Analysis of covariance with pre-treatment/demographic measurements in parallel clinical pharmacology comparability studies for biologics

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Objectives: In randomized clinical efficacy trials, analysis of covariance is commonly used to reduce the residual variability and correct for potential bias in baseline covariates. However, it is not common to assess the impact of pre-treatment/demographic measurements in the clinical pharmacology comparability studies. The objective of this research was to evaluate the impact of including important covariates in bioequivalence test in parallel clinical pharmacology comparability studies for biologics.

Methods: We examined the most up-to-date package inserts for the FDA-approved biologics available at the time of the study to extract quantitative information about demographic and/or baseline disease characteristics on systemic clearance. Based on the observed range of correlation, simulation was conducted to evaluate the reduction of sample size if the analysis of covariance was used in the PK comparability study instead of the typical analysis without including any covariates.

Results: Body weight was identified as a significant covariate in about one-third of approved biologics evaluated (n=130). A few other disease-specific characteristics were also identified as significant covariates affecting exposure for some biologics, such as tumor burden. Our simulation showed that required sample size decreased nonlinearly with increasing correlation between the pre-treatment/demographic measurements and drug exposure in order to achieve 80% power to demonstrate bioequivalence. The sample size could decrease 10% if including a baseline covariate with a correlation coefficient of 0.30 and 47% if including a baseline covariate with a correlation coefficient of 0.68.

Conclusions: Using analysis of covariance with pre-treatment/demographic measurements could reduce sample size up to 47% in parallel clinical pharmacology comparability studies for biologics.