

ABSTRACT:

The existing standard bioequivalence (BE) analysis uses non-compartmental analysis (NCA) to compute the area under the concentration-time curve (AUC) and the maximal concentration (C_{max}). While this method is associated with fewer assumptions/hypotheses and performs adequately well in the majority of cases, it requires dense pharmacokinetic (PK) samples for all individuals in the study, which is not always feasible, such as in studies involving patients or children. Therefore, it is important to develop and evaluate new approaches for assessment of BE in sparse PK designs.

The objective of the research project is to develop, evaluate and compare model-based methods to analyse BE studies with different types of designs. We aim to find relevant statistical approaches for model based (MB) BE guarantying control of type I error and sufficient power for sparse PK designs.

Our approaches are based on the population approach using nonlinear mixed effect models which borrow strength across time and across patients to increase the ability to estimate parameters and allows the use of sparse PK samples. Two different modelling approaches will be developed as well as the corresponding tests: 1) a global model fit of all data with a treatment effect on all PK parameters, followed by a two one-sided tests (TOST) on the treatment effect on AUC and C_{max}; 2) a global model fit of all data with constrained optimisation under the null hypothesis of non-equivalence, followed by i) a TOST on AUC and C_{max} based on parametric bootstrap or ii) a direct assessment of the similarity between the two PK profile curves. The first two approaches using TOST mimicking what is recommended in guidelines for NCA BE will also be extended to sequential study designs.

Each method will be evaluated by clinical trial simulation with various designs and scenarios in order to evaluate the type I error and the power of MBBE tests. The approaches that showed the most promising performance through this clinical trial simulation study will be applied and compared on real clinical trial data provided by Servier, Roche and Novartis Pharma and as well as in house FDA data of ophthalmic drugs.

The project involves academic statistician experts in the field and key scientists from the industry. We will summarize pros and cons of all investigated methods, and recommendations will be proposed when assessing BE under various scenarios.