

Vivli Results Report Form

Lead Investigator Name: Mary Ann Lukas

Institution: GlaxoSmithKline

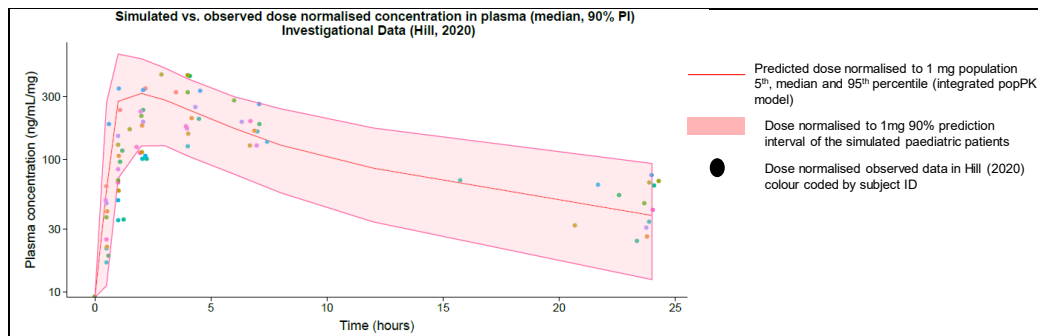
Vivli Data Request ID: 00007396

Title of Data Request: Modeling and Simulation of ambrisentan pharmacokinetics in young children

Date: 07/19/2022

An integrated population pharmacokinetic (popPK) model has been developed for ambrisentan incorporating previous data from the adult and 8 to less than 18 year population. In brief, the PK profile of ambrisentan is adequately described by a two compartmental model with first-order oral absorption and elimination, incorporating bodyweight as a covariate on clearance (CL/F) and volume of distribution (V2/F) with allometric powers of 0.75 and unity, respectively. Clearance was also influenced by both renal function (as indicated by creatinine clearance baseline levels) and hepatic function (as indicated by bilirubin baseline levels). The integrated popPK model was used to simulate the PK of ambrisentan based on the population demographic distribution in the Hill study (2020). Age range in the Hill study (2020) is different to the age group for which the popPK model has been developed (4 to less than 8-year-old population), however, there is an overlap to the range of weight which is used as input to the popPK model. 1000 simulations were performed using the parameter estimates from the final integrated popPK model including the inter-subject variability and residual errors. Dose normalised to 1mg observed data from Hill study (2020) (n=13, weight range 11-19 kg) were overlaid over the 90% prediction interval of the integrated popPK model and results are presented in Figure 1. Overall, the majority of the observed data from the Hill study (2020) fall within the envelope of popPK model predictions providing confidence on the model predictability for this new population.

Figure 1 Overlay of simulated paediatric data, with weight within 11-36 kg, from Hill (2020, n=13) study using the integrated popPK model^a versus corresponding observed investigational data colour coded by individual



a. In the absence of baseline creatinine clearance and bilirubin levels, an assumption was made, and these values were set to the median values observed in historic study in paediatric population with PAH (GSK, study AMB112529). Sensitivity analysis of these two covariates show there is minimal effect on oral clearance (CL/F), therefore, this assumption is expected not to significantly influence the exposure results from the integrated popPK model.

Reference

Hill K.D, Maharaj A.R, Li J.S. et al. A randomised, controlled pharmacokinetic and pharmacodynamic trial of ambrisentan after Fontan surgery. *Pediatric Critl Care Med.* 2020 , 21(9): 795-803.

