Population Pharmacokinetic-Pharmacodynamic Modeling of a Novel TAFIa Inhibitor DS-1040 in Healthy Subjects

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Objectives: DS-1040 is a novel inhibitor of the activated form of thrombin-activatable fibrinolysis inhibitor (TAFIa), currently being developed for the treatment of acute ischemic stroke and venous thromboembolism. The objectives of this analysis were to characterize the population pharmacokinetics (PopPK) of DS-1040, and the relationships between DS-1040 plasma concentrations and pharmacodynamic (PD) measures, total TAFIa activity and clot lysis time.

Methods: The PopPK dataset consisted of 5 phase I studies with 3,077 PK samples from 214 healthy subjects. Log-transformed plasma concentrations of DS-1040 following intravenous and oral administration were analyzed simultaneously. Stepwise forward addition and backwards elimination were used for covariate model building, at the significance levels of p<0.01 and p<0.005 respectively. Total TAFIa activity and clot lysis time measures were available from 213 and 78 subjects respectively. These PD measures were analyzed sequentially, using final PopPK model predicted plasma concentrations and sigmoid E\text{max} type function. FOCE INTER as implemented in NONMEM V.7.2 was used in both PopPK and PKPD modeling.

Results: A 3-compartment PK model best described the concentration-time profiles of DS-1040. Residual error was estimated to be 14.6% for intravenous administration and 24.1% for oral administration. Inter-subject variability was modest (17% to 35%) in all PK parameters, with the exception of K\text{a}(99%). Asian race was identified as a covariate on V\text{c}(23.5% lower V\text{c} in Asian subjects), but it is not expected to affect the total exposure (AUC) of DS-1040 and hence is not clinically important. Concentration dependent decreases in total TAFIa activity and clot lysis time were rapid (Figure 1). Model estimated IC\text{50} values were 3 ng/mL and 15 ng/mL respectively, and Imax values were 99% and 76% respectively, for total TAFIa activity and clot lysis time.

Conclusions: The analyses provided an adequate description of the observed data. The established PopPK and PKPD models will be used to inform future study design and dose/regimen selections.

Figure 1 Total TAFIa activity and clot lysis time versus DS-1040 plasma concentrations