Population pharmacokinetic analysis of inhaled budesonide in asthma patients

***Konstantina Soulele*[1], *Panos Macheras*[1,2], *Vangelis Karalis*[1]**

(1) Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Greece, (2) Pharma-Informatics Unit of Research & Innovation Center ATHENA

Objectives: To apply population pharmacokinetic modeling in order to describe the absorption and disposition kinetics of budesonide (BUD) in asthma patients after administration of two different dry powder inhalers (DPI): the multi-dose (Budesonide/Formoterol via Symbicort® Turbuhaler® 400/12 mcg/inhalation, Reference device) and a single-dose device (Budesonide/Formoterol via Pulmoton® Elpenhaler® 400/12 mcg/inhalation, ELPEN, Greece, Test device).

Methods: BUD plasma concentration (C) – time (t) data were obtained from a single dose, 2x2 bioequivalence study comparing two dry powder inhalers Test (T) and Reference (R) 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 pharmacokinetic model capable of describing the parallel fast and slow lung absorption of budesonide was developed. The C-t data of BUD were fitted to one- and two-compartment PK models assuming different lung absorption processes and first order elimination kinetics. The relative fractions of dose absorbed either fast or slowly through the lungs (R_{fast} and R_{slow}) along with their relative ratio ($z = R_{fast}/R_{slow}$) were set as parameters estimated by the optimization process. 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: A two-compartment disposition model with two parallel first order absorption processes (fast and slow) from the lungs was found to describe successfully the C-t profiles of budesonide. An MLXTRAN code, describing the parallel fast and slow absorption of BUD through the lungs was developed. Gastrointestinal absorption was excluded due to the co-administration of the activated charcoal scheme. A schematic representation of the final model is depicted in **Figure 1**.

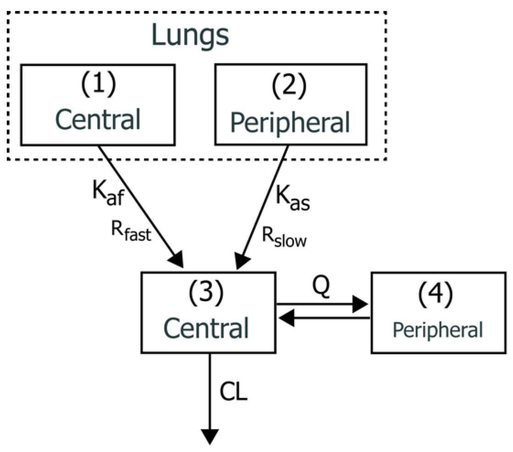

Fig. 1 Schematic representation of the two-compartment model of BUD describing the complex absorption kinetics from lungs after inhaled administration.

The final model was parameterized in terms of the fast (K_{af}) and slow (K_{as}) lung absorption rate constants, the apparent volume of distribution in the central (Vc/F) and peripheral (Vp/F) compartments, the apparent clearance (CL/F), the inter-compartmental clearance (Q/F), the relative fractions of dose absorbed either slowly (R_{slow}) or fast (R_{fast}) through the lungs, and the ratio ($z = R_{fast}/R_{slow}$). The application of a combined error model led to the best performance. The estimates of the population parameters and their statistics are listed in **Table 1**.

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

Table 1. Estimated population pharmacokinetic parameters for BUD.

Parameter	Mean (RSE%)	BSV% (RSE%)
Kaf (h^{-1})	19.7 (8)	72.34 (12)
Kas (h^{-1})	0.11 (11)	51.38 (12)
R_{slow}	0.67 (3)	63.75 (17)
z	0.27 (5)	49.72 (11)
Vc/F (L)	228 (3)	28.24 (10)
Vp/F (L)	182 (6)	35.77 (10)
Q/F (L/h)	254 (6)	50.90 (10)
CL/F (L/h)	154 (3)	22.79 (9)

PK Random Effects Correlation	
Kaf-Rslow	0.45 (38)
Vp/F - Q/F	0.84 (6)
Covariates effects	
Gender on Kas	-0.58 (23) ($p = 1.6 \cdot 10^{-5}$)
Gender on Vp/F	0.22 (28) (p = 0.00031)
Residual error model	
a	0.90 (18)
b	0.13 (2)

The estimated R_{slow} value was found equal to 67%, which suggests that over half of an inhaled dose of BUD is slowly absorbed through the lungs. Gender was found a significant covariate on Kas and Vp/F, with men exhibiting higher Kas and lower Vp/F compared to women. No difference in the performances of the two DPIs was observed. The derived population PK model was capable of adequately describing the plasma C-t data of BUD (**Figures 2-4**). The goodness-of-fit results showed an adequate predictive ability of the final PK model.

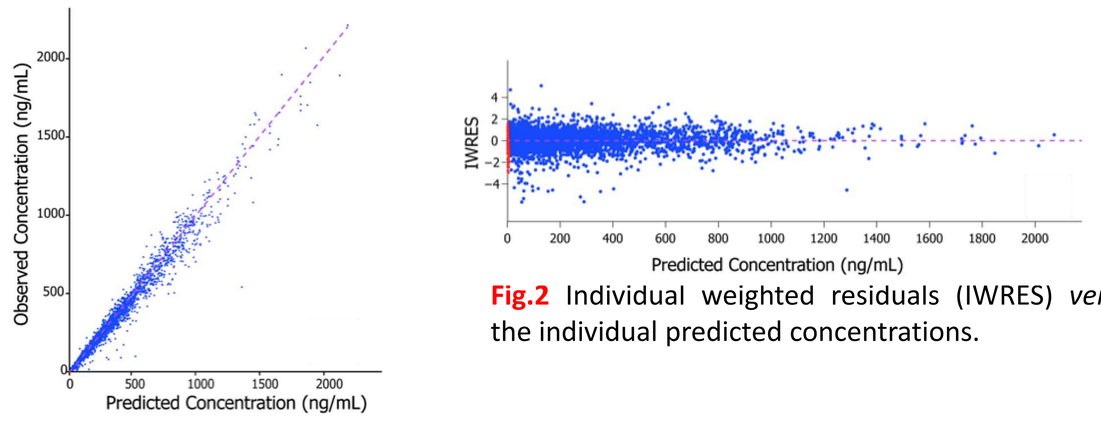

Fig.2 Individual weighted residuals (IWRES) *versus* the individual predicted concentrations.

Fig.3 Individual predicted vs. observed plot.

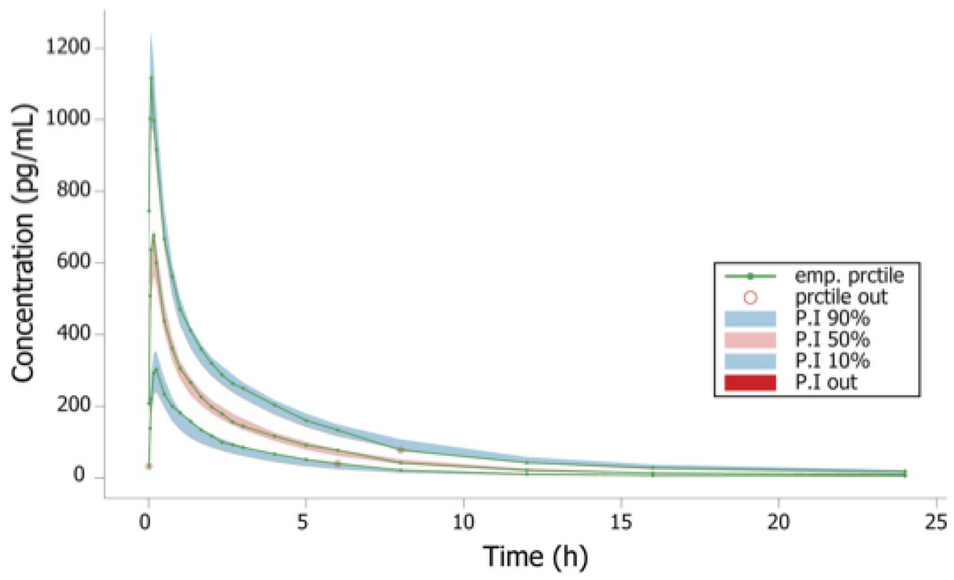

Fig.4 Visual predictive check (VPC).

Conclusions: A population pharmacokinetic model, with two parallel lung absorption processes was found to describe successfully the C-t profile of BUD in asthma patients. Following an initial fast pulmonary absorption, a second slower absorption phase was evident most probably attributed to the lung deposition (central/peripheral) of budesonide and the formation of fatty acid conjugated esters in the airways. Significant covariates affecting the pharmacokinetic parameters were identified.

***Key*: K_{af}**: fast first order absorption rate constant; **K_{as}**: slow first order absorption rate constant; **R_{slow}**: relative fraction of dose absorbed slowly from the lungs; **z**: ratio of dose fractions absorbed either fast (i.e. R_{fast}/R_{slow}); **Vc, Vp**: volume of drug distribution of the central and peripheral compartments; **Q**: inter-compartmental clearance; **CL**: clearance; **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.