CHF5993, a triple combination therapy for COPD patients: population PK modelling of formoterol following pMDI inhalation.

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Background & objectives

Formoterol fumarate (FF) is a long-acting β2-agonist (LABA) with a rapid onset of bronchodilation. FF has been shown to be highly efficacious and safe, especially in combination with inhaled corticosteroids. An extrafine triple combination of beclometasone dipropionate (BDP, 100 µg/dose), FF (6 µg/dose) and glycopyrronium bromide (GB, 12.5 µg/dose) in a pressurized metered dose inhaler (pMDI), referred to as CHF5993 100/6/12.5 pMDI, has been developed. The objectives of the analysis were:

- to evaluate the population pharmacokinetics (PK) of FF using data collected in phase II and III studies in patients with COPD,
- to evaluate the influence of selected covariates on FF PK 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**: 187 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**: 200 COPD patients receiving two puffs twice daily of CHF5993 pMDI (BDP/FF/GB 100/6/12.5 µg).

Model development and parameter estimations were performed with NONMEM 7.3.

Modelling Characteristics:

- Population approach, accounting for inter-individual variability (IIV) on PK parameters and evaluation of Inter-occasion variability (IOV)
- M3-method to account for data below the limit of quantification
- Both sides log-transformation; additive residual error on the log-scale

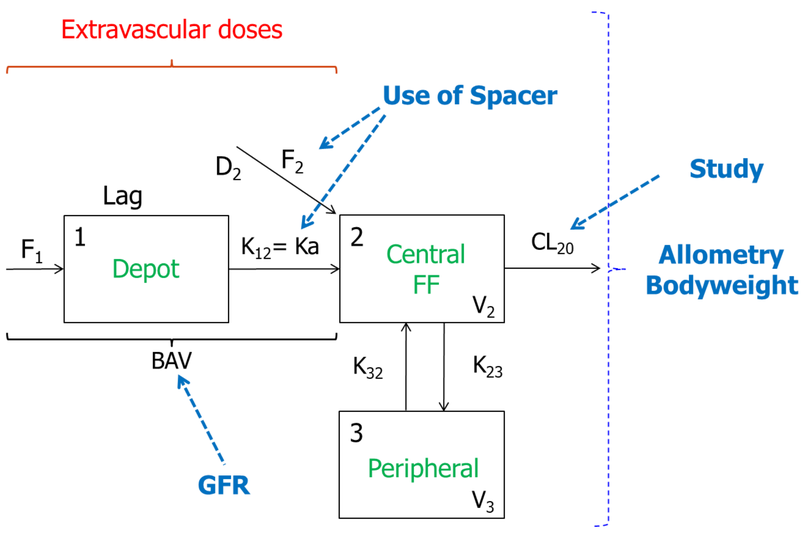
Covariate selection:

- Explored covariates: *age, smoking status, sex, body weight (BW), body mass index, concomitant medications, study effect, use of spacer, baseline forced expiratory volume in 1 second (FEV_1), concomitant diseases and glomerular filtration rate (GFR).*

Results

A two-compartment disposition model with a combined first-order and zero-order absorption was used (Figure 1). IOV was implemented on relative bioavailability (BAV).

Figure 1: Pop PK model for FF



- ✓ Allometric scaling (with fixed exponents) of BW on clearances and volumes.
- ✓ CL was 36% lower in TRINITY study compared to CARSAF.
- ✓ Use of spacer decreased Ka by 39.6%, but increased F2 by 33.0%.
- ✓ BAV was found to increase when GFR decreased.

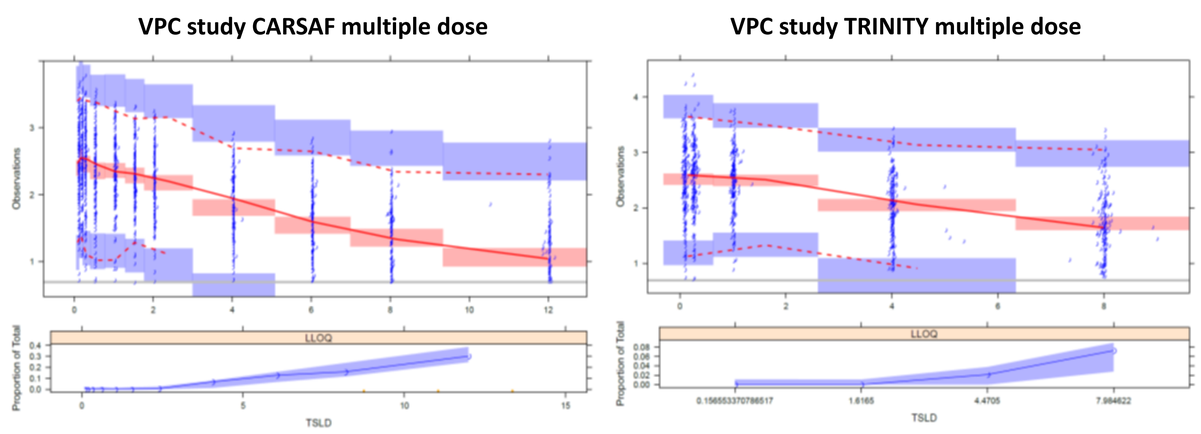
Table 1: Estimates of model parameters (typical values)

	Estimate (RSE%)	IIV CV% (RSE%)	IOV CV% (RSE%)
CL (L/h) (1)	162 (4.3)	50 (9.3)	
V2 (L) (1)	248 (6.6)	43 (14.3)	
K23 (1/h))	1.10 (6.2)	-	
K32 (1/h))	0.193 (6.6)	-	
D2 (h)	0.118 fix	-	
Ka (1/h)	0.483 (7.3)	35 (16.9)	
F2	0.274 (5.7)	36 (13.3)	
Lag time (h)	0.376 fix	-	
BAV	1 fix	-	23 (9.1)
residual error (%CV)	27.7 (0.6)		
CL~BW	+ 0.75 fix	-	
V~BW	+ 1 fix		
CL~Trinity	- 0.36 (9.4)	-	
Ka~Spacer	- 0.396 (26.5)	-	
F2~Spacer	+ 0.33 (27.9)	-	
BAV~GFR	- 0.422 (26.3)	-	

(1) Correlation CL/V2: 0.713

Ka: absorption rate; K23 and K32: rate of transfer between central and peripheral compartments; CL: clearance; V2: volume of central compartment; D2: duration and F2: fraction of zero-order absorption; BAV: relative bioavailability (BAV=F1+F2); RSE: relative standard error; CV%: coefficient of variation as percentage

Figure 2: Visual Predictive Checks of FF plasma concentration as a function of time since last dose (TSLD)



Simulations were performed to visualize the impact of these covariates on the PK of FF, at steady-state, using a FF dose of 12 µg bid (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), FF exposure increases by ~2.5-fold compared to the reference patients (70 kg, 84 mL/min/1.73 m^2). This higher exposure is of no clinical concern, because individual therapeutic doses of up to 2-fold the FF doses used in CHF5993 formulation are available on the market and thus this doubling in exposure can be considered safe.

Table 2: Simulated FF exposure after multiple administrations of 12 µg bid

	Body weight (kg)	GFR (mL/min/1.73m²)	FF AUC_{tau} (pg.h/mL) CARSAF	FF AUC_{tau} (pg.h/mL) TRINITY
Influence of body weight	40	84	112.7	176.1
	70	84	74.1	115.7
	139	84	44.3	69.2
Influence of GFR	70	27	119.6	186.9
	70	84	74.1	115.7
	70	161	56.3	88.0
Influence of body weight and GFR	40	27	182.0	284.3
	70	84	74.1	115.7
	139	161	33.7	52.6

Conclusions

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