# Supplementary material

## Simulation-based Assessment of the Impact of Non-adherence on Endoxifen Target Attainment in Different Tamoxifen Dosing Strategies

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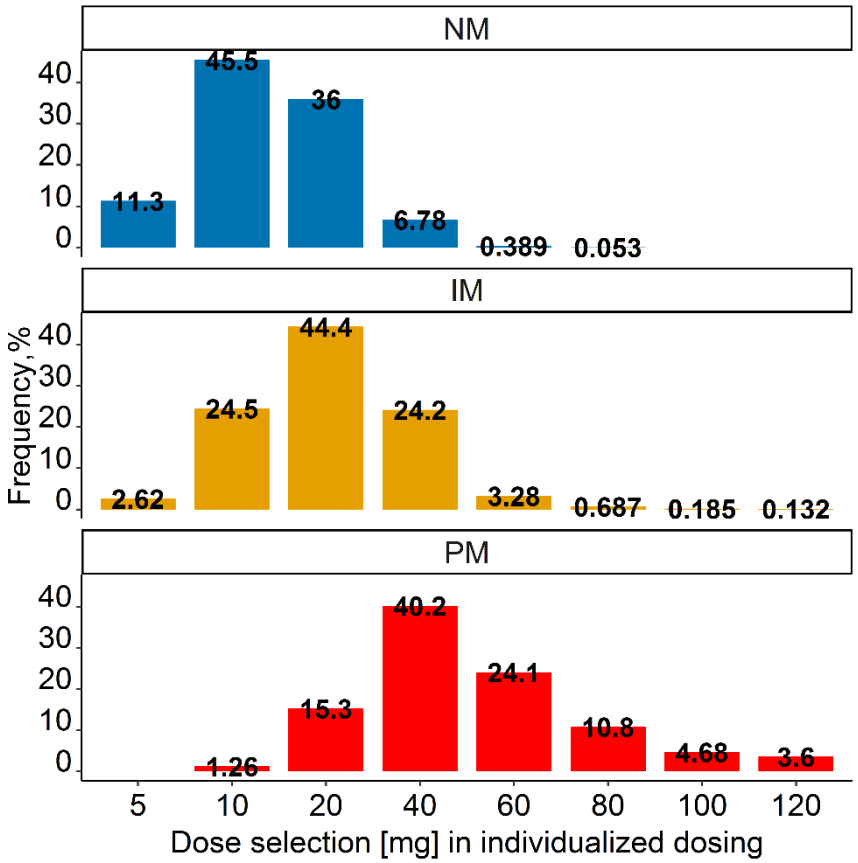
**Table S1.** Comparison of $C_{SS,min\ ENDX}$, interindividual variability and proportion in fully adherent patients with subtarget concentrations in the five dosing strategies stratified in the three CYP2D6 genotype-predicted phenotypes with their individual doses.

| | **(1) Standard dosing** | | | | **(2) CYP2D6-guided dosing** | | | | **(3) Model-informed precision dosing (5.97 ng/mL target)** | | | | **(4) Model-informed precision dosing (5.97 ng/mL target) + 10 mg** | | | | **(5) Model-informed precision dosing (9 ng/mL target)** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **CYP2D6** | gNM | gIM | gPM | all | gNM | gIM | gPM | all | gNM | gIM | gPM | all | gNM | gIM | gPM | all | gNM | gIM | gPM | all |
| $n_{patients}$ | 3396 | 2269 | 333 | 5998 | 3396 | 2269 | 333 | 5998 | 3396 | 2269 | 333 | 5998 | 3396 | 2269 | 333 | 5998 | 3396 | 2269 | 333 | 5998 |
| **Dose (mg)** | 20 | 20 | 20 | 20 | 20 | 30 | 60 | 20-60 | 5-120 | 5-120 | 5-120 | 5-120 | 15-130 | 15-130 | 15-130 | 15-130 | 5-120 | 5-120 | 5-120 | 5-120 |
| $C_{SS,minENDX}$ | | | | | | | | | | | | | | | | | | | | |
| **-Median** | 13.1 | 8.52 | 3.81 | 10.7 | 13.1 | 12.8 | 11.4 | 12.9 | 8.52 | 8.39 | 7.74 | 8.41 | 15.3 | 13.0 | 9.71 | 14.1 | 12.7 | 12.3 | 10.6 | 12.4 |
| **-IQR** | 9.06-19.1 | 5.48-12.8 | 2.36-5.36 | 6.80-16.2 | 9.06-19.1 | 8.22-19.2 | 7.07-16.1 | 8.65-19.0 | 7.05-10.2 | 7.06-9.98 | 6.80-9.29 | 7.03-10.1 | 12.8-19.0 | 10.8-15.8 | 8.33-11.9 | 11.5-17.6 | 10.6-15.0 | 10.4-14.8 | 9.48-12.4 | 10.4-14.8 |
| **-CV, %** | 54.0 | 60.5 | 57.2 | 62.5 | 54.0 | 60.5 | 57.2 | 56.8 | 24.2 | 24.2 | 22.6 | 24.2 | 30.1 | 29.4 | 25.8 | 32.0 | 23.7 | 24.0 | 22.7 | 24.1 |
| $n_{risk,\ \%}$ | 7.69 | 28.9 | 81.7 | 19.8 | 7.60 | 10.5 | 16.5 | 9.19 | 7.60 | 10.5 | 16.5 | 9.19 | 0.0294 | 0.220 | 2.40 | 0.233 | 0.00 | 0.132 | 1.50 | 0.133 |

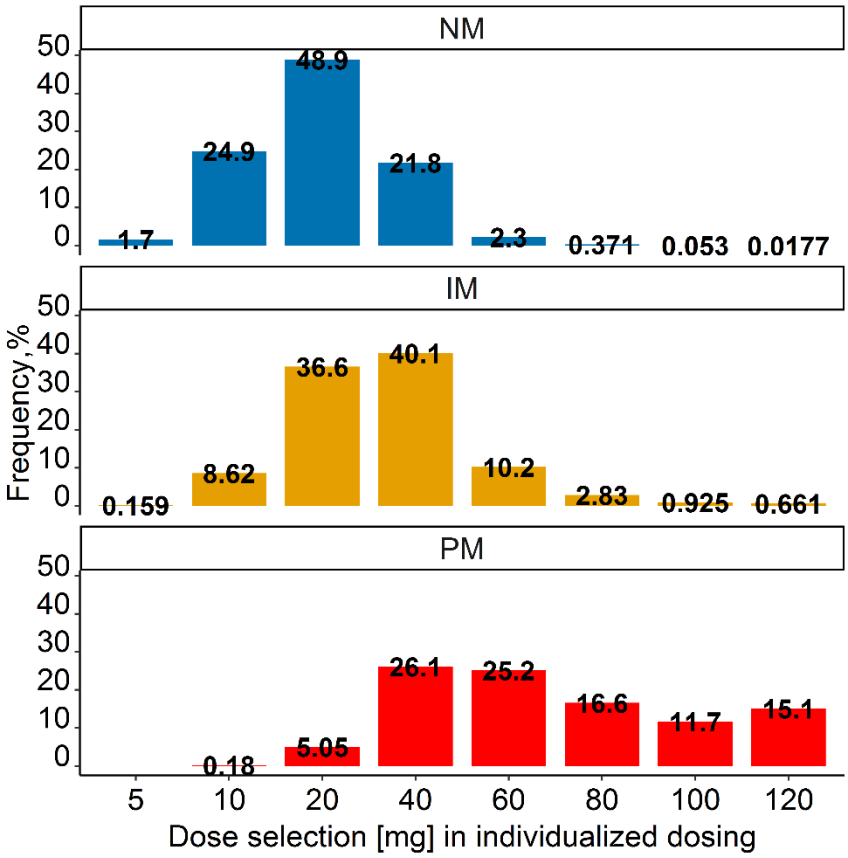
*Abbreviations*: $C_{SS,min\ ENDX}$: minimum endoxifen concentrations at steady-state [ng/mL]; CV: coefficient of variation; IQR: inter-quartile range; gXM: genotype predicted metaboliser; NM: normal metaboliser; IM: intermediate metabolisers, PM: poor metabolisers; $n_{risk}$, %: proportion of patients at risk for $C_{SS,min\ ENDX}$ below the proposed therapeutic threshold of 5.97 ng/mL [1]

**Figure S1.** Range and proportions of the individual dose selection in MIPD targeting the proposed therapeutic target threshold of 5.97 ng/mL [1].



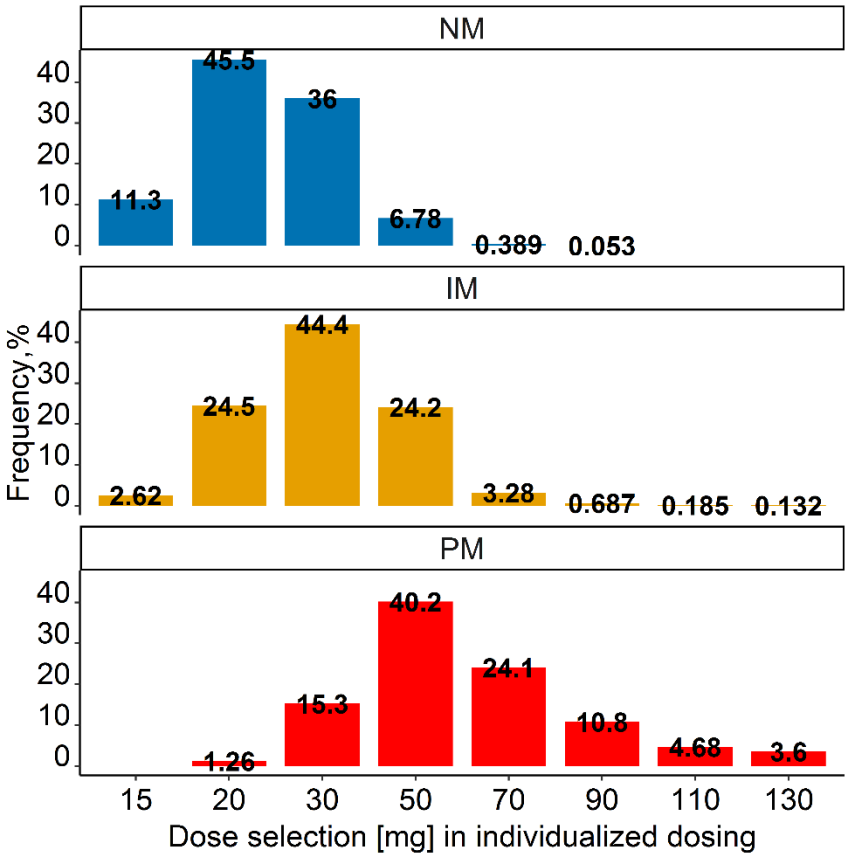

*Abbreviations*: gXM: genotype predicted metaboliser; NM: normal metaboliser; IM: intermediate metabolisers, PM: poor metabolisers.

**Figure S2.** Range and proportions of the individual dose selection in MIPD targeting the lowest reported mean $C_{SS,min\ ENDX}$ in gNM of 9 ng/mL [2].




*Abbreviations*: gXM: genotype predicted metaboliser; NM: normal metaboliser; IM: intermediate metabolisers, PM: poor metabolisers.

**Supplementary Figure 3.** Range and proportions of the individual dose selection in MIPD targeting the proposed therapeutic target threshold of 5.97 ng/mL [1] and adding 10 mg to each selected dose.




*Abbreviations*: gXM: genotype predicted metaboliser; NM: normal metaboliser; IM: intermediate metabolisers, PM: poor metabolisers.

## References


1. Madlensky, L.; Natarajan, L.; Tchu, S.; Pu, M.; Mortimer, J.; Flatt, S.W.; Nikoloff, D.M.; Hillman, G.; Fontecha, M.R.; Lawrence, H.J.; et al. Tamoxifen metabolite concentrations, CYP2D6 genotype, and breast cancer outcomes. *Clin. Pharmacol. Ther.* **2011**, *89*, 718–725, doi:10.1038/clpt.2011.32.

2. Hertz, D.L.; Deal, A.; Ibrahim, J.G.; Walko, C.M.; Weck, K.E.; Anderson, S.; Magrinat, G.; Olajide, O.; Moore, S.; Raab, R.; et al. Tamoxifen Dose Escalation in Patients With Diminished CYP2D6 Activity Normalizes Endoxifen Concentrations Without Increasing Toxicity. *Oncologist* **2016**, *21*, 795–803.