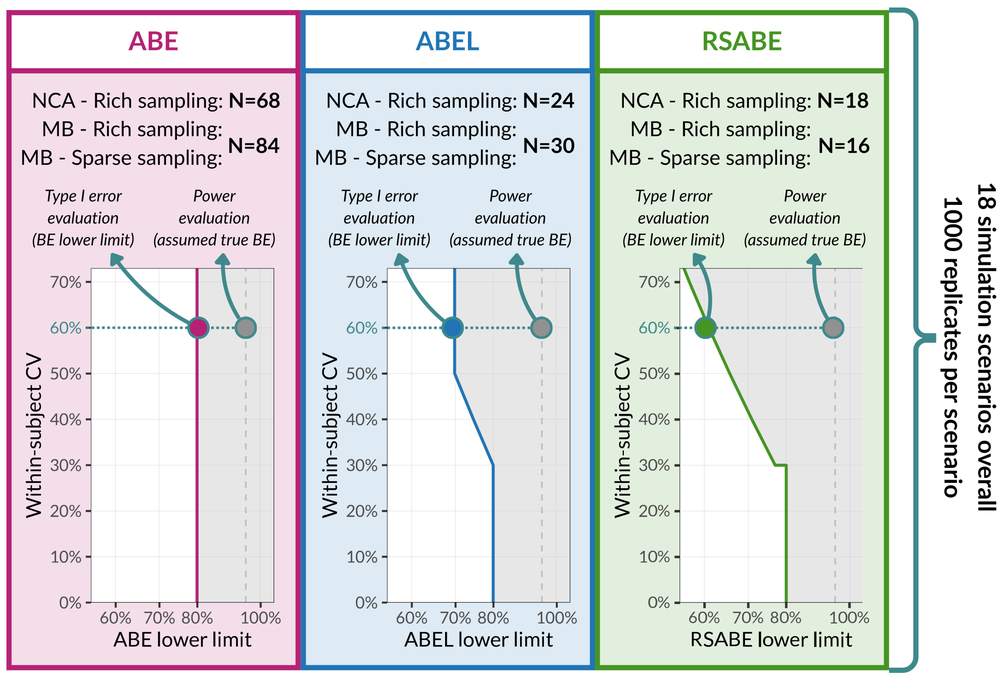
  ⇒ **model-based** (MB) TOST [1] using nonlinear mixed-effect model (NLMEM)
- TOST needs higher sample size in the case of **highly variable drugs** (HVDs), with over 30% within-subject variability (WSV)

  ⇒ alternative WSV-driven BE tests for HVDs
  - ABE with Expanding Limits (**ABEL**) [2] (EMA guidelines [3])
  - Reference-Scaled ABE (**RSABE**) [4] (FDA guidelines [5])

Objective: combine scaled BE tests with the MB framework on C_{max} for a HVD and evaluate their performance through simulated BE clinical trials

SIMULATION STUDY

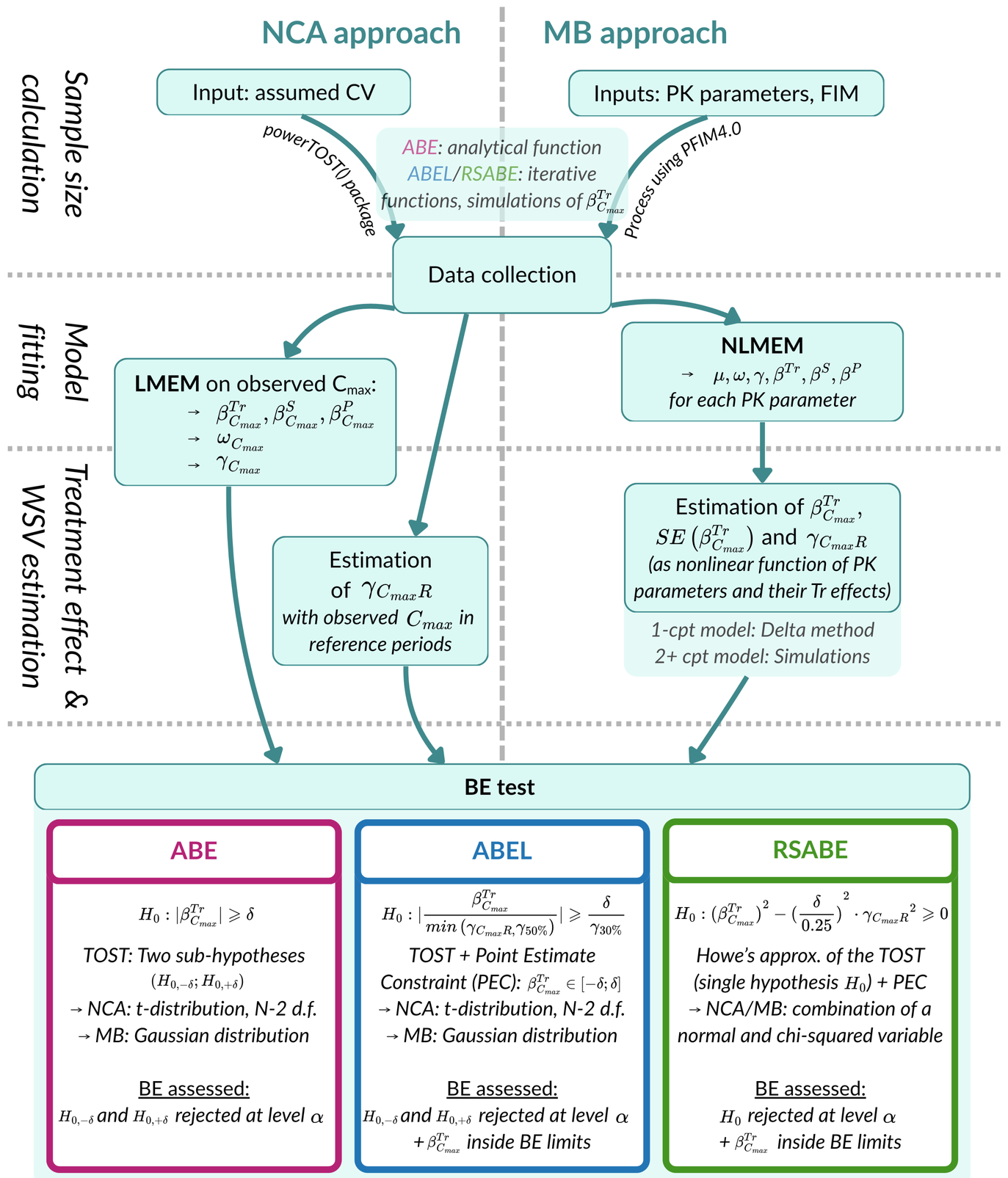
- PK model of **dasatinib**, HVD in oncology: two compartments, 1-order absorption and lag time [6]
- Fully replicated crossover design: four periods, two sequences [5]
- 60% WS CV on C_{max} [7]
- n=19 times for rich sampling and n=6 for sparse sampling, optimized using PFIM4.0
- Treatment effect on PK parameters with bioavailability ($Cl/F, V_1/F, Q/F, V_2/F$)



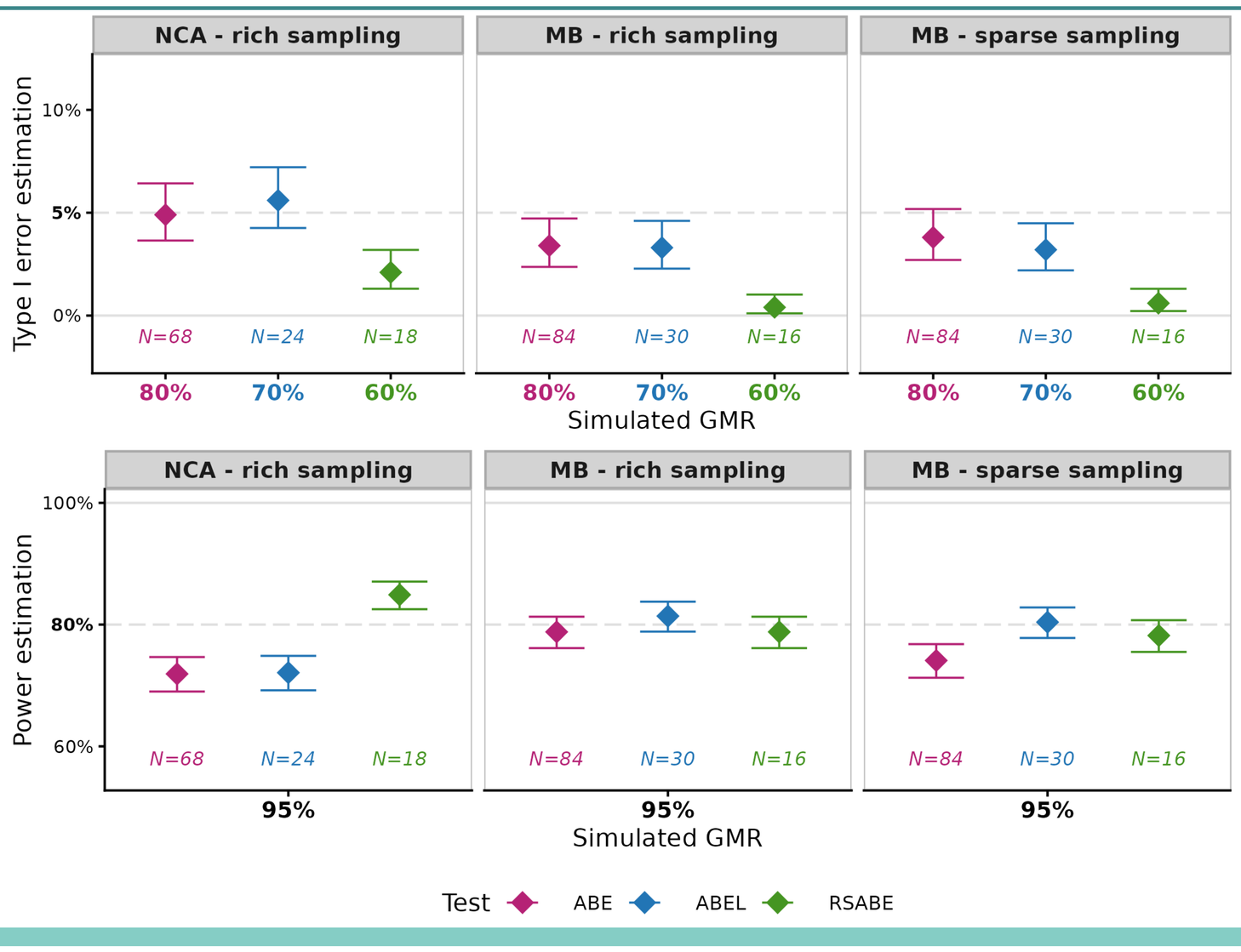
METHODS

Notations: • μ, ω, γ the population parameter, BSV and WSV for a PK parameter

• $\gamma_{C_{max}R}$ the WSV of C_{max} on the reference drug, $\gamma_{x\%} = \sqrt{log[1 + (x\%)^2]}$ the WSV for a given CV $x\%$



RESULTS



- MB-approaches obtained type I errors below 5% but only MB-ABE on sparse sampling studies failed to reach the target power of 80%
- RSABE obtained low type I error with both NCA and MB

Conclusions

- Comparable performances of MB tests on rich sampling compared to NCA counterparts
- MB-ABEL and MB-RSABE viable on sparse sampling
- Perspectives:
  - Controlling type I error around 30% WSV [8, 9]
  - **Design optimization** for BE studies
  - Introducing **two-stage** protocols [10]

REFERENCES

1. Dubois, A. et al. *Statistics in Medicine* (2011).
2. Endrenyi, L. et al. *Journal of Pharmacy & Pharmaceutical Sciences* (2009).
3. European Medicines Agency. *Guideline on the investigation of bioequivalence.* (2010).
4. Davit, B. M. et al. *The AAPS Journal* (2012).
5. U.S. Food and Drug Administration. *Draft guidance for industry: bioequivalence recommendations for progesterone oral capsules.* (2011).
6. Hassouneh, W. B. et al. *Pharmaceuticals* (2024).
7. Lennernäs, H. et al. *Clinical Pharmacology in Drug Development* (2024).
8. Labes, D. et al. en. *Pharmaceutical Research* (Nov. 2016).
9. Ocaña, J. et al. *Pharmaceutical Statistics* (2019).
10. Loingeville, F. et al. *Statistical Methods in Medical Research.* Epub ahead of print (2025).