An Improved Approach for Confirmatory Phase III Population Pharmacokinetics Analysis

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Abstract

Phase III POPPK analyses are often treated as if confirmatory analyses, especially in phase III, use the interpretation that results are final. Common POPPK analyses revise, implicitly or explicitly, estimates in exploratory approaches. In this methodology, two major goals for phase III POPPK analysis are the following: (1) estimation of covariate effect on long-term systemic drug exposure; (2) attainment of uncorrelated covariates. In practice, several limitations have been noted: (1) non-normally distributed data; (2) non-linear relationship; (3) non-independence of the observations; (4) assumption that the model is appropriate. A previous POPPK model based on phase I/II data was developed. However, the simulated data in the proposed analysis was not observed to accept accurate covariance analysis. In this study, we developed the following simple model:

\[ Y_{ij} = \beta_0 + \beta_1 D_{ij} + \epsilon_{ij} \]

for analysis (a), where \( Y_{ij} \) is the observed concentration of the ith subject and \( D_{ij} \) is the dose level of the jth observation. In this model, the effect of dose is modeled as a linear function. Parameter \( \beta_0 \) represents the intercept, \( \beta_1 \) represents the effect of dose, and \( \epsilon_{ij} \) represents the error term. The proposed approach was also tested on other phase III subpenetrating datasets using real-world data. The results are summarized according to the corresponding significance level of the proposed approach (a). The results are similar to those of other phase III POPPK analyses.

Method

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Introduction

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