Clinical Trial Simulations to Guide Dose Escalation in First Time In Human (FTIH) for a Drug With Absolute Individual Exposure Limits

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Objectives: Simulate with uncertainty to guide dose escalation in a FTIH study

Methods: Toxicology studies in a single species for a novel mechanism drug showed cardiovascular toxicities at relatively high doses/exposures. Exposures in the FTIH study were limited to predefined levels (a 30-fold margin from the corresponding NOAEL exposures at which no cardiovascular toxicities were detected) such that a proposed dose was acceptable if the predicted probability of any individual exceeding the AUC and Cmax limits was no more than 10%.

The placebo-controlled, cross-over FTIH study provided concentration-time data from 6, 12 (9 unique), and 18 (11 unique) subjects for three single dose levels. Fit-for-purpose population pharmacokinetic (PK) models were developed (NONMEM v7.2) after each single dose escalation step. Clinical trial simulations were conducted by incorporating parameter uncertainty (mrgsolve in R) and provided the probabilities for individual subjects to exceed exposure limits for higher single and repeat doses.

Results: Concentration-time data were adequately described by a 2 compartment model with first-order absorption. Parameters were generally well defined with standard errors typically less than 30% with increasing precision as the data size increased. Inter-individual variability was estimated on up to four parameters [oral clearance (CL/F), central and peripheral volume of distribution (Vc/F and Vp/F), and absorption rate constant (KA)] and was typically <30% except on KA (77 to 101%). Visual and numerical predictive checks demonstrated adequate model performance.

FTIH clinical trial simulation demonstrated that Cmax was the dose escalation limiting parameter for single dose and AUC for repeat dose. Confidence in the predicted probabilities increased with accumulating data, primarily via the bootstrap procedure employed to provide uncertainty estimates in the simulations.

Conclusions: Clinical trial simulations by incorporating uncertainty with fit-for-purpose PK models allowed for safe dose escalation during a FTIH study with restrictive exposure limits. This approach allowed predictions with better approximation of variability in data. Future work will compare this approach with Bayesian methods for dose escalation.