

Assessment of probability of success for the outcome of a noninferiority trial comparing two bioequivalent, fixed-dose combination drugs

William M. Sallas (1), Joseph Kahn (1), Steven Kern (2)

(1) Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; (2) Novartis AG, Basel, Switzerland

Objectives: A new formulation for a fixed-dose combination drug (10 mg compound X + 10 mg compound Y) was determined from a bioequivalence (BE) study to be lower in its exposure to X and equal in its exposure to Y compared with an old formulation. The objective for this work was to determine the probability of success (POS) for a proposed noninferiority study comparing the proportion of responders for new vs. old formulations.

Methods: Different dose combinations to assess the relative contribution of X and Y to clinical outcome were not available. Clinical efficacy and demographic data were pooled from two studies of the old formulation. Limited PK data for X and Y were available in each trial in a subset of patients. However, due to small sample sizes relationships of PK with demographics and response were inconclusive. Therefore, AUC of X was predicted in all patients in the trials based on a previous population PK model assuming clearance proportional to body weight. Efficacy vs. (population predicted) AUC was fit by logistic regression. This assumed that AUC (or mg/kg dose) of X was the most important predictor of clinical outcome.

For sensitivity analysis to this assumption, a population prediction of compound Y AUC based on a previous population PK model assuming clearance as a function of weight and age was evaluated for goodness of fit for efficacy. The logistic regression model contained the same number of parameters as that used for X AUC; therefore, $-2 \times \log(\text{likelihood})$ was used to compare the goodness of fit for efficacy.

For the assessment of POS for a noninferiority design, first an optimistic approach was taken using a traditional power calculation assuming known and equal response rates for the two formulations, a protocol-specified noninferiority margin, 4 possible sample sizes, and the current, body-weight dependent, dosing table. This optimistic approach is relevant if the new formulation was exactly equivalent to the old or if compound Y AUC completely accounted for the clinical outcome. Second, for a model-based assessment of POS, a simulation of 10,000 trials was conducted for each combination of 4 sample sizes with the current dosing table, and 2 alternative dosing tables for the new formulation. For each trial, the log of the ratio of X AUC (new/old) was drawn from a normal distribution with mean and standard deviation plugged in from associated estimates in its prior BE statistical analysis. Similarly, for each trial, the intercept and slope from the logistic regression model were drawn from a bivariate normal distribution with mean and variance-covariance matrix plugged in from estimates in its prior statistical analysis. A patient was simulated by a draw of body weight from a log normal distribution and randomized to old or new formulation with a dose assigned by the relevant dosing table. The patient AUC was computed based on the population predicted X AUC for the associated formulation. The probability of the patient being a responder was computed from the patient's X AUC and the trial-specific logistic regression model. The patient was classified a responder if a draw from a uniform (0,1) distribution was less than this probability. The trial was classified as a success if noninferiority was concluded as determined from the noninferiority margin and the lower-endpoint of the 95% confidence interval derived from the normal approximation. The fraction of successful trial outcomes gave the model-based POS for the trial. Finally, an average of the model-based POS and optimistic POS was calculated, representing indifference of belief.

Results: The goodness-of-fit comparison supported X AUC as determined from mg/kg dose as the better predictor of clinical response, although compound Y AUC was competitive (Table 1). For the current dosing table, the probabilities of success for each sample size and degree of optimism were computed (Table 2). Finally, probabilities of success with alternative dosing tables were computed.

Table 1. Goodness of fit for clinical response model¹

Population PK model used to predict AUC	-2 × log (likelihood)
Compound X: Clearance proportional to weight, i.e., AUC proportional to mg/kg dose	239.91
Compound Y: Clearance based on weight and age	240.45

¹ $\text{logit}(p) = \beta_0 + \beta_1 \log(\text{AUC})$ where AUC determined separately from previous population PK models for X and Y

Table 2. Probability of success by sample size and degree of optimism for the current dosing table

N per arm	Probability of success		
	Optimistic	Model-based	Indifference
100	40%	23%	31%
200	67%	34%	51%
300	84%	44%	64%
600	99%	62%	80%

Conclusions: Probability of success for the new noninferiority study was computed under a range of underlying assumptions. It was decided that the risk of failing to attain noninferiority was too high to proceed.