

Population pharmacokinetic analysis of BGF MDI (PT010), an inhaled triple fixed-dose combination product, in patients with chronic obstructive pulmonary disease

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Introduction

BGF MDI (PT010) is a triple fixed-dose combination of budesonide/glycopyrronium/formoterol fumarate dihydrate delivered by metered dose inhaler using co-suspension delivery technology [1], in development for the inhaled treatment of chronic obstructive pulmonary disease (COPD).

Objective

To evaluate the population pharmacokinetic (popPK) properties of BGF MDI, and the impact of covariates on each of its components, budesonide (BD), glycopyrronium (GP), and formoterol fumarate dihydrate (FF), in patients with COPD.

Methods

Data

- Pharmacokinetic (PK) data from 9 clinical studies in subjects with mild-to-very severe COPD. Each study contained data on one or more of the following triple-, dual- and mono-

therapies: (i) BGF MDI, (ii) budesonide/formoterol fumarate dihydrate (BFF) MDI, (iii) glycopyrronium/formoterol fumarate dihydrate (GFF) MDI (Bevespi Aerosphere®[2]), (iv) BD MDI, (v) GP MDI, and (vi) FF MDI.

- In total, the BD analysis included 3930 samples from 220 subjects, the GP analysis included 7612 samples from 481 subjects, and the FF analysis included 10277 samples from 652 subjects (Figure 1).

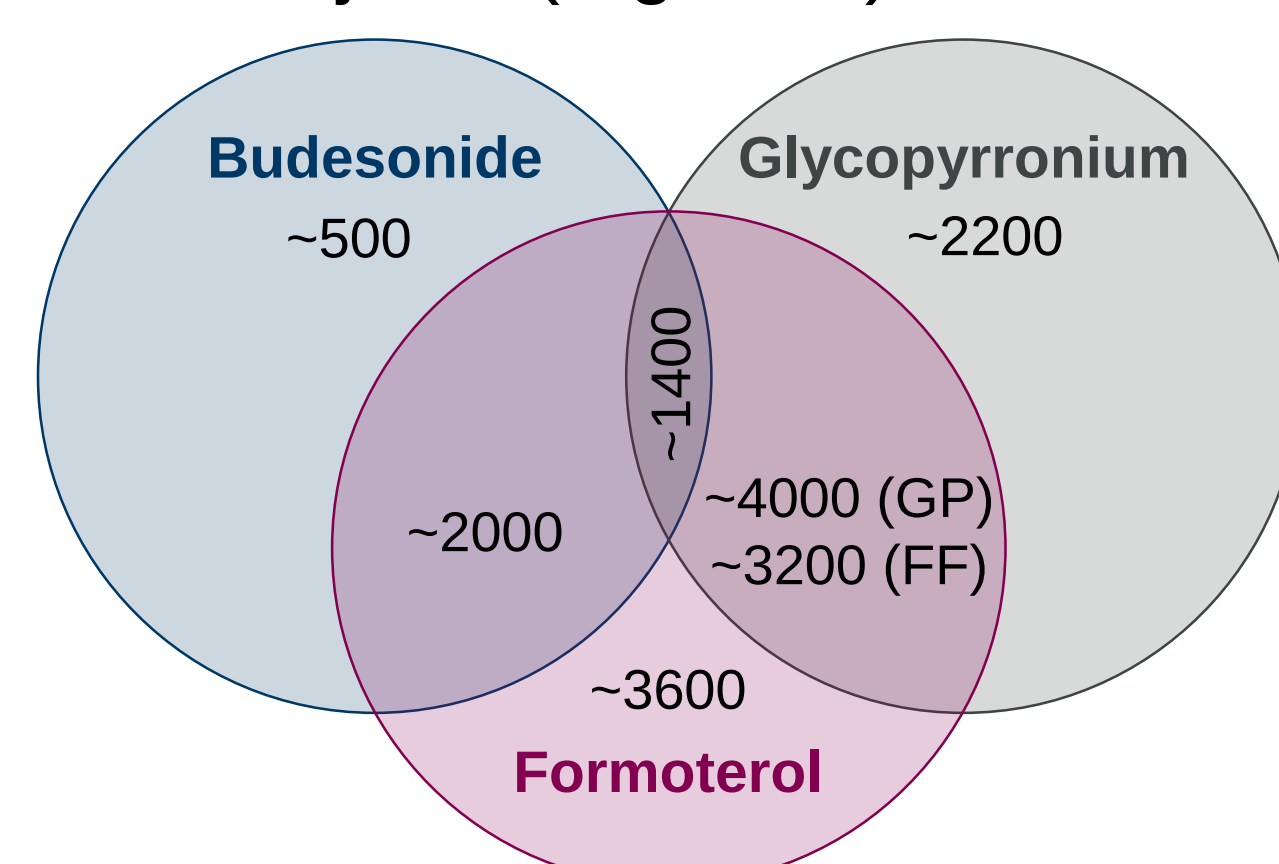


Figure 1. Approximate number of samples included in the analysis from each of the triple-, dual- and mono-therapies.

Modelling & Simulations

- Model analyses were conducted in NONMEM (v 7.3.0); model evaluations and simulations were conducted in R (v 3.2.4).

- Structural base models investigated: 1-, 2-, and 3-compartment models.
- Covariates considered: age, body weight, absolute estimated glomerular filtration rate (eGFR), sex, smoking status, COPD severity, formulation effects of products (ii)-(vi) versus (i) on relative bioavailability (F_{rel}).
- Simulations were conducted to assess the impact of identified covariates on AUC, C_{max} , and C_{min} , at steady state during twice-daily dosing of the anticipated to be licensed dose of BGF MDI (320/14.4/10 µg).
- The “worst case” combination of covariates, selected to obtain the highest C_{max} /AUC, were identified, and the exposure was evaluated relative the typical patient, considering the 10th/90th percentile for continuous covariates.

Conclusions

The popPK properties of BGF MDI, in patients with COPD, were thoroughly evaluated and none of the identified covariate effects were deemed clinically relevant.

Results

Budesonide

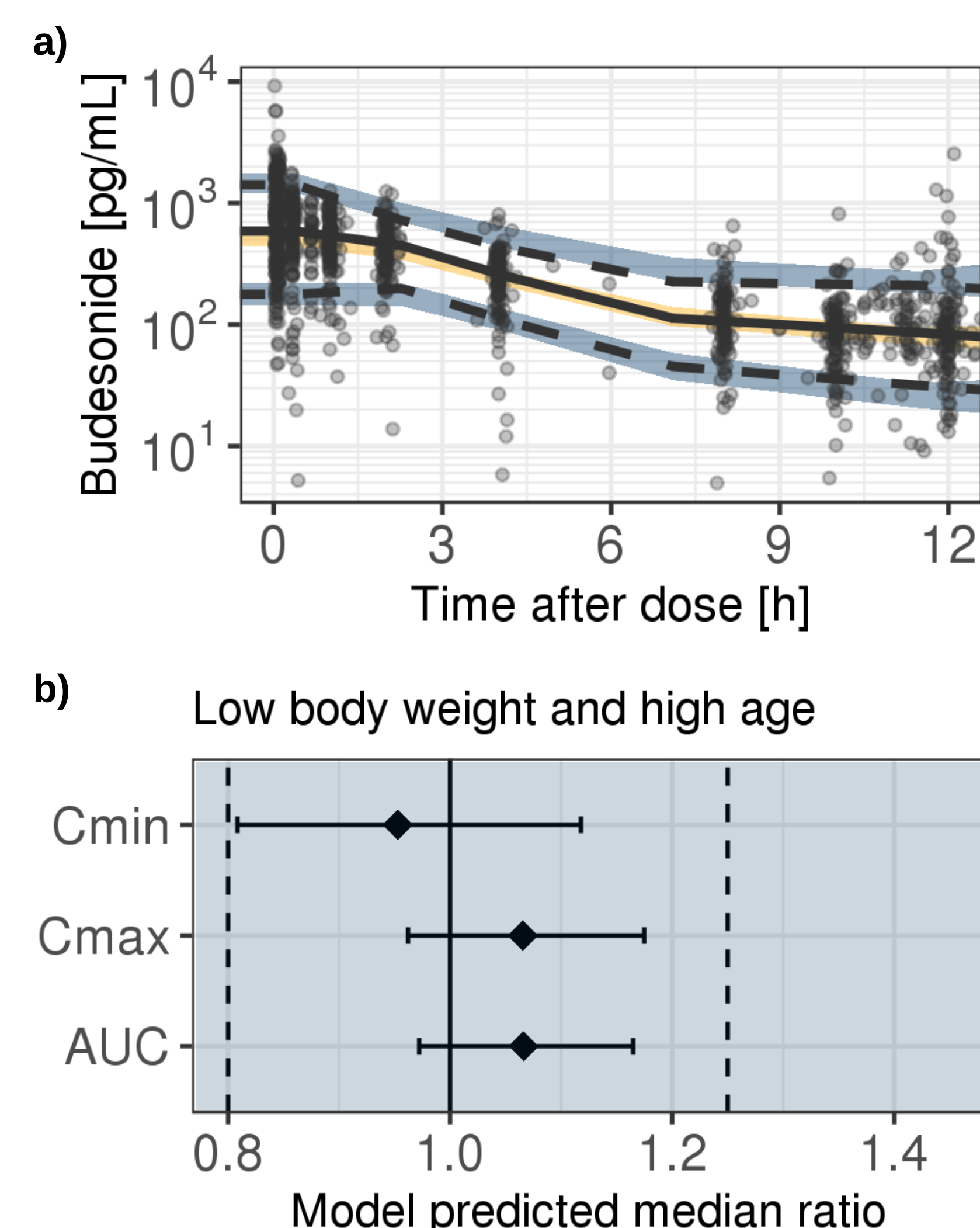


Figure 2 a) Prediction corrected VPC for the final BD model. **b)** Predicted impact of “worst case” covariates combination on BD exposure, median ratio relative to typical patient.

Glycopyrronium

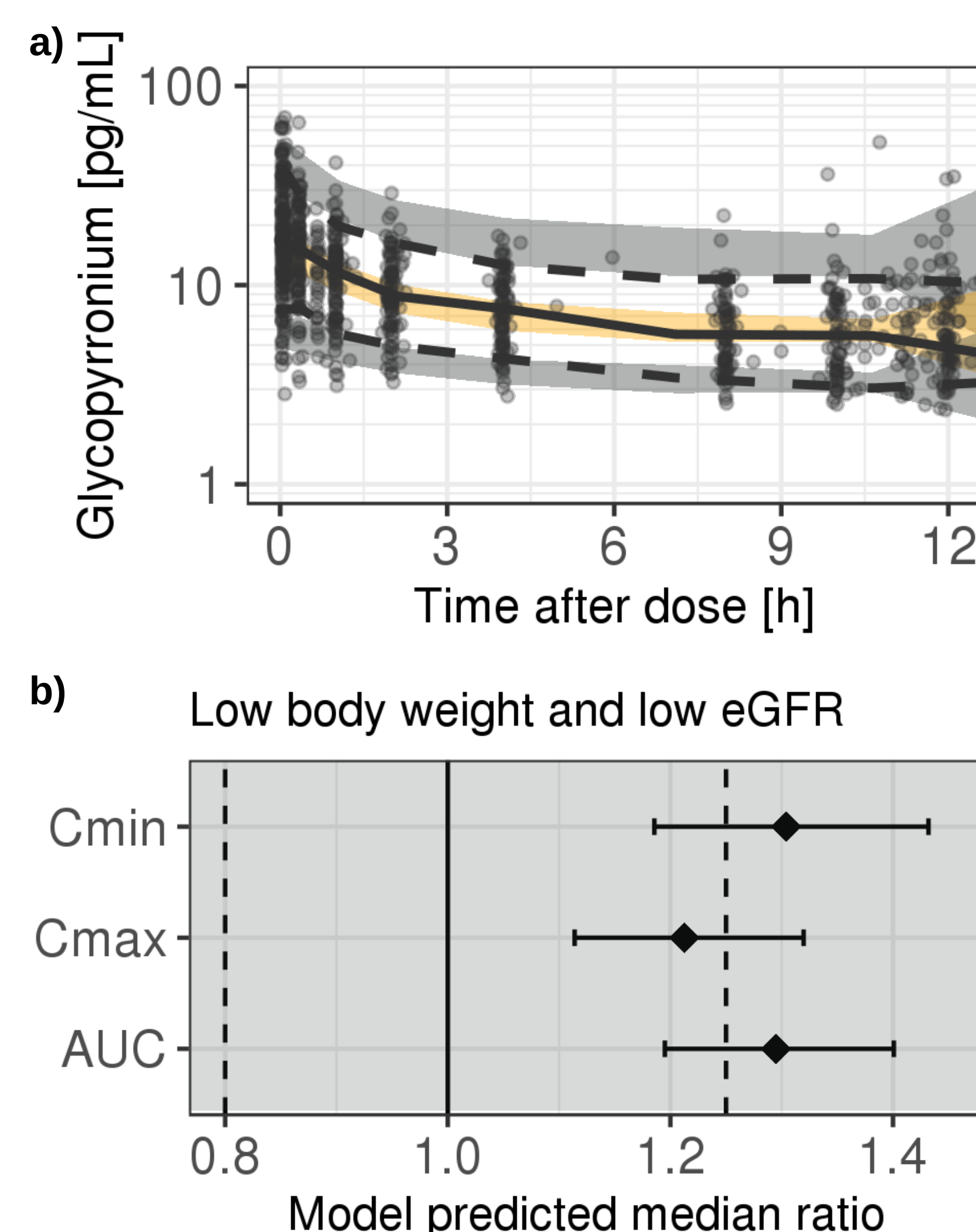


Figure 3 a) Prediction corrected VPC for the final GP model. **b)** Predicted impact of “worst case” covariate combination on GP exposure, median ratio relative to typical patient.

Formoterol

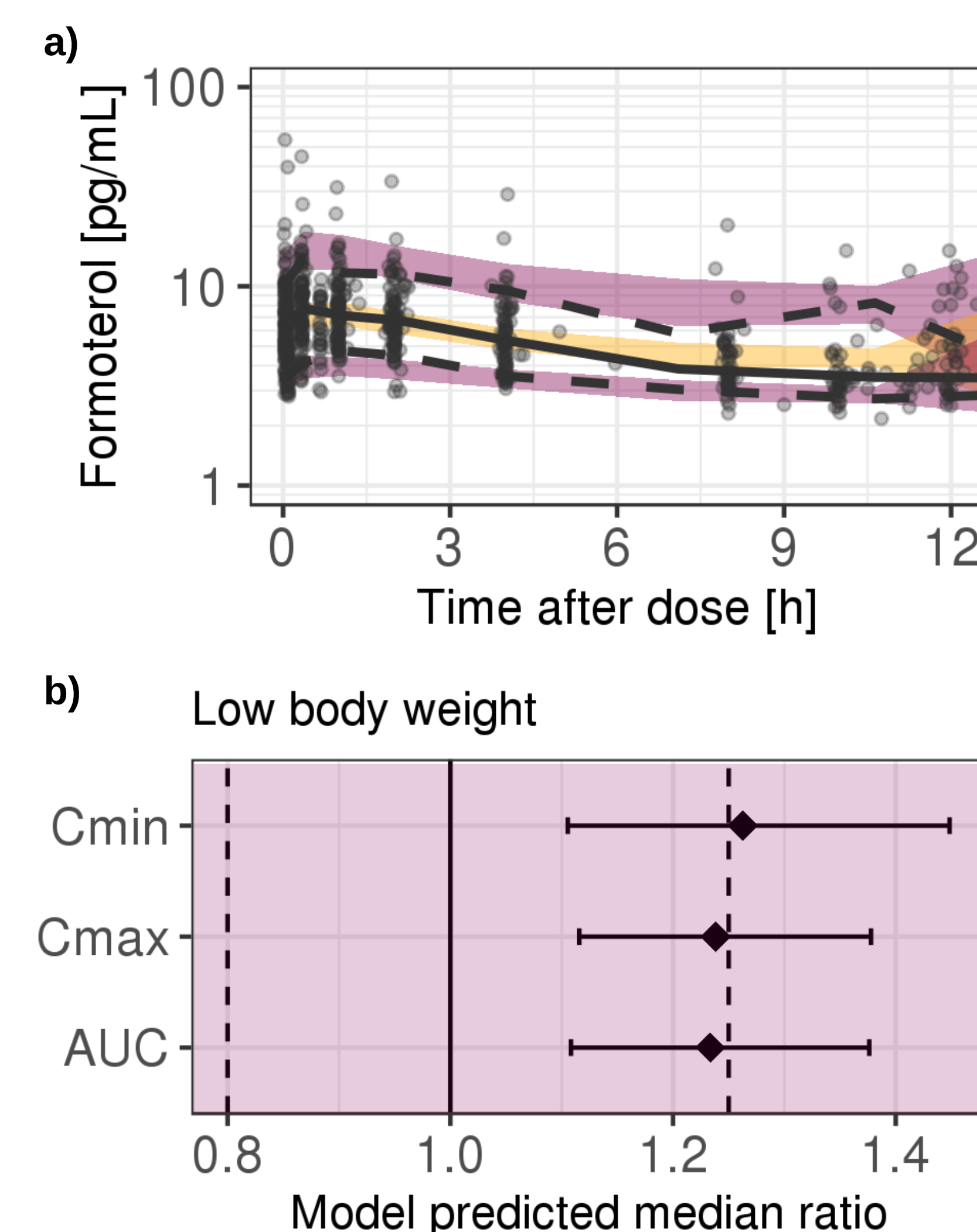


Figure 4 a) Prediction corrected VPC for the final FF model. **b)** Predicted impact of “worst case” covariates combination on FF exposure, median ratio relative to typical patient.

- The final popPK model was a 3-compartment model with 1st-order absorption, including body weight affecting inter-compartmental clearance parameters (Q_{p1}/F and Q_{p2}/F), and age affecting clearance (CL/F). A Visual Predictive Check (VPC) for the final model is presented in Figure 2a.
- None of the identified covariates expressed any important impact on BD exposure. The predicted effects of the “worst case” combination of covariates (body weight 57.6 kg, age 74 years), relative to the typical patient, were approx. -5%, 7%, and 7%, for median C_{min} , C_{max} , and AUC, respectively (Figure 2b).

- The final popPK model was a 2-compartment model with 1st-order absorption, including absolute eGFR affecting CL/F , body weight affecting volumes of distribution (V_c/F and V_p/F) and Q/F , and smoking status affecting the absorption rate constant (k_a) and F_{rel} . A VPC for the final model is presented in Figure 3a.
- Absolute eGFR was the covariate that had the greatest impact on GP exposure. The predicted effects of the “worst case” combination of covariates (body weight 57.6 kg, eGFR 63.7 mL/min, former smoker), relative to the typical patient, were approx. 30%, 21%, and 29%, for median C_{min} , C_{max} , and AUC, respectively (Figure 3b). These differences were expected since GP is renally cleared.

- The final popPK model was a 2-compartment model with 1st-order absorption, including body weight affecting CL/F and V_c/F , smoking status affecting k_a and CL/F , and COPD severity affecting k_a . Formulation effects for BFF MDI, GFF MDI, and FF MDI on F_{rel} (<16% increase relative to PT010) were also included. A VPC for the final model is presented in Figure 4a.
- Body weight was the covariate that had the greatest impact on FF exposure. The predicted effects of the “worst case” combination of covariates (body weight 58.0 kg, mild or moderate COPD, former smoker), relative to the typical patient, were approx. 26%, 24%, and 23%, for median C_{min} , C_{max} , and AUC, respectively (Figure 4b).

References

- Ferguson GT, et al. Respiratory Medicine 134 (2018) 16-23
- Bevespi Aerosphere is a trademark of the AstraZeneca group of companies.

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