

THERAPEUTIC DRUG MONITORING OF ENDOXIFEN IN ER+ BREAST CANCER PATIENTS: COMPARING DATA FROM CLINICAL PRACTICE TO MODEL-BASED PREDICTIONS

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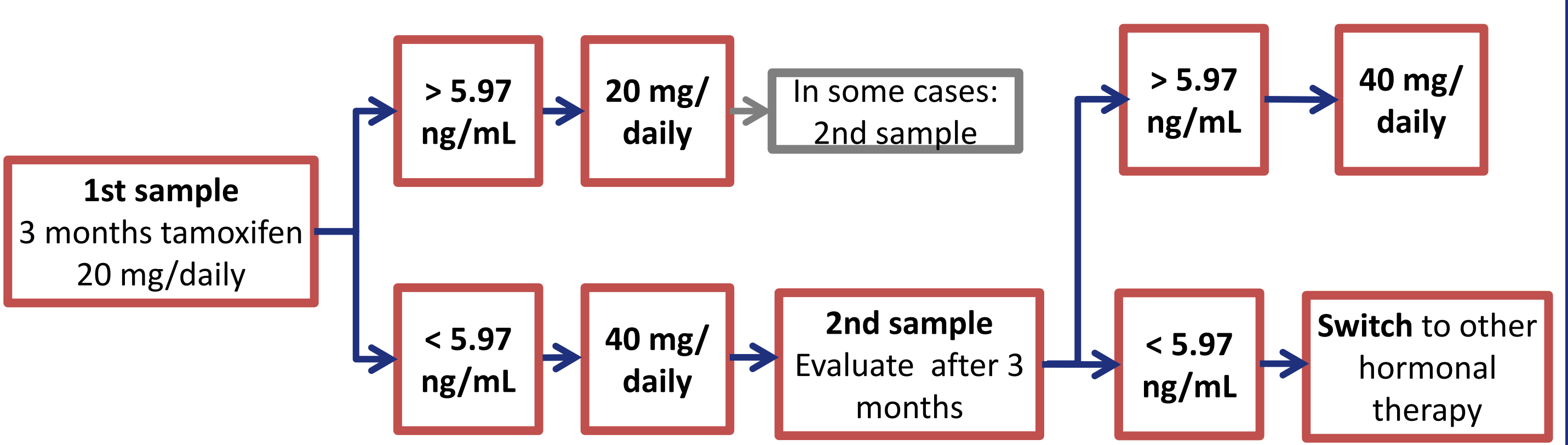
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Background

- 5 years of **adjuvant treatment** with tamoxifen lowers estrogen receptor (ER)-positive breast cancer recurrence and mortality rates
- Variability in response has been attributed to variability in exposure to **endoxifen**, an active metabolite of tamoxifen.
- An endoxifen concentration **>5.97 ng/mL** has been associated with 26% lower risk of breast cancer recurrence in a retrospective analysis [1].
- Therapeutic Drug Monitoring (TDM) is currently implemented in several hospitals based on this target.

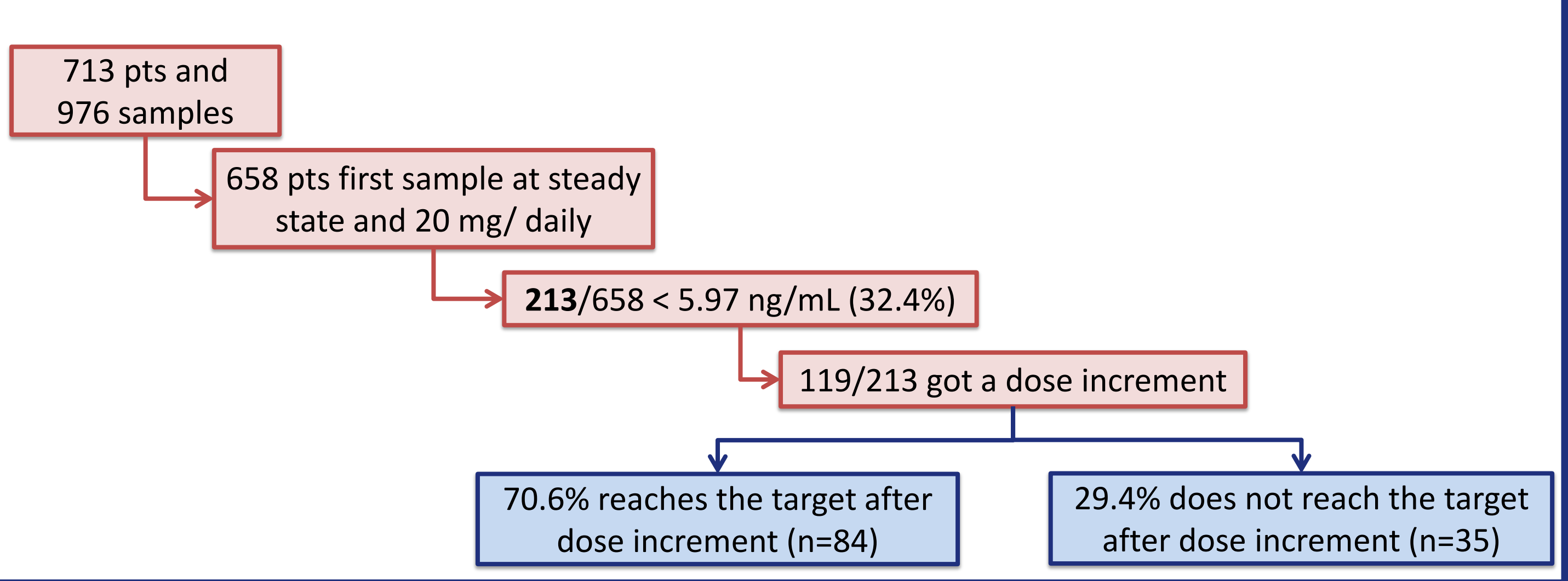
Therapeutic Drug Monitoring (TDM)



Aim

- Models describing pharmacokinetics (PK) of tamoxifen and its metabolites are sparse and based on data from trials only: target attainment might be different in clinical setting.
- The aim of this analysis is to evaluate target attainment based on endoxifen TDM applied in a clinical cohort and compare to model-based predictions from a PK model based on trial data.
- Ultimately we want to be able to evaluate study design, power and required sample size using model-based clinical trial simulations (CTS).

Methods I - Data



Methods II - PK model

PK model

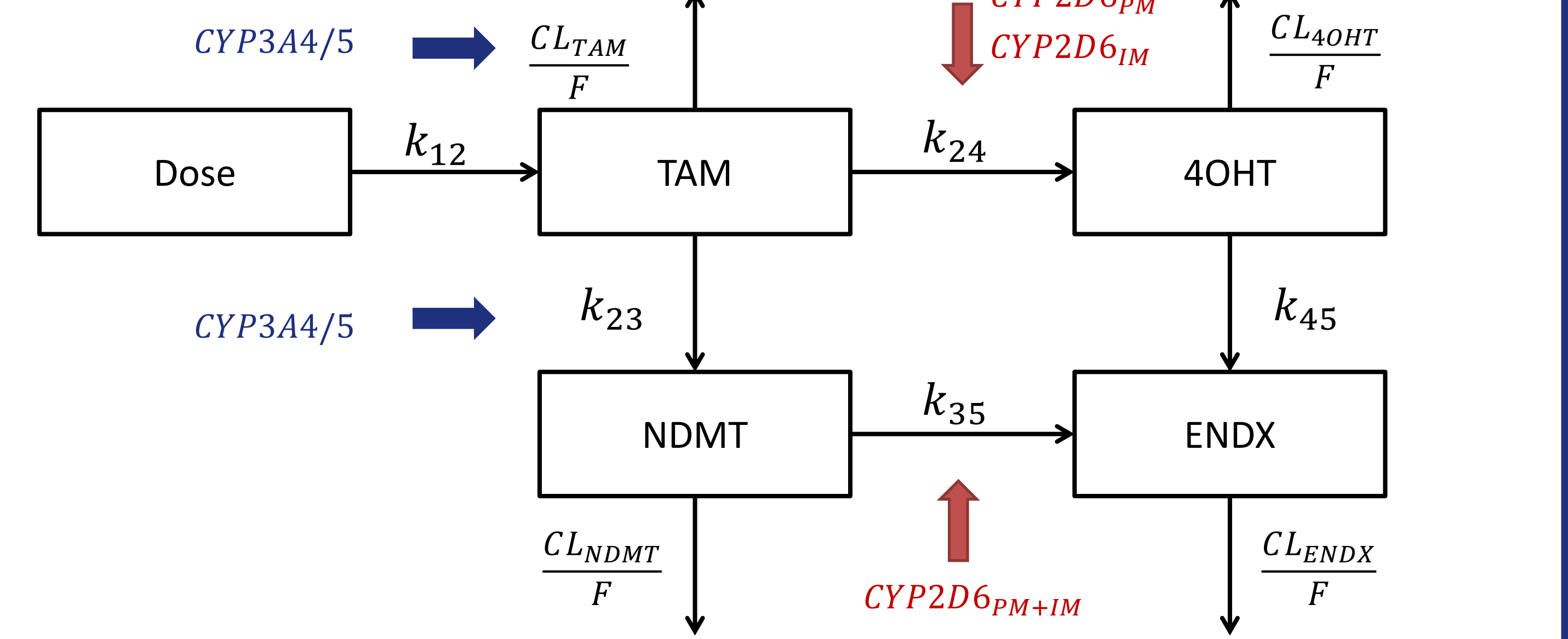


Figure 1: TAM = tamoxifen, 4OHT = 4-hydroxy-tamoxifen, NDMT = N-desmethyl-tamoxifen, ENDX = endoxifen. PM = poor metabolizers, IM = intermediate metabolizer. [2]

Covariates

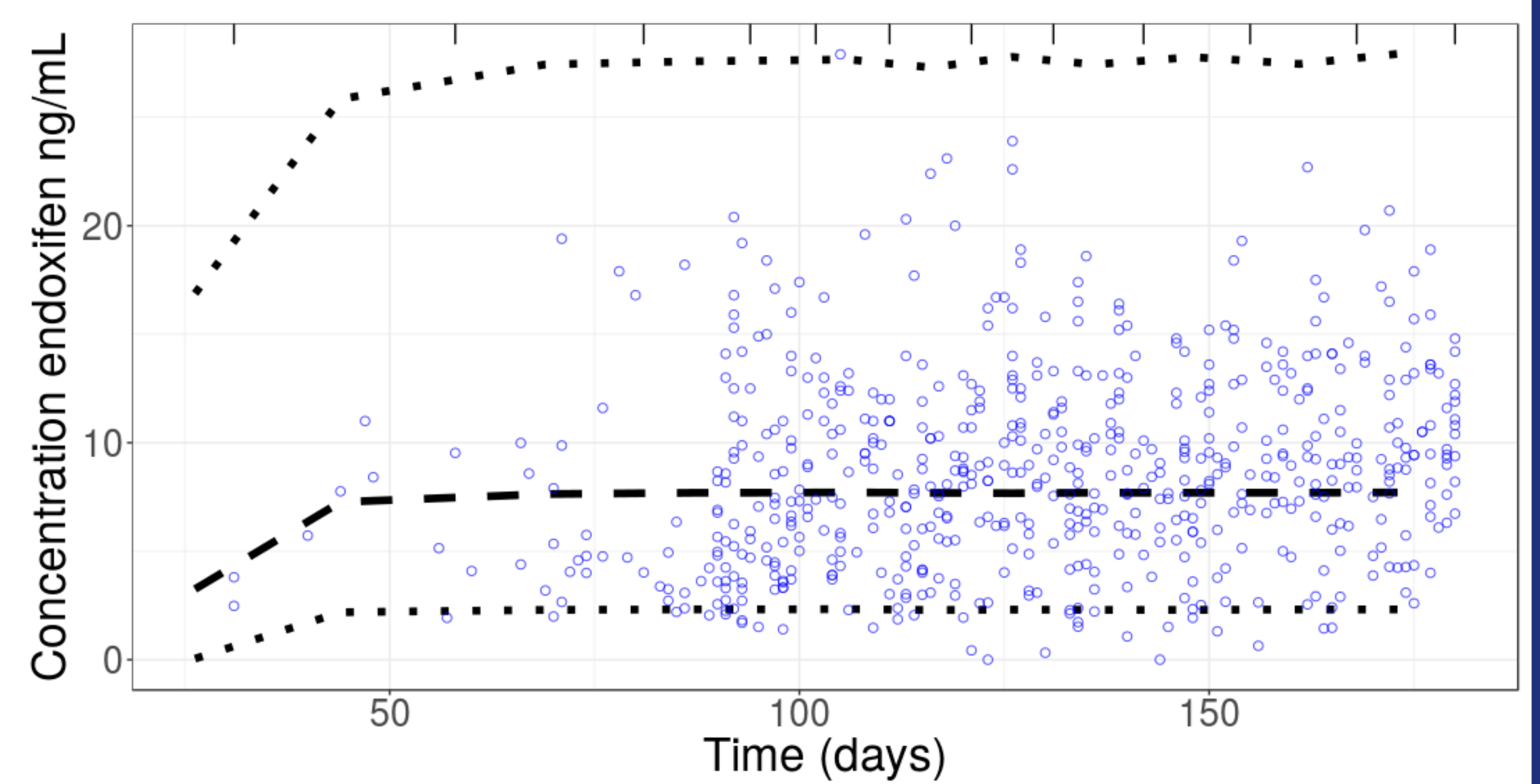
- CYP2D6: an underlying distribution was assumed based on literature [3] 52.5% extensive/rapid, 45% intermediate and 2.5% poor metabolizers.
- CYP3A4 activity: activity was assumed to be log linearly distributed $\ln N(\mu = 1.57, \omega = 0.44)$, similar to previously described [4]
- The other covariates were fixed to the median value.

Methods III – Simulations and comparisons

Simulations

- A population of n=1000 was simulated 100 times, using a dose adaptation simulation script including inter-individual and residual variability. (R version 3.3.4).
- Dose was adapted based on a sample at day 90 and reevaluated on day 180
- Percentages of target attainment at day 90 and day 180 were compared to steady state concentrations from the clinical database.

Results – Visual predictive check



Visual Predictive Check for endoxifen concentrations: observations (blue dots) are all first measured endoxifen concentration up to 6 months of treatment of patients that received tamoxifen 20 mg/daily (including non steady state concentrations). Dashed line = median of the simulated concentrations endoxifen, dotted lines = the 5th and the 95th percentile of the simulated data.

Results – Target attainment proportions

Table 1 Proportions of patients above target observed vs. simulated

	Clinical data % above target (#/n)	Simulated data Median [range] % above target
	n=658	n=1000 (sim=100x)
1st sample	67.6 (445/658)	67.8 [63.6-70.8]
2nd sample (increased pts)	70.6 (84/119)	84.9 [79.9-88.5]
2nd sample ^A	82.1 (540/658)	88.2 [85.8-90.7]
2nd sample ^B	88.8 (584/658)	88.2 [85.8-90.7]

^A For patients for whom a second sample was missing and did not undergo a dose increment, it was assumed that the endoxifen concentration remained the same during first and (hypothetical) second sample.

^B A sensitivity analysis was conducted, since only 119/213 of patients below the target received a dose increment in the clinical setting. The sensitivity analysis assumed that all patient < target received a doses increment and account for the % of patients with a first sample above the target (dose not increased) but a second sample below the target due to sampling error.

Conclusions

- The PK model simulates **similar proportions** of patients that > 5.97 ng/mL endoxifen before dose adaption, compared to clinical practice.
- The absolute difference in target attainment after applying TDM was **6.1%** (82.1% in the clinical setting vs. 88.2% simulated)
- This difference is mainly caused by **not applying a dose increment** to patients < target concentration, due to: side effects, borderline concentration < target and patients or physicians' preference.
- After a **sensitivity analysis** the proportion was within simulated range.
- These findings should be considered when evaluating the feasibility of a RCT to prove benefit of TDM for endoxifen in this patient group and show validity of using a **model-based approach** to evaluate study design, sample size, power for future RCTs.

References

- [1] Madlensky L, Natarajan L, Tchu S, et al. Clin Pharmacol Ther. 2011 May;89(5):718–25.
- [2] Dahmane EBA. 2013;1–184. Available from: <http://archive-ouverte.unige.ch/unige:33429>
- [3] Ter Heine R, Binkhorst L, de Graan AJM, et al Br J Clin Pharmacol. 2014 Sep;78(3):572–86.
- [4] Klopp-Schulze L, Joerger M, et al. Clin Pharmacokinet. 2018 Feb;57(2):229-242