Target-Mediated Drug Disposition (TMDD) Population Pharmacokinetics (PopPK) Model Using the Quasi-Steady-State (QSS) Approximation of Alirocumab in Healthy Volunteers or Patients: Pooled Analysis of Randomized Phase I/II/III Studies

Nassim Djebli, Jean-Marie Martinez, Laura Lohan, Sonia Khier, Aurélie Brunet, Fabrice Hurbin, David Fabre
Sanofi, Montpellier, France

Objectives: Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibition with monoclonal antibodies such as alirocumab significantly reduces low-density lipoprotein cholesterol levels both with and without other lipid-lowering therapies. We aimed to develop and qualify a PopPK model for alirocumab in healthy volunteers or patients, taking into account the mechanistic TMDD process.

Methods: This TMDD model was developed using a subset of the alirocumab clinical trial database, including 9 Phase I/II/III studies (N=527): NCT01026597; NCT01074372; NCT01161082; NCT01448317; NCT01723735; NCT01288443; NCT01288469; NCT01266876; NCT01644474. Subsequently, the model was expanded to a larger data set of 13 studies (N=2870), including 4 additional studies: NCT01812707; NCT01623115; NCT01644188; NCT01507831. Potential model parameters and covariates relationships were explored, and predictive ability was validated using Visual Predictive Check (VPC).

Results: The TMDD model was built using the QSS approximation, occurring in the central compartment of a two-compartment model. The final TMDD-QSS model included only 1 significant parameter-covariate relationship between the disease state and the distribution volume of the central compartment (Vc): 3.16 L for healthy subjects versus 4.93 L for patients (i.e. 1.56-fold higher Vc in patients). Separately, application of the model to the expanded data set revealed a significant relationship between statin co-administration and linear clearance (CLL): 0.176 L/day without statin versus 0.224 L/day with statin (i.e. 1.27-fold higher CLL with statin). The good predictive performance of the TMDD model was assessed based on graphical and numerical quality criteria, together with the VPC and comparison of the predictions to those from a PopPK model with parallel linear and Michaelis-Menten clearances (i.e. simplification of the TMDD PopPK model).

Conclusions: This mechanistic TMDD PopPK model integrates the interaction of alirocumab with PCSK9 and accurately predicts alirocumab and total PCSK9 concentrations in healthy subjects and patients. This is the first published TMDD model developed on such a large population.