

# Tamoxifen and endoxifen pharmacokinetics: Exploration of differences in model performance using simulations

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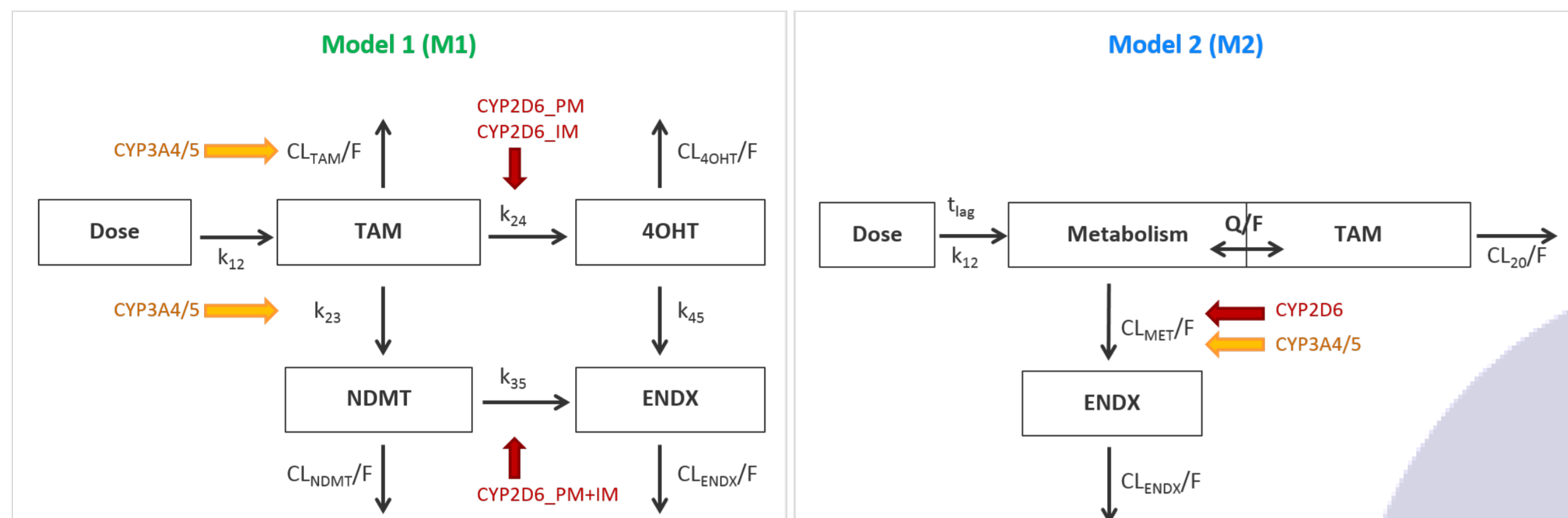
## Background and Objectives

Two published population pharmacokinetic (PK) models of tamoxifen (TAM) and its major metabolite endoxifen (ENDX) - Model 1 ("M1", [1]) and Model 2 ("M2", [2]) - have been built from data at steady-state; both implemented the impact of CYP2D6 and CYP3A4/5 activity but using different structural models. A previous investigation comparing the performance of M2 and M1 revealed considerable differences in predicted trough concentrations at

steady-state ( $C_{ss,min}$ ) of TAM (-40%) and ENDX (-20%). Furthermore, M1 was in high agreement with previous reported results [3]. Accurate model predictions are crucial for model reuse as prior knowledge to apply to sparse data situations.

The aim of this work was to explore potential reasons for the unexpected differences in model predictions and their impact on future use.

## Methods



**Figure 1. Schematic representation of the two population PK models for tamoxifen (TAM) and its metabolites N-desmethyltamoxifen (NMDT), 4-hydroxytamoxifen (4OHT) and endoxifen (ENDX) modified from [1,2].**  $CL_x/F$ , relative clearance of compound from compartment x; CYP2D6, continuous covariate for CYP2D6 activity; CYP3A4/5, continuous covariate for CYP3A4/5 activity; CYP2D6\_PM, categorical covariate for CYP2D6 poor metaboliser; CYP2D6\_IM, categorical covariate for CYP2D6 intermediate metaboliser; CYP2D6\_PM+IM, categorical covariate for CYP2D6 poor and intermediate metaboliser; Dose, TAM dose; Metabolism, hypothetical liver compartment;  $k_{12}$ , absorption rate constant;  $k_{21}$ , formation rate constant of metabolising compound from compartment x to metabolite in compartment y;  $Q/F$ , intercompartmental flow;  $t_{lag}$ , lag time.

## Simulation scenarios

Reference scenario and population:

- The standard TAM therapy regimen, 20 mg TAM p.o. once daily, was used to simulate  $C_{ss}$  with M1 and M2 (Table 1 and Figure 1).
- Simulated populations were assumed (i) to represent similar CYP phenotype distributions, (ii) to be >80% adherent to their daily TAM intake, (iii) to show a bioavailability of 100% and (iv) to have reached PK steady-state conditions.

Modifications to the reference scenario:

- **Three hypotheses** were tested to explore lower  $C_{ss}$  predictions of M2:
  - (1) Modified bioavailability (F),
  - (2) Poor adherence to TAM intake,
  - (3) Assumption of steady-state.

➤ For hypotheses (1) and (2):

- Several populations of factor tiers with ranges from 0% (reference) to 50% (each  $n_{patients}=1000$ ) were simulated using M1 in Berkeley Madonna (v. 8.3.18) to reproduce predictions of M2.
- Adherence to daily drug intake was simulated as a binary outcome ('taken'/'not taken') with a constant probability of non-adherence.

➤ For hypothesis (3):

- M2 was used to extrapolate PK profiles (each  $n_{patients}=100$ ) from reported steady-state conditions to earlier time points, i.e. before reaching steady-state.
- PK parameters were re-estimated assuming steady-state at different days (5, 10, reference: 20) in NONMEM (v. 7.3).

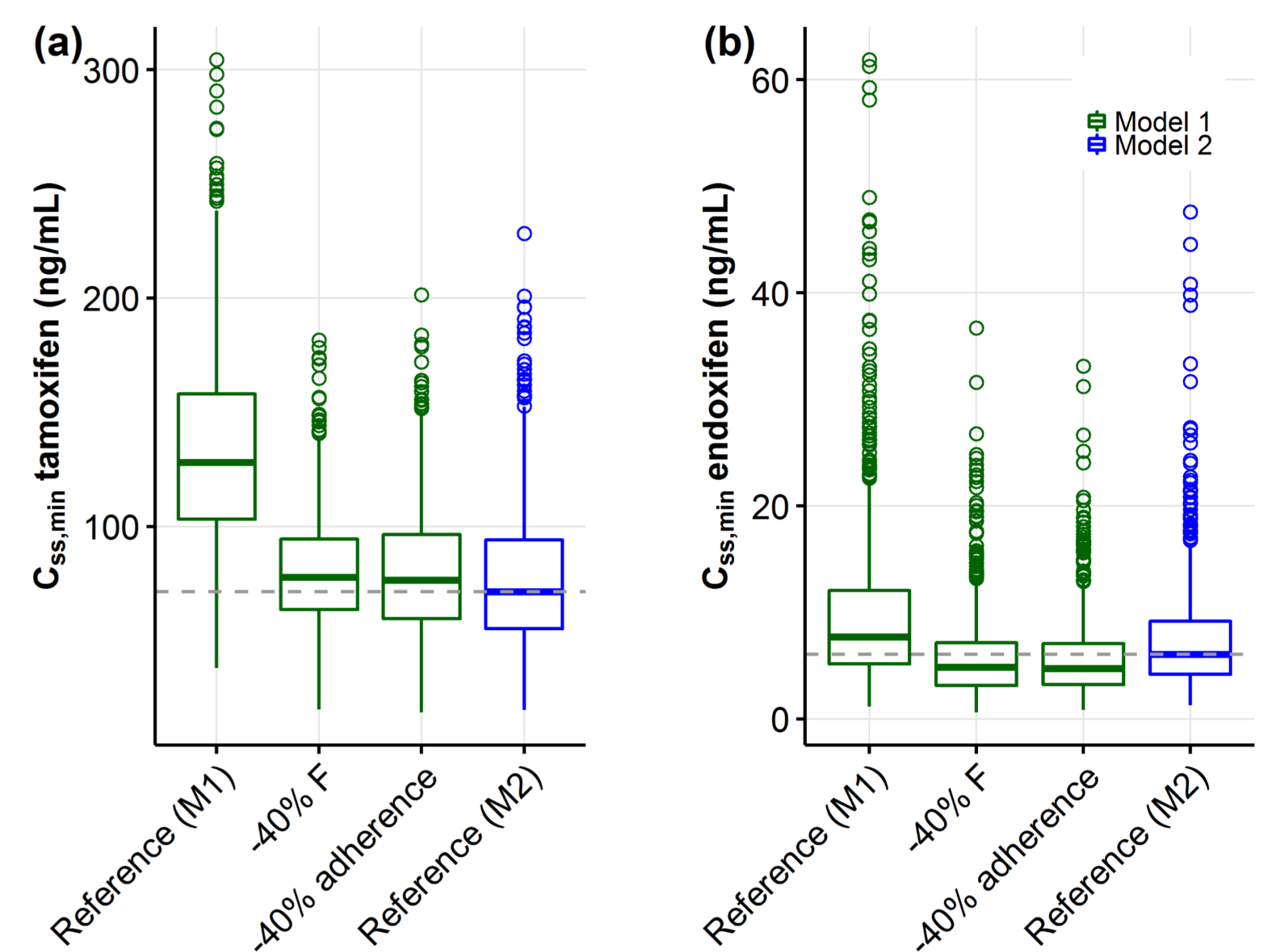
**Table 1. Parameter estimates and covariate distributions of Model 1 [1] and Model 2 [2] as used in presented simulation study.**

Parameter	Model 1 Estimates	Model 2 Estimates
<b>Fixed effects</b>		
$t_{lag}$ [h]		0.455
$k_{12}$ [1/h]	0.7 <sup>a</sup>	1.90
$CL_{TAM}/F$ [L/h]	5.8 <sup>b</sup>	9.64 <sup>c</sup>
$CL_{20}/F$ [L/h]		9.34
$V_{TAM}/F$ [L]	724	753
$V_{4OHT}/F$ [L]	$= V_{TAM}/F$	
$V_{NMDT}/F$ [L]	$= V_{TAM}/F$	
$V_{ENDX}/F$ [L]	$= V_{TAM}/F$	400 <sup>a</sup>
$k_{23}$ [1/h]	0.007	
$k_{24}$ [1/h]	0.000055	
$k_{35}$ [1/h]	0.0003	
$k_{45}$ [1/h]	0.015	
$CL_{NMDT}/F$ [L/h]	3.4	
$CL_{4OHT}/F$ [L/h]	2.9	
$CL_{ENDX}/F$ [L/h]	6.2	5.1 <sup>a</sup>
$CL_{MET}/F$ [L/h]		0.300
$Q/F$ [L/h]		61.8
<b>Interindividual variability (IIV)</b>		
IIV $CL_{TAM}/F$ , %CV	25	
IIV $CL_{20}/F$ , %CV		37.8
IIV $V_{TAM}/F$ , %CV		26.7
IIV $CL_{MET}/F$ , %CV		25.4
IIV $k_{23}$ , %CV	16	
IIV $k_{24}$ , %CV	26	
IIV $k_{35}$ , %CV	59	
$\rho$ ( $CL_{TAM}/F$ , $V_{TAM}/F$ ), %		61.2
$\rho$ ( $k_{24}$ , $k_{35}$ ), %	51	
<b>Covariate effects on PK</b>		
CYP3A4/5 on $CL_{TAM}/F$	0.16	
CYP3A4/5 on $k_{23}$	0.07	
CYP2D6_PM+IM on $k_{35}$	-0.26	
CYP2D6_PM on $k_{24}$	-0.96	
CYP2D6_IM on $k_{24}$	-0.56	
CYP2D6 on $CL_{MET}/F$		0.262
CYP3A4/5 on $CL_{MET}/F$		0.157
<b>Covariate distribution</b>		
$P(x = \text{CYP2D6 EM})$	0.525	
$P(x = \text{CYP2D6 IM})$	0.450	
$P(x = \text{CYP2D6 PM})$	0.250	
CYP2D6 [L/h]		1560 <sup>d</sup>
CYP3A4/5, MR	4.81 <sup>e</sup>	
CYP3A4/5 [L/h]		44.7 <sup>d</sup>
IIV CYP2D6, %CV		166 <sup>d</sup>
IIV CYP3A4/5, %CV	64.0 <sup>e</sup>	
IIV CYP3A4/5, %CV		89.8 <sup>d</sup>

%CV, coefficient of variation; MR, midazolam metabolic ratio;  $P$ , probability;  $\rho$ , correlation coefficient;  
a: Originally fixed to value from [4].  
b:  $CL_{TAM}/F = (k_{23} + k_{24} + k_{35}) \cdot V_{TAM}$ .  
c: Calculated by  $CL_{TAM}/F = CL_{20} + \frac{CL_{23} \cdot Q/F}{CL_{23} + Q/F}$ .  
d: Median and CV% of  $CL_{p-xn}$ , i.e. CYP2D6 or CYP3A4/5, from dextromethorphan (D) and metabolites (Xn) model using an exponential variability model [2].  
e: Median and CV% approximated from reported distribution (median and range) [1] assuming a log-normal distribution of individual  $MR_{CYP3A4/5}$ .

## Results and Discussion

**Figure 2. Simulation scenarios using Model 1 (M1) to reproduce predictions of Model 2 (M2).** Steady-state concentrations of (a) tamoxifen and (b) endoxifen in 1000 virtual patients with scenarios of reduced (i) adherence and (ii) bioavailability (F). Scenarios (i - ii) are compared to reference populations of M1 (assuming >80% adherence and F of ~100%) and of M2.

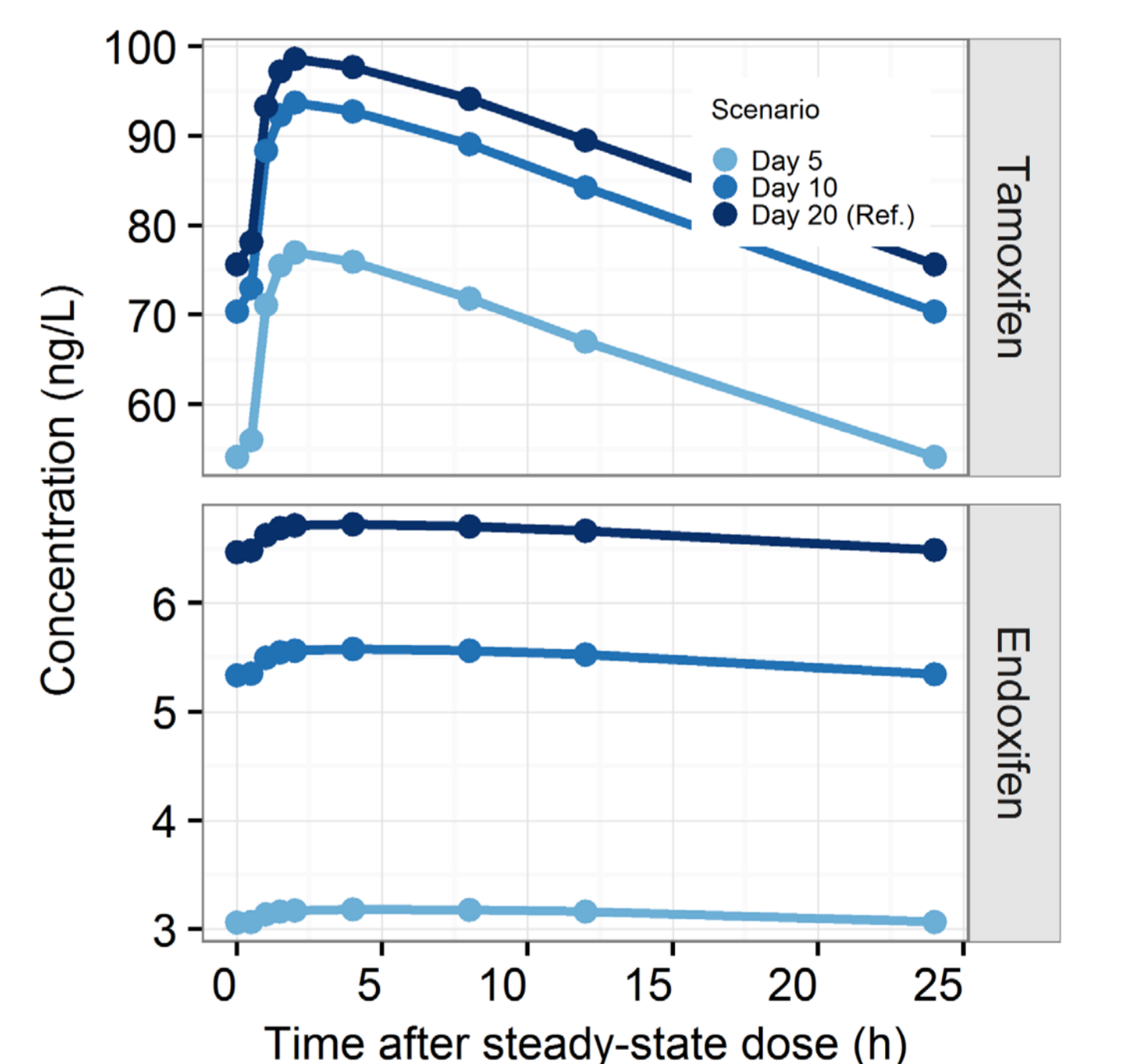


## Hypothesis (1) and (2)

- Modified bioavailability or poor adherence, both with decreases of 40% in M1, were able to reproduce predictions of  $C_{ss,min}$  of TAM in M2, but not of  $C_{ss,min}$  of ENDX as these were underpredicted by ~20% (Figure 2).

## Hypothesis (3)

- Scenarios with earlier assumption of steady-state, i.e. day 5 and 10, showed increased population  $CL_{TAM}$  estimates with 13.2 and 10.4 L/h, respectively in comparison to the reference with 9.75 L/h (day 20, i.e. reported steady-state conditions of TAM and ENDX according to M2).
- Consequently, with assuming steady-state too early (day 5 and 10)  $C_{ss,min}$  of TAM decreased by -26% and 5.9%, respectively, and  $C_{ss,min}$  of ENDX even more profound by -52% and -17%, respectively compared to the reference (day 20) (Figure 3).
- The %decrease from reference did not match the change needed (TAM>ENDX) to explain the predictions of M2 either.
- However,  $CL_{ENDX}/F$  has been originally fixed in M2 to a literature value [4] which might explain the less profound differences in predicted  $C_{ss,min}$  of ENDX between M1 and M2.



**Figure 3. Impact of assuming steady-state at different days on model predictions.** Three scenarios with steady-state assumed at day 5 and 10 (too early) and 20 (reference) were explored using M2. For each scenario steady-state concentrations (within 24 hours) of tamoxifen (top panel) and endoxifen (bottom panel) were predicted for 100 patients taking 20 mg once daily tamoxifen (median profile displayed).

## Conclusions

- None of the three hypotheses *per se* were able to capture both the predictions  $C_{ss}$  of TAM and ENDX for M2.
- The differences in model predictions might be **due to a combination of the hypothesised factors**, rather than explained by one factor alone, or additional factors.
- This simulation **exercise exemplifies** that factors such as steady-state assumption, differences in F or adherence have a **considerable impact on model predictions** of TAM and ENDX emphasising the **need to reliably document and account for them** in clinical trials, clinical practice and data analysis.

## References:

- [1] E. B. A. Dahmane. Thèse de doctorat: Univ. Genève. No. Sc. 4617 (2013).
- [2] R. Ter Heine *et al.* Brit J Clin Pharmacol 78: 572-86 (2014).
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- [4] A. Ahmad *et al.* Clin Pharmacol. Ther. 88: 814-817 (2010).



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