

# Population pharmacokinetic analysis of tamoxifen and its six metabolites in breast cancer patients: quantification of the impact of genetic polymorphisms and co-medications on tamoxifen metabolism

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## Background

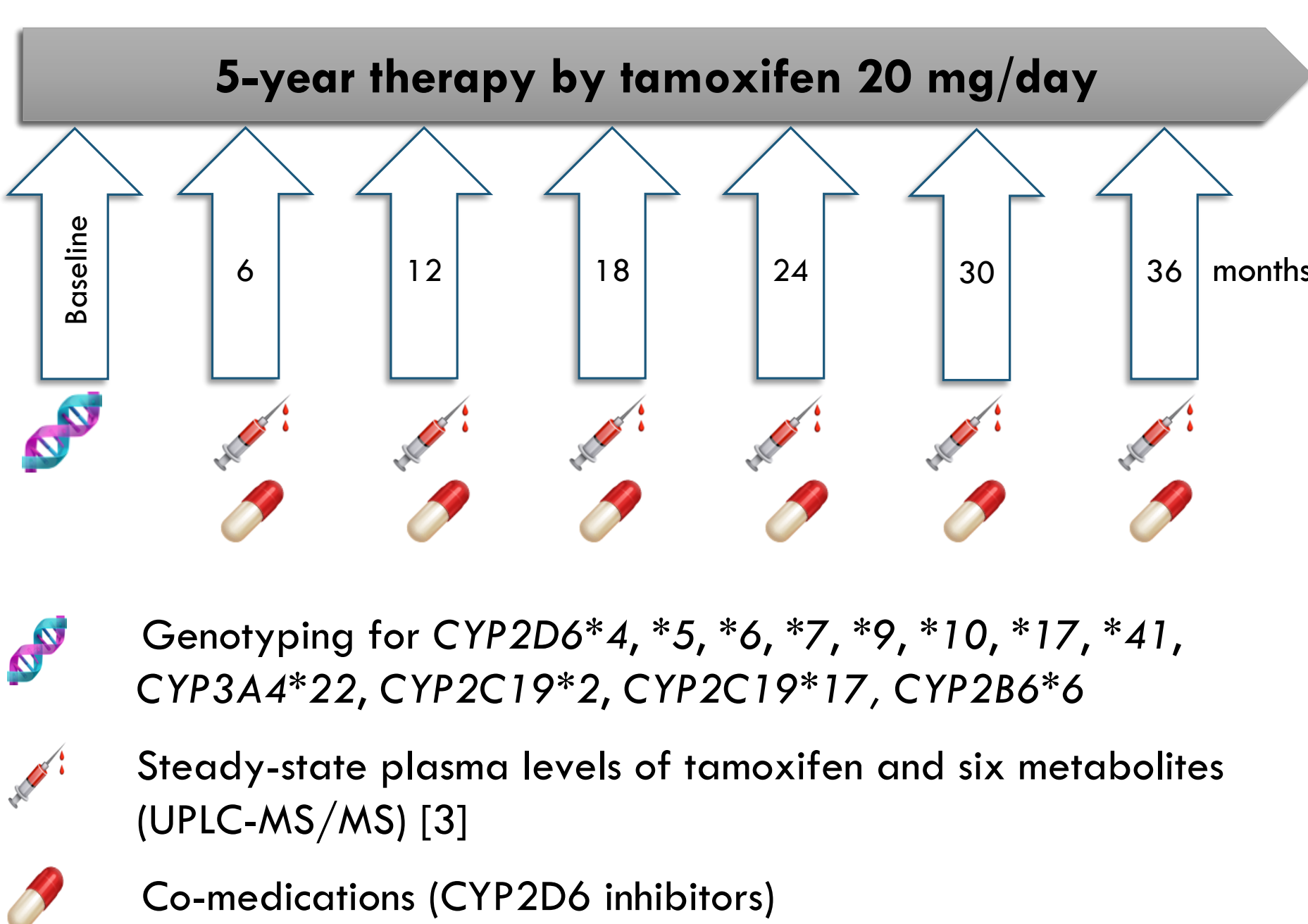
- 5-year therapy by tamoxifen is a cornerstone in the adjuvant treatment of estrogen receptor (ER)-positive breast cancer [1].
- The metabolism of tamoxifen is mediated by multiple cytochromes P450 (CYP2D6, CYP3A4, CYP2C19, CYP2B6) and the variability in their enzymatic activity may impact the formation of tamoxifen metabolites, in particular endoxifen (the major active component), and *in fine* the therapeutic outcome.
- The optimisation of tamoxifen therapy could be achieved by dose-adjustment based on individual characteristics and subsequent therapeutic drug monitoring (TDM) of plasma endoxifen levels, although a universally accepted therapeutic threshold for endoxifen still needs to be confirmed [2].

### The objectives:

- Development of a population PK model for tamoxifen and its six major metabolites
- Quantification of the impact of genetic polymorphisms and co-medications on tamoxifen metabolism
- Dose-adjustment simulations in patients at increased risk of subtherapeutic exposure based on their genetic characteristics

## Methods: Model development in NONMEM

### PHACS study



### PK analysis

- The preliminary data included 917 patients providing 3 868 samples (27 076 concentrations)
- Data were analysed in NONMEM version 7.4.1 using FOCE-I
- A seven-compartment model with linear conversion rate constants and linear elimination (Fig. 1) was fit to the data

### Covariates

- CYP2D6 phenotype (poor (PM), intermediate (IM), normal (NM) and ultrarapid (UM))
- CYP3A4\*22, CYP2C19\*2, CYP2C19\*17 and CYP2B6\*6 genotypes
- Body weight, age
- Concomitant CYP2D6 inhibitors (weak/moderate or potent)

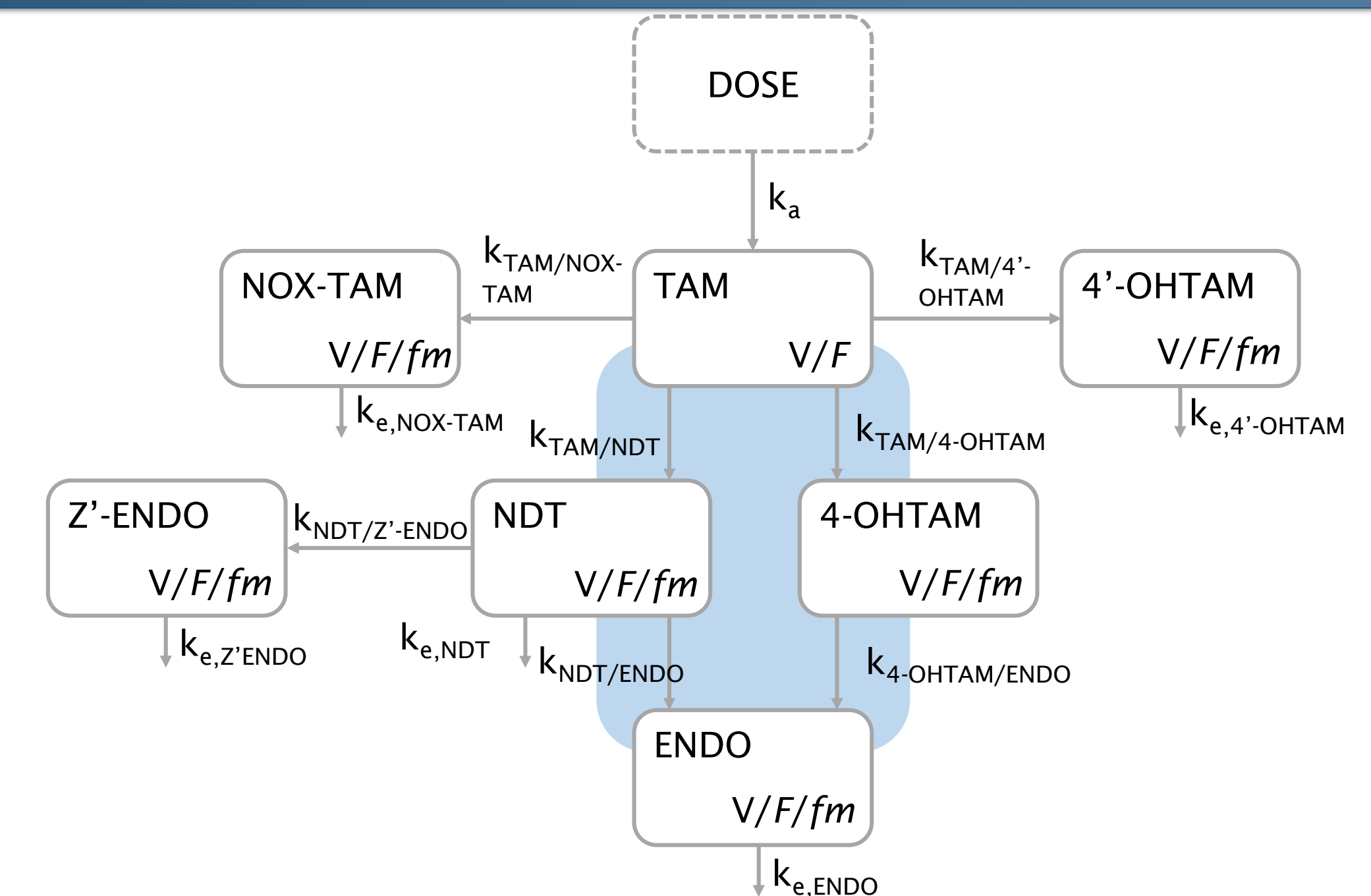


Fig. 1 Schematic representation of the structural model. Apparent volumes of distribution of the metabolites (V/F) were fixed to the value of V/F of tamoxifen.

## Results

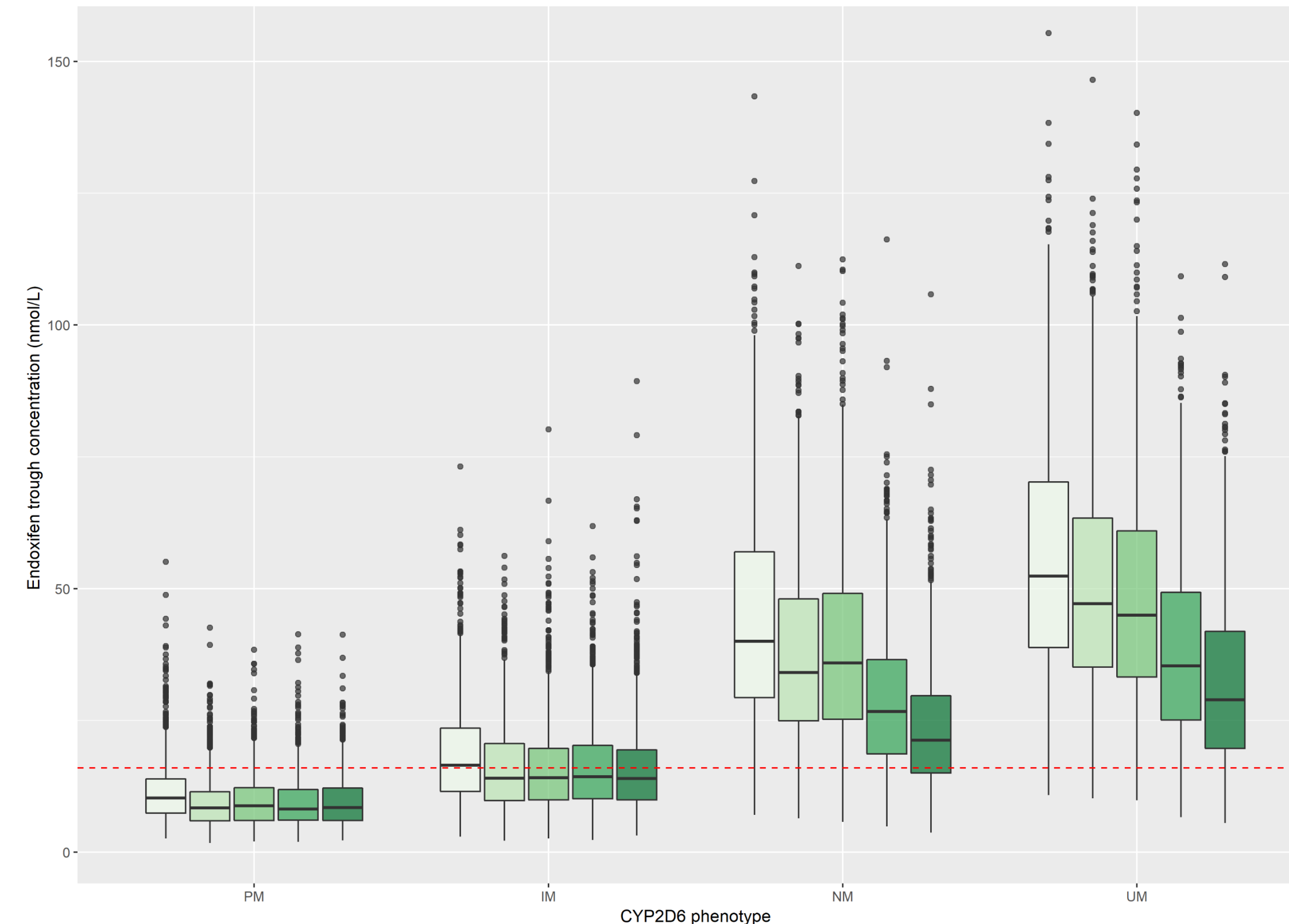
Table 1. Estimates of the final model with significant covariates.

Parameter	Mean estimate (%RSE)	Inter-individual variability, %CV (%RSE) [ $\eta$ -shrinkage]
$k_a$ (h <sup>-1</sup> )	0.9 (fixed)	-
V/F (L)	966 (fixed)	-
$k_{TAM/NDT}$ (h <sup>-1</sup> )	$7.28 \times 10^{-3}$ (2.2)	30.8 (2.8) [6.5]
CYP3A4*22 carriers <sup>a</sup>	0.79 (5.8)	-
Age	-0.25 (24)	-
$k_{TAM/4-OHTAM}$ (h <sup>-1</sup> )	$6.17 \times 10^{-5}$ (20)	51.5 (3.1) [8.2]
CYP2D6 IM or PM phenotype <sup>b</sup>	0.72 (6.1)	-
CYP2D6 missing phenotype <sup>b</sup>	1.35 (6.5)	-
Age	-0.43 (28)	-
$k_{TAM/4'-OHTAM}$ (h <sup>-1</sup> )	$6.1 \times 10^{-8}$ (1.6)	19.7 (4.8) [29]
$k_{TAM/NOX-TAM}$ (h <sup>-1</sup> )	$2.47 \times 10^{-7}$ (2.3)	44.8 (3.2) [14]
CYP2B6*6/*6 genotype <sup>c</sup>	0.74 (7.0)	-
$k_{NDT/ENDO}$ in CYP2D6 UM (h <sup>-1</sup> )	$10.4 \times 10^{-4}$ (10)	47.7 (3.2) [12]
$k_{NDT/ENDO}$ in CYP2D6 NM (h <sup>-1</sup> )	$7.06 \times 10^{-4}$ (6.9)	
$k_{NDT/ENDO}$ in CYP2D6 IM (h <sup>-1</sup> )	$2.47 \times 10^{-4}$ (8.9)	
$k_{NDT/ENDO}$ in CYP2D6 PM (h <sup>-1</sup> )	$1.31 \times 10^{-4}$ (12)	
$k_{NDT/ENDO}$ in missing CYP2D6 (h <sup>-1</sup> )	$9.02 \times 10^{-4}$ (13)	-
Weak/moderate CYP2D6 inhibitor in NM and UM patients	0.71 (6.0)	-
Potent CYP2D6 inhibitor in NM and UM patients	0.53 (6.4)	-
Age	-0.42 (25)	-
$k_{NDT/Z'-ENDO}$ (h <sup>-1</sup> )	$4.09 \times 10^{-7}$ (1.0)	-
$k_{4-OHTAM/ENDO}$ (h <sup>-1</sup> )	$3.36 \times 10^{-3}$ (19)	-
$k_{e,NDT}$ (h <sup>-1</sup> )	$3.48 \times 10^{-3}$ (4.5)	46.4 (2.9) [4.6]
CYP3A4*22 carriers <sup>a</sup>	0.81 (8.3)	-
Body weight	0.23 (24)	-
$k_{e,ENDO}$ (h <sup>-1</sup> )	$11.9 \times 10^{-3}$ (6.1)	-
$k_{e,4'-OHTAM}$ (h <sup>-1</sup> )	$2.01 \times 10^{-6}$ (fixed)	-
$k_{e,NOX-TAM}$ (h <sup>-1</sup> )	$1.77 \times 10^{-6}$ (fixed)	-
$k_{e,Z'-ENDO}$ (h <sup>-1</sup> )	$1.08 \times 10^{-5}$ (fixed)	-
<b>Residual variability, %CV [<math>\epsilon</math>-shrinkage]</b>		
$\sigma_{prop,TAM}$	30.9 (1.6) [6.3]	-
$\sigma_{prop,NDT}$	34.6 (2.1) [4.8]	-
$\sigma_{prop,4-OHTAM}$	38.2 (1.8) [8.4]	-
$\sigma_{prop,ENDO}$	41.4 (1.9) [7.3]	-
$\sigma_{prop,Z'-ENDO}$	40.5 (1.6) [3.5]	-
$\sigma_{prop,4'-OHTAM}$	34.9 (1.8) [6.6]	-
$\sigma_{prop,NOX-TAM}$	59.5 (2.0) [5.9]	-

<sup>a</sup> reference: CYP3A4\*22 non-carriers; <sup>b</sup> reference: CYP2D6 NM phenotype; <sup>c</sup> reference: CYP2B6\*1/\*1 and \*1/\*6

### Covariate analysis

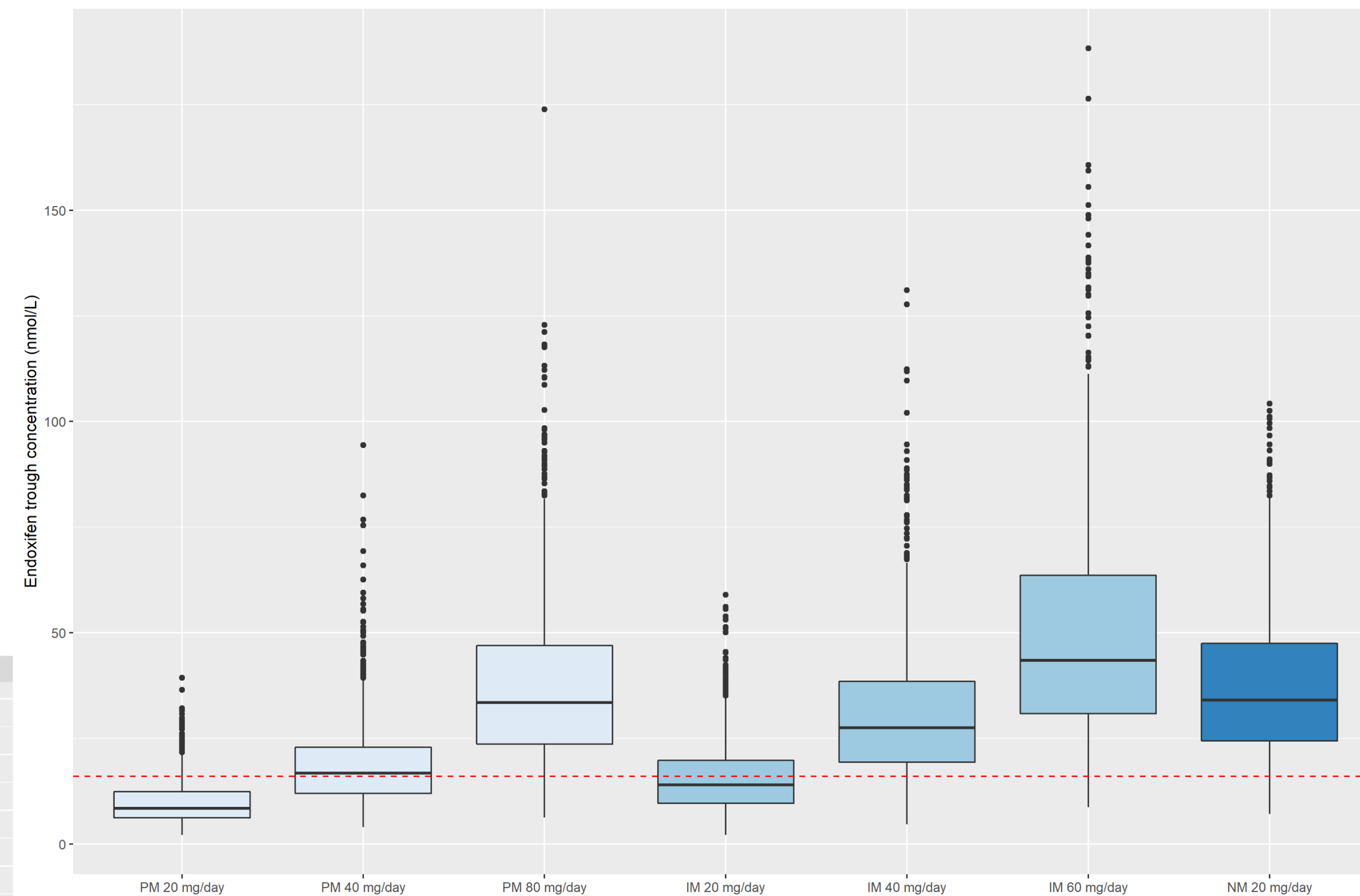
TAM to 4-OHTAM conversion	↘ by 28% in CYP2D6 IM and PM
TAM to NDT conversion	↘ by 21% in CYP3A4*22 carriers
TAM to NOX-TAM conversion	↘ by 26% in CYP2B6*6/*6 carriers
NDT to ENDO conversion	↘ by 81% and 65% in CYP2D6 IM and PM, respectively, and ↗ by 47% in CYP2D6 UM ↘ by 29% and 47% for weak/moderate and potent CYP2D6 inhibitors (in CYP2D6 NM and UM)
NDT elimination	↘ by 19% in CYP3A4*22 carriers



### Impact of CYP2D6, CYP3A4\*22, CYP2B6\*6 and CYP2D6 inhibitors on endoxifen levels

Fig. 3 Simulated endoxifen concentrations according to CYP2D6 phenotype, CYP3A4\*22 and CYP2B6\*6 genotypes and CYP2D6 inhibitors. For each combination, n=1000 endoxifen concentrations were simulated. The red dashed line represents the previously proposed plasma endoxifen threshold [1].

- According to simulations, only 11% and 40% of CYP2D6 PM and IM, respectively, reach the endoxifen therapeutic threshold at standard dose of 20 mg/day



### Dose-adjustment simulations according to CYP2D6 phenotype

Fig. 4 Simulated endoxifen concentrations according to CYP2D6 phenotype and different dosing regimens. The red dashed line represents the previously proposed plasma endoxifen threshold [1].

- A dose increase from the recommended dose of 20 mg/day to 40 and 80 mg/day in CYP2D6 PM patients increased the number of patients reaching the endoxifen therapeutic threshold to 54% and 94%, respectively
- In CYP2D6 IM patients, a dose increase to 40 and 60 mg/day increased the number of patients reaching the endoxifen therapeutic threshold to 85% and 98% patients, respectively

**Conclusions:** Based on simulations, a dose increase to 80 and 40 mg/day in CYP2D6 PM and IM patients, respectively, could help to increase the number of patients reaching the endoxifen therapeutic threshold consistently with previous reports [4]. Research with efficacy data is needed to confirm the clinical benefit of CYP2D6 phenotype guided dosing.

**References:** [1] EBCTCG 1998; [2] Madlensky *et al.* CPT 2011; [3] Arellano *et al.* JPBA 2014; [4] Klopp-Schulze *et al.* CPK 2017.

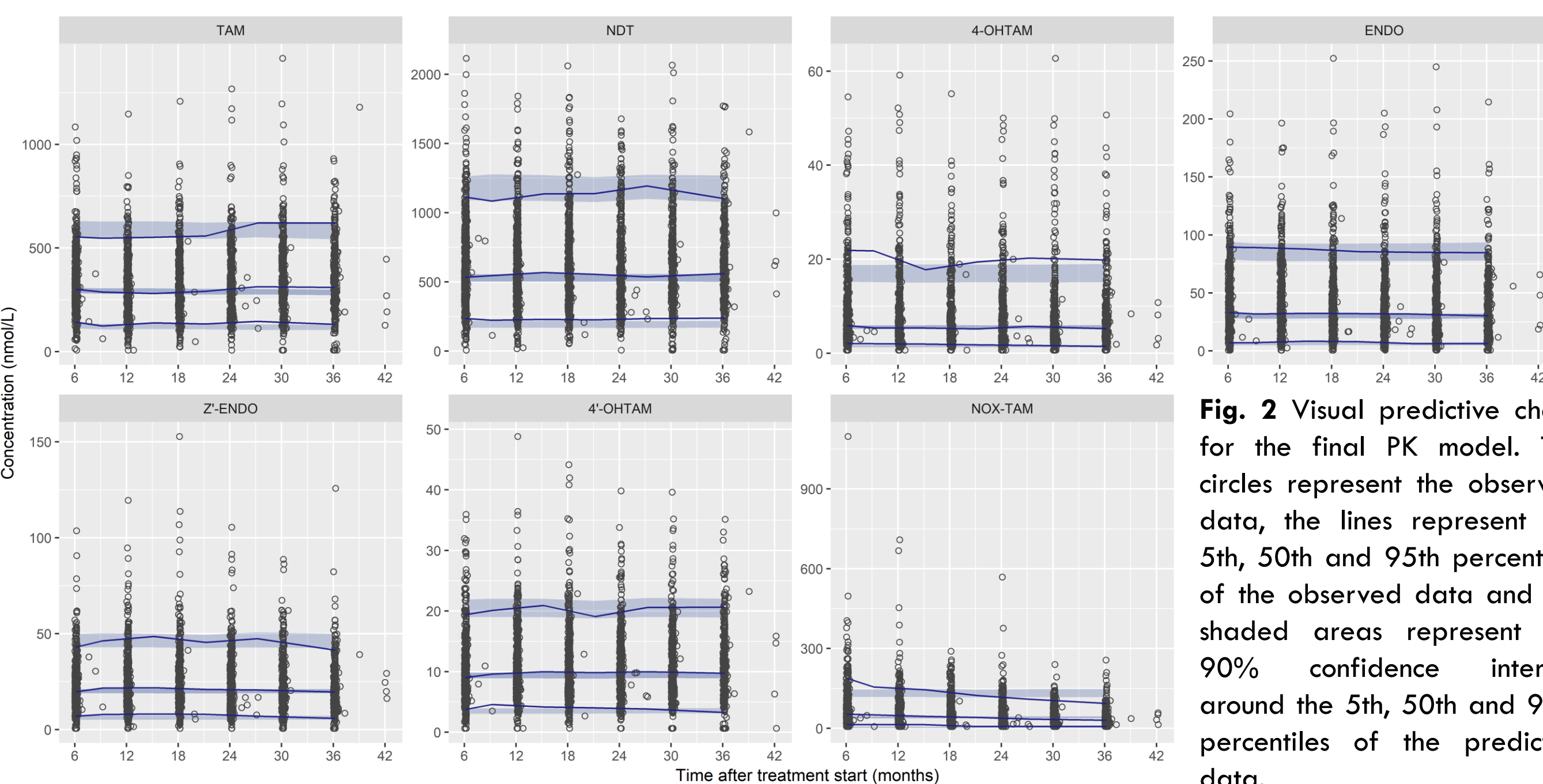


Fig. 2 Visual predictive check for the final PK model. The circles represent the observed data, the lines represent the 5th, 50th and 95th percentiles of the observed data and the shaded areas represent the 90% confidence interval around the 5th, 50th and 95th percentiles of the predicted data.