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Introduction

- Wilson disease (WD)** is an autosomal recessive disorder in which mutations of the ATP7B gene results in an **impaired copper homeostasis** and **copper accumulation** in the body.
- Treatment with chelators, such as **trientine dihydrochloride (TETA-2HCl)** aims to **reduce copper levels** by its sequestration and enhanced elimination.
 - While the effects of TETA-2HCl have been demonstrated in both non-clinical and clinical studies, no dedicated pharmacokinetic (PK) – pharmacodynamic (PD) modelling was performed.
- The **UNITED study** is an open label, multicentre, prospective study, assessing PK, PD, efficacy and safety of TETA-2HCl as well as the dose-response relationship.
 - During the **first 4 weeks** of the UNITED study, the treatment with TETA-2HCl was **up-titrated** according to a set scheme.
 - In Week 0 (Baseline) patients started treatment with 3 mg/kg/day, which was increased to 8 mg/kg/day in Week 2 and to 13 mg/kg/day in Week 4.

Objectives

- To reveal and quantify the relationships between systemic trientine (TETA) exposure and its effect on serum copper markers as well as urinary copper excretion, using a model-based PK-PD analysis.
- To evaluate the influence of patient characteristics on relevant model parameters, such as baseline copper clearance and drug potency, in a broad WD patient population during the up-titration phase of the UNITED study.

Final popPK and popPK-PD model structure

- The **final popPK model** was a **linear 2-CMT model** with **1st-order absorption** and IIV on the absorption rate constant (K_a) and bioavailability (F_1).
 - Exposure for visit 2 was observed to be higher than for the other visits, which was described by a higher F_1 .
- The **final popPK-PD model** described a baseline CUCL (BL), extended by a TETA-induced CUCL (Figure 2).
 - Serum NCC was expressed as a balance between copper influx and copper efflux and was the driver for BL. In this model, CUCL was affected by TETA in a multiplicative fashion: $CUCL = BL * (1 + SL * TETA)$.
 - Inter-individual variability (IIV) was included on K_{in} and serum EC, but not on SL.

Methods

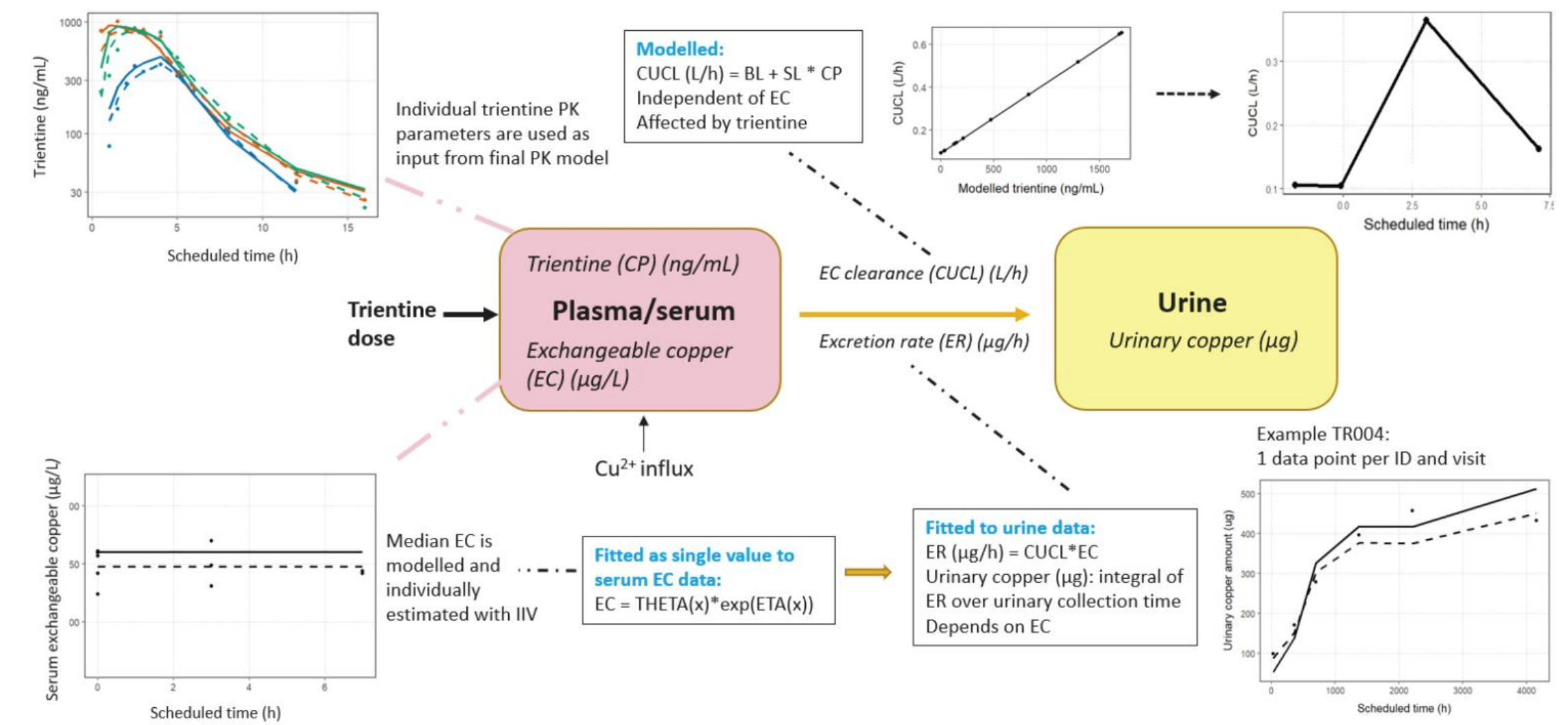


Figure 1: PopPK-PD modelling plan.

- A **population PK-PD** (popPK-PD) model was developed and fitted to the UNITED study up-titration phase data.
- The **individual TETA PK** model parameters were related to **total 24-hour urinary copper excretion** (24h-UCE) and **serum non-ceruloplasmin bound copper** (NCC) concentrations using the popPK-PD model.
- Main characteristic of the model: **urinary exchangeable copper clearance** (CUCL), which was related to **24h-UCE** through a **modelled median serum NCC** (µg/L).
- 24h-UCE and NCC were fitted** to the data of the up-titration phase of the UNITED study.
- The **influence of patient characteristics**, like weight, age, and copper parameters, on relevant model parameters, such as serum NCC and CUCL, was evaluated.

Final popPK-PD model structure:
 $CUCL = BL * (1 + SL * CP)$
With $BL = K_{in}/EC$

K_{in} (copper inflow from liver)

Serum EC → $CLR = CUCL$ (BL dependent on serum EC)

Figure 2: Final popPK-PD model structure.

$dEC/dt = K_{in} - CLH * EC - CLR * EC$
 $CLR = BL * (1 + SL * CP)$
 $CLH \sim 0$
At SS ($dEC/dt = 0$): $K_{in}/EC - CLH = BL$
 $BL = K_{in}/EC$ (dashed line)

Estimate K_{in}
Estimate EC
Derive BL

CUCL = Urinary exchangeable copper clearance.
BL = BaseLine urinary exchangeable copper (L^2/h).
SL = slope - effect of trientine on CUCL.
CP = predicted plasma trientine concentration (ng/mL).

Covariate analysis

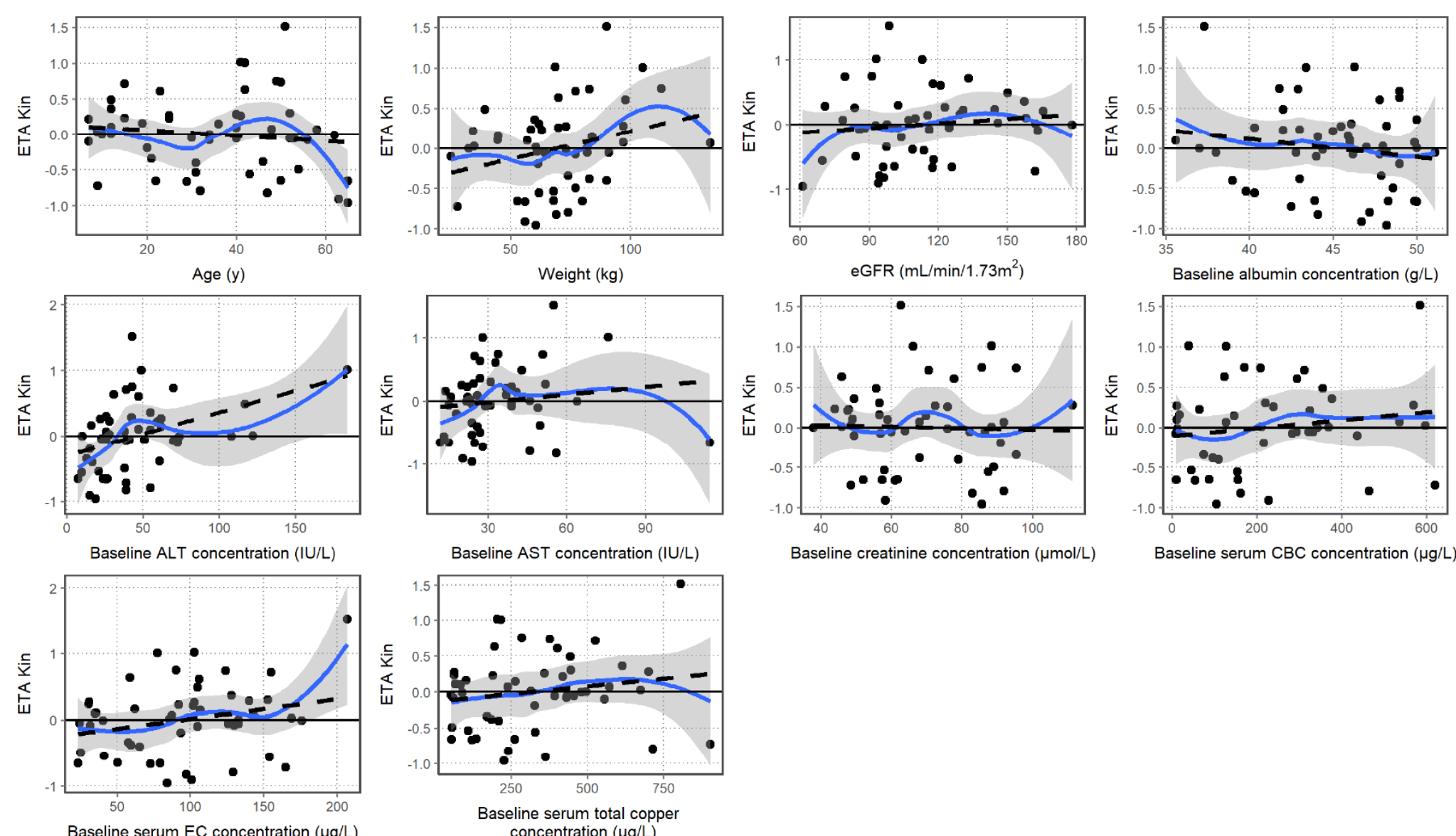


Figure 3: Relationship between ETA K_{in} and selected continuous covariates for the final base popPK-PD model.

- No covariates** were found to affect trientine PK (not shown).
- Exploratory covariate analysis revealed a positive relationship between the **baseline alanine transferase (ALT)** and K_{in} (Figure 3).
- Exploration of the observed data revealed a positive relationship between **age group** and SL (effect of trientine on urinary copper clearance, $\mu g/h$ - Figure 4).
- A formal covariate analysis resulted in the final popPK-PD model including **ALT on K_{in}** and **weight on SL**.
- An **effect of age on SL** (Figure 5, top) could be explained by a positive relationship between **weight and SL** (Figure 5, bottom).

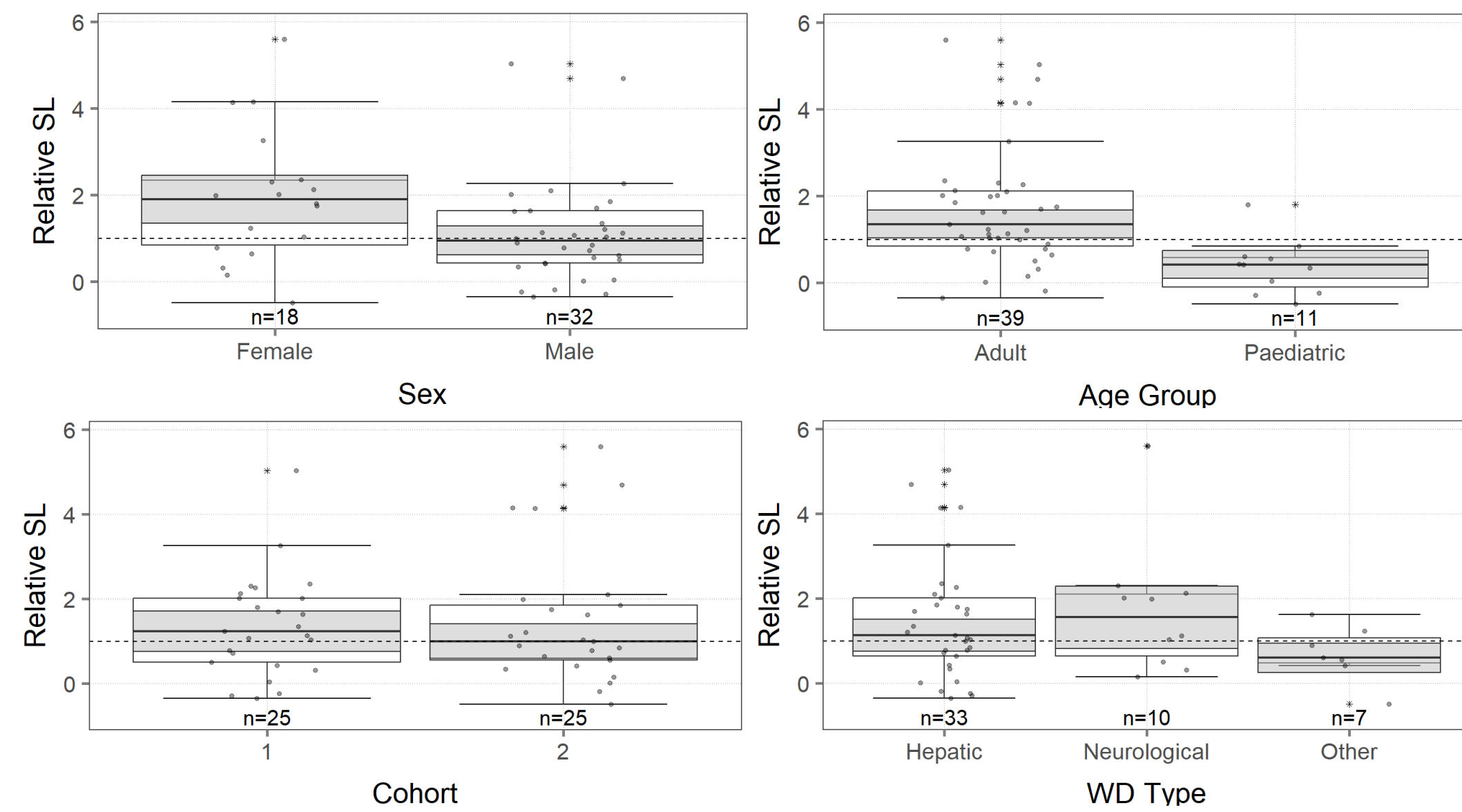


Figure 4: Relationship between observed SL ($L^2/\mu g$; relative to population value) and selected categorical covariates. SL was calculated as (average CUCL*observed median serum EC)/(observed urinary collection time (UCT)). Average CUCL was calculated as observed 24h-UCE/serum EC AUC. Serum EC AUC was calculated as the median serum EC*observed UCT.

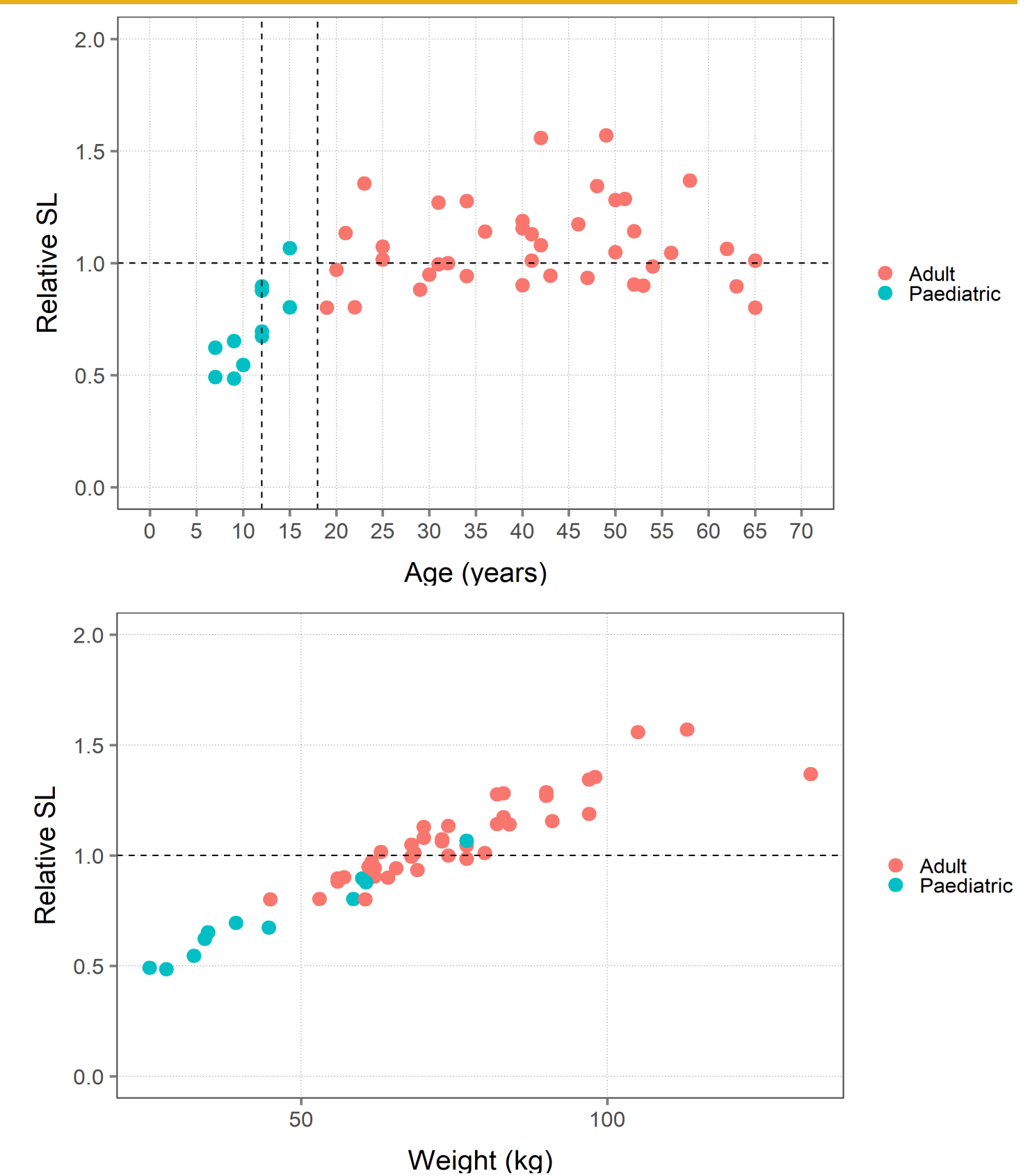


Figure 5: SL ($L^2/\mu g$; relative to population value) versus age and weight in adult and paediatric patients from the UNITED study using the final full popPK-PD model.

Final popPK and final popPK-PD model fits

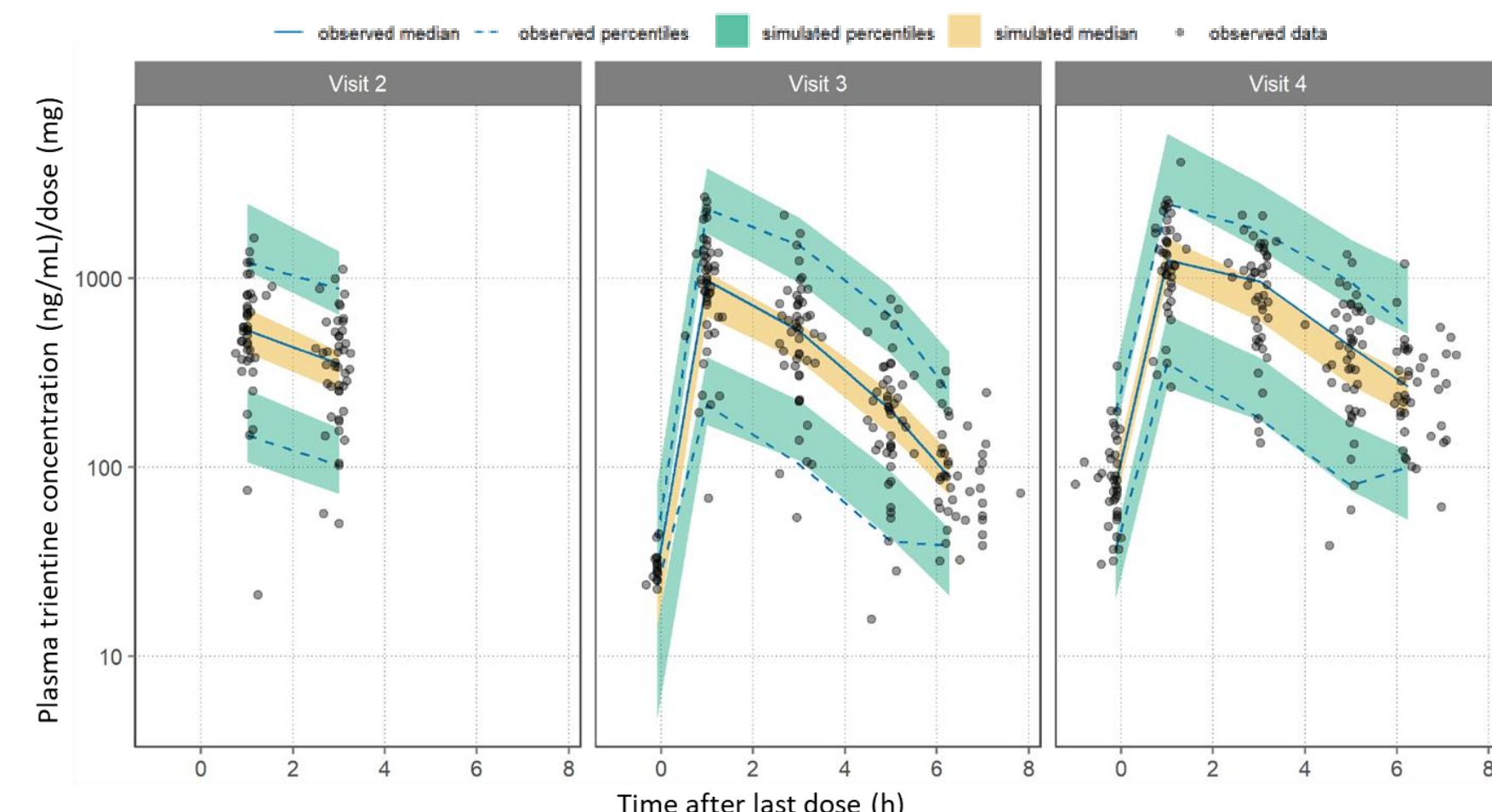


Figure 6: Prediction-Corrected Visual Predictive Checks of final popPK model per visit.

- The **final popPK model** included no covariates and hence equalled the **base popPK model**.
 - Plasma TETA concentrations were well described for all three visits (Figure 6).
- The **final popPK-PD model** (structure given in Figure 2) included an effect of **ALT on K_{in}** as well as an effect of **weight on slope**.
 - This model described both the 24h-UCE and the serum EC data of the up-titration phase of the UNITED study well (Figures 7 and 8).
- All parameter estimates were estimated with **good precision** (RSE <50%, not shown)

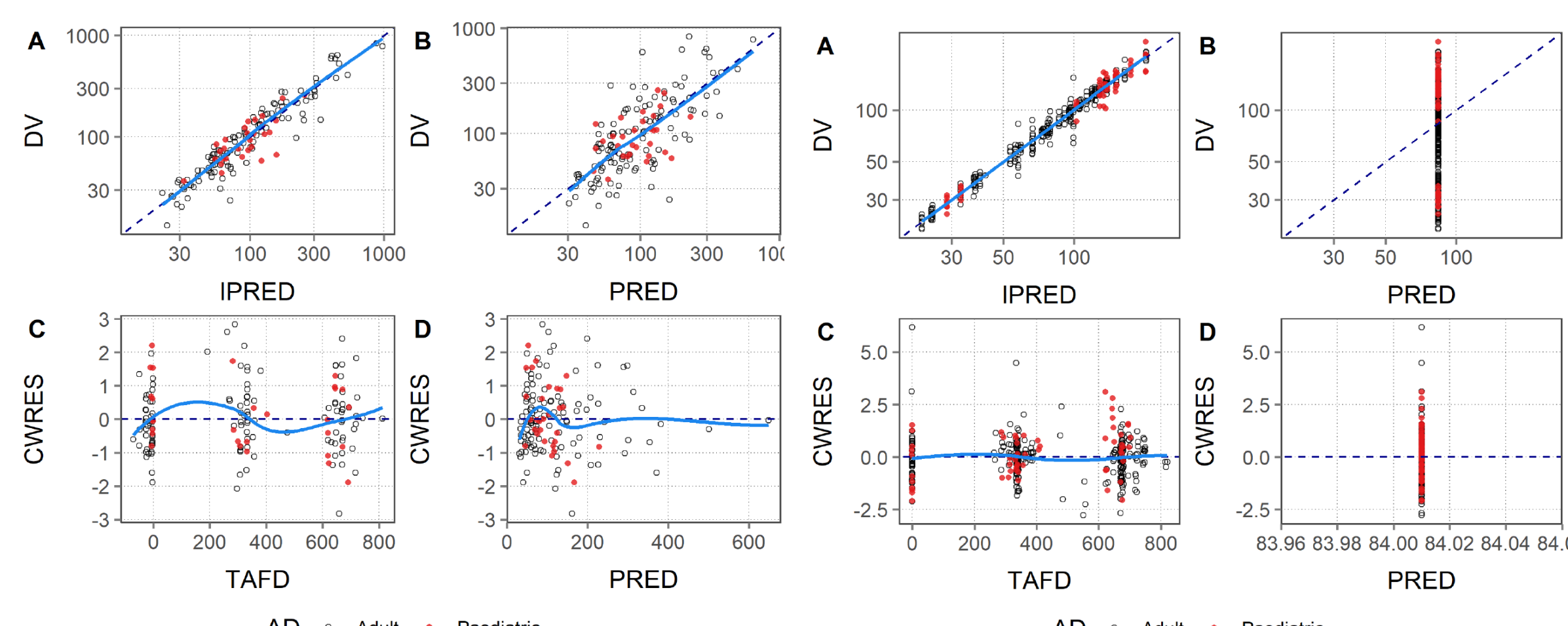


Figure 7: Goodness-of-fit plots of (1) 24h-UCE and (2) of serum EC concentrations.

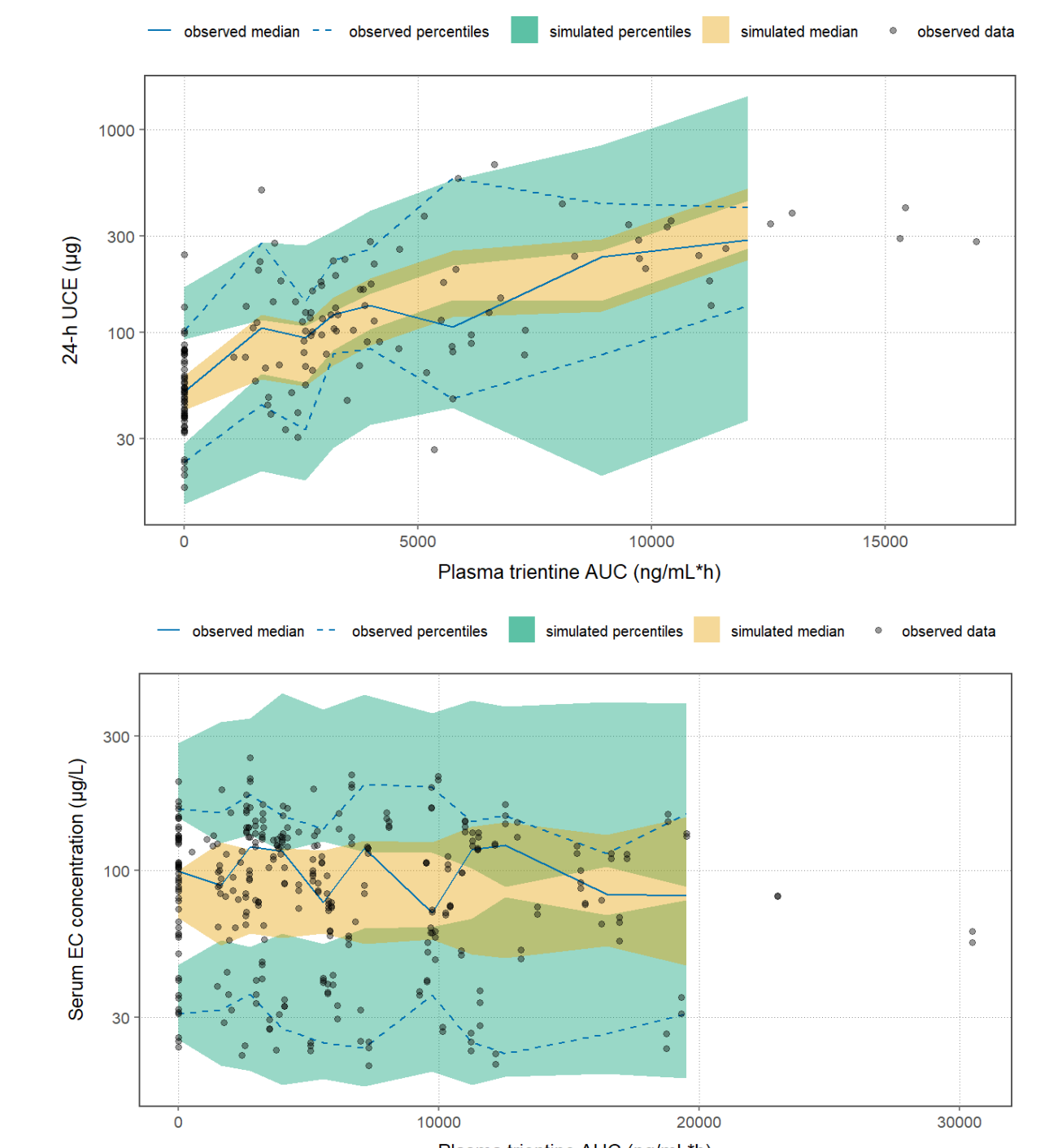


Figure 8: Prediction-Corrected Visual Predictive Checks: (A) 24h-UCE and (B) Serum EC concentration versus plasma trientine exposure (AUC; ng/mL*h) in all WD patients.

Conclusions

In this study, we were able to establish a final popPK-PD model that may form the basis of a response-guided dosing for TETA-2HCl in Wilson Disease. Using the final popPK-PD model we were able to describe the relationship between TETA and 24h-UCE well. Furthermore, the final popPK-PD model indicated potential effects of baseline ALT on K_{in} and weight on SL (drug effect).