

# Population Pharmacokinetics of Tamoxifen and three of its metabolites in Breast Cancer patients

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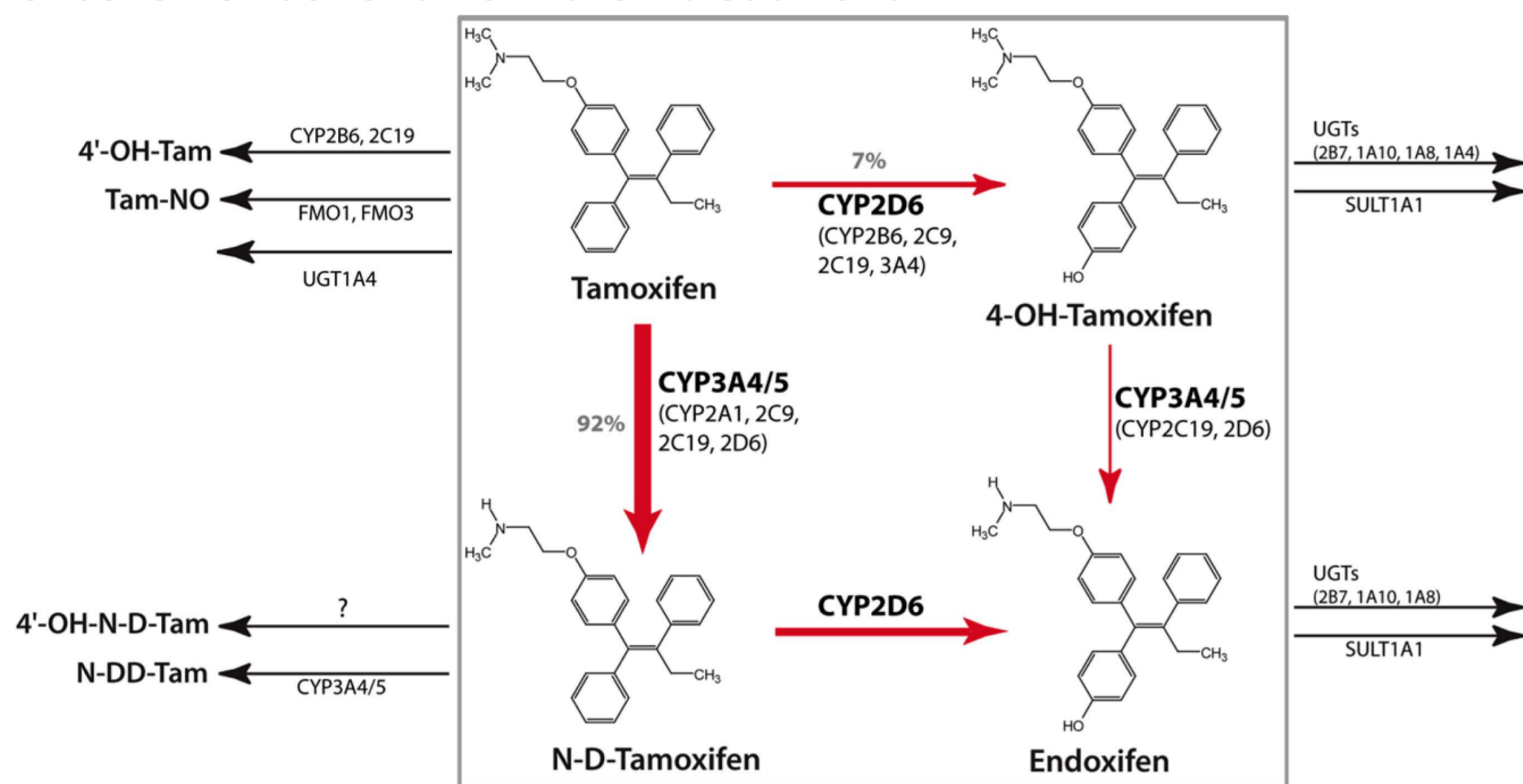
## Background

Tamoxifen (tam) remains a mainstay in the adjuvant treatment and prevention of hormone-sensitive breast cancer.

Tam is a pro-drug metabolized into active metabolites: 4-hydroxy-tamoxifen and mainly endoxifen.

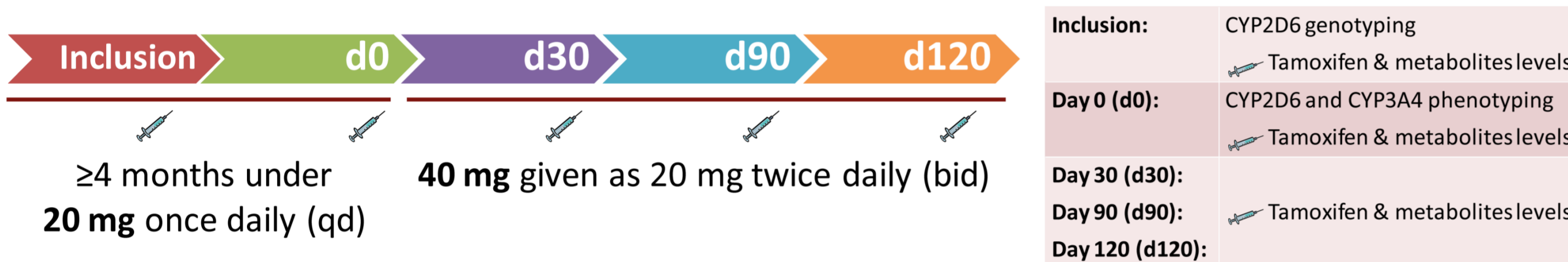
CYP2D6 is a key enzyme responsible for Tam bioactivation into endoxifen.

CYP2D6 gene is highly polymorphic and patients with null (PM) or reduced (IM) CYP2D6 activity display lower endoxifen concentrations and thus might experience lower benefit from their treatment<sup>1</sup>.



## Methods

### Study design:



### Data:

457 blood samples were collected from 97 patients. Plasma levels measurements of Tam, NDTam (N-D-tamoxifen), 4OHTam (4-OH-tamoxifen) and EDF (endoxifen) were measured by liquid chromatography-tandem mass spectrometry<sup>2</sup>.

### Covariates:

✓ **Patients characteristics:** Ethnicity, sex, age, menopausal status, body weight (BW), height.

✓ **Co-medications:** CYP2D6 inhibitors: potent [paroxetine (n=2), fluoxetine(n=1)], moderate [citalopram and escitalopram (n=6), sertraline (n=1)], weak to null [risperidone (n=1), venlafaxine (n=8)]. CYP2C19 inhibitors: moderate [omeprazole and esomeprazole (n=8)]. CYP2C9 inhibitors: weak [pantoprazole (n=3), cotrimoxazole (n=1)].

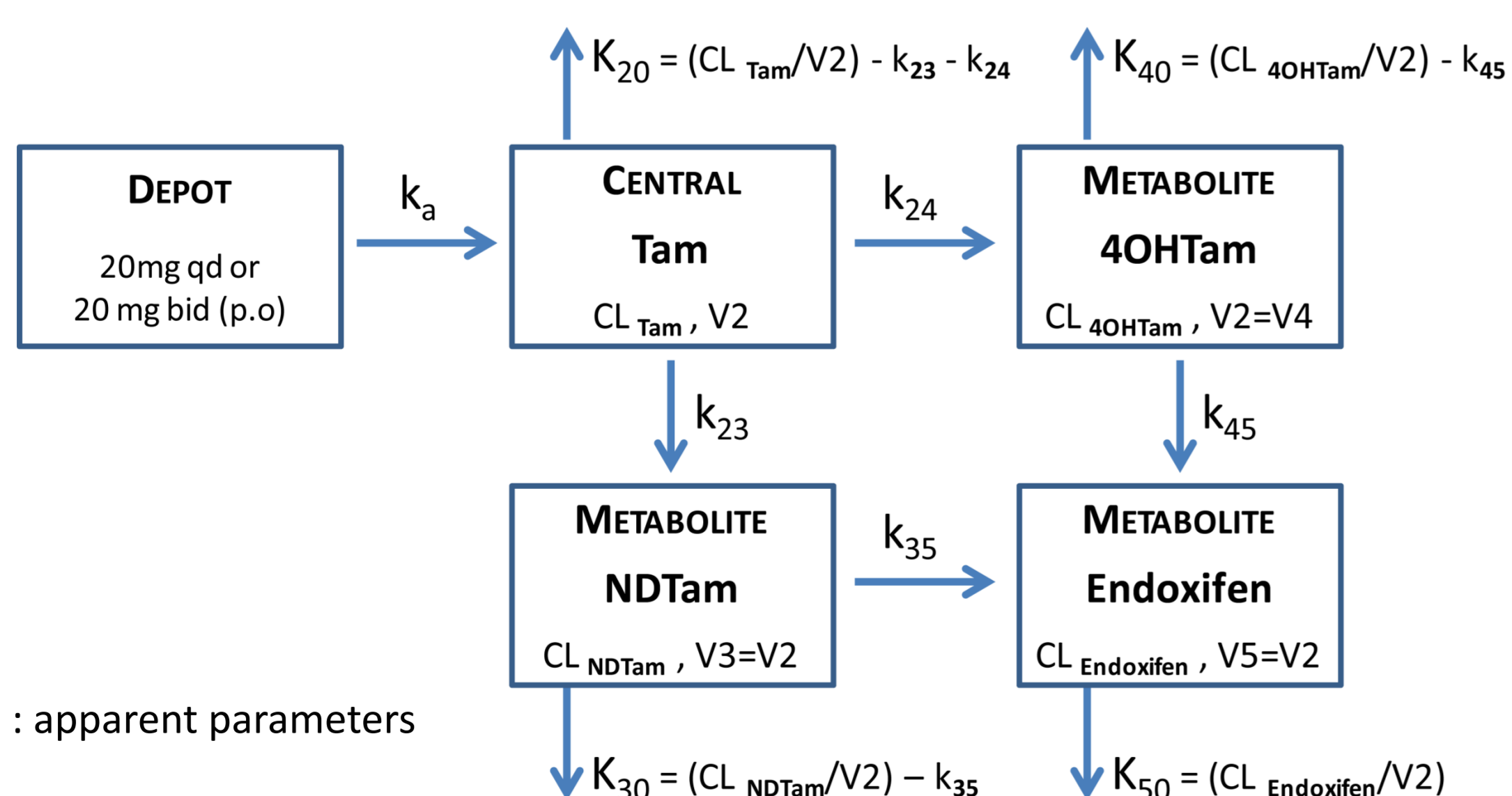
✓ **Genetic polymorphisms:** CYP2D6 genotypes were categorized and scored on the basis of the number of functional alleles (PM=homozygous loss of functional allele, IM=heterozygous loss (\*1/\*4), EM=homozygous reference allele, UM=multiple functional alleles). Heterozygous genotypes (\*4/\*XN) have been scored according to the dextromethorphan metabolic ratio test. CYP3A4/5 phenotype expressed as a midazolam metabolic ratio<sup>3</sup> was used as a continuous variable.

✓ **Other covariates:** liver function tests (ASAT, ALAT, GGT, total bilirubin, alkaline phosphatase), treatment adherence (self reported through a semi-quantitative drug intake frequency questionnaire).

### Population pharmacokinetics analysis:

✓ The full model consisted of a 4 compartment model with a first order-absorption of Tam, and a mono-exponential elimination and linear conversion to the three metabolites.

✓ The Vd of Tam and its three metabolites were assumed to be equal, in order to address the issue of global identifiability of the model.



\* CL and V2 : apparent parameters

✓ Inter-patient variability (IIV) was assigned to CL<sub>Tam</sub>, k<sub>23</sub>, k<sub>24</sub> and k<sub>35</sub> with a correlation between CL<sub>Tam</sub> and k<sub>23</sub> and between k<sub>24</sub> and k<sub>35</sub>.

✓ A proportional error model with correlation between residual errors was employed to describe intra-patients variability for Tam and NDTam and for 4OHTam and EDF.

## Objectives

✓ To characterize the population pharmacokinetics of Tam and its major metabolites, with an emphasis on the active moiety endoxifen.

✓ To quantify the inter- and intra-individual variability and explore the influence of genetic and non-genetic factors on their disposition.

Reported data are preliminary results from an ongoing prospective, open-label trial studying tamoxifen metabolism in breast cancer patients and the impact of tamoxifen dose on the level of the active metabolites (NCT00963209).

## Results

Forward covariates model building on the structural model (table1) identified :

✓ CYP2D6 genotype (PM, n=4 and IM, n=30) and CYP2D6 drug inhibitors (potent, n=3 and moderate, n=7) have the most significant impact on NDTam transformation to EDF (k<sub>35</sub>). CYP2D6 PM and IM have a reduced EDF formation by 87% and 28%, respectively. Potent and moderate CYP2D6 inhibitors reduced EDF formation by 61% and 36%. Both covariates explained 25% of the IIV on k<sub>35</sub>.

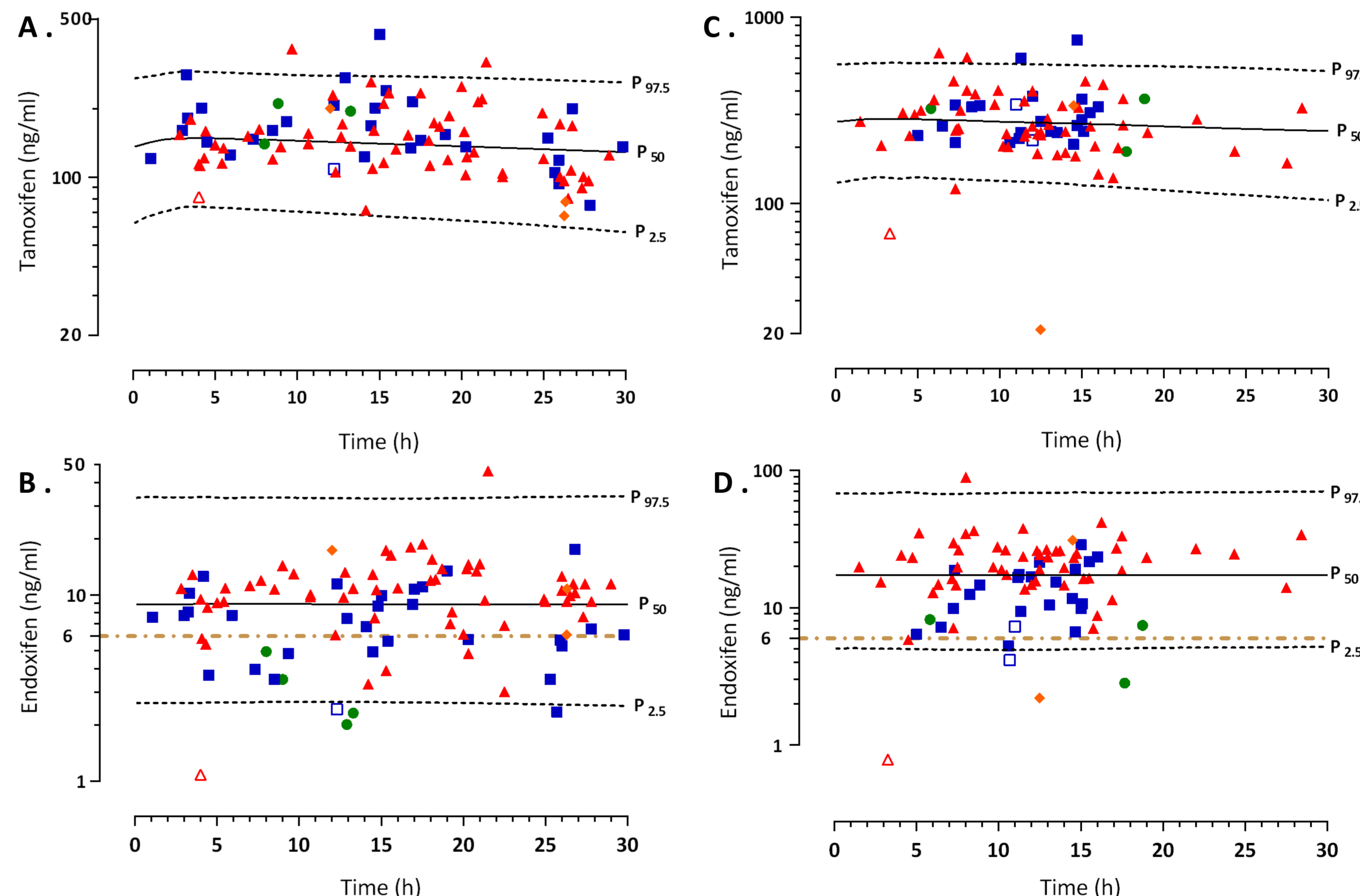
✓ BW and CYP2C19 drug inhibitors have been found to influence Tam transformation to 4OHTam (k<sub>24</sub>) by 40% and 15%, respectively.

✓ Age and CYP3A4 activity affected, respectively, the apparent CL<sub>Tam</sub> by 43% and Tam to NDTam transformation (k<sub>23</sub>) by 6%.

These results must be confirmed in the backward deletion steps.

Parameter	Population mean			
	Estimate	RSE (%)	IIV (%)	RSE (%)
CL/F <sub>Tam</sub> (l/h)	5.8	3	31	42
V2/F (l)	996	41		
k <sub>a</sub> (h <sup>-1</sup> ) (FIX)	0.7	-		
k <sub>23</sub> (h <sup>-1</sup> )	9.5E-03	52	17	40
k <sub>24</sub> (h <sup>-1</sup> )	6.04E-05	39	30	43
k <sub>35</sub> (h <sup>-1</sup> )	2.2E-04	26	72	42
k <sub>45</sub> (h <sup>-1</sup> ) (FIX)	0.007	-		
CL/F <sub>NDTam</sub> (l/h)	6.3	88		
CL/F <sub>4OHTam</sub> (l/h)	4.9	75		
CL/F <sub>Endoxifen</sub> (l/h)	7.7	48		
σ <sub>Tam</sub> (CV%)	19	37		
σ <sub>NDTam</sub> (CV%)	18	38		
σ <sub>4OHTam</sub> (CV%)	19	37		
σ <sub>Endoxifen</sub> (CV%)	20	36		
		ρ (%)	RSE (%)	
ω (CL/F <sub>Tam</sub> , k <sub>23</sub> )	22	54		
ω (k <sub>24</sub> , k <sub>35</sub> )	72	8		
σ <sub>Tam</sub> · σ <sub>NDTam</sub>	88	3		
σ <sub>4OHTam</sub> · σ <sub>Endoxifen</sub>	77	4		

Figure1. VPC plots for Tam and EDF steady-state levels under a Tamoxifen dose of 20 mg qd (A. ; B.) and under 20 mg bid (C. ; D.). PM, IM, EM, UM. Open symbols: patients under potent CYP2D6 inhibitor.



The value of 6 ng/ml in endoxifen VPC plots corresponds to an identified threshold that have been correlated to treatment efficacy<sup>1,4</sup>

## Conclusions

✓ Tam and its metabolites pharmacokinetics exhibit high inter-patient variability.

✓ CYP2D6 polymorphism and CYP2D6 drug inhibitors are the most significant covariates that influence endoxifen formation, with a greater impact of CYP2D6 PM and potent CYP2D6 inhibitors. However, these covariates account for only part of this variability.

✓ A larger proportion of patients have EDF levels under the 6 ng/ml threshold under the 20mg daily dose, when compared to the 20 mg twice daily Tamoxifen dose.

✓ Due to the large variability, direct EDF monitoring seems to be a better approach to evaluate EDF exposure.