Optimizing Sampling Designs for Apixaban Phase III Studies using Trial Simulation

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Objectives: Define an optimal sparse sampling strategy to maximize knowledge gained on apixaban exposure in a diverse patient population, while limiting cost and maintaining compatibility with study logistics. Apixaban is an oral direct factor Xa inhibitor, intended to treat deep venous thrombosis (DVTtx) and to prevent DVT in post-surgical and acutely ill medical patients (DVTp). In addition, apixaban is intended for the prevention of stroke in patients with atrial fibrillation (AFib), and for secondary prevention in patients with acute coronary syndrome (ACS).

Methods: A one-compartment exposure model was used for trial simulation. Optimal sparse sampling designs were selected using trial simulation: (step 1) narrow down sampling designs to a reasonable number of options (WinPOPT), (step 2) identify optimal sampling design with model-based trial simulation (NONMEM) based on accuracy (BIAS) and precision (mean absolute error (MAE)) criteria for the population exposure parameters, (step 3) identify optimal number of subjects with sparse sampling to be enrolled in each trial (WinPOPT). The quality of the apixaban exposure parameters for the selected optimal sparse sampling designs was compared to that for a design with one random sample only (reference).

Results: The single random sample design (reference) showed a high bias (~80%) and MAE (~>100%) in exposure parameters. Sampling designs with 4 sparse samples provided good estimation of exposure, with both BIAS and MAE remaining generally low, e.g. ~<20% and ~30%, respectively. Enrollment of more patients (300-500) in the study trial allowed improvement of precision. The optimal sampling strategy for clinical trials recommended four samples to be drawn in at least 300 patients at specific time points and on two separate occasions.

Conclusions: Model-based trial simulation allowed optimal sampling to be proposed that could conveniently be implemented in apixaban Phase III studies, so that knowledge on exposure in the target patient population be maximized, while avoiding excessive costs and preserving study logistics.