Supplementary material

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

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

$C_{SS,min\ ENDX}$: 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) (n=435)	**Eval. dataset (all) (n=935)**	**Eval. dataset (African) (n=12)**	**Eval. dataset (Arab) (n=77)**	**Eval. dataset (Asian) (n=153)**	**Eval. dataset (Caucasian) (n=681)**	**Eval. dataset (Indian) (n=12)**
Pre-menopausal Median (IQR) [kg]	72.2 (63.4-83.8)	63.0 (57.0-72.3)	62.5 (55.8-68.8)	68.0 (61.0-76.0)	57.4 (51.4-62.8)	65 (59.0-76.0)	61.4 (53.9-64.7)
Post-menopausal Median (IQR) [kg]	70 (62.0-80.1)	70 (63.0-78.5)	-	-	-	70 (63.0-78.5)	
p-Value	ns	p<0.001				p<0.001	

$C_{SS,min\ ENDX}$: 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 $C_{SS,min\ ENDX}$ 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				
- **Median**	**36.9%**	**+15.7%**	**+75.0%**	**7**
- 90% CI	(34.6% - 39.2%)	(13.7% - 17.8%)	(63.7% - 86.3%)	(6 - 8)
Heavy				
- **Median**	**33.4%**	**+12.3%**	**+58.1%**	**9**
- 90% CI	(31.5% - 35.2%)	(10.6% - 13.8%)	(49.8% - 66.8%)	(8 - 10)
Young				
- **Median**	**23.8%**	**+2.70%**	**+13.0%**	**37**
- 90% CI	(22.2% - 25.5%)	(1.40% - 4.10%)	(6.50% - 19.4%)	(25 - 72)
IQR				
- **Median**	**21.1%**	**-**	**-**	**-**
- 90% CI	(19.8% - 22.4%)			
Elderly				
- **Median**	**19.1%**	**-2.00%**	**-9.63%**	**50**
- 90% CI	(17.7% - 20.6%)	(-3.10% - -0.90%)	(-14.6% - -4.39%)	(33 - 112)
Light				
- **Median**	**13.5%**	**-7.60%**	**-36.1%**	**14**
- 90% CI	(12.4% - 14.8%)	(-8.60% - -6.60%)	(-40.2% - -31.8%)	(12 - 16)
Light elderly				
- **Median**	**12.1%**	**-9.10%**	**-43.0%**	**11**
- 90% CI	(10.8% - 13.4%)	(-10.1% - -8.00%)	(-47.4% - -38.2%)	(10 - 13)

$C_{SS,min\ ENDX}$: Endoxifen minimum concentrations at steady-state;
Subpopulation characteristics: Heavy young: 22-39 years, 77-150 kg; *Heavy*: 40-65 years, 77-150 kg; *Young*: 22-39 years, 60-76 kg; *IQR:* 40-65 years, 60-76 kg; *Elderly*: 66-95 years, 60-76 kg; *Light:* 40-65 years, 39-60 kg; *Light elderly:* 66-95 years, 39-60 kg.
Abbreviations: CI: confidence interval; *IQR*: interquartile range;
NNH: number needed to harm (1/Absolute change in risk; if absolute change in risk is positive);
NNT: 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 $C_{SS,min\ ENDX}$ 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	**gNM**				
	- Median	**22.5%**	**+13.1%**	**+141%**	**8**
	- 90% CI	(20.1% - 25.0%)	(11.2% - 15.4%)	(114% - 173%)	(5 - 9)
	gIM				
	- Median	**50.1%**	**+20.3%**	**+68.2%**	**5**
	- 90% CI	(46.9% - 53.4%)	(17.3% - 23.0%)	(56.3% - 81.0%)	(5 - 6)
	gPM				
	- Median	**92.4%**	**+11.2%**	**+13.8%**	**9**
	- 90% CI	(89.7% - 95.1%)	(7.60% - 15.2%)	(9.00% - 19.7%)	(6 - 14)
Heavy	**gNM**				
- Median	**- Median**	**19.4%**	**+10.1%**	**+107%**	**10**
- 90% CI	- 90% CI	(17.3% - 21.5%)	(8.40% - 11.6%)	(86.5% - 131%)	(9 - 12)
	gIM				
	- Median	**45.8%**	**+16.0%**	**+53.7%**	**7**
	- 90% CI	(43.1% - 48.9%	(13.8% - 18.3%)	(44.9% - 63.6%)	(6 - 8)
	gPM				
	- Median	**90.6%**	**+9.40%**	**+11.6%**	**11**
	- 90% CI	(87.4% - 93.5%)	(6.20% - 13.4%)	(7.21% - 17.3%)	(8 - 17)
Young	**gNM**				
- Median	**- Median**	**11.4%**	**+1.97%**	**+21.2%**	**51**
- 90% CI	- 90% CI	(9.82% - 12.9%)	(0.850% - 3.20%)	(8.90% - 35.5%)	(32 - 118)
	gIM				
	- Median	**33.6%**	**+3.80%**	**+12.7%**	**27**
	- 90% CI	(30.9% - 36.4%)	(1.60% - 6.01%)	(5.21% - 21.1%)	(17 - 63)
	gPM				
	- Median	**84.3%**	**+2.90%**	**+3.64%**	**35**
	- 90% CI	(80.0% - 88.1%)	(-0.7% - 7.0%)	(-0.838% - 8.86%)	(*ns*) [2]
IQR	**gNM**				
	- Median	**9.36%**	-	-	-
	- 90% CI	(8.18% - 10.8%)			
	gIM				
	- Median	**29.8%**	-	-	-
	- 90% CI	(27.4% - 32.2%)			
	gPM				
	- Median	**81.1%**	-	-	-
	- 90% CI	(76.8% - 85.2%)			
Elderly	**gNM**				
	- Median	**7.98%**	**-1.42%**	**-15.1%**	**71**
	- 90% CI	(6.82% - 9.27%)	(-2.30% - -0.42%)	(-23.5% - -4.97%)	(44 - 239)
	gIM				
	- Median	**26.9%**	**-2.90%**	**-9.79%**	**35**
	- 90% CI	(24.6% - 29.6%)	(-4.90% - -0.90%)	(-16.1% - -3.15%)	(21 - 112)
	gPM				
	- Median	**78.9%**	**-2.20%**	**-2.72%**	**46**
	- 90% CI	(84.2% - 83.4%)	(-6.50% - 1.50%)	(-7.84%-1.86%)	(*ns*) [2]
Light	**gNM**				
	- Median	**4.52%**	**-4.82%**	**-51.5%**	**21**
	- 90% CI	(3.66% - 5.53%)	(-5.71% - -3.97%)	(-58.1% - -44.7%)	(18 - 26)

	gIM	**18.7%**	**-11.1%**	**-37.1%**	**9**
	- **Median**	(16.6% - 21.1%)	(-13.0% - -9.30%)	(-42.6% - -31.9%)	(8 - 11)
	- 90% CI				
	gPM	**69.4%**	**-11.9%**	**-14.7%**	**9**
	- **Median**	(63.4% - 74.2%)	(-16.2% - -7.60%	(-20.1% - -9.29%)	(7 - 14)
	- 90% CI				
Light elderly	**gNM**				
	- **Median**	**3.73%**	**-5.62%**	**-60.0%**	**18**
	- 90% CI	(2.97% - 4.63%)	(-6.56% - -4.69%)	(-66.7% - -53.0%)	(16 - 22)
	gIM				
	- **Median**	**16.5%**	**-13.3%**	**-44.4%**	**8**
	- 90% CI	(14.5% - 18.9%)	(-15.2% - -11.4%)	(-50.3% - -38.8%)	(7 - 9)
	gPM				
	- **Median**	**65.9%**	**-15.1%**	**-18.7%**	**7**
	- 90% CI	(60.2% - 71.9%)	(-20.0% - -10.6%)	(-24.5% - -13.0%)	(5 - 10)

$C_{SS,min\ ENDX}$: Endoxifen minimum concentrations at steady-state;
Subpopulation characteristics: Heavy young: 22-39 years, 77-150 kg; *Heavy*: 40-65 years, 77-150 kg; *Young*: 22-39 years, 60-76 kg; *IQR:* 40-65 years, 60-76 kg; *Elderly*: 66-95 years, 60-76 kg; *Light:* 40-65 years, 39-60 kg; *Light elderly:* 66-95 years, 39-60 kg.
Abbreviations: *CI*: confidence interval; *gXM*: genotype-predicted phenotype; *gNM*: normal metaboliser (incl. ultrarapid metaboliser); *gIM*: intermediate metaboliser; *gPM*: poor metaboliser; *IQR*: interquartile range; *NNH*: number needed to harm (1/Absolute change in risk; if absolute change in risk is positive); *NNT*: number needed to treat (1/(-Absolute change in risk); if absolute change in risk is negative); *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 $C_{SS,min\ ENDX}$ 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				
- **Median**	**70.6%**	**+49.7%**	**+238%**	**2**
- 90% CI	(66.2% - 75.1%)	(45.0% - 54.2%)	(208% - 268%)	(2 - 3)
Heavy				
- **Median**	**62.4%**	**+41.5%**	**+198%**	**3**
- 90% CI	(58.5% - 66.4%)	(+37.4% - 45.4%)	(+174% - 223%)	(3 - 3)
Young				
- **Median**	**27.4%**	**+6.50%**	**+30.7%**	**16**
- 90% CI	(24.8% - 30.2%)	(+3.80% - 9.20%)	(17.7% - 44.5%)	(11 – 27)
Median				
- **Median**	**20.9%**	**-**	**-**	-
- 90% CI	(19.7% - 22.3%)			
Elderly				
- **Median**	**17.6%**	**-3.30%**	**-15.9%**	**34**
- 90% CI	(16.0% - 19.4%)	(-4.60 - -2.00%)	(-21.8% - -9.18%)	(22 - 50)
Light				
- **Median**	**6.39%**	**-14.5%**	**-69.4%**	**7**
- 90% CI	(5.42% - 7.46%)	(-15.7% - 13.3%)	(-73.6% - -65.1%)	(7 - 8)
Light elderly				
- **Median**	**5.10%**	**-15.8%**	**-75.6%**	**7**
- 90% CI	(4.18% - 6.22%)	(-17.0% - -14.6%)	(-79.5% - -71.1%)	(6 - 7)

$C_{SS,min\ ENDX}$: 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;
NNH: number needed to harm (1/Absolute change in risk; if absolute change in risk is positive);
NNT: 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 $C_{SS,min\ ENDX}$ and absolute and relative risk changes for different patient subpopulations in SU2, stratified for CYP2D6 phenotype.

Scenario	CYP2D6 phenotype	Number of patients at risk	Absolute change in risk compared to median	Relative change in risk compared to median	NNH/NNT
Heavy young	**gNM**				
	- Median	**59.2%**	**+50.0**	**+542%**	**2**
	- 90% CI	(53.9% - 64.9%	(44.5% - 55.7%)	(447% - 659%)	**(2-3)**
	gIM				
	- Median	**83.4%**	**+53.9%**	**+182%**	**2**
	- 90% CI	(79.6% - 87.3%)	(49.6 – 58.0%)	(158% - 207%)	(2-2)
	gPM				
	- Median	**99.3%**	**+17.8%**	**+21.8%**	**6**
	- 90% CI	(98.6% - 99.8%)	(13.8% - 22.3%)	(16.1% - 29.1%)	(5-8)
Heavy	**gNM**				
	- Median	**49.4%**	**+40.2%**	**+436%**	**3**
	- 90% CI	(44.4% - 54.0%)	(35.3% - 44.8%)	(364% - 527%)	(3-3)
	gIM				
	- Median	**76.7%**	**+47.1%**	**+159%**	**3**
	- 90% CI	(72.8% - 80.6%)	(42.8% - 51.1%)	(138% - 182%)	(2-3)
	gPM				
	- Median	**98.7%**	**+17.2%**	**+21.1%**	**6**
	- 90% CI	(97.5% - 99.5%)	(13.3% - 21.6%)	(15.6% - 28.0%)	(5-8)
Young	**gNM**				
	- Median	**14.1%**	**+4.92%**	**+53.1%**	**21**
	- 90% CI	(11.7% - 16.6%)	(2.86% - 7.19%)	(29.5% - 82.0%)	(14 – 35)
	gIM				
	- Median	**38.4%**	**+8.80%**	**+29.7%**	**12**
	- 90% CI	(34.7% - 42.3%)	(5.20% - 12.6%)	(16.9% - 43.6%)	(8 - 20)
	gPM				
	- Median	**87.6%**	**+6.00%**	**+7.38%**	**17**
	- 90% CI	(83.4% - 91.0%)	(1.90% - 10.1%)	(2.27% - 12.9%)	(10 – 53)
Median	**gNM**				
	- Median	**9.21%**	**-**	**-**	**-**
	- 90% CI	(8.00% - 10.5%)			
	gIM				
	- Median	**29.6%**	**-**	**-**	**-**
	- 90% CI	(27.3% - 32.2%)			
	gPM				
	- Median	**81.4%**	**-**	**-**	**-**
	- 90% CI	(76.9% - 85.6%)			
Elderly	**gNM**				
	- Median	**6.96%**	**-2.23%**	**-24.4%**	**45**
	- 90% CI	(5.76% - 8.35%)	(-3.23% - -1.17%)	(-34.15 - -13.0%)	(31 – 86)
	gIM				
	- Median	**24.8%**	**-4.80%**	**-16.2%**	**21**
	- 90% CI	(22.1% - 27.7%)	(-7.00% - -2.40%)	(-23.3% - -8.24%)	(15 – 42)
	gPM				
	- Median	**77.1%**	**-4.30%**	**-5.34%**	**24**
	- 90% CI	(71.5% - 82.0%)	(-8.60% - -0.4%)	(-10.4% - -0.49%)	(11-250)
Light	**gNM**				
	- Median	**1.24%**	**-7.95%**	**-86.7%**	**13**
	- 90% CI	(0.812% - 1.71%)	(-9.04% - -6.94%	(-90.6% - -82.3%)	(12 – 15)

	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 elderly	**gNM**				
	- Median	**0.812%**	**-8.38%**	**-91.1%**	**12**
	- 90% CI	(0.495% - 1.22%)	(-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% CI	(35.3% - 49.7%)	(-44.6% - -32.8%)	(-55.4% - -40.1%)	(2-3)

$C_{SS,min\ ENDX}$: 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; *gXM:* genotype-predicted phenotype; *gNM:* normal metaboliser (incl. ultrarapid metaboliser); *gIM:* intermediate metaboliser; *gPM*: poor metaboliser;
NNH: number needed to harm (1/Absolute change in risk; if absolute change in risk is positive);
NNT: 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

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