CHF5993, a triple combination therapy for COPD patients: population PK modelling of beclometasone-17-monopropionate (B17MP) following pMDI inhalation

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Background & objectives

Beclometasone dipropionate (BDP) is a synthetic corticosteroid that is hydrolyzed via esterase enzymes to an active metabolite B17MP and has been the mainstay of anti-inflammatory therapy for asthma for many years. An extrafine triple combination of BDP (100 µg/dose), formoterol fumarate (FF, 6 µg/dose) and glycopyrronium bromide (GB, 12.5 µg/dose) in a pressurized metered dose inhaler (pMDI), referred to as CHF 5993 100/6/12.5 pMDI, has been developed. The objectives of the analysis were:

- to evaluate the population pharmacokinetics (PK) of B17MP using data collected in phase II and III studies in patients with COPD
- to evaluate the influence of selected covariates on B17MP pharmacokinetic parameters and their potential clinical impact requiring dose adaptation

Methods

Patients & Data: Data issued from phase II (CARSAF) and III (TRINITY) double-blind, randomized, active-controlled studies.

- **CARSAF**: 191 COPD patients receiving a fixed combination of Foster® pMDI (BDP/FF 100/6µg – 2 puffs bid) plus either 25 or 50 µg bid of GB.
- **TRINITY**: 203 COPD patients receiving two puffs twice daily of CHF 5993 pMDI (BDP/FF/GB 100/6/12.5 µg)

In total, 5549 B17MP plasma concentrations, collected in 394 COPD patients, were included.

Model development and parameter estimations were performed with NONMEM 7.3.

Model Characteristics:

- Population approach, accounting for inter-individual variability (IIV) on PK parameters
- Study specific IIV and inter-occasion variability (IOV) were examined: single/multiple dose and at trough

Covariate selection:

- Explored covariates: *age, smoking status, sex, body weight, body mass index, concomitant medications, study effect, use of spacer, baseline forced expiratory volume in 1 second (FEV1), concomitant diseases and glomerular filtration rate (GFR)*
- Forward selection - backward deletion procedure

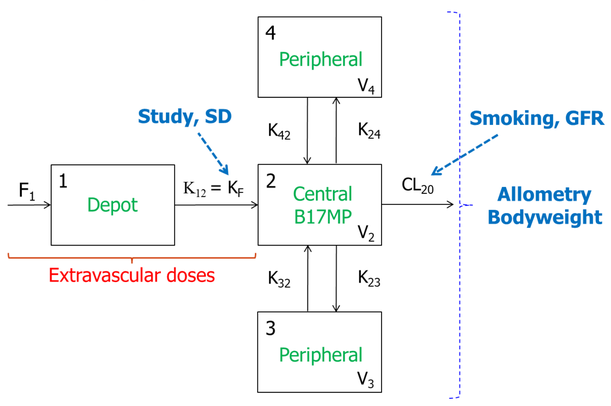
Results

A three-compartment disposition model, with first-order formation and first-order elimination was proposed (Figure 1). Allometric scaling (estimated exponents) accounted for bodyweight influence on clearances and volumes of distribution. Inter-occasion variability was implemented on relative bioavailability.

Significant covariates were GFR and smoking habit on total clearance, while study effect and single dose (SD) versus repeated administration on the formation rate constant (KF).

Parameter estimates are reported in Table 1, and visual predictive checks stratified on study and occasion in Figure 2.

Figure 1: Scheme of the pop PK model for B17MP.



Simulated typical B17MP exposures at steady state as a function of covariates were performed (Table 2). For simulated patients with extremely low values of body weight (below 40 kg) and concomitant low GFR (below 27 mL/min/1.73 m^2), B17MP exposure increases ~1.8-fold compared to reference patients (70 kg, 84 mL/min/1.73m^2). This is of no clinical concern because, in other studies, B17MP doses up to 2-fold the one used in CHF5993 didn't show any safety signal.

Table 2: Simulated B17MP exposure after multiple administrations of 25 µg bid

	Body weight (kg)	GFR (mL/min/1.73m²)	B17MP AUC_{tau} (pg.h/mL) - CARSAF	B17MP AUC_{tau} (pg.h/mL) – TRINITY
Influence of body weight	40	84	3189	3203
	70	84	2170	2177
	139	84	1352	1356
Influence of GFR	70	27	2492	2542
	70	84	1964	2013
	70	161	1710	1758
Influence of body weight and GFR	40	27	3972	3985
	70	84	2170	2177
	139	161	1193	1196

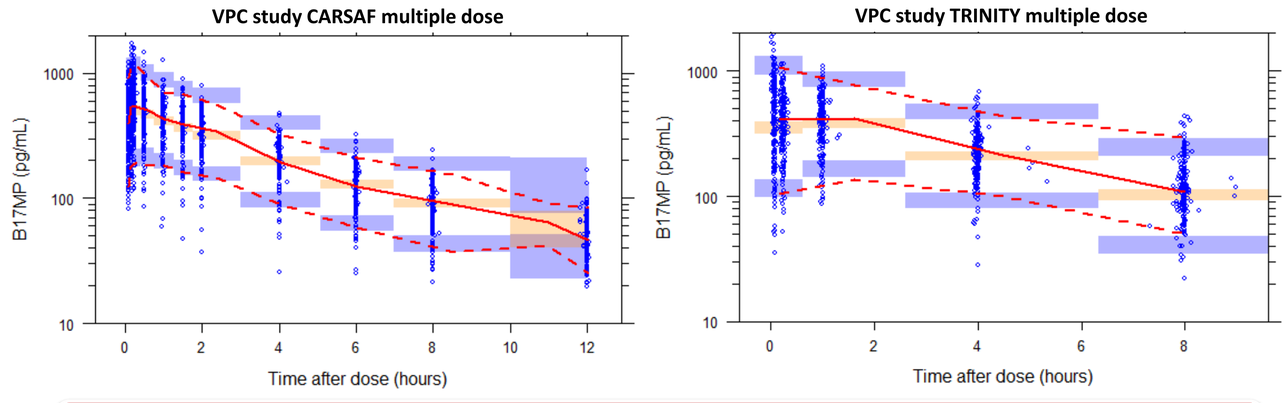
Table 1: Estimates of model parameters (typical values)

	Estimate (RSE%)	IIV (CV%) CARSAF	IIV (CV%) TRINITY	IOV (CV%)
CL (L/h)	91.2 (1.9)	10	15	
V2 (L)	97.9 (5.5)	13	22	
K23 (1/h))	9.49 (5.8)	-	-	
K32 (1/h))	3.96 (5.4)	-	-	
K24 (1/h))	0.408 (13.4)	-	-	
K42 (1/h))	0.257 (12.4)	-	-	
KF (1/h)	2.62 (8.1)	11	11	
F1 (relative bioavailability)	1 FIX	-	-	10
Residual error proportional	0.217 (0.7)	-	-	
Residual error additive	6.07 (8.2)	-	-	
CL_BW	+0.69 (14.7)	-	-	
V_BW	+1.17 (11.0)	-	-	
Microconstants_BW	-0.48	-	-	
COV GFR on CL (COV_{GFR}) [1]	0.191 (27.2)	-	-	
COV Smoking on CL (COV_{SMK}) [1]	-0.067 (27.2)	-	-	
COV Study on KF (COV_{Study}) [1]	0.488 (28.9)	-	-	
COV SD on KF (COV_{SD}) [1]	-0.109 (11.8)	-	-	

[1]: $CL = TH_{CL} * ((BW/70)^{**}0.69) * ((GFR/84)^{**}COV_{GFR}) * (1+\text{smoking habits}*COV_{SMK})$
$V2 = TH_{V2} * ((BW/70)^{**}1.17)$
$KF = TH_{KF} * (1+Study*COV_{Study}) * (1+SD*COV_{SD})$

KF: formation rate; K23, K32, K24 and K42: rate of transfer between central and peripheral compartments; CL: clearance; V2: volume of central compartment; F1: relative bioavailability; SD: single dose

Figure 2: Visual Predictive Checks of B17MP plasma concentration as a function of time since last dose (TSLD) in CARSAF and TRINITY



Conclusions

The PK model built on data from COPD patients described the B17MP data well and was able to explain part of the variability in exposure. Based on simulated profiles, no clinical dose adjustments were deemed necessary.