# CHF5993, a triple combination therapy for COPD patients: population PK modelling of glycopyrronium bromide following pMDI inhalation

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## Background & objectives

Glycopyrronium bromide (GB) is a long acting muscarinic antagonist for the treatment of chronic obstructive pulmonary disease (COPD), providing clinically significant bronchodilation with a rapid onset of effect as well as being safe and well-tolerated. An extrafine triple combination of beclometasone dipropionate (BDP, 100 µg/dose), formoterol fumarate (FF, 6 µg/dose) and 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 GB using data collected in phase II and III studies in patients with COPD
- to evaluate the influence of selected covariates on GB 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**: 124 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 25µg bid of GB in the novel fixed-dose formulation (CHF5993 100/6/12.5 pMDI – 2 puffs bid)

In total, 4194 GB plasma concentrations (including 618 observations below the limit of quantification - BLQ), collected in 324 COPD patients, were considered.

Model development and parameter estimations were performed with NONMEM 7.3.

Model Characteristics:

- Population approach, accounting for inter-individual variability (IIV) on PK parameters. Inter-occasion variability (IOV) was also examined: single/multiple dose and at trough
- M3-method for BLQ data, additive residual error on the log-scale (log-transformation both sides)

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 ($FEV_1$), concomitant diseases and glomerular filtration rate (GFR)*
- Forward selection - backward deletion procedure

## Results

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

A study effect was found significant on the volume of distribution of central compartment ($V_2$). GFR was significant for bioavailability (implemented as a simultaneous influence of covariate on CL and V2).

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

**Figure 1: Schema of the pop PK model for GB.**

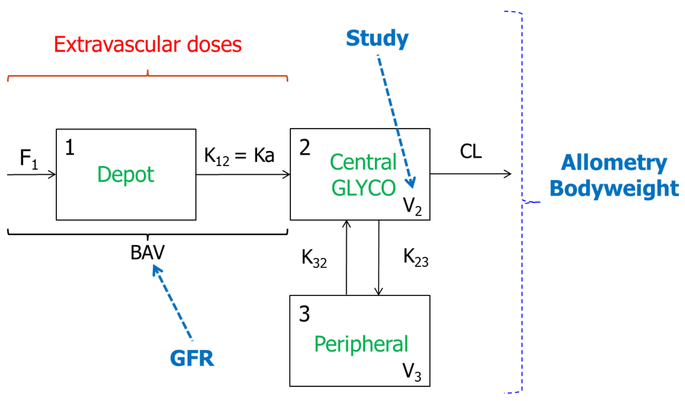
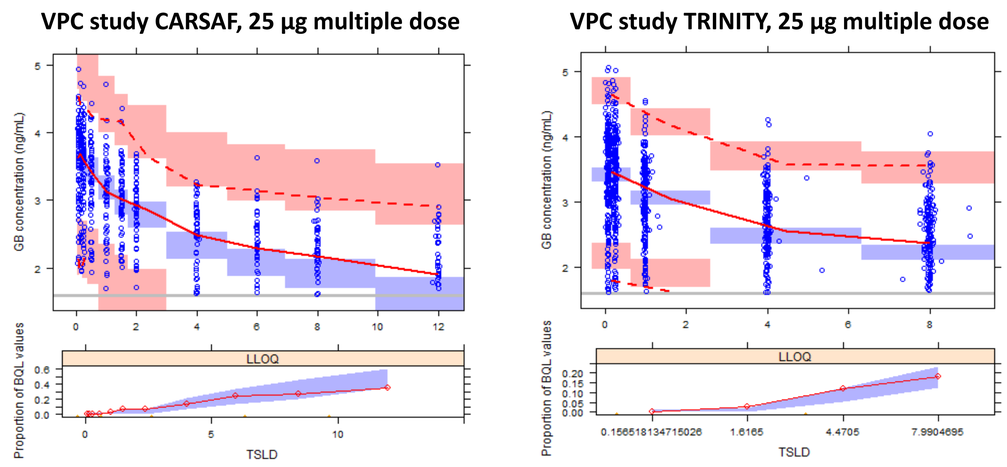



**Figure 2: Visual Predictive Checks of GB plasma concentration as a function of time since last dose (TSLD), in CARSAF and TRINITY study**




Simulated typical GB 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 $m^2$), GB exposure increased ~2.7-fold compared to reference patients (70 kg, 83.7 mL/min/1.73$m^2$). This is of no clinical concern because, in other studies, GB doses of up to 4-fold the one used in CHF5993 didn't show any safety signal.

**Table 1: Estimates of model parameters (typical values)**

| | Estimate (RSE%) | IIV CV% (RSE%) | IOV CV% (RSE%) |
|---|---|---|---|
| **CL (L/h)** | 170 (3.5) | 26 (11) | |
| **V2 (L)** | 1.86 (81) | 29 (1536) | |
| **K23 (1/h))** | 369 (81) | - | |
| **K32 (1/h))** | 0.165 (21) | - | |
| **Ka (1/h)** | 0.705 (4.0) | 21 (12) | |
| **F1 (relative bioavailability)** | 1 FIX | - | 13 (9.3) |
| **Residual error (%)** | 22 (0.5) | - | |
| **CL_BW** | +0.75 FIX | - | |
| **V_BW** | +1 FIX | - | |
| **COV STUDY on V2 ($COV_{Study}$) [1]** | 0.637 (7.7) | - | |
| **COV GFR on BAV ($COV_{GFR}$) [1]** | -0.505 (27) | - | |

[1]: $CL = TH_{CL} * ((BW/70)^{**}0.75) / ((GFR/83.7)^{**}COV_{GFR})$
$V2 = TH_{V2} * ((BW/70)^{**}1) * COV_{Study}{}^{**}STUDY / ((GFR/83.7)^{**}COV_{GFR})$

Ka: absorption rate, K23 and K32: rate of transfer between central and peripheral compartments, CL: clearance, V2: volume of distribution of central compartment; F1: relative bioavailability, BAV: bioavailability; BW: bodyweight; CV: coefficient of variation; RSE: relative standard error

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

| | Bodyweight (kg) | GFR (mL/min/1.73$m^2$) | GB $AUC_{tau}$ (pg.h/mL) |
|---|---|---|---|
| **Influence of bodyweight** | 40 | 83.7 | 223.8 |
| | 70 | 83.7 | 147.1 |
| | 139 | 83.7 | 87.9 |
| **Influence of GFR** | 70 | 27 | 260.4 |
| | 70 | 83.7 | 147.1 |
| | 70 | 161 | 105.7 |
| **Influence of bodyweight and GFR** | 40 | 27 | 396.2 |
| | 70 | 83.7 | 147.1 |
| | 139 | 161 | 63.2 |

## Conclusions

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