## Supplementary material

Table S1: $\mathrm{C}_{\mathrm{SS}, \text { min }} \mathrm{ENDX}$ across different subpopulations in the development and evaluation dataset, respectively.

|  | Dev. dataset (all) ( $\mathrm{n}=435$ ) | Eval. dataset (all) ( $\mathrm{n}=935$ ) | Eval. dataset (African) ( $\mathrm{n}=12$ ) | Eval. dataset (Arab) ( $\mathrm{n}=77$ ) | Eval. dataset (Asian) ( $\mathrm{n}=153$ ) | Eval. dataset (Caucasian) ( $\mathrm{n}=681$ ) | Eval. dataset (Indian) ( $\mathrm{n}=12$ ) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Pre- menopausal Median (IQR) $[\mathrm{ng} / \mathrm{mL}]$ | $\begin{gathered} 8.09 \\ (5.67- \\ 12.1) \\ (\mathrm{n}=67) \end{gathered}$ | $\begin{gathered} 10.6 \\ (7.15- \\ 16.9) \\ (\mathrm{n}=568) \end{gathered}$ | $\begin{gathered} 5.74(4.40- \\ 9.01) \end{gathered}$ | $\begin{gathered} 13.5 \\ (8.24- \\ 17.4) \end{gathered}$ | $\begin{gathered} 15.6 \\ (9.49- \\ 23.9) \end{gathered}$ | $\begin{gathered} 9.22 \\ (5.60-12.8) \\ (\mathrm{n}=314) \end{gathered}$ | $\begin{gathered} 24.4 \\ (16.9- \\ 27.1) \end{gathered}$ |
| Postmenopausal Median (IQR) [ng/mL] | $\begin{gathered} 11.7 \\ (6.90- \\ 17.2) \\ (\mathrm{n}=368) \end{gathered}$ | $\begin{gathered} 10.8 \\ (7.27- \\ 14.5) \\ (\mathrm{n}=367) \end{gathered}$ | - | - | - | $\begin{gathered} 10.8 \\ (7.27-14.5) \\ (\mathrm{n}=367) \end{gathered}$ | - |
| p-Value | $\mathrm{p}<0.001$ | ns |  |  |  | $\mathrm{p}<0.001$ |  |

$C_{S S, \text { min ENDX: }}$ Endoxifen minimum concentrations at steady-state; Dev. Dataset: development dataset; Eval. dataset: evaluation dataset; IQR: interquartile range.

Table S2: Body weights across different subpopulations in the development and evaluation dataset, respectively.

|  | Dev. dataset (all) ( $\mathrm{n}=435$ ) | Eval. <br> dataset <br> (all) $(n=935)$ | Eval. dataset (African) $(\mathrm{n}=12)$ | Eval. dataset (Arab) ( $\mathrm{n}=77$ ) | Eval. dataset (Asian) ( $\mathrm{n}=153$ ) | Eval. dataset (Caucasian) ( $\mathrm{n}=681$ ) | Eval. <br> dataset <br> (Indian) $(\mathrm{n}=12)$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Premenopausal Median (IQR) [kg] | $\begin{gathered} 72.2 \\ (63.4- \\ 83.8) \end{gathered}$ | $\begin{gathered} 63.0 \\ (57.0- \\ 72.3) \end{gathered}$ | $\begin{gathered} 62.5 \\ (55.8- \\ 68.8) \end{gathered}$ | $\begin{gathered} 68.0 \\ (61.0- \\ 76.0) \end{gathered}$ | $\begin{array}{r} 57.4 \\ (51.4- \\ 62.8) \end{array}$ | $\begin{gathered} 65 \\ (59.0-76.0) \end{gathered}$ | $\begin{gathered} 61.4 \\ (53.9- \\ 64.7) \end{gathered}$ |
| Postmenopausal Median (IQR) [kg] | $\begin{gathered} 70 \\ (62.0- \\ 80.1) \end{gathered}$ | $\begin{gathered} 70 \\ (63.0- \\ 78.5) \end{gathered}$ | - | - | - | $\begin{gathered} 70 \\ (63.0-78.5) \end{gathered}$ |  |
| p -Value | ns | $\mathrm{p}<0.001$ |  |  |  | $\mathrm{p}<0.001$ |  |

$C_{S S, \text { min ENDX: }}$ Endoxifen minimum concentrations at steady-state, Dev. Dataset: development dataset; Eval. dataset: evaluation dataset; IQR: interquartile range.

Table S3: Number of patients at risk for subtarget $\mathrm{C}_{\mathrm{SS}, \min \operatorname{ENDX}}$ and absolute and relative risk changes for different patient subpopulations in SU1.

| Scenario | Number of patients at risk | Absolute change in risk compared to IQR | Relative change in risk compared to IQR | NNH/NNT |
| :---: | :---: | :---: | :---: | :---: |
| Heavy young <br> - Median <br> - 90\% CI | $\begin{gathered} \mathbf{3 6 . 9 \%} \\ (34.6 \%-39.2 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 5 . 7 \%} \\ (13.7 \%-17.8 \%) \end{gathered}$ | $\begin{gathered} +75.0 \% \\ (63.7 \%-86.3 \%) \end{gathered}$ | $\begin{gathered} 7 \\ (6-8) \end{gathered}$ |
| Heavy <br> - Median <br> - 90\% CI | $\begin{gathered} \mathbf{3 3 . 4 \%} \\ (31.5 \%-35.2 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 2 . 3 \%} \\ (10.6 \%-13.8 \%) \end{gathered}$ | $\begin{gathered} \mathbf{+ 5 8 . 1 \%} \\ (49.8 \%-66.8 \%) \end{gathered}$ | $\begin{gathered} 9 \\ (8-10) \end{gathered}$ |
| Young <br> - Median <br> - $90 \%$ CI | $\begin{gathered} \mathbf{2 3 . 8 \%} \\ (22.2 \%-25.5 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{2 . 7 0 \%} \\ (1.40 \%-4.10 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 3 . 0 \%} \\ (6.50 \%-19.4 \%) \end{gathered}$ | $\begin{gathered} 37 \\ (25-72) \end{gathered}$ |
| $\begin{aligned} & \text { IQR } \\ & \text { - Median } \\ & -90 \% \text { CI } \end{aligned}$ | $\begin{gathered} \mathbf{2 1 . 1 \%} \\ (19.8 \%-22.4 \%) \end{gathered}$ | - | - | - |
| Elderly <br> - Median <br> - 90\% CI | $\begin{gathered} \text { 19.1\% } \\ (17.7 \%-20.6 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 2 . 0 0 \%} \\ (-3.10 \%- \\ -0.90 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 9 . 6 3 \%} \\ (-14.6 \% \text { - } \\ -4.39 \%) \end{gathered}$ | $\begin{gathered} \mathbf{5 0} \\ (33-112) \end{gathered}$ |
| Light <br> - Median <br> - $90 \%$ CI | $\begin{gathered} \mathbf{1 3 . 5 \%} \\ (12.4 \%-14.8 \%) \end{gathered}$ | $\begin{aligned} & -7.60 \% \\ & (-8.60 \%- \\ & -6.60 \%) \end{aligned}$ | $\begin{aligned} & \mathbf{- 3 6 . 1 \%} \\ & (-40.2 \%- \\ & -31.8 \%) \end{aligned}$ | $\begin{gathered} 14 \\ (12-16) \end{gathered}$ |
| Light elderly <br> - Median <br> - $90 \%$ CI | $\begin{gathered} \mathbf{1 2 . 1 \%} \\ (10.8 \%-13.4 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 9 . 1 0 \%} \\ (-10.1 \% \text { - } \\ -8.00 \%) \\ \hline \end{gathered}$ | $\begin{gathered} -43.0 \% \\ (-47.4 \% \\ -38.2 \%) \\ \hline \end{gathered}$ | $\begin{gathered} 11 \\ (10-13) \end{gathered}$ |

$C_{S S, \min E N D X:}$ Endoxifen minimum concentrations at steady-state;
Subpopulation characteristics: Heavy young: 22-39 years, $77-150 \mathrm{~kg}$; Heavy: 40-65 years, $77-150 \mathrm{~kg}$;
Young: 22-39 years, $60-76 \mathrm{~kg}$; IQR: 40-65 years, $60-76 \mathrm{~kg}$; Elderly: $66-95$ years, $60-76 \mathrm{~kg}$;
Light: 40-65 years, $39-60 \mathrm{~kg}$; Light elderly: 66-95 years, $39-60 \mathrm{~kg}$.
Abbreviations: CI: confidence interval; IQR: interquartile range;
$N N H$ : number needed to harm (1/Absolute change in risk; if absolute change in risk is positive); $N N T$ : number needed to treat (1/(-Absolute change in risk); if absolute change in risk is negative) SU1: Study set-up 1: endoxifen subtarget concentrations for subpopulations with different age and body weight distributions

Table S4: Number of patients at risk for subtarget $\mathrm{C}_{\mathrm{SS}, \min \operatorname{ENDX}}$ and absolute and relative risk changes for different patient subpopulations in SU1, stratified for CYP2D6 phenotype.

| Scenario | CYP2D6 phenotype | Number of patients at risk | Absolute change in risk compared to IQR | Relative change in risk compared to IQR | NNH/NNT |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Heavy young | $\begin{aligned} & \text { gNM } \\ & - \text { Median } \\ & -90 \% \mathrm{Cl} \\ & \text { gIM } \end{aligned}$ | $\begin{gathered} \mathbf{2 2 . 5 \%} \\ (20.1 \%-25.0 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 3 . 1 \%} \\ (11.2 \%-15.4 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 4 1 \%} \\ (114 \%-173 \%) \end{gathered}$ | $\begin{gathered} \mathbf{8} \\ (5-9) \end{gathered}$ |
|  | $\begin{aligned} & \text { - Median } \\ & \text { - 90\% Cl } \\ & \text { gPM } \end{aligned}$ | $\begin{gathered} \mathbf{5 0 . 1 \%} \\ (46.9 \%-53.4 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{2 0 . 3 \%} \\ (17.3 \%-23.0 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{6 8 . 2 \%} \\ (56.3 \%-81.0 \%) \end{gathered}$ | $\begin{gathered} \mathbf{5} \\ (5-6) \end{gathered}$ |
|  | $\begin{aligned} & \text { - Median } \\ & \text { - } 90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{9 2 . 4 \%} \\ (89.7 \%-95.1 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 1 . 2 \%} \\ (7.60 \%-15.2 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 3 . 8 \%} \\ (9.00 \%-19.7 \%) \end{gathered}$ | $\begin{gathered} 9 \\ (6-14) \end{gathered}$ |
| Heavy <br> - Median <br> - $90 \%$ CI | gNM <br> - Median <br> - $90 \%$ CI | $\begin{gathered} \mathbf{1 9 . 4 \%} \\ (17.3 \%-21.5 \%) \end{gathered}$ | $+10.1 \%$ | $+\mathbf{1 0 7 \%}$ | $10$ |
|  | gIM |  |  |  |  |
|  | $\begin{aligned} & \text { - Median } \\ & -90 \% \mathrm{Cl} \\ & \text { gPM } \end{aligned}$ | $\begin{gathered} \mathbf{4 5 . 8 \%} \\ (43.1 \%-48.9 \% \end{gathered}$ | $\begin{gathered} +\mathbf{1 6 . 0 \%} \\ (13.8 \%-18.3 \%) \end{gathered}$ | $\begin{gathered} +53.7 \% \\ (44.9 \%-63.6 \%) \end{gathered}$ | $\begin{gathered} 7 \\ (6-8) \end{gathered}$ |
|  | $\begin{aligned} & \text { - Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{9 0 . 6 \%} \\ (87.4 \%-93.5 \%) \end{gathered}$ | $\begin{gathered} \mathbf{+ 9 . 4 0 \%} \\ (6.20 \%-13.4 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 1 . 6 \%} \\ (7.21 \%-17.3 \%) \end{gathered}$ | $\begin{gathered} 11 \\ (8-17) \end{gathered}$ |
| Young <br> - Median <br> - $90 \%$ CI | $\begin{aligned} & \text { gNM } \\ & \quad-\text { Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{1 1 . 4 \%} \\ (9.82 \%-12.9 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 . 9 7 \%} \\ (0.850 \%-3.20 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{2 1 . 2 \%} \\ (8.90 \%-35.5 \%) \end{gathered}$ | $\begin{gathered} \mathbf{5 1} \\ (32-118) \end{gathered}$ |
|  | $\begin{aligned} & \text { gIM } \\ & \quad-\text { Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{3 3 . 6 \%} \\ (30.9 \%-36.4 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{3 . 8 0 \%} \\ (1.60 \%-6.01 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 2 . 7 \%} \\ (5.21 \%-21.1 \%) \end{gathered}$ | $\begin{gathered} 27 \\ (17-63) \end{gathered}$ |
|  | gPM <br> - Median <br> - $90 \% \mathrm{Cl}$ | $\begin{gathered} \mathbf{8 4 . 3 \%} \\ (80.0 \%-88.1 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{2 . 9 0 \%} \\ (-0.7 \%-7.0 \%) \end{gathered}$ | $\begin{gathered} \mathbf{+ 3 . 6 4 \%} \\ (-0.838 \%-8.86 \%) \end{gathered}$ | $\begin{gathered} 35 \\ (n s)^{2} \end{gathered}$ |
| IQR | $\begin{aligned} & \text { gNM } \\ & \quad-\text { Median } \\ & -90 \% \mathrm{Cl} \\ & \text { gIM } \end{aligned}$ | $\begin{gathered} \mathbf{9 . 3 6 \%} \\ (8.18 \%-10.8 \%) \end{gathered}$ | - | - | - |
|  | $\begin{aligned} & \text { - Median } \\ & \text { - } 90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{2 9 . 8 \%} \\ (27.4 \%-32.2 \%) \end{gathered}$ | - | - | - |
|  | gPM <br> - Median <br> - 90\% CI | $\begin{gathered} \mathbf{8 1 . 1 \%} \\ (76.8 \%-85.2 \%) \end{gathered}$ | - | - | - |
| Elderly | $\begin{aligned} & \text { gNM } \\ & - \text { Median } \\ & -90 \% \mathrm{Cl} \\ & \text { gIM } \end{aligned}$ | $\begin{gathered} \text { 7.98\% } \\ (6.82 \%-9.27 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 1 . 4 2 \%} \\ (-2.30 \%--0.42 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 1 5 . 1 \%} \\ (-23.5 \%--4.97 \%) \end{gathered}$ | $\begin{gathered} 71 \\ (44-239) \end{gathered}$ |
|  | $\begin{aligned} & \text { - Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{2 6 . 9 \%} \\ (24.6 \%-29.6 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 2 . 9 0 \%} \\ (-4.90 \%--0.90 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 9 . 7 9 \%} \\ (-16.1 \%--3.15 \%) \end{gathered}$ | $\begin{gathered} 35 \\ (21-112) \end{gathered}$ |
|  | $\begin{aligned} & \text { gPM } \\ & \quad-\text { Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \text { 78.9\% } \\ (84.2 \%-83.4 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 2 . 2 0 \%} \\ (-6.50 \%-1.50 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 2 . 7 2 \%} \\ (-7.84 \%-1.86 \%) \end{gathered}$ | $\begin{gathered} 46 \\ (n s)^{2} \end{gathered}$ |
| Light | $\begin{aligned} & \text { gNM } \\ & \quad-\text { Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \text { 4.52\% } \\ (3.66 \%-5.53 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 4 . 8 2 \%} \\ (-5.71 \%--3.97 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 5 1 . 5 \%} \\ (-58.1 \%--44.7 \%) \end{gathered}$ | $\begin{gathered} 21 \\ (18-26) \end{gathered}$ |


|  | gIM | 18.7\% | -11.1\% | -37.1\% | 9 |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | $\begin{aligned} & \text { - Median } \\ & \text { - } 90 \% \mathrm{Cl} \end{aligned}$ | (16.6\%-21.1\%) | (-13.0\%--9.30\%) | (-42.6\%--31.9\%) | (8-11) |
|  | gPM <br> - Median <br> - 90\% Cl | $\begin{gathered} \mathbf{6 9 . 4 \%} \\ (63.4 \%-74.2 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 1 1 . 9 \%} \\ (-16.2 \%--7.60 \% \end{gathered}$ | $\begin{gathered} \mathbf{- 1 4 . 7 \%} \\ (-20.1 \%--9.29 \%) \end{gathered}$ | $\begin{gathered} 9 \\ (7-14) \end{gathered}$ |
| Light elderly | $\begin{aligned} & \text { gNM } \\ & \text { - Median } \\ & -90 \% \mathrm{Cl} \\ & \text { gIM } \end{aligned}$ | $\begin{gathered} \mathbf{3 . 7 3 \%} \\ (2.97 \%-4.63 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 5 . 6 2 \%} \\ (-6.56 \%--4.69 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 6 0 . 0 \%} \\ (-66.7 \%--53.0 \%) \end{gathered}$ | $\begin{gathered} 18 \\ (16-22) \end{gathered}$ |
|  | $\begin{aligned} & \text { - Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ <br> gPM | $\begin{gathered} \mathbf{1 6 . 5 \%} \\ (14.5 \%-18.9 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 1 3 . 3 \%} \\ (-15.2 \%--11.4 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 4 4 . 4 \%} \\ (-50.3 \%--38.8 \%) \end{gathered}$ | $\begin{gathered} \mathbf{8} \\ (7-9) \end{gathered}$ |
|  | $\begin{aligned} & \text { - Median } \\ & \text { - } 90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{6 5 . 9 \%} \\ (60.2 \%-71.9 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 1 5 . 1 \%} \\ (-20.0 \%--10.6 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 1 8 . 7 \%} \\ (-24.5 \%--13.0 \%) \end{gathered}$ | $\begin{gathered} 7 \\ (5-10) \end{gathered}$ |

$C_{S S, m i n}$ ENDX: Endoxifen minimum concentrations at steady-state;
Subpopulation characteristics: Heavy young: 22-39 years, $77-150 \mathrm{~kg}$; Heavy: 40-65 years, $77-150 \mathrm{~kg}$; Young: 22-39 years, $60-76 \mathrm{~kg}$; IQR: $40-65$ years, $60-76 \mathrm{~kg}$; Elderly: $66-95$ years, $60-76 \mathrm{~kg}$; Light: 40-65 years, $39-60 \mathrm{~kg}$; Light elderly: $66-95$ years, $39-60 \mathrm{~kg}$.
Abbreviations: CI: confidence interval; gXM: genotype-predicted phenotype; gNM: normal metaboliser (incl. ultrarapid metaboliser); gIM: intermediate metaboliser; $g P M$ : poor metaboliser; IQR: interquartile range; $N N H$ : number needed to harm (1/Absolute change in risk; if absolute change in risk is positive);
 ns: not significant
SU1: Study set-up 1: endoxifen subtarget concentrations for subpopulations with different age and body weight distributions

Table S5: Number of patients at risk for subtarget $\mathrm{C}_{\mathrm{SS}, \min \mathrm{ENDX}}$ and absolute and relative risk changes for different patient subpopulations in SU2.

| Scenario | Number of patients at risk | Absolute change in risk compared to median | Relative change in risk compared to median | NNH/NNT |
| :---: | :---: | :---: | :---: | :---: |
| Heavy young <br> - Median <br> - $90 \%$ CI | $\begin{gathered} \text { 70.6\% } \\ (66.2 \%-75.1 \%) \end{gathered}$ | $\begin{gathered} +49.7 \% \\ (45.0 \%-54.2 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{2 3 8 \%} \\ (208 \%-268 \%) \end{gathered}$ | $\begin{gathered} \mathbf{2} \\ (2-3) \end{gathered}$ |
| Heavy <br> - Median <br> - 90\% CI | $\begin{gathered} \mathbf{6 2 . 4 \%} \\ (58.5 \%-66.4 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{4 1 . 5 \%} \\ (+37.4 \%-45.4 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 9 8 \%} \\ (+174 \%-223 \%) \end{gathered}$ | $\begin{gathered} \mathbf{3} \\ (3-3) \end{gathered}$ |
| Young <br> - Median <br> - 90\% CI | $\begin{gathered} \mathbf{2 7 . 4 \%} \\ (24.8 \%-30.2 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{6 . 5 0 \%} \\ (+3.80 \%-9.20 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{3 0 . 7 \%} \\ (17.7 \%-44.5 \%) \end{gathered}$ | $\begin{gathered} \mathbf{1 6} \\ (11-27) \end{gathered}$ |
| Median <br> - Median <br> - 90\% CI | $\begin{gathered} \mathbf{2 0 . 9 \%} \\ (19.7 \%-22.3 \%) \end{gathered}$ | - | - | - |
| Elderly <br> - Median <br> - 90\% CI | $\begin{gathered} \mathbf{1 7 . 6 \%} \\ (16.0 \%-19.4 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 3 . 3 0 \%} \\ (-4.60--2.00 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 1 5 . 9 \%} \\ (-21.8 \%--9.18 \%) \end{gathered}$ | $\begin{gathered} 34 \\ (22-50) \end{gathered}$ |
| Light <br> - Median <br> - 90\% CI | $\begin{gathered} \mathbf{6 . 3 9 \%} \\ (5.42 \%-7.46 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 1 4 . 5 \%} \\ (-15.7 \%-13.3 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 6 9 . 4 \%} \\ (-73.6 \%--65.1 \%) \end{gathered}$ | $\begin{gathered} 7 \\ (7-8) \end{gathered}$ |
| Light elderly <br> - Median <br> - $90 \%$ CI | $\begin{gathered} \mathbf{5 . 1 0 \%} \\ (4.18 \%-6.22 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 1 5 . 8 \%} \\ (-17.0 \%--14.6 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 7 5 . 6 \%} \\ (-79.5 \%--71.1 \%) \end{gathered}$ | $\begin{gathered} 7 \\ (6-7) \end{gathered}$ |

$C_{S S, \min \text { ENDX: }}$ Endoxifen minimum concentrations at steady-state;
Subpopulation characteristics: Heavy young: 22 years, 150 kg ; Heavy: 55 years, 150 kg ; Young: 22
years, 68 kg ; Median: 55 years, 68 kg ; Elderly: 95 years, 68 kg ; Light: 55 years, 39 kg ;
Light elderly: 95 years, 39 kg .
Abbreviations: CI: confidence interval;
$N N H$ : number needed to harm (1/Absolute change in risk; if absolute change in risk is positive);
$N N T$ : number needed to treat ( $1 /(-)$ Absolute change in risk; if absolute change in risk is negative)
SU2: Study set-up 2: endoxifen subtarget concentrations for subpopulations with extreme age and body weight values

Table S6: Number of patients at risk for subtarget $\mathrm{C}_{\mathrm{SS}, \text { min }} \mathrm{ENDX}$ and absolute and relative risk changes for different patient subpopulations in SU2, stratified for CYP2D6 phenotype.

| Scenario | CYP2D6 <br> phenotype | Number of patients at risk | Absolute change in risk compared to median | Relative change in risk compared to median | NNH/NNT |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Heavy young | $\begin{aligned} & \text { gNM } \\ & - \text { Median } \\ & -90 \% \mathrm{Cl} \\ & \text { gIM } \end{aligned}$ | $\begin{gathered} \mathbf{5 9 . 2 \%} \\ (53.9 \%-64.9 \% \end{gathered}$ | $\begin{gathered} +50.0 \\ (44.5 \%-55.7 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{5 4 2 \%} \\ (447 \%-659 \%) \end{gathered}$ | $\begin{gathered} 2 \\ (2-3) \end{gathered}$ |
|  | - Median <br> - 90\% CI | $\begin{gathered} \mathbf{8 3 . 4 \%} \\ (79.6 \%-87.3 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{5 3 . 9 \%} \\ (49.6-58.0 \%) \end{gathered}$ | $\begin{gathered} \mathbf{+ 1 8 2 \%} \\ (158 \%-207 \%) \end{gathered}$ | $\begin{gathered} \mathbf{2} \\ (2-2) \end{gathered}$ |
|  | $\begin{aligned} & \text { gPM } \\ & \quad-\text { Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{9 9 . 3 \%} \\ (98.6 \%-99.8 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 7 . 8 \%} \\ (13.8 \%-22.3 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{2 1 . 8 \%} \\ (16.1 \%-29.1 \%) \end{gathered}$ | $\begin{gathered} 6 \\ (5-8) \end{gathered}$ |
| Heavy | $\begin{aligned} & \text { gNM } \\ & - \text { Median } \\ & -90 \% \mathrm{Cl} \\ & \text { gIM } \end{aligned}$ | $\begin{gathered} \text { 49.4\% } \\ (44.4 \%-54.0 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{4 0 . 2 \%} \\ (35.3 \%-44.8 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{4 3 6 \%} \\ (364 \%-527 \%) \end{gathered}$ | $\begin{gathered} \mathbf{3} \\ (3-3) \end{gathered}$ |
|  | $\begin{aligned} & \text { - Median } \\ & \text { - } 90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \text { 76.7\% } \\ (72.8 \%-80.6 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{4 7 . 1 \%} \\ (42.8 \%-51.1 \%) \end{gathered}$ | $\begin{gathered} \mathbf{+ 1 5 9 \%} \\ (138 \%-182 \%) \end{gathered}$ | $\begin{gathered} \mathbf{3} \\ (2-3) \end{gathered}$ |
|  | $\begin{aligned} & \text { gPM } \\ & \quad-\text { Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{9 8 . 7 \%} \\ (97.5 \%-99.5 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{1 7 . 2 \%} \\ (13.3 \%-21.6 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{2 1 . 1 \%} \\ (15.6 \%-28.0 \%) \end{gathered}$ | $\begin{gathered} 6 \\ (5-8) \end{gathered}$ |
| Young | $\begin{aligned} & \text { gNM } \\ & - \text { Median } \\ & -90 \% \mathrm{Cl} \\ & \text { gIM } \end{aligned}$ | $\begin{gathered} \mathbf{1 4 . 1 \%} \\ (11.7 \%-16.6 \%) \end{gathered}$ | $\begin{gathered} +4.92 \% \\ (2.86 \%-7.19 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{5 3 . 1 \%} \\ (29.5 \%-82.0 \%) \end{gathered}$ | $\begin{gathered} 21 \\ (14-35) \end{gathered}$ |
|  | $\begin{aligned} & \text { - Median } \\ & \text { - 90\% CI } \\ & \text { gPM } \end{aligned}$ | $\begin{gathered} \mathbf{3 8 . 4 \%} \\ (34.7 \%-42.3 \%) \end{gathered}$ | $\begin{gathered} \mathbf{+ 8 . 8 0 \%} \\ (5.20 \%-12.6 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{2 9 . 7 \%} \\ (16.9 \%-43.6 \%) \end{gathered}$ | $\begin{gathered} 12 \\ (8-20) \end{gathered}$ |
|  | $\begin{aligned} & \text { - Median } \\ & \text { - } 90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{8 7 . 6 \%} \\ (83.4 \%-91.0 \%) \end{gathered}$ | $\begin{gathered} +\mathbf{6 . 0 0 \%} \\ (1.90 \%-10.1 \%) \end{gathered}$ | $\begin{gathered} +7.38 \% \\ (2.27 \%-12.9 \%) \end{gathered}$ | $\begin{gathered} 17 \\ (10-53) \end{gathered}$ |
| Median | $\begin{aligned} & \text { gNM } \\ & - \text { Median } \\ & -90 \% \mathrm{Cl} \\ & \text { gIM } \end{aligned}$ | $\begin{gathered} \mathbf{9 . 2 1 \%} \\ (8.00 \%-10.5 \%) \end{gathered}$ | - | - | - |
|  | $\begin{aligned} & \text { - Median } \\ & \text { - } 90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{2 9 . 6 \%} \\ (27.3 \%-32.2 \%) \end{gathered}$ | - | - | - |
|  | $\begin{aligned} & \text { gPM } \\ & \quad-\text { Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{8 1 . 4 \%} \\ (76.9 \%-85.6 \%) \end{gathered}$ | - | - | - |
| Elderly | $\begin{aligned} & \text { gNM } \\ & - \text { Median } \\ & -90 \% \mathrm{Cl} \\ & \text { gIM } \end{aligned}$ | $\begin{gathered} \mathbf{6 . 9 6 \%} \\ (5.76 \%-8.35 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 2 . 2 3 \%} \\ (-3.23 \%--1.17 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 2 4 . 4 \%} \\ (-34.15--13.0 \%) \end{gathered}$ | $\begin{gathered} 45 \\ (31-86) \end{gathered}$ |
|  | $\begin{aligned} & \text { - Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ gPM | $\begin{gathered} \mathbf{2 4 . 8 \%} \\ (22.1 \%-27.7 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 4 . 8 0 \%} \\ (-7.00 \%--2.40 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 1 6 . 2 \%} \\ (-23.3 \%--8.24 \%) \end{gathered}$ | $\begin{gathered} 21 \\ (15-42) \end{gathered}$ |
|  | - Median <br> - $90 \%$ CI | $\begin{gathered} \text { 77.1\% } \\ (71.5 \%-82.0 \%) \end{gathered}$ | $\begin{gathered} -\mathbf{4 . 3 0 \%} \\ (-8.60 \%--0.4 \%) \end{gathered}$ | $\begin{gathered} \mathbf{- 5 . 3 4 \%} \\ (-10.4 \%--0.49 \%) \end{gathered}$ | $\begin{gathered} 24 \\ (11-250) \end{gathered}$ |
| Light | $\begin{aligned} & \text { gNM } \\ & \quad-\text { Median } \\ & -90 \% \mathrm{Cl} \end{aligned}$ | $\begin{gathered} \mathbf{1 . 2 4 \%} \\ (0.812 \%- \\ 1.71 \%) \end{gathered}$ | $\begin{gathered} -7.95 \% \\ (-9.04 \%--6.94 \% \end{gathered}$ | $\begin{gathered} \mathbf{- 8 6 . 7 \%} \\ (-90.6 \%--82.3 \%) \end{gathered}$ | $\begin{gathered} 13 \\ (12-15) \end{gathered}$ |


|  | gIM |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: |
|  | - Median | 7.93\% | -21.7\% | -73.2\% | 5 |
|  | - 90\% CI | (6.26\%-9.83\%) | (-23.8\%--19.5\%) | (-78.1\%--68.0\%) | (5-6) |
|  | gPM |  |  |  |  |
|  | - Median | 48.3\% | -33.1\% | -40.6\% | 3 |
|  | - 90\% CI | (41.4\%-55.1\%) | (-38.6\%--26.9\%) | (-47.5\%--33.3\%) | (3-4) |
| Light | gNM |  |  |  |  |
| elderly | - Median | 0.812\% | -8.38\% | -91.1\% | 12 |
|  | - $90 \% \mathrm{Cl}$ | $\begin{gathered} (0.495 \%- \\ 1.22 \%) \end{gathered}$ | (-9.53\%--7.29\%) | (-94.3\%--87.2\%) | (11-14) |
|  | gIM |  |  |  |  |
|  | - Median | 6.05\% | -23.5\% | -79.6\% | 5 |
|  | -90\% CI | (4.55\%-7.88\%) | (-25.8\%--21.4\%) | (-84.0\%--74.5\%) | $(4-5)$ |
|  | gPM |  |  |  |  |
|  | - Median | 42.2\% | -39.1\% | $-47.9 \%$ | 3 |
|  | - 90\% Cl | (35.3\%-49.7\%) | (-44.6\%--32.8\%) | (-55.4\%--40.1\%) | (2-3) |

$C_{S S, \min E N D X:}$ Endoxifen minimum concentrations at steady-state;
Subpopulation characteristics: Heavy young: 22 years, 150 kg ; Heavy: 55 years, 150 kg ; Young: 22 years, 68 kg ; Median: 55 years, 68 kg ; Elderly: 95 years, 68 kg ; Light: 55 years, 39 kg ; Light elderly: 95 years, 39 kg .
Abbreviations: CI: confidence interval; gXM: genotype-predicted phenotype; $g N M$ : normal metaboliser (incl. ultrarapid metaboliser); gIM: intermediate metaboliser; gPM: poor metaboliser;
$N N H$ : number needed to harm (1/Absolute change in risk; if absolute change in risk is positive); $N N T$ : number needed to treat ( $1 /(-$ Absolute change in risk); if absolute change in risk is negative)
SU2: Study set-up 2: endoxifen subtarget concentrations for subpopulations with extreme age and body weight values

## References:

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