

Quantitative evaluation of the impact of CYP2D6 genetic polymorphisms on pharmacokinetics of tamoxifen and its metabolites in breast cancer patients

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Background

- ✓ Treatment of hormone-dependent breast cancer with **tamoxifen (TAM)** is associated with **high interindividual variability (IIV)** in treatment outcome (**efficacy, toxicity**)
- ✓ **Genetic polymorphisms of the CYP2D6** metabolising enzyme contribute to differences in **plasma exposure to TAM active metabolite endoxifen [ENDO]**
- ✓ **Due to inconsistent results** regarding the impact of genetic polymorphisms of CYP2D6 on TAM efficacy and toxicity, **it has not been possible to establish dose recommendations**
- ✓ **The detailed quantification** of the impact of **CYP2D6 genetic polymorphisms** on plasma levels of ENDO remains to be determined by a PK model in order to perform **PK-guided dose adjustment of TAM**

Objective

To develop a **population PK (PopPK) model** describing the steady-state concentrations of **TAM and three of its metabolites** in breast cancer patients and to **quantify the detailed impact of genetic polymorphisms of CYP2D6** on plasma levels of ENDO.

Methods

Patients and data

- PK and pharmacogenetic (PG) data come from a **prospective, multicenter, 3-year follow up study (PHACS study, NCT01127295)** including breast cancer patients starting treatment with TAM at 20 mg once daily in adjuvant setting.
- Plasma concentrations of TAM, N-desmethyl TAM (NDT), 4OH-TAM and ENDO were measured by a validated UPLC-MS/MS method [1].

CYP2D6 genetic polymorphisms

- Patients were genotyped for single nucleotide polymorphisms (SNP) in the **CYP2D6** gene at study inclusion
- A phenotype was assigned to each **CYP2D6** allele according to its activity (Table 1). Each patient has two alleles therefore two associated phenotypes; the combination of these phenotypes represents the diplophenotype. These diplophenotypes were then collapsed into metaboliser status (MS) with four classes based on the previously proposed classification system [2] (Table 2).

Table 1. CYP2D6 alleles analysed in the study with their respective activity and phenotype.

Enzyme activity	Allele	Phenotype
normal	*1	Extensive (EM)
reduced	*9, *10, *17, *41	Intermediate (IM)
none	*4, *5, *6, *7	Poor (PM)
increased	gene duplication (*1xN)	Ultra rapid (UM)

Table 2. Classification of CYP2D6 diplophenotype into metaboliser status.

CYP2D6 diplophenotype	Metaboliser status (MS)
EM/EM	EM
EM/IM	
EM/PM	
IM/IM	IM
IM/PM	PM
PM/PM	UM

PK analysis

- Longitudinal **concentration-time data for 209 patients** (n=934, one trough concentration every 6 months up to 36 months) were analysed in NONMEM version 7.4 using FOCE with INTERACTION option.
- Data were described by a **four-compartment model** with linear conversion of TAM into NDT and 4OH-TAM, both converted to ENDO, and linear elimination (Fig. 1).

Covariate analysis

- A separate fixed effect was estimated for each **CYP2D6 phenotype**. Two different classifications were tested:
 - **MS** (four classes: IM, PM, UM with EM as the reference group)
 - **diplophenotype** (seven classes: EM/IM, EM/PM, IM/IM, IM/PM, PM/PM, UM with EM/EM as the reference group).

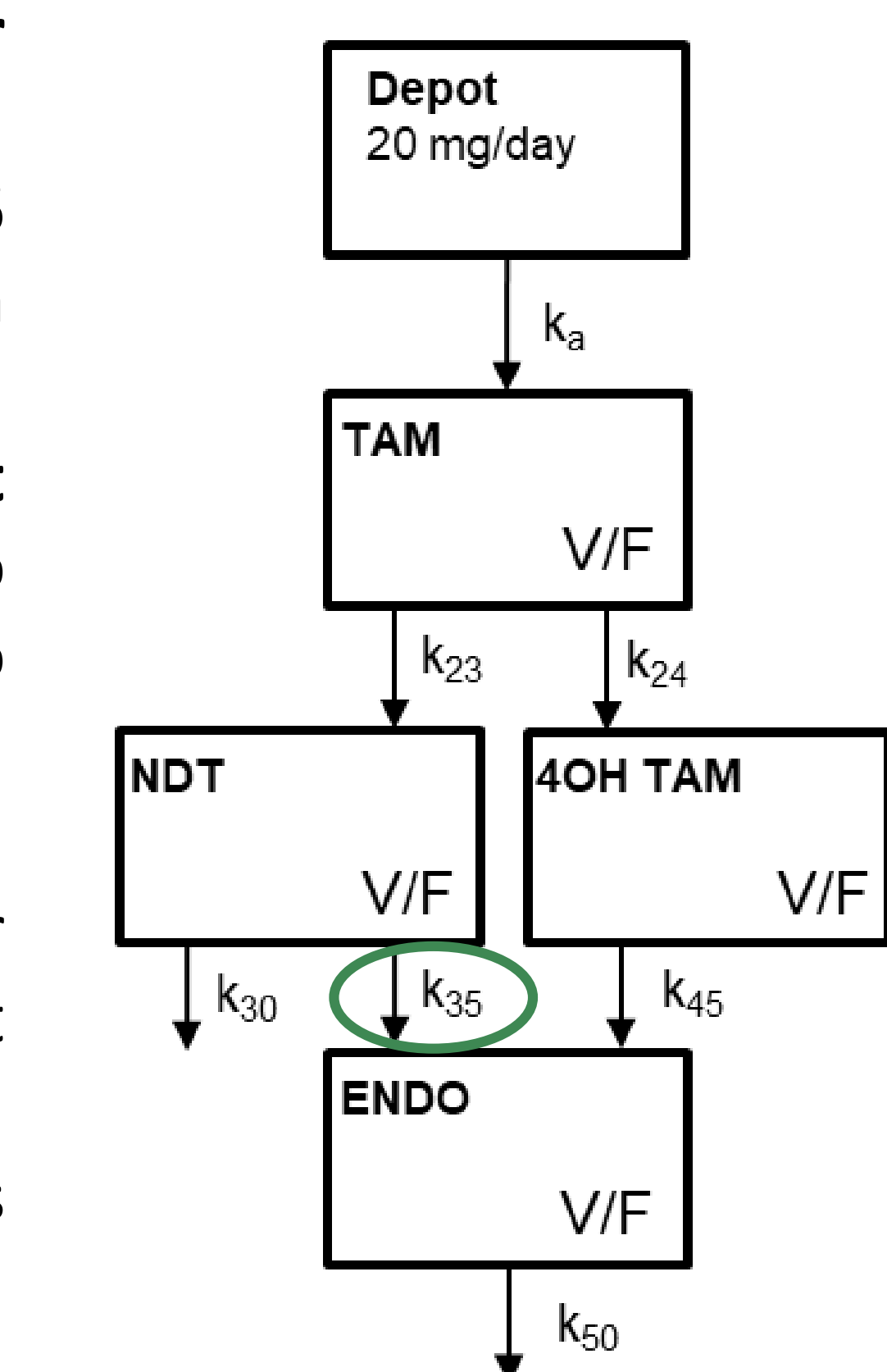


Fig. 1 Schematic representation of the structural model.

Results

→ **CYP2D6 activity was significantly associated with NDT to ENDO conversion rate constant (k_{35})**

→ **The CYP2D6 activity classified as diplophenotype was retained in the final model as it explained 47% of the IIV on k_{35} compared to 33% explained by CYP2D6 MS classification**

CYP2D6 diplophenotype	Effect on k_{35} value comparing to EM/EM
EM/IM and EM/PM	↓ 35%
IM/IM	↓ 66%
IM/PM	↓ 75%
PM/PM	↓ 86%
UM	↑ 27%

Table 3. Parameter estimates of the base and final model.

Parameter	Mean estimate (%RSE)	
	Base model	Final model
ka (h ⁻¹)	0.7 fixed	0.7 fixed
V/F (L)	996 fixed	996 fixed
k ₂₃ (h ⁻¹)	6.99 x 10 ⁻³ (2%)	7.0 x 10 ⁻³ (4%)
k ₂₄ (h ⁻¹)	2.28 x 10 ⁻⁵ (35%)	2.06 x 10 ⁻⁵ (77%)
k ₃₅ (h ⁻¹)	4.06 x 10 ⁻⁴ (30%)	7.14 x 10 ⁻⁴ (35%)
EM/IM and EM/PM on k₃₅		0.648 (7%)
IM/IM on k₃₅		0.344 (21%)
IM/PM on k₃₅		0.246 (14%)
PM/PM on k₃₅		0.137 (15%)
UM on k₃₅		1.27 (11%)
k ₃₀ (h ⁻¹)	3.92 x 10 ⁻³ (6%)	3.84 x 10 ⁻³ (9%)
k ₄₅ (h ⁻¹)	7.86 x 10 ⁻⁴ (34%)	7.07 x 10 ⁻⁴ (76%)
k ₅₀ (h ⁻¹)	8.08 x 10 ⁻³ (27%)	9.23 x 10 ⁻³ (35%)
Interindividual variability (%RSE) [shrinkage]		
k ₂₃	29.5% (7%) [6%]	29.7% (6%) [5%]
k ₂₄	72.2% (4%) [2%]	73.5% (8%) [2%]
k₃₅	71.1% (6%) [3%]	37.4% (6%) [10%]
k ₃₀	44.6% (7%) [3%]	46.0% (9%) [3%]
Residual error	Mean estimate (%RSE) [shrinkage]	Correlation (%RSE)
TAM	25.2% (6%) [9%]	79.4% (9%)
NDT	26.2% (7%) [9%]	
4OH TAM	29.6% (6%) [9%]	81.0% (8%)
ENDO	31.5% (6%) [9%]	

Simulated steady-state PK profiles

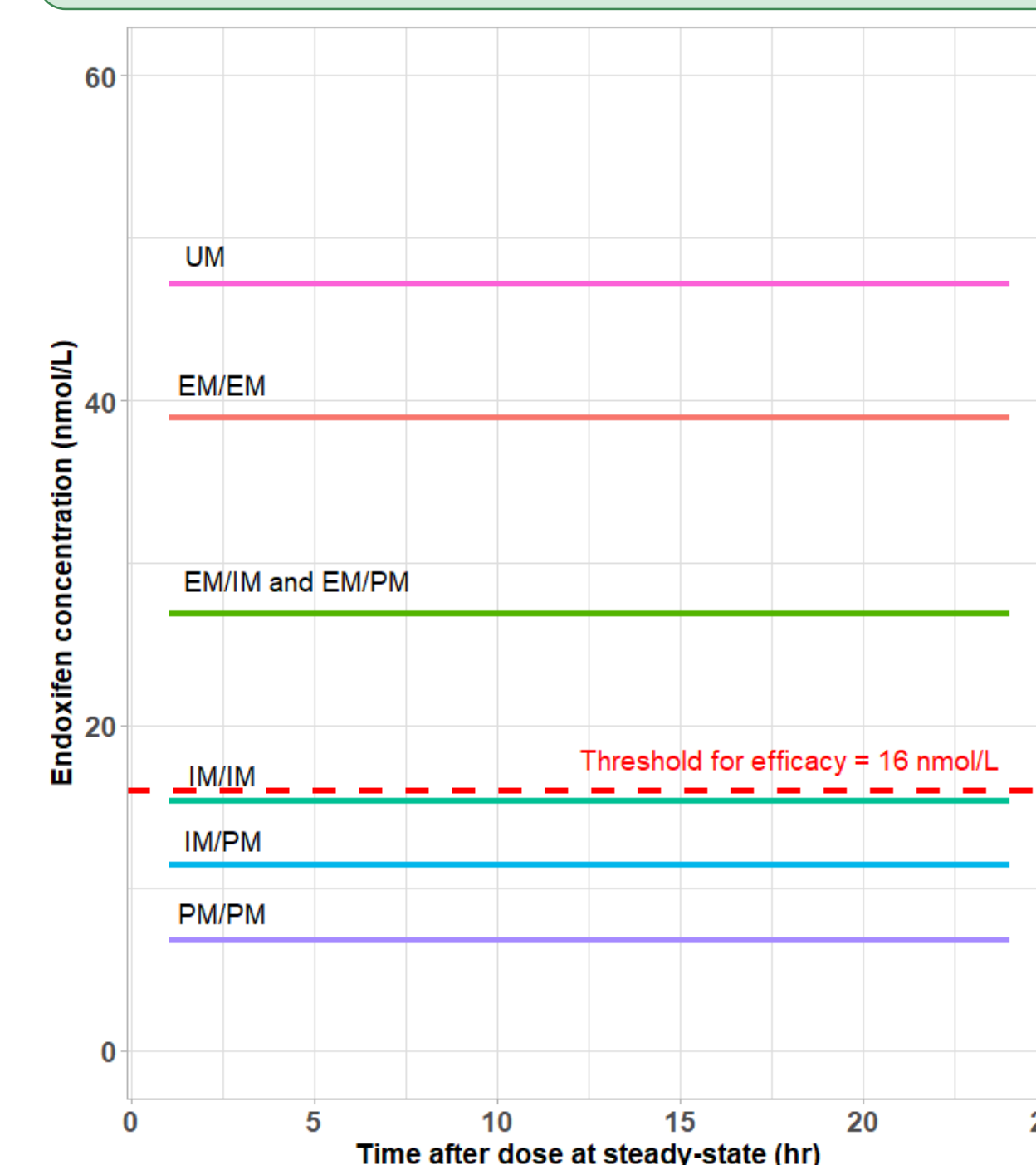


Fig. 2 Simulated mean PK profiles of ENDO at steady-state according to CYP2D6 diplophenotype.

Based on the mean simulated PK ENDO profiles at steady-state, **IM/IM, IM/PM and PM/PM patients may not achieve the plasma ENDO concentration threshold** associated with better efficacy [3] (Fig 2).

Evaluation of the final model

Fig. 3 Goodness-of-fit plots of the final model.

CWRES conditional weighted residuals, PRED population predictions

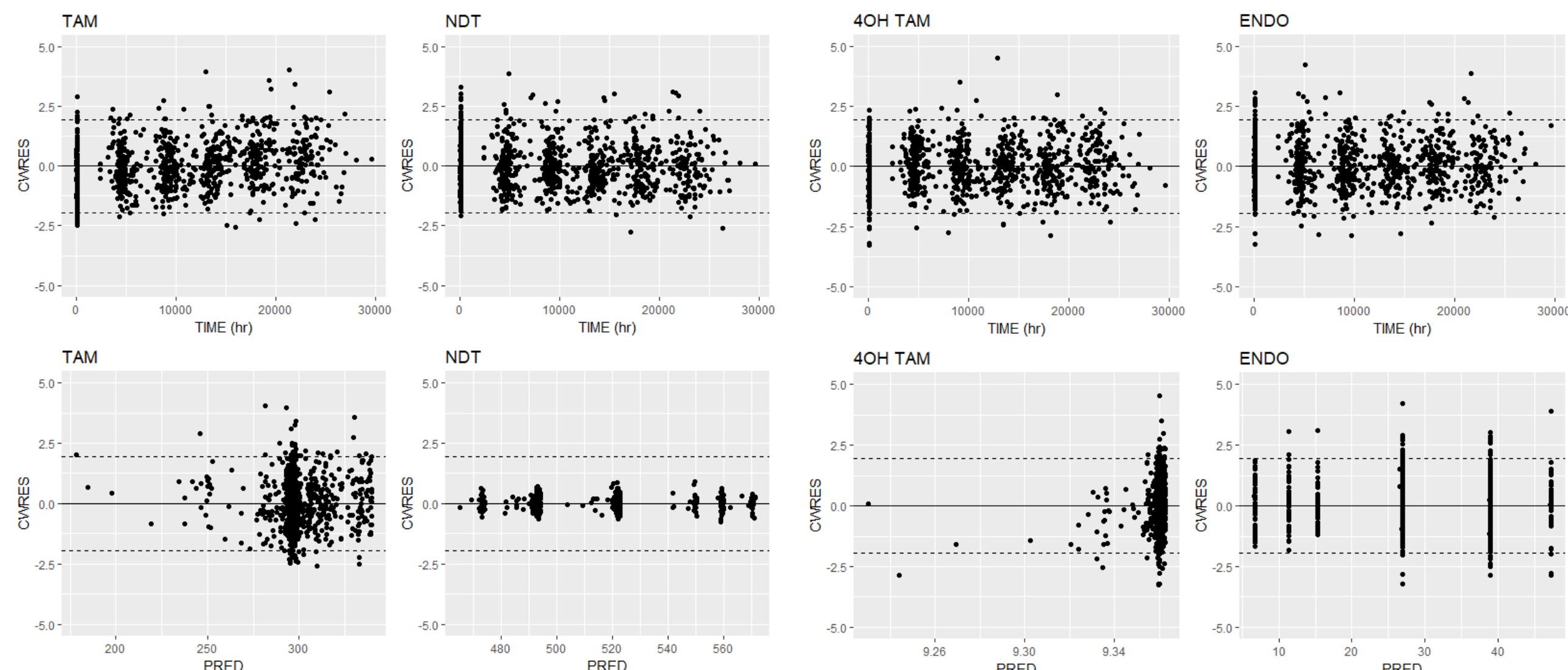
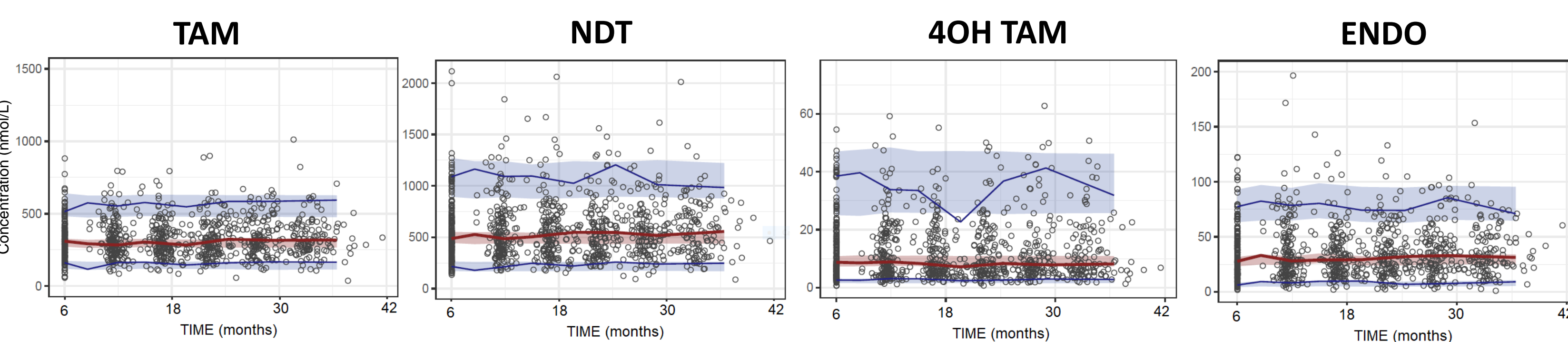


Fig. 4 Visual Predictive Check based on 1000 simulations of the original data set using the final model.



Conclusions

- ✓ The developed PopPK model could be useful to perform TAM dose simulations based on individual genetic characteristics
- ✓ Further analyses will focus on the inclusion of the genetic polymorphisms of CYP2D6 and other genes on the remaining conversion rate constants

References

[1] Arellano et al. JPBA 2014; [2] Gaedigk et al. CPT 2008; [3] Madlensky et al. CPT 2011;