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How can modeling and simulation optimize the clinical development of adalimumab biosimilar candidates?

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Generally, Pharmacokinetics (PK) trials for adalimumab biosimilar candidates are oversized as high variability is expected. Sample size /arm varies from 60 to 108 subjects. An inadequate sample size could jeopardize the trial outcome. In this context, a population pharmacokinetic model of adalimumab in rheumatoid arthritis (RA) patients was used to obtain empirical Bayesian estimates (EBE) from in recent adalimumab biosimilar development. Consequently, EBEs of PK parameters for adalimumab EU- and US-approved formulations were implemented in the simulation software Simulo, and simulations of adalimumab PK were carried out at the dose proposed in the adalimumab product information monograph in RA of 40 mg subcutaneus (sc) injection. In addition, the effect of subject´s weight was implemented in the simulation software. These simulations were carried out to explore the effects of the simulated adalimumab serum concentrations on the PK pivotal study design in terms of sample size, in order to estimate the PK parameters required to address PK similarity between adalimumab biosimilar candidates and adalimumab. Then the likelihood of simulated study design scenarios was evaluated following the regulatory exercise to demonstrate PK similarity. The influence of neutralizing anti-adalimumab antibodies (AAA+) was also explored. The population PK model was qualified using different approaches, including comparison of the predicted versus observed adalimumab serum concentrations and PK parameters validation. They demonstrated good accuracy in capturing the adalimumab PK in the population. Therefore the existing model was considered well suited for this simulation task. Power analysis of the results for PK similarity tests showed that larger trials (+150 subjects) did not improve significantly the probability to obtain bioequivalence when compared with smaller trials. A maximum difference of 15% in AAA+ could decrease the chance to obtain successful results for all pairwise comparisons. Model-based simulations approach, incorporating available information of adalimumab, yield a reduced sample size (40-60% decreased), compared to traditional methods. Overall, this can be considered as the optimum rationale for supporting the design for a PK pivotal study of adalimumab biosimilar candidate to address PK similarity.

Biography

Bernardo Miguel-Lillo has his expertise in evaluation and optimizing study designs, especially in the field of Oncology. He has applied model and simulation after years of experience in research, evaluation and analyzing pharmacokinetic and pharmacodynamic data in pharmaceutical industry. His main focus of interest is in the contribution of pharmacometrics in the decision making process for drug development.

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