Population pharmacokinetics and pharmacodynamics of the CFTR potentiator ivacaftor in patients with cystic fibrosis and a G551D-CFTR mutation

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Objectives: Ivacaftor (IVA) is a CFTR potentiator that improves lung function in patients with mutations resulting in a gating defect or residual CFTR activity as measured by percent predicted forced expiratory volume in 1 second (ppFEV₁). The objectives of this study were to (1) develop a population pharmacokinetic (popPK) model of IVA, (2) quantify the exposure-response (E-R) relationship for ppFEV₁ in patients with CF and a G551D-CFTR mutation, and (3) determine the optimality of the recommended dose for patients ≥12 years-of-age (IVA 150mg q12h).

Methods: PopPK analysis was based on 5386 samples from 424 subjects. Different structural models were evaluated using NONMEM. Covariate effects were evaluated using a full-model approach. The E-R relationship of ppFEV₁ to the IVA trough concentration was modeled with a maximum effect (Eₘₐₓ) model, with IVA concentrations generated from individual Bayesian parameter estimates. The E-R model was fit to ppFEV₁ data from G551D subjects, and the optimality of IVA 150mg q12h was determined.

Results: IVA PK followed a two-compartment model with absorption driven by a sequential zero-order/first-order process. Body weight was the most important predictor of variability for the apparent oral clearance of IVA. The Eₘₐₓ model reasonably fit the E-R data, with an EC₅₀ of 40 ng/mL (95% CI: 24.7, 81.1). For IVA 150mg q12h, the model predicted a mean change from baseline ppFEV₁ (ppFEV₁) response of 9.6 percentage points (95% CI: 8.3, 10.9) for the population ≥12 years of age, which is consistent with the within-group ∆ppFEV₁ of 10.4 percentage points observed in a Phase 3 study (Ramsey et al., NEJM 2011;365:1663-72). Additionally, the ∆ppFEV₁ response corresponded to 93% (95% CI: 89%, 97%) of the model-predicted maximum response.

Conclusions: PopPK and E-R models of IVA reasonably described the PK and ppFEV₁ data. These models predicted that the IVA 150mg q12h dose achieves near maximal response for ∆ppFEV₁.

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