On the population pharmacokinetics and the enterohepatic recirculation of inhaled formoterol in asthma patients

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Objectives: To develop a population pharmacokinetic (PK) model for describing the absorption kinetics and enterohepatic recirculation (EHC) of formoterol (FOR) following inhaled administration.of two different dry powder inhalers (DPI): the multi-dose (Budesonide/Formoterol via Symbicort® Turbuhaler® 400/12 mcg/inhalation, Reference device) and a novel single-dose device (Budesonide/Formoterol via Pulmoton® Elpenhaler® 400/12 mcg/inhalation, ELPEN, Greece, Test device).

Methods: Plasma concentration (C) – time (t) data of FOR were obtained from a single dose, 2x2 bioequivalence study comparing the two DPIs in 90 asthma patients under fasting conditions, with co-administration of activated charcoal. Non-linear mixed-effect modeling was applied to the C-t dataset and a PK model able to describe the kinetics of FOR was developed. Different EHC models were tested, including multi-compartment models with an EHC loop using first or zero order transfer rate constants, sine function models for gallbladder control, gallbladder emptying time, presence or absence of bile elimination, etc. Several error models were tested, whereas the period and treatment effects, as well as, demographic characteristics were explored as potential covariates. The entire work was implemented in Monolix 2016 R1.

Results: The FOR C-t profiles revealed a second lesser peak at four hours post-dose (**Figure 1**). Since gastrointestinal absorption was excluded due to the co-administration of the activated charcoal scheme, this second peak was attributed to the presence of EHC of FOR. Finally, FOR PK following inhalation was best described by a two-compartment disposition model linked to an EHC loop with the introduction of two additional compartments, a bile and a gastrointestinal (GI) compartment. Elimination from the central and bile compartment, as well as the transfer rates between the compartments of the EHC loop were considered to follow first order kinetics (**Figure 2**).

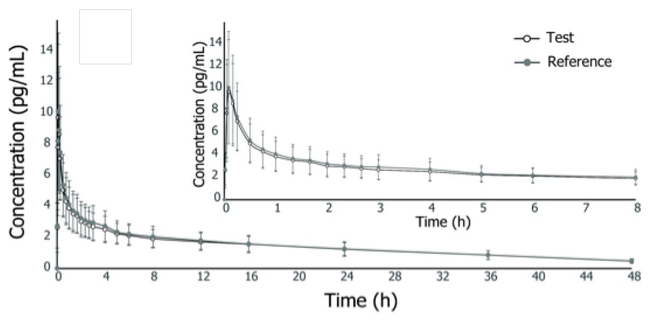

Fig. 1 Mean plasma C-t profile of FOR following inhaled administration. The inset magnifies the time zone 0- 8 hours.

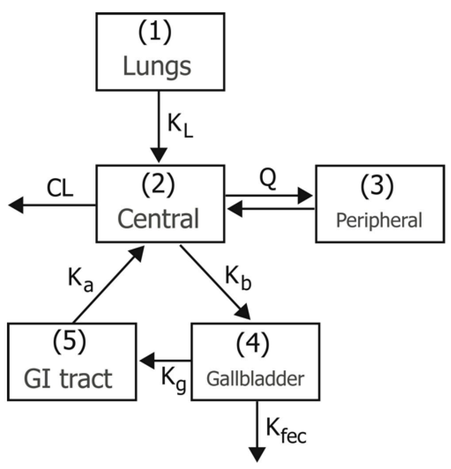

Fig. 2 Schematic representation of the five-compartment model of FOR describing the EHC process.

The model was finally parameterized in terms of the lung absorption rate constant (K_L), the apparent volume of distribution in the central (Vc/F) and peripheral (Vp/F) compartment, the apparent clearance from the central compartment (CL/F), the inter-compartmental clearance (Q/F), the transfer rate constant to bile (Kb), the excretion rate constant from bile to the intestine (Kg), the GI absorption (Ka) and fecal elimination (Kfec) rate constants. A combined error model led to the optimum performance.

Acknowledgment: We wish to thank Elpen Pharmaceutical Co, Greece for providing us the data to perform this computational analysis.

The estimates of the population parameters and their statistics are listed in **Table 1**. A gallbladder time interval between 2-5 hours post-dose was considered based on the observed second concentration peak of the C-t plot, whereas intestinal absorption was initiated at 3 hours post-dose, following termination of the activated charcoal scheme. No significant covariate was found and no difference in the performances of the two DPIs was observed.

Table 1. Estimated population pharmacokinetic parameters for FOR.

Parameter	Mean (RSE%)	BSV% (RSE%)
K_L (h^{-1})	14.8 (3)	15.08 (23)
Vc/F (L)	619 (4)	32.30 (14)
Vp/F (L)	1,130 (4)	36.65 (10)
Q/F (L/h)	2,350 (6)	48.89 (10)
CL/F (L/h)	93 (3)	24.66 (9)
Kb (h^{-1})	0.37 (5)	48.31 (8)
Kg (h^{-1})	0.70 (8)	61.83 (15)
Ka (h^{-1})	0.26 (6)	48.89 (13)
Kfec (h^{-1})	0.01 (14)	88.42 (20)
PK Random Effects Correlation		
Vp/F - Q/F	0.74 (11)	-
Residual error model		
a	0.12 (7)	-
b	0.15 (2)	-

The derived population PK model was capable of adequately describing adequately the plasma C-t data of BUD (Fig. 3-5). The goodness-of-fit results showed an adequate predictive ability of the final PK model.

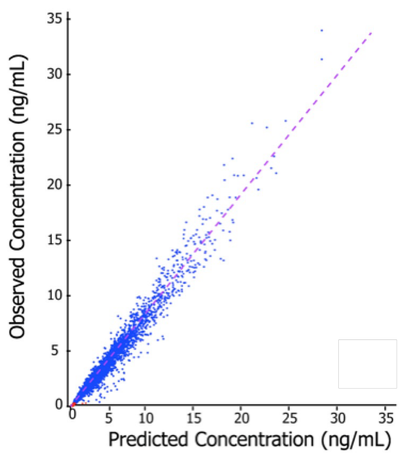

Fig.3 Individual predicted vs. observed plot.

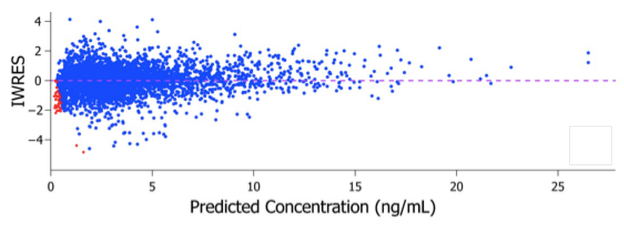

Fig.3 Individual weighted residuals (IWRES) *versus* the individual predicted concentrations.

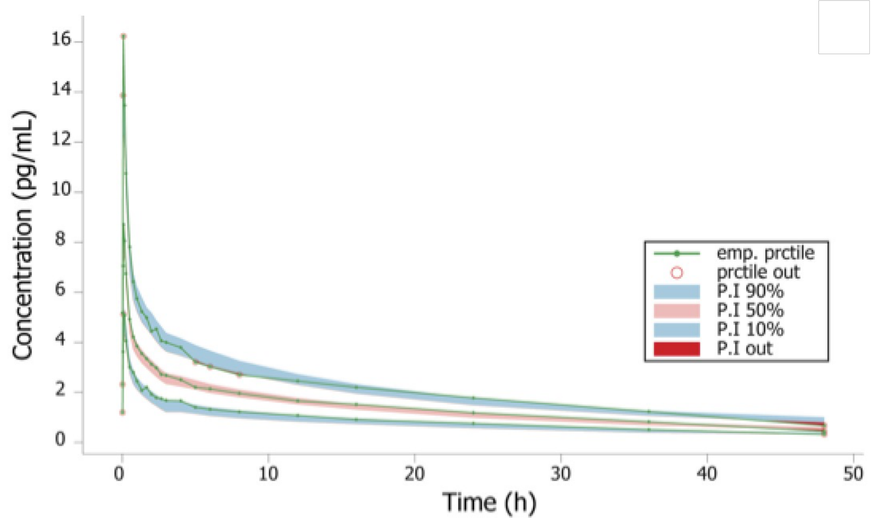

Fig.5 Visual predictive check (VPC).

Conclusions: A population PK model with an EHC component was found to fit suitably the plasma C-t data of inhaled FOR. Several EHC scenarios were developed and their performance was evaluated in terms of physiological soundness and goodness-of-fit criteria. No significant covariates were identified.

***Key*: F**: bioavailable fraction of dose; **BSV(%)**: Between subject variability; **RSE(%)**: percent relative standard error; **a** and **b**: Residual error parameters for the combined error model.