# Quantifying the impact of CYP2D6 allele activity on Z-endoxifen formation leveraging the multi-study CEPAM database: Towards treatment optimisation of tamoxifen

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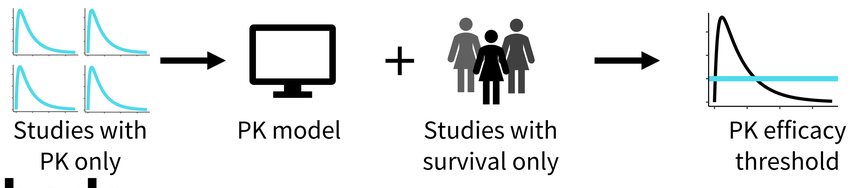
## Background and Objectives

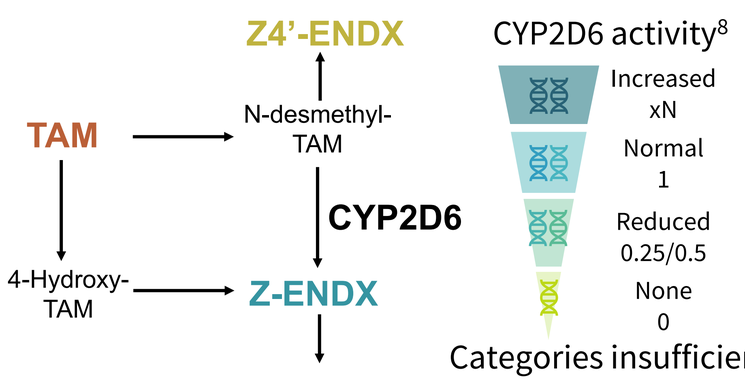
### Tamoxifen treatment individualisation?

**Prodrug TAM:** Breast cancer recurrence (≤ 25%) at 20 mg QD standard dosing[1]
**Active Z-ENDX:** Clinical studies found heterogeneous PK efficacy thresholds[2-5]
**Large prospective study for TAM treatment individualisation unrealistic**[6]

**New approach needed: Modelling + simulation of multi-study data**[7,8]




### Role of varying CYP2D6 allele activities




Develop PK model for TAM and Z-ENDX from large multi-study dataset

Investigate quantitative impact of CYP2D6 alleles on Z-ENDX formation

## Methods

### CEPAM analysis dataset

36 studies n=8451 n=10574

19.4%
TAM <1 month
No PK measurements
Unexplained outliers
No *CYP2D6* genotype

31 studies n=6841 n=8791

### PK samples

**94%** one sample

**6%** multiple samples [2-20]

**Z-ENDX 66.5%**
**TAM + Z-ENDX and Z4'-ENDX 19.8%**
**Total ENDX 13.8%** (Z-ENDX + Z4'-ENDX)

### Developing CYP2D6 percentage allele activity

**Modelling CYP2D6 activity**
NONMEM® 7.5.1, FOCE-I

Single CYP2D6 allele activity:
$= Activity * NxCNV$

Combined allele activity:
$= \frac{+}{2}$

CYP2D6-dependent Z-ENDX formation:
$CL_{CYP2D6} = CL_{CYP2D6} * * e^{CYP2D6\ inhibitor}$

**CYP2D6 inibitor**
**54%** none
**42%** imputed
**2.9%** weak
**0.1%** moderate
**0.9%** strong

| CYP2D6 alleles | | CEPAM,% |
|---|---|---|
| xN | CNV | 2.1 |
| | *1 (WT) | 44 |
| | *2 | 13 |
| | *35 | 1.8 |
| | *9 | 2.2 |
| | *10 | 7.3 |
| | *17 | 1.2 |
| | *41 | 7.6 |
| | *3 | 1.0 |
| | *4 | 15 |
| | *5 | 3.8 |

## Results

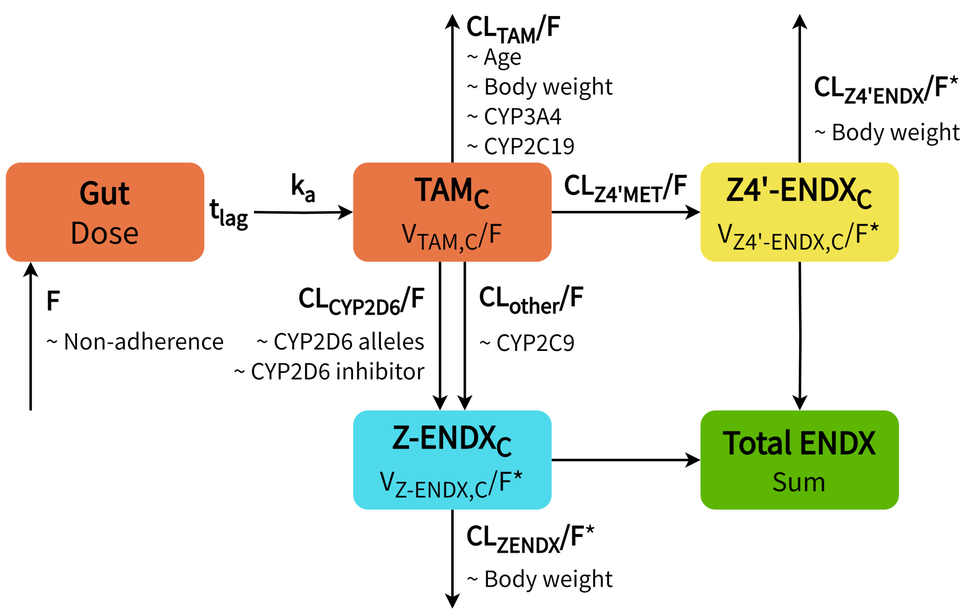



**Figure 1** Parent-metabolite model of TAM and ENDX. All exponential and power covariate relationships were median-normalised. All RSEs: ≤30%. *: Parameter values fixed.
**Structural parameters:** $t_{lag}$: 0.385 h; $k_a$: 1.09 $h^{-1}$; $CL_{TAM}/F$: 5.78 L/h; CYP2D6-dependent apparent Z-ENDX formation $CL_{CYP2D6}/F$: 0.442 L/h; CYP2D6-independent apparent Z-ENDX formation $CL_{other}/F$: 0.163 L/h; $CL_{ZENDX}/F$: 5.1 L/h; $CL_{Z4'MET}/F$: 0.318 L/h; $CL_{Z4'ENDX}/F$: 5.1 L/h; $V_{TAM,C}/F$: 743 L; $V_{ZENDX,C}/F$: 400 L; $V_{Z4'ENDX,C}/F$: 400 L.
**Covariates on F:** Non-adherence (-0.697) as relative change; **on $CL_{TAM}/F$:** Age (-0.282) and body weight (0.177) as power functions; CYP3A4 and CYP2C19 phenotype (0.133 and 0.001) as exponential models; **on $CL_{CYP2D6}/F$:** CYP2D6 inhibitor (-0.565) as exponential model; CYP2D6 alleles as relative change, Fig. 4; **on $CL_{other}/F$:** CYP2C9 phenotype (0.380) as exponential model; **on $CL_{ZENDX}/F$ and $CL_{Z4'ENDX}/F$:** Body weight (0.385 and 0.226) as power functions.
**IIV**: On $CL_{TAM}/F$ (51.0% CV) and on Z-ENDX formation $CL_{CYP2D6}/F$+ $CL_{other}/F$ (28.1% CV) as exponential model. **RUV:** Proportional model separated for patients with one sample (29.9-58.6% CV)and multiple samples (≤17.3% CV).

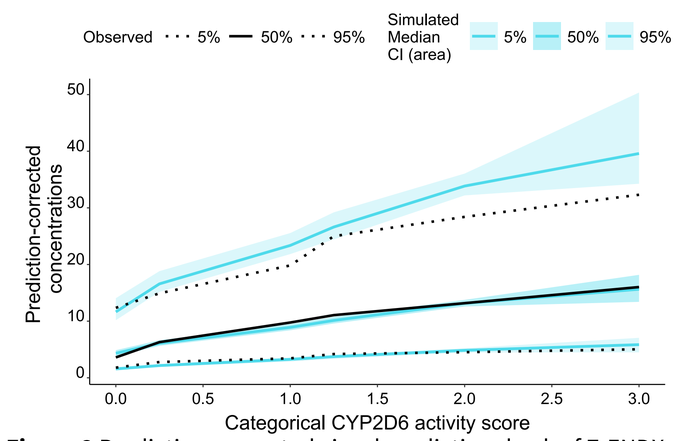



**Figure 2** Prediction-corrected visual predictive check of Z-ENDX.

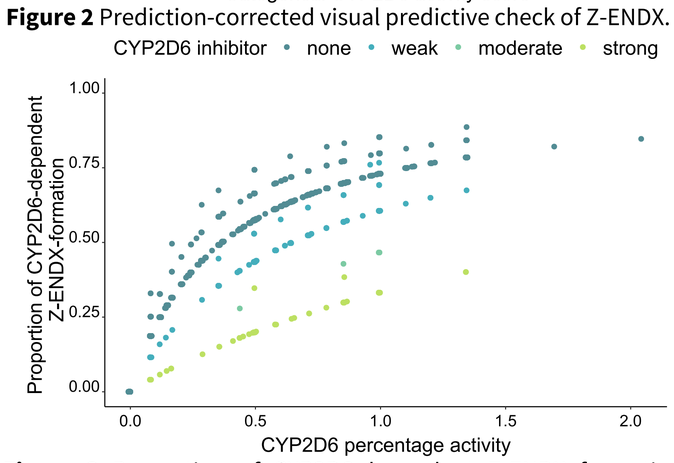



**Figure 3** Proportion of CYP2D6-dependent Z-ENDX formation with increasing allele activity stratified by CYP2D6 inhibitor.

**CYP2D6 allele activity**

| Alleles | | Activity | |
|---|---|---|---|
| | | Category | Percentage |
| xN | CNV | | **Nx 0.70** |
| *1 (WT) | | 1 | **1 fix** |
| *35 | | 1 | **0.74** |
| *2 | | 1 | **0.72** |
| *9 | | 0.25 | **0.58** |
| *17 | | 0.5 | **0.30** |
| *10 | | 0.25 | **0.25** |
| *41 | | 0.25 | **0.17** |
| *3,*4,*5 | | 0 | **0 fix** |

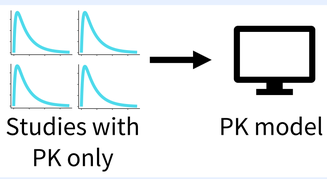
**Figure 4** CYP2D6 categorical and percentage allele activities and impact of gene duplication (CNV).

## Conclusions

**PK model for Z-ENDX was developed based on global multi-study data**

**CYP2D6 percentage activity holds high potential for optimising TAM treatment**

**PK model was successfully developed:**

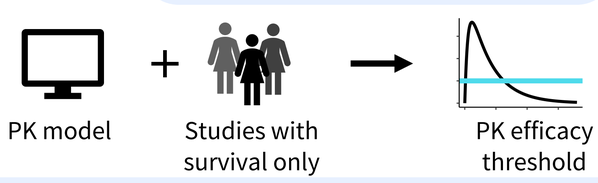



## Perspective

**Treatment simulations and survival analysis for studies with reported outcome and covariate information**

**Investigate potential for individualised TAM dosing**

**Application of PK model to studies with survival data :**




References

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[2] Madlensky et al. Clin. Pharmacol. Ther. 89: 718-725 (2011).
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[4] Helland et al. Breast Cancer Res. 19 (2011).
[5] Love et al. Springerplus 2: 1-5 (2013).
[6] Helland et al. J. Pers. Med. 11 (2021).
[7] de Vries Schultink et al. PAGE 28 (2019).
[8] Mc Laughlin et al. Clin. Pharmacol. Ther. (2024).
[9] Caudle et al. Clin. Transl. Sci. 13: 116-124 (2020).

Abbreviations

| | | | |
|---|---|---|---|
| CNV | Copy number variation | PK | Pharmacokinetic(s) |
| CL | Clearance | QD | Once daily |
| ENDX | Endoxifen | RSE | Relative standard error |
| F | Bioavailability | RUV | Residual standard error |
| FOCE-I | First-order conditional estimation with interaction | TAM | Tamoxifen |
| | | $t_{lag}$ | Absorption lag time |
| IIV | Interindividual variability | V | Volume of distribution |
| $k_a$ | Absorption rate constant | WT | wildtype |
| N | Number of gene duplications | | |

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