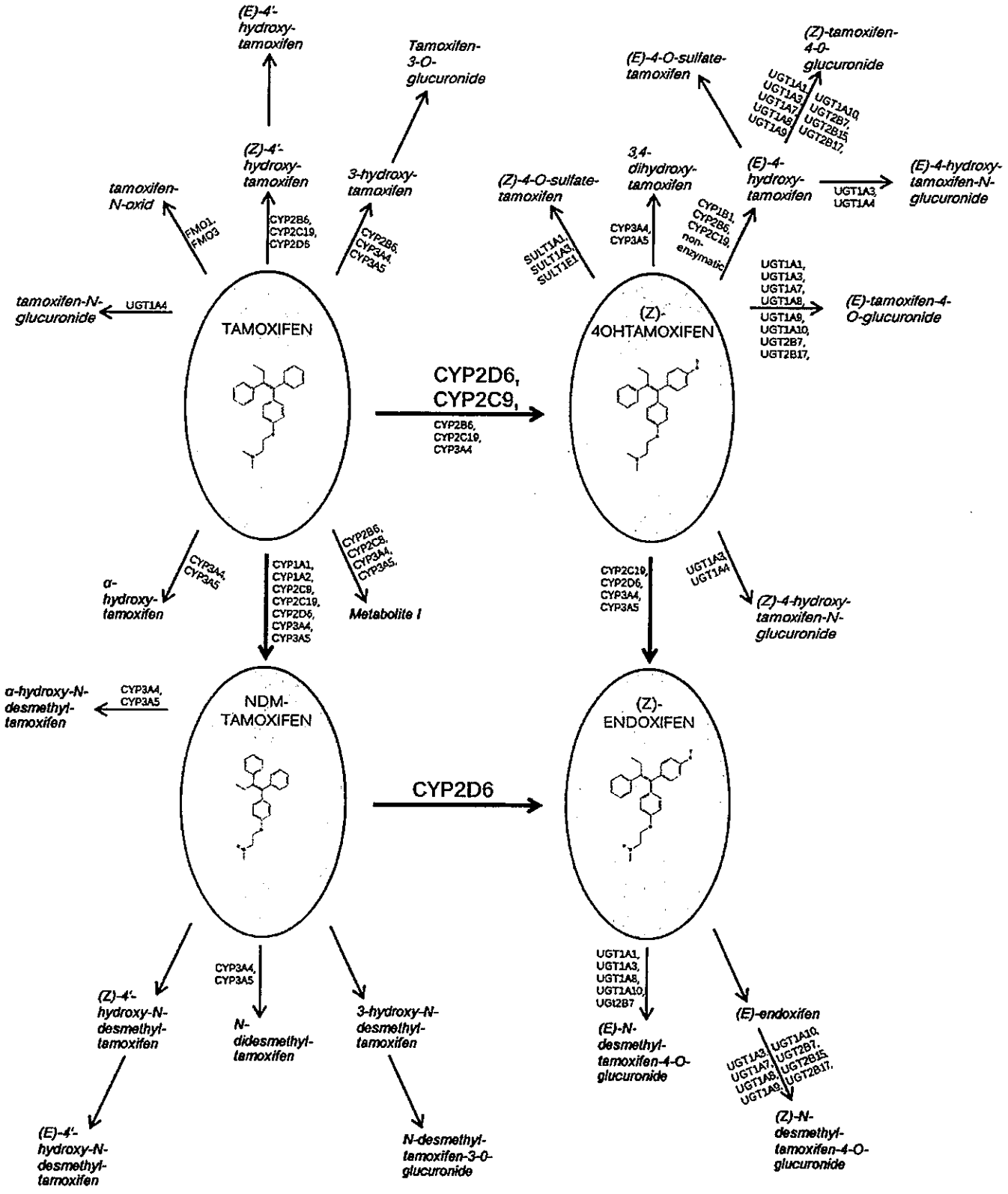

(E)-4'-hydroxy-tamoxifen
Tamoxifen-3-O-glucuronide
(Z)-4'-hydroxy-tamoxifen
3-hydroxy-tamoxifen
tamoxifen-N-oxid
FMO1, FMO3
CYP2B6, CYP2C19, CYP2D6
CYP2B6, CYP3A4, CYP3A5
tamoxifen-N-glucuronide
UGT1A4
TAMOXIFEN
CYP2D6, CYP2C9,
CYP2B6, CYP2C19, CYP3A4
(Z)-4OHTAMOXIFEN
(E)-4-O-sulfate-tamoxifen
(Z)-tamoxifen-4-O-glucuronide
UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, UGT2B15, UGT2B17,
(Z)-4-O-sulfate-tamoxifen
3,4-dihydroxy-tamoxifen
(E)-4-hydroxy-tamoxifen
(E)-4-hydroxy-tamoxifen-N-glucuronide
UGT1A3, UGT1A4
SULT1A1, SULT1A3, SULT1E1
CYP3A4, CYP3A5
CYP1B1, CYP2B6, CYP2C19, non-enzymatic
UGT1A1, UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, UGT2B17,
(E)-tamoxifen-4-O-glucuronide
CYP3A4, CYP3A5
α-hydroxy-tamoxifen
CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5
CYP2B6, CYP2C9, CYP3A4, CYP3A5,
Metabolite I
CYP2C19, CYP2D6, CYP3A4, CYP3A5
UGT1A3, UGT1A4
(Z)-4-hydroxy-tamoxifen-N-glucuronide
α-hydroxy-N-desmethyl-tamoxifen
CYP3A4, CYP3A5
NDM-TAMOXIFEN
CYP2D6
(Z)-ENDOXIFEN
UGT1A1, UGT1A3, UGT1A8, UGT1A10, UGt2B7
(E)-N-desmethyl-tamoxifen-4-O-glucuronide
(E)-endoxifen
UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, UGT2B15, UGT2B17,
(Z)-N-desmethyl-tamoxifen-4-O-glucuronide
(Z)-4'-hydroxy-N-desmethyl-tamoxifen
CYP3A4, CYP3A5
N-didesmethyl-tamoxifen
3-hydroxy-N-desmethyl-tamoxifen
(E)-4'-hydroxy-N-desmethyl-tamoxifen
N-desmethyl-tamoxifen-3-O-glucuronide

Figure 1

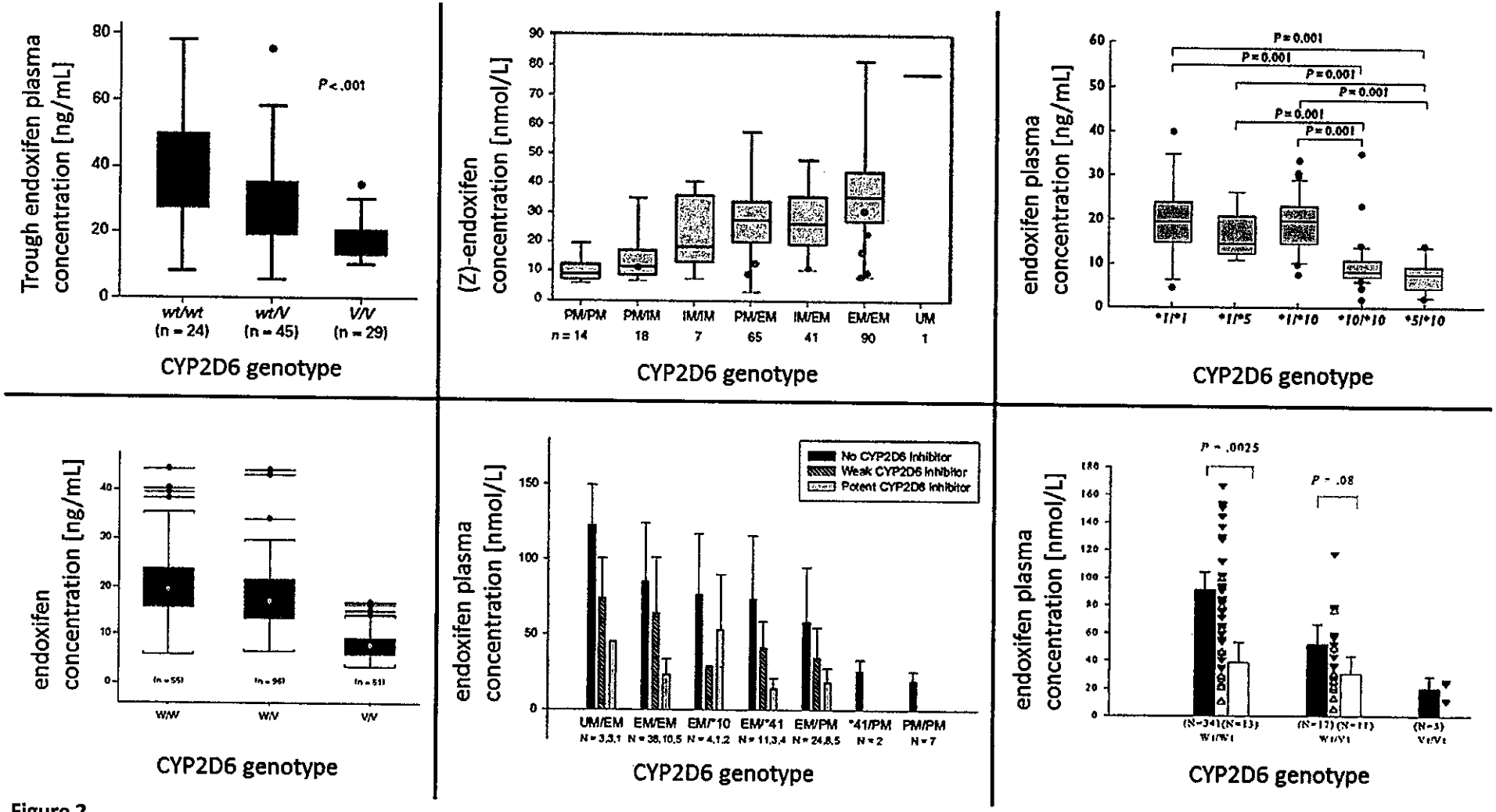

Trough endoxifen plasma concentration [ng/mL]
P<.001
wt/wt (n = 24)
wt/V (n = 45)
V/V (n = 29)
CYP2D6 genotype
(Z)-endoxifen concentration [nmol/L]
PM/PM n = 14
PM/IM 18
IM/IM 7
PM/EM 65
IM/EM 41
EM/EM 90
UM 1
CYP2D6 genotype
endoxifen plasma concentration [ng/mL]
P = 0.001
*1/*1
*1/*5
*1/*10
*10/*10
*5/*10
CYP2D6 genotype
endoxifen concentration [ng/mL]
W/W
W/V
V/V
CYP2D6 genotype
endoxifen plasma concentration [nmol/L]
No CYP2D6 Inhibitor
Weak CYP2D6 Inhibitor
Potent CYP2D6 Inhibitor
UM/EM
EM/EM
EM/*10
EM/*41
EM/PM
*41/PM
PM/PM
CYP2D6 genotype
endoxifen plasma concentration [nmol/L]
P = .0025
P = .08
CYP2D6 genotype

Figure 2

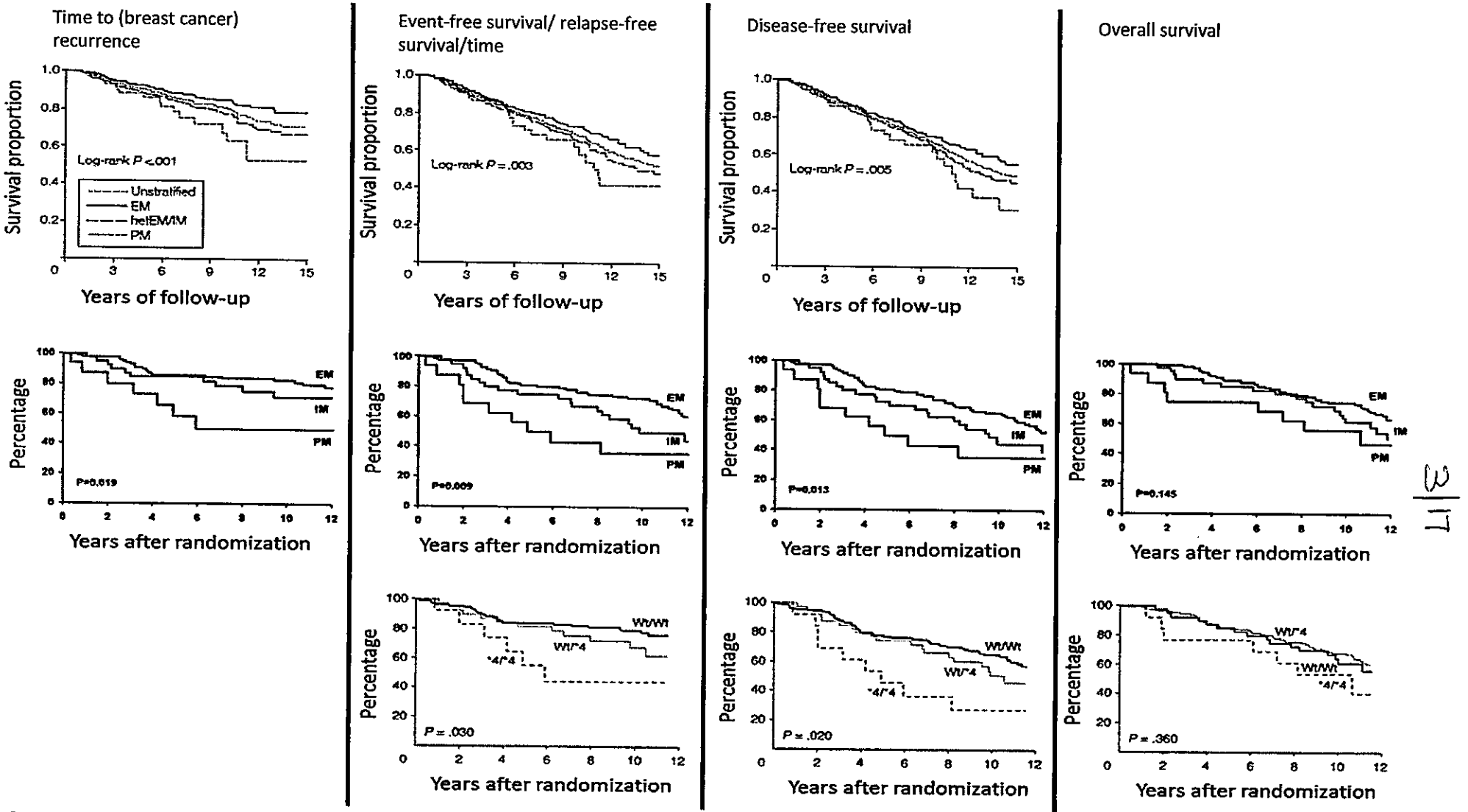
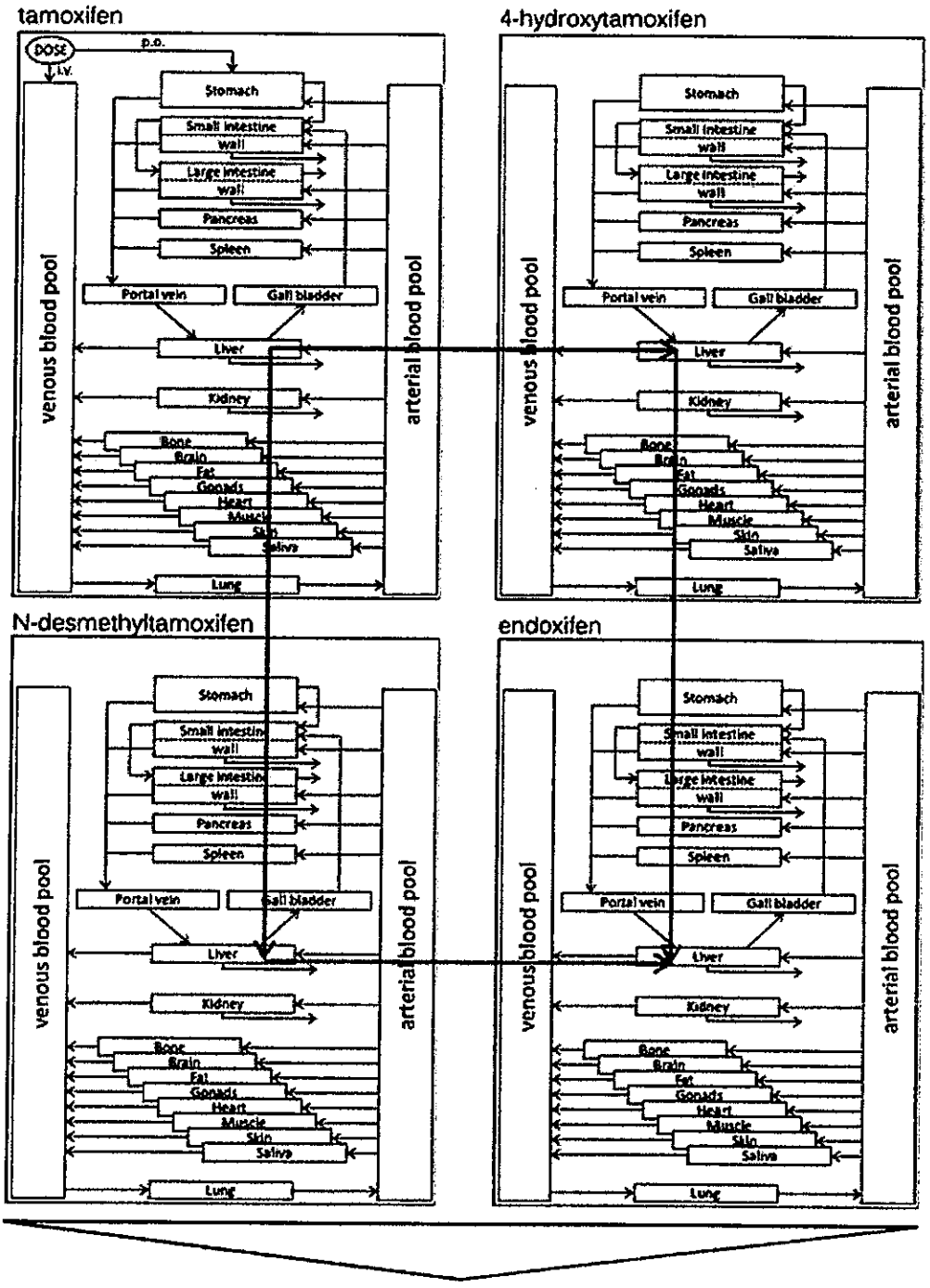

Time to (breast cancer) recurrence
Event-free survival/ relapse-free survival/time
Disease-free survival
Overall survival
Survival proportion
Log-rank P <.001
Unstratified
EM
hetEM/IM
PM
Log-rank P = .003
Log-rank P = .005
Years of follow-up
Percentage
P=0.019
P=0.009
P=0.013
P=0.145
Years after randomization
Wt/Wt
Wt/*4
*4/*4
P = .030
P = .020
P = .360

Figure 3


tamoxifen
4-hydroxytamoxifen
N-desmethyltamoxifen
endoxifen
DOSE
p.o.
i.v.
Stomach
Small intestine wall
Large intestine wall
Pancreas
Spleen
Portal vein
Gall bladder
Liver
Kidney
Bone
Brain
Fat
Gonads
Heart
Muscle
Skin
Saliva
Lung
venous blood pool
arterial blood pool

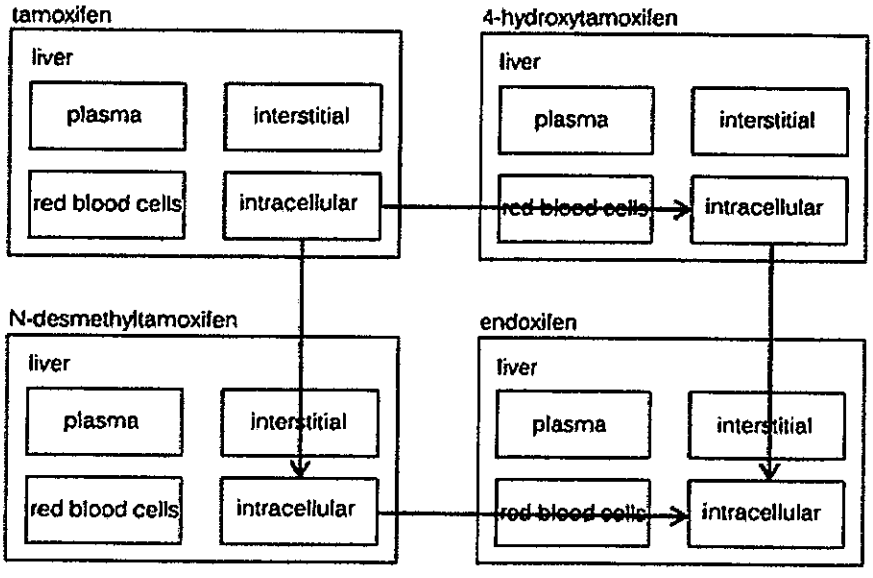

tamoxifen
liver
plasma
interstitial
red blood cells
intracellular
4-hydroxytamoxifen
liver
plasma
interstitial
red blood cells
intracellular
N-desmethyltamoxifen
liver
plasma
interstitial
red blood cells
intracellular
endoxifen
liver
plasma
interstitial
red blood cells
intracellular

Figure 4

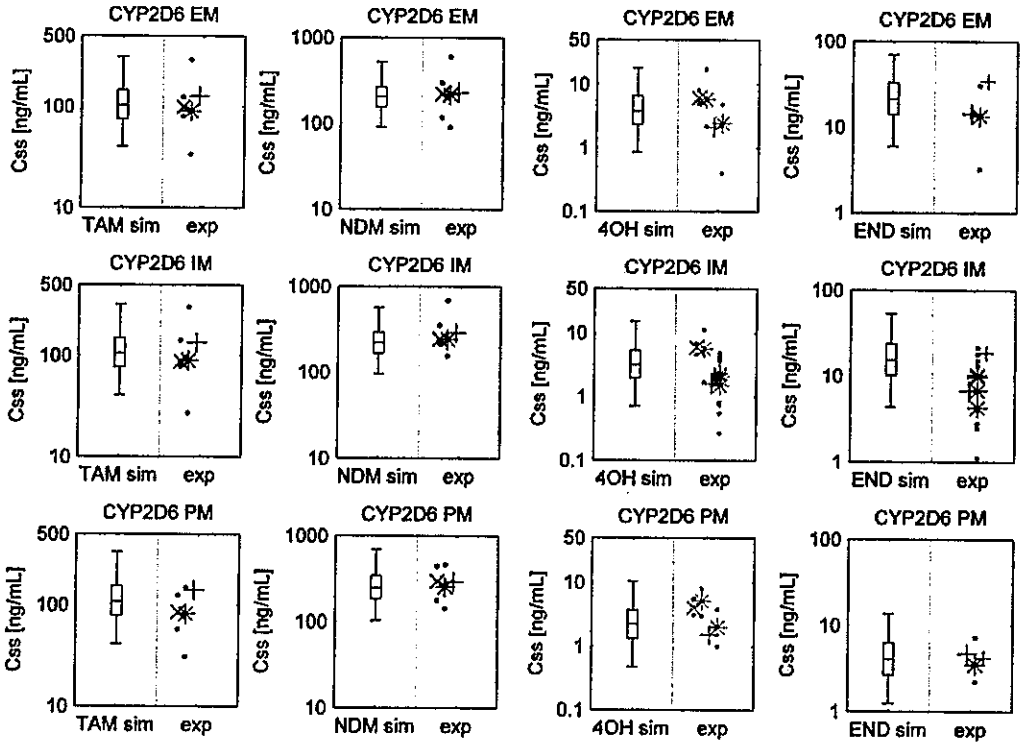


Figure 5A

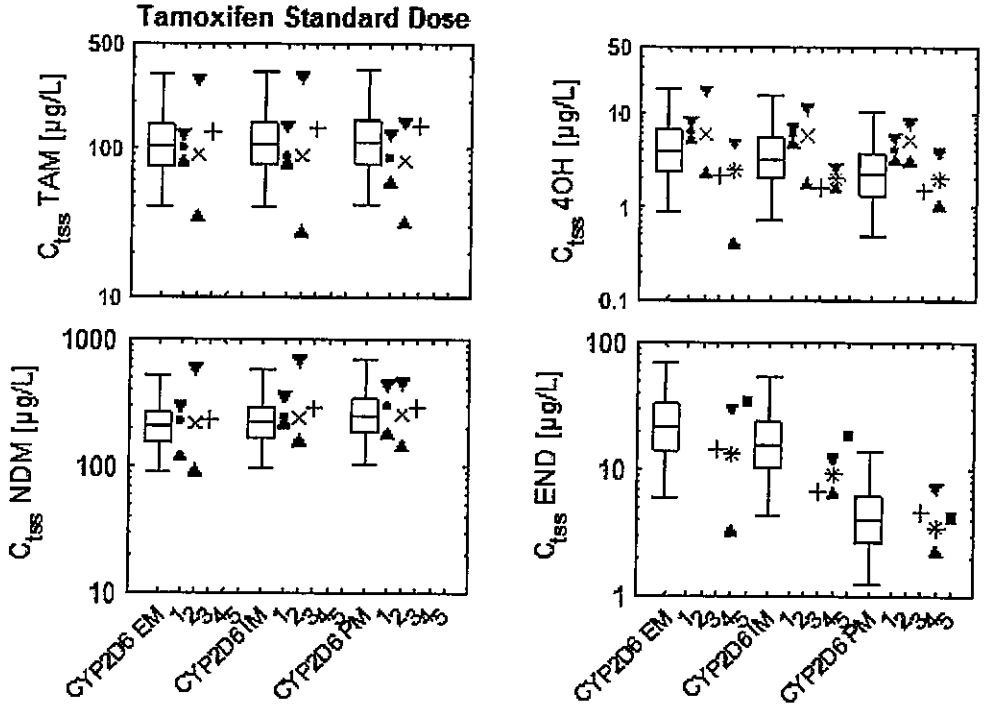


Figure 5B

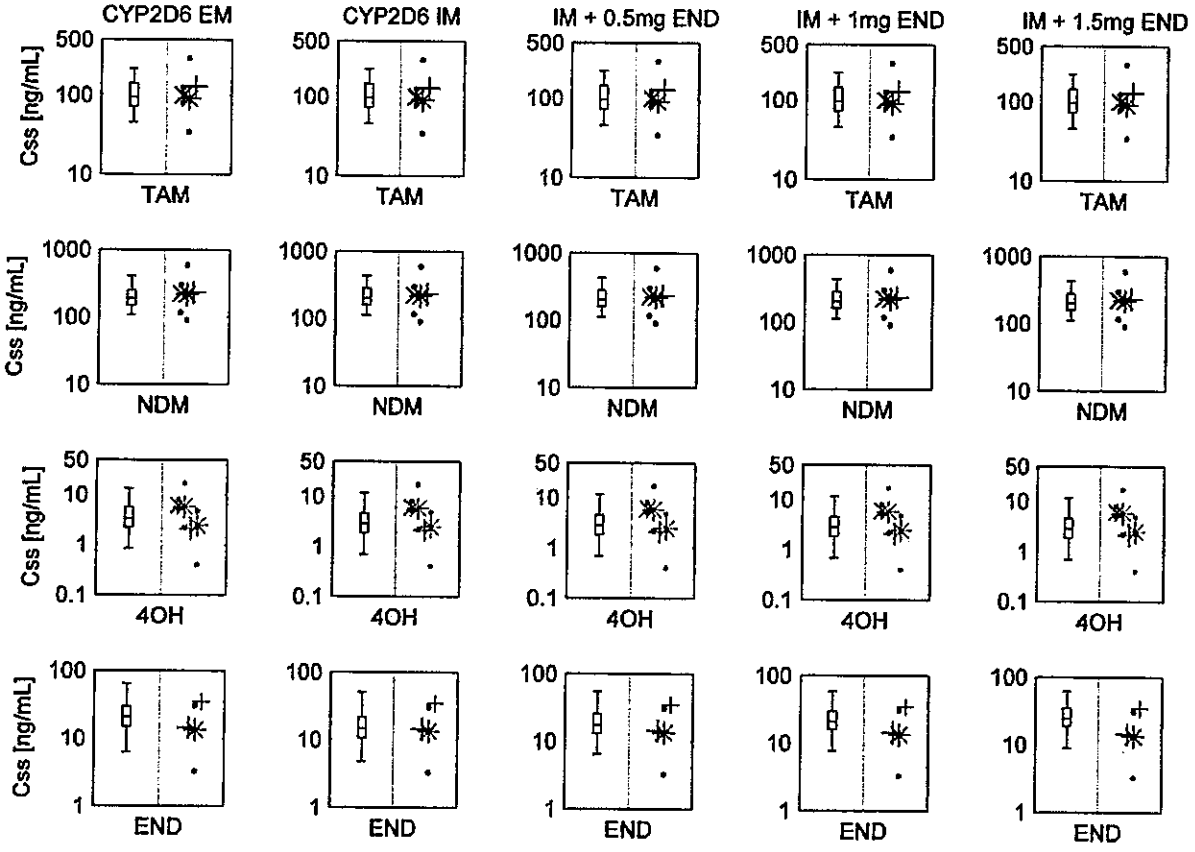


Figure 6A

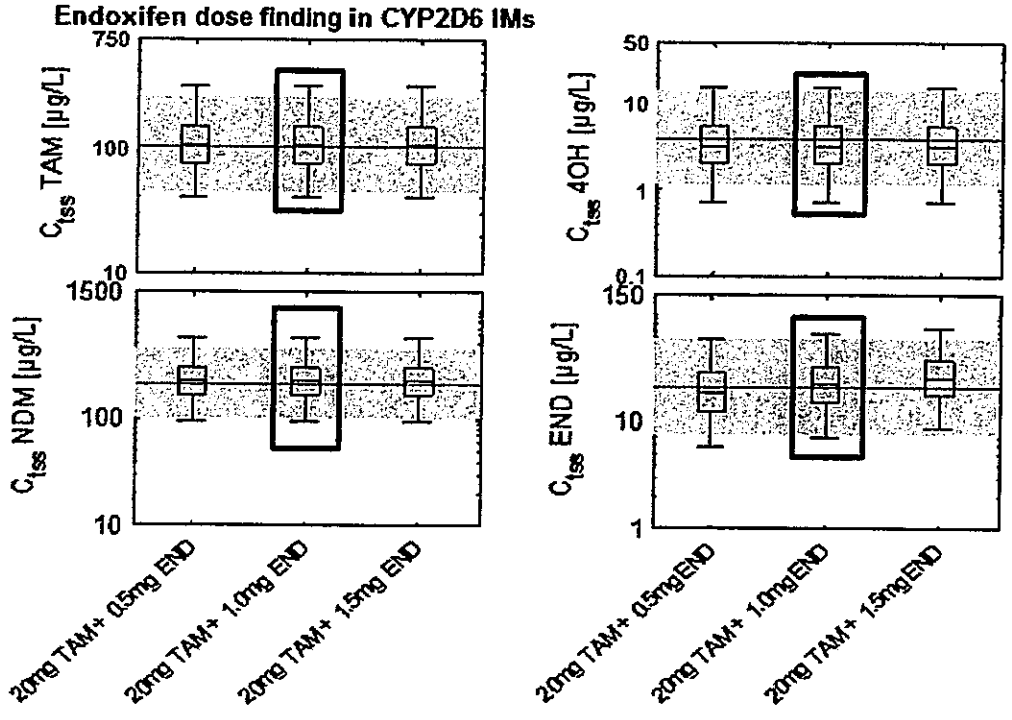


Figure 6B

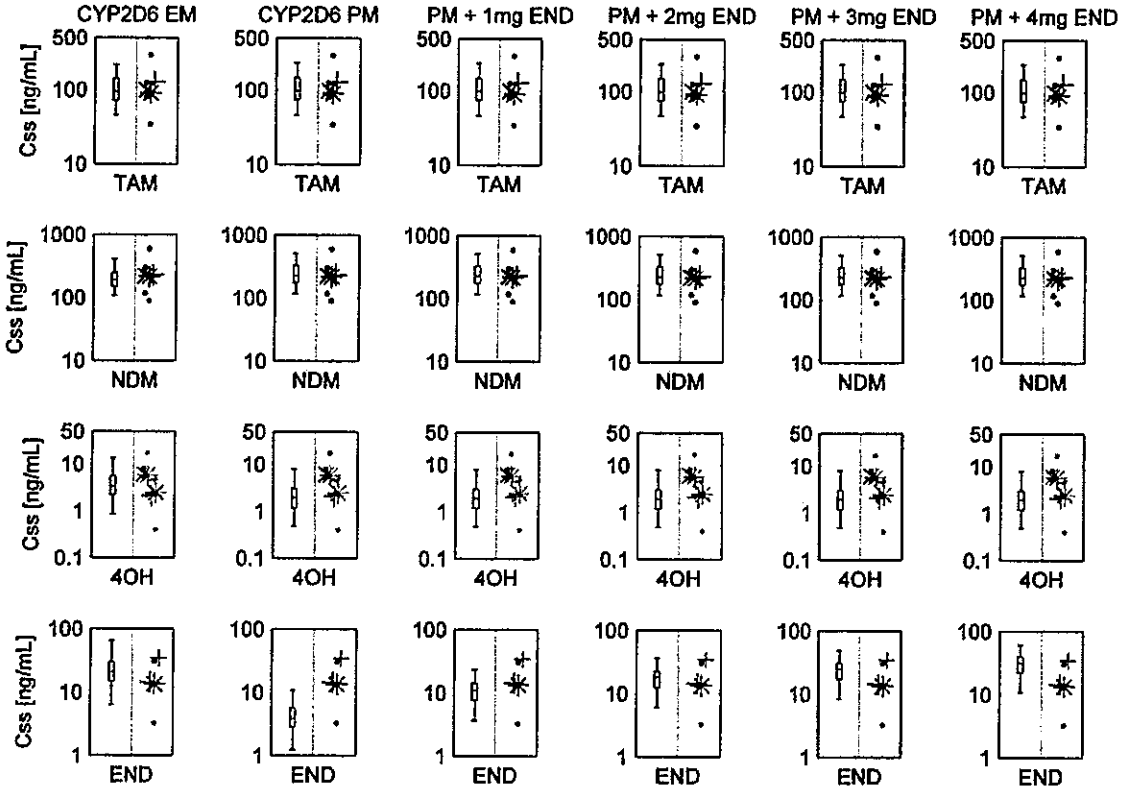


Figure 7A

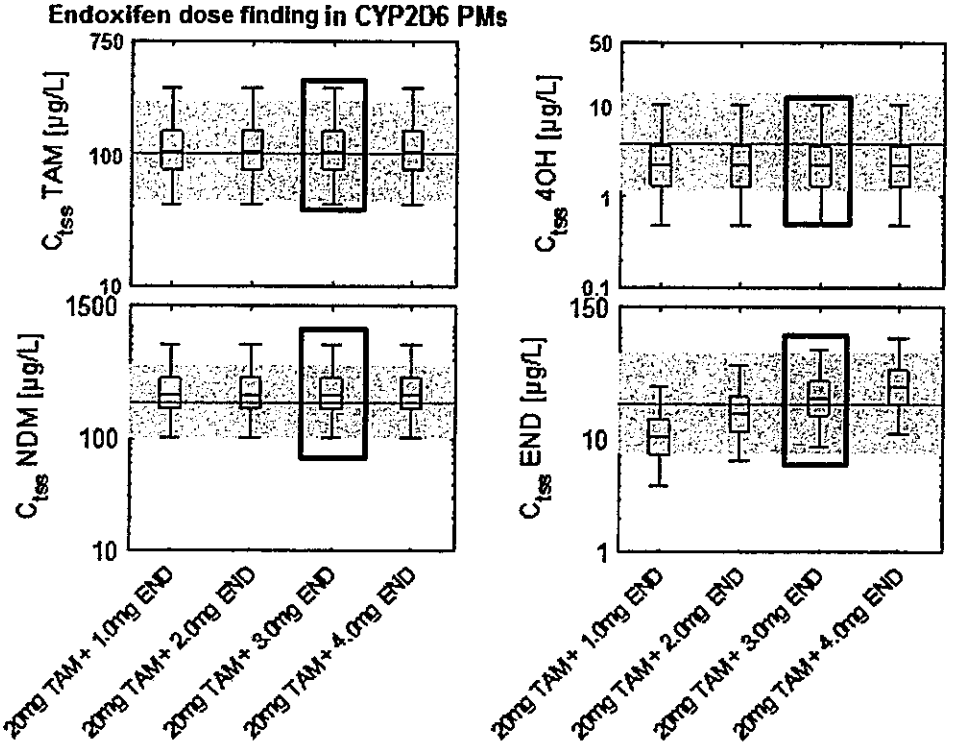


Figure 7B

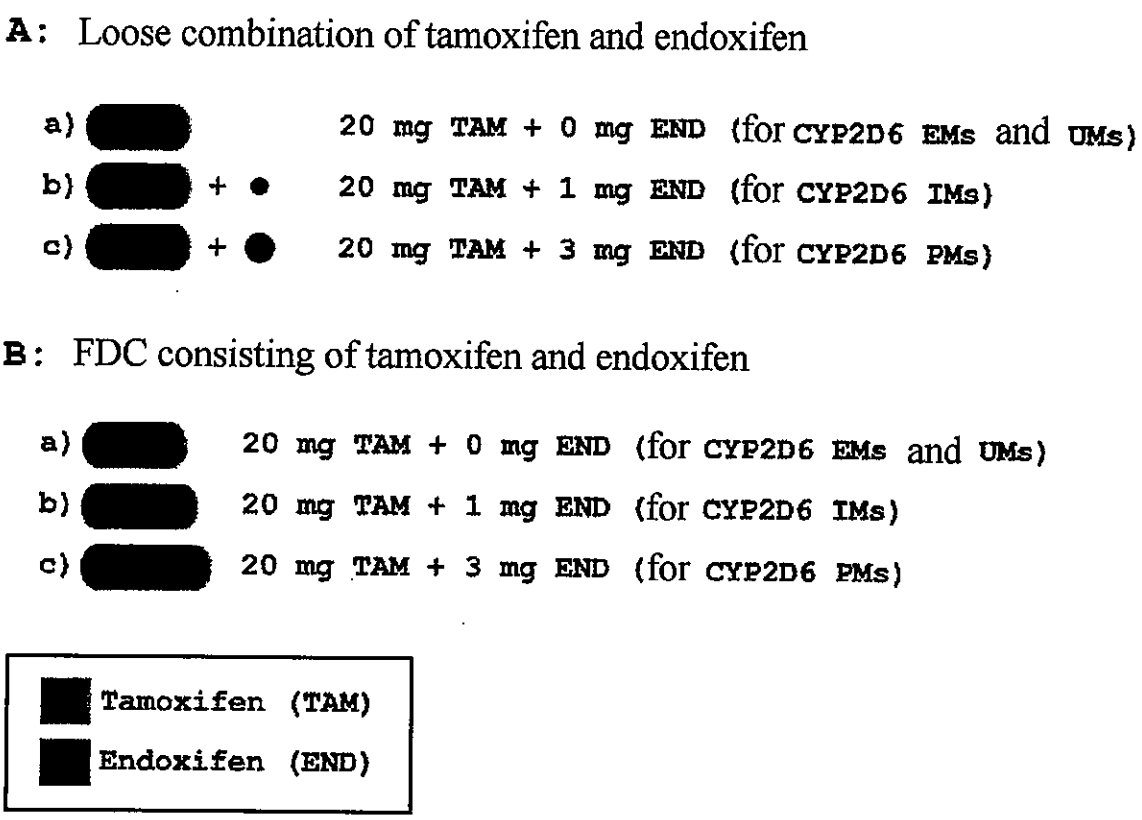

A: Loose combination of tamoxifen and endoxifen
a) 20 mg TAM + 0 mg END (for CYP2D6 EMs and UMs)
b) + 20 mg TAM + 1 mg END (for CYP2D6 IMs)
c) + 20 mg TAM + 3 mg END (for CYP2D6 PMs)
B: FDC consisting of tamoxifen and endoxifen
a) 20 mg TAM + 0 mg END (for CYP2D6 EMs and UMs)
b) 20 mg TAM + 1 mg END (for CYP2D6 IMs)
c) 20 mg TAM + 3 mg END (for CYP2D6 PMs)
Tamoxifen (TAM)
Endoxifen (END)

Figure 8

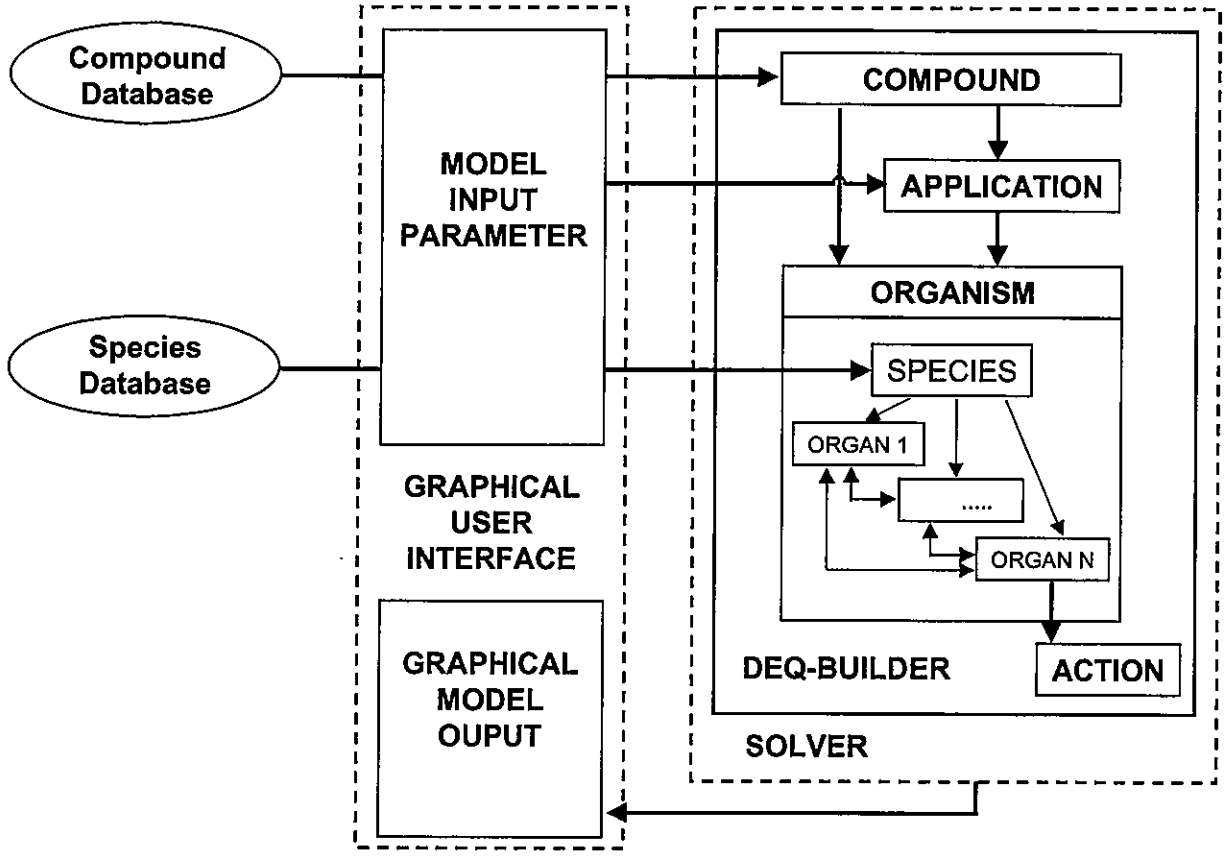

Compound Database
Species Database
MODEL INPUT PARAMETER
GRAPHICAL USER INTERFACE
GRAPHICAL MODEL OUPUT
COMPOUND
APPLICATION
ORGANISM
SPECIES
ORGAN 1
.....
ORGAN N
DEQ-BUILDER
ACTION
SOLVER

Figure 9

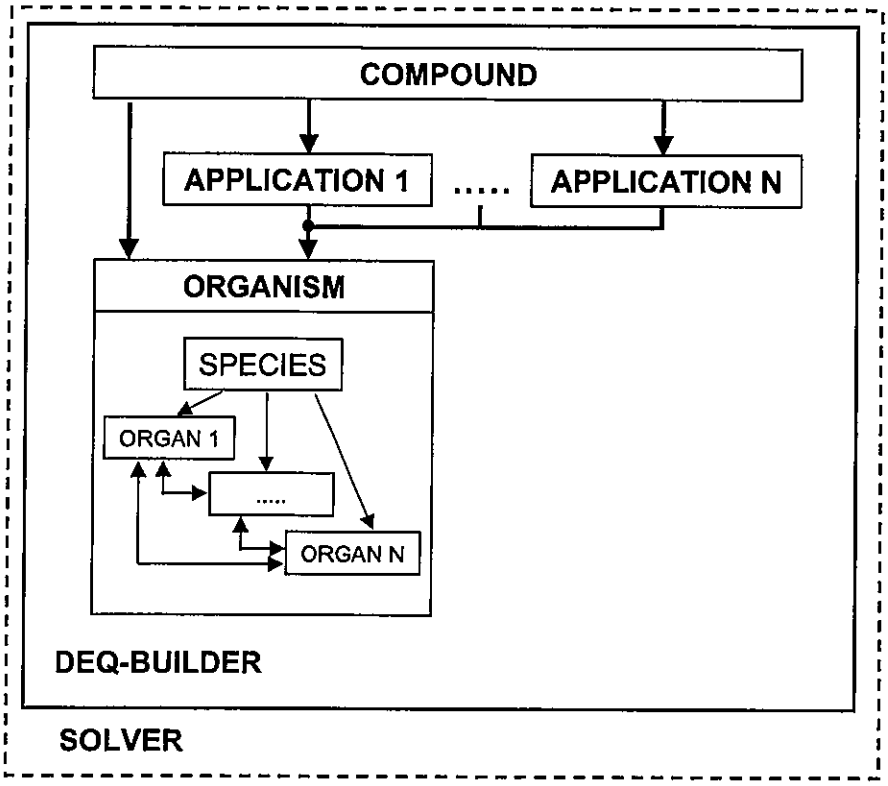


Figure 10

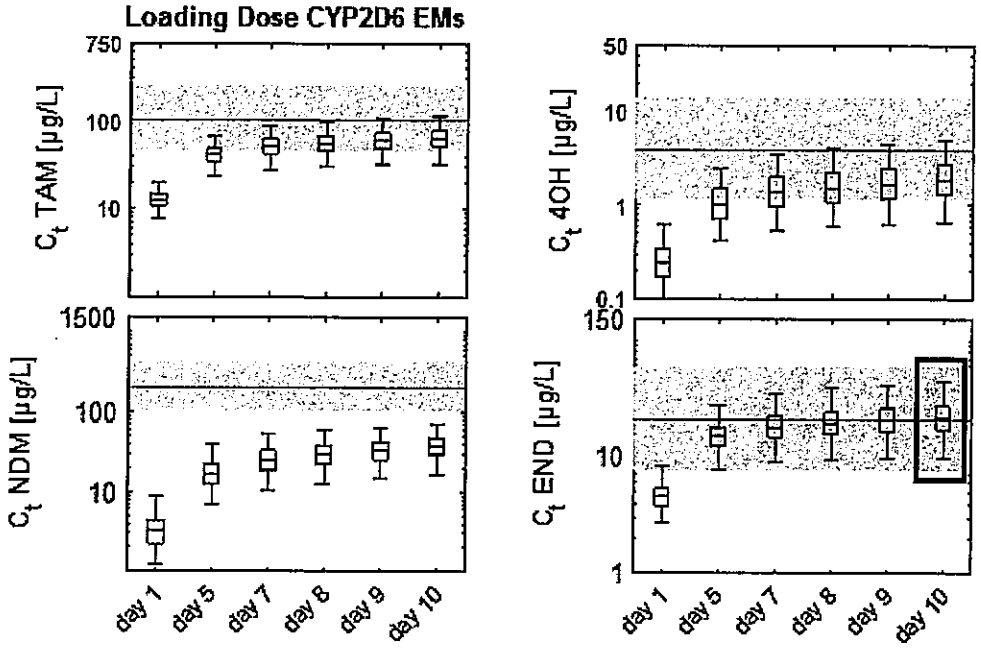


Figure 11

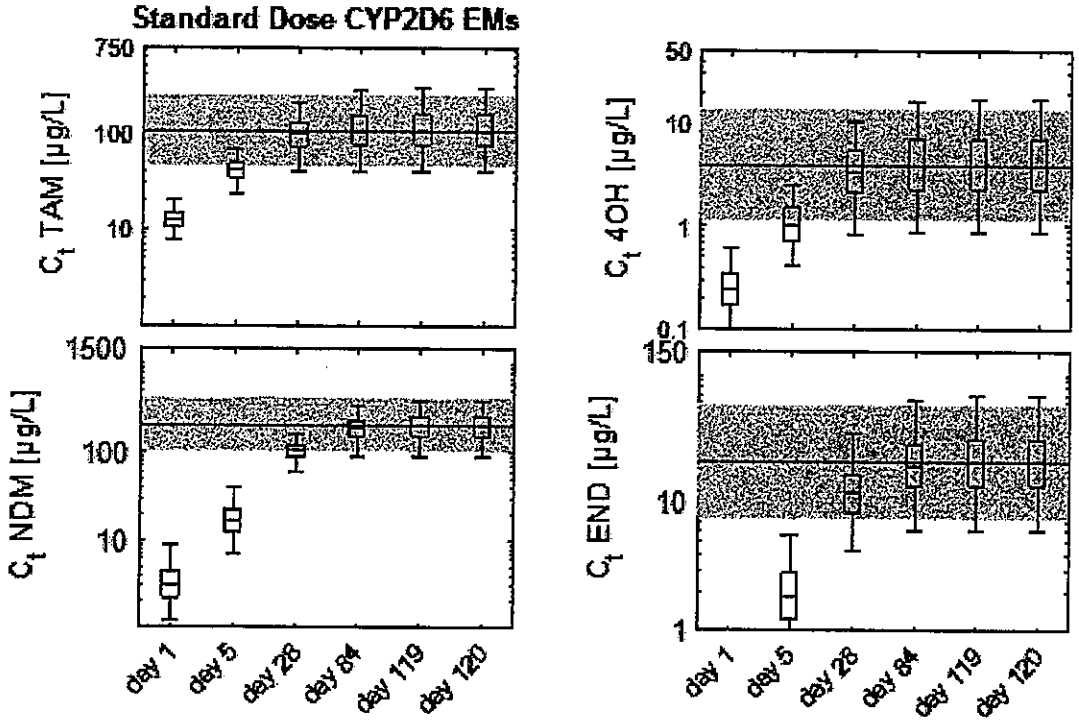

Standard Dose CYP2D6 EMs
C_t TAM [µg/L]
750
100
10
C_t NDM [µg/L]
1500
100
10
C_t 4OH [µg/L]
50
10
1
0.1
C_t END [µg/L]
150
10
1
day 1
day 5
day 28
day 84
day 119
day 120

Figure 12

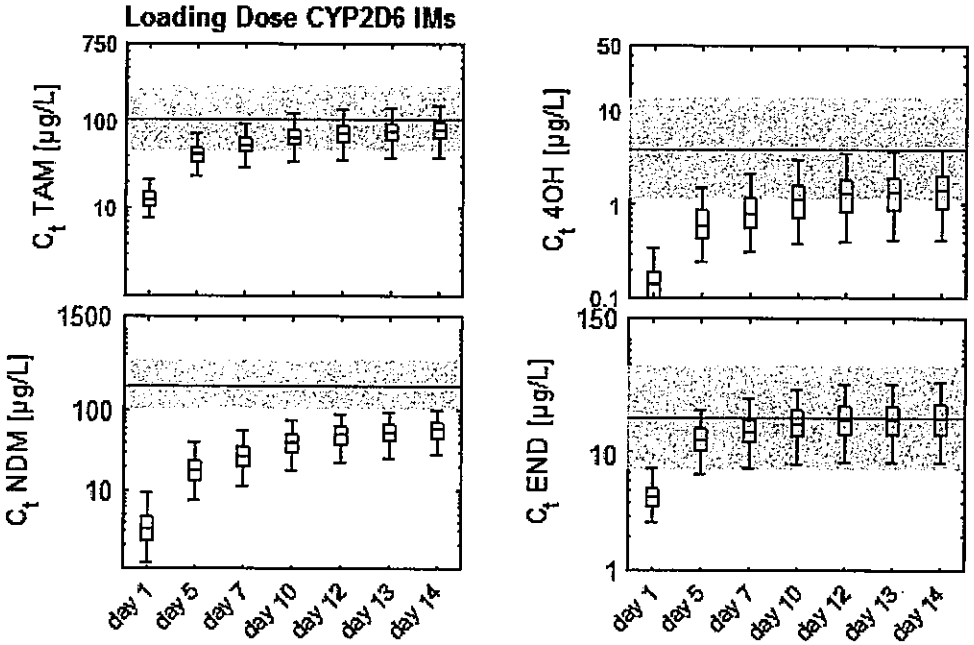

Loading Dose CYP2D6 IMs
C_t TAM [µg/L]
750
100
10
C_t NDM [µg/L]
1500
100
10
C_t 4OH [µg/L]
50
10
1
0.1
C_t END [µg/L]
150
10
1
day 1
day 5
day 7
day 10
day 12
day 13
day 14

Figure 13

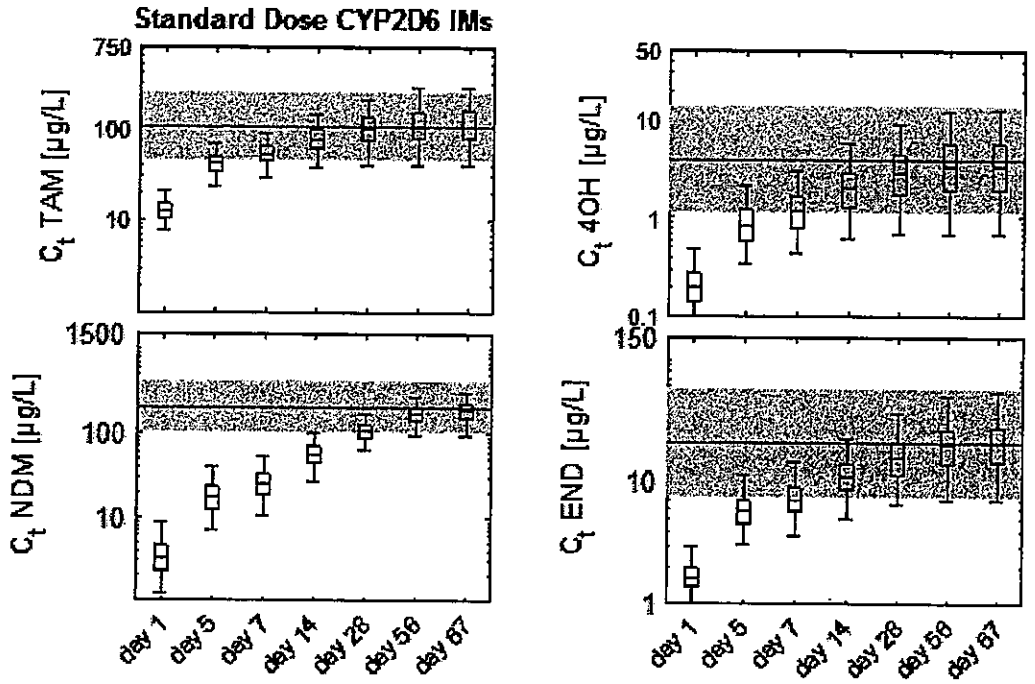

Standard Dose CYP2D6 IMs
C_t TAM [µg/L]
750
100
10
C_t NDM [µg/L]
1500
100
10
C_t 4OH [µg/L]
50
10
1
0.1
C_t END [µg/L]
150
10
1
day 1
day 5
day 7
day 14
day 28
day 56
day 67

Figure 14

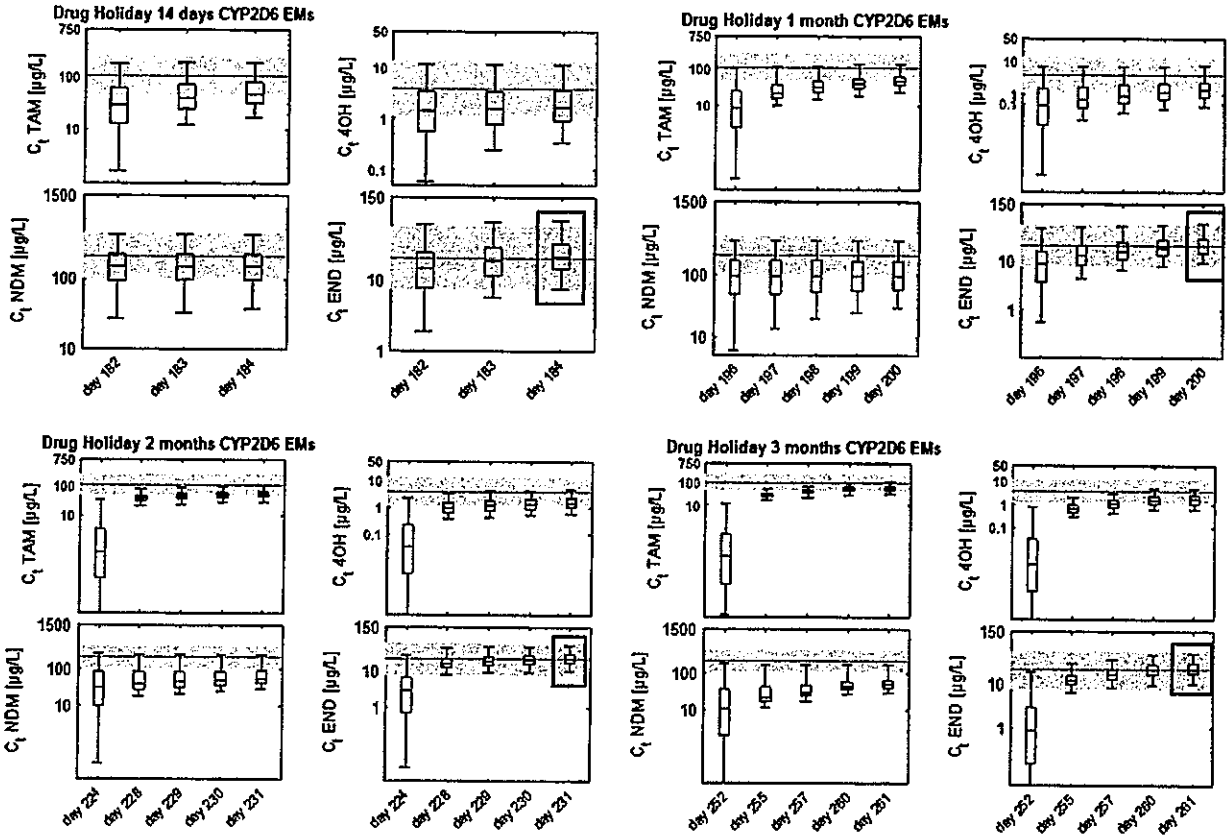

Drug Holiday 14 days CYP2D6 EMs
Drug Holiday 1 month CYP2D6 EMs
Drug Holiday 2 months CYP2D6 EMs
Drug Holiday 3 months CYP2D6 EMs
C_t TAM [µg/L]
C_t 4OH [µg/L]
C_t NDM [µg/L]
C_t END [µg/L]
day 182
day 183
day 184
day 196
day 197
day 198
day 199
day 200
day 224
day 226
day 228
day 230
day 231
day 252
day 255
day 257
day 260
day 261

Figure 15

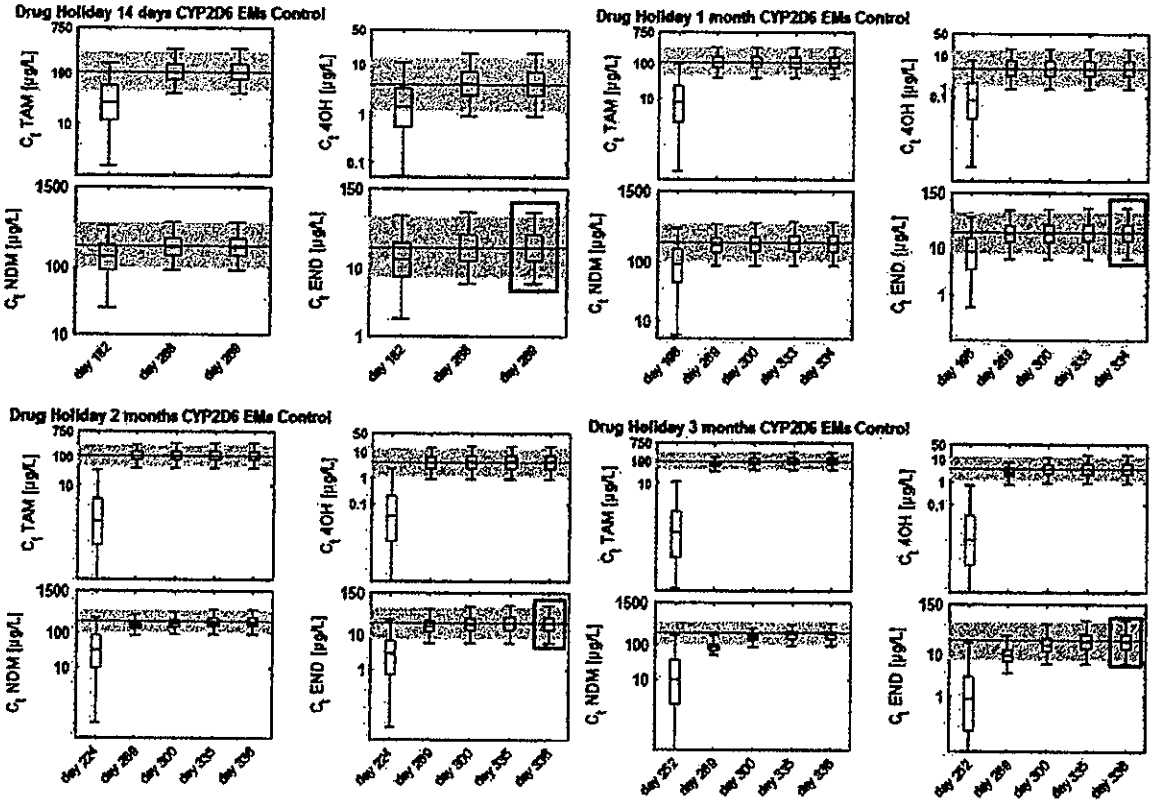

Drug Holiday 14 days CYP2D6 EMs Control
Drug Holiday 1 month CYP2D6 EMs Control
Drug Holiday 2 months CYP2D6 EMs Control
Drug Holiday 3 months CYP2D6 EMs Control
Ct TAM [µg/L]
Ct 4OH [µg/L]
Ct NDM [µg/L]
Ct END [µg/L]

Figure 16

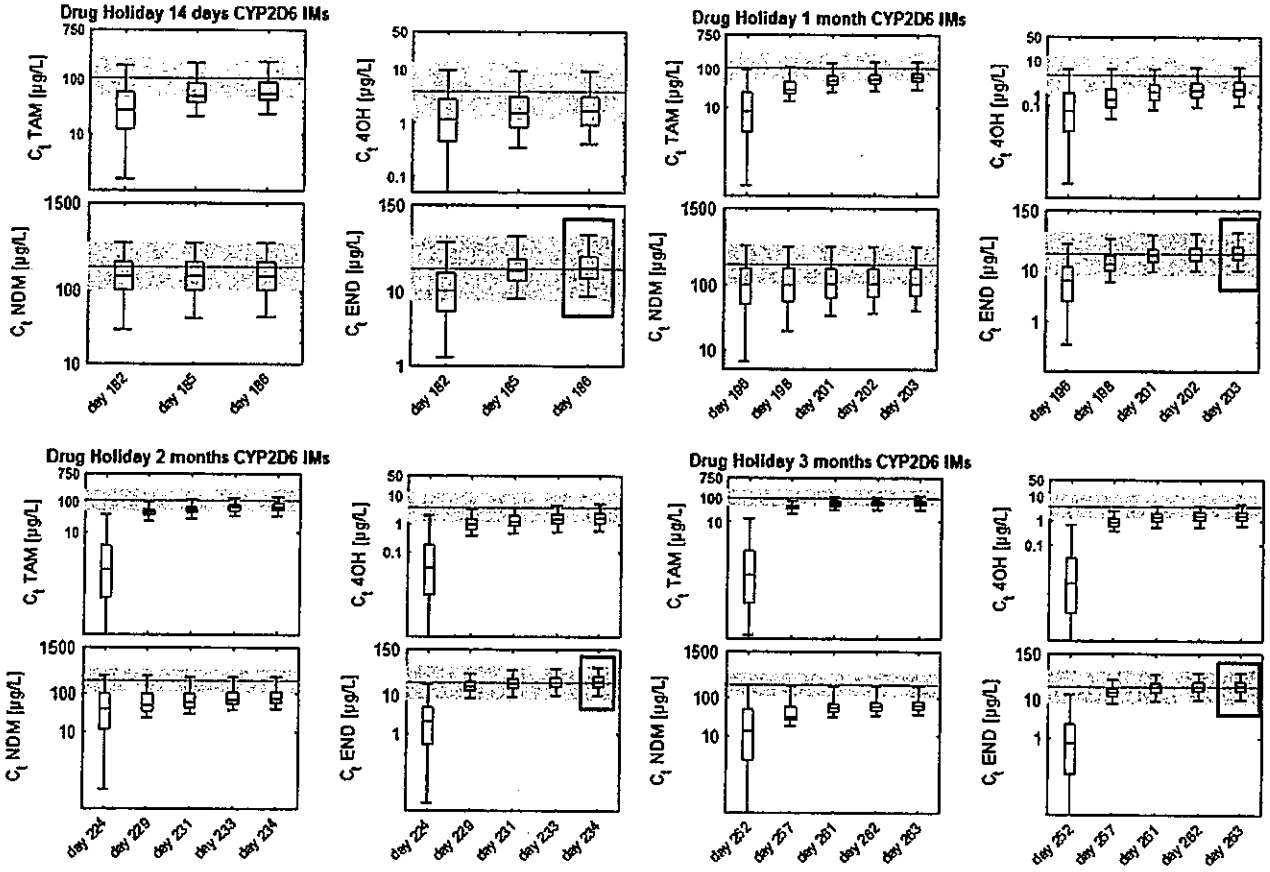

Drug Holiday 14 days CYP2D6 IMs
Drug Holiday 1 month CYP2D6 IMs
Drug Holiday 2 months CYP2D6 IMs
Drug Holiday 3 months CYP2D6 IMs
C_t TAM [µg/L]
C_t 4OH [µg/L]
C_t NDM [µg/L]
C_t END [µg/L]

Figure 17

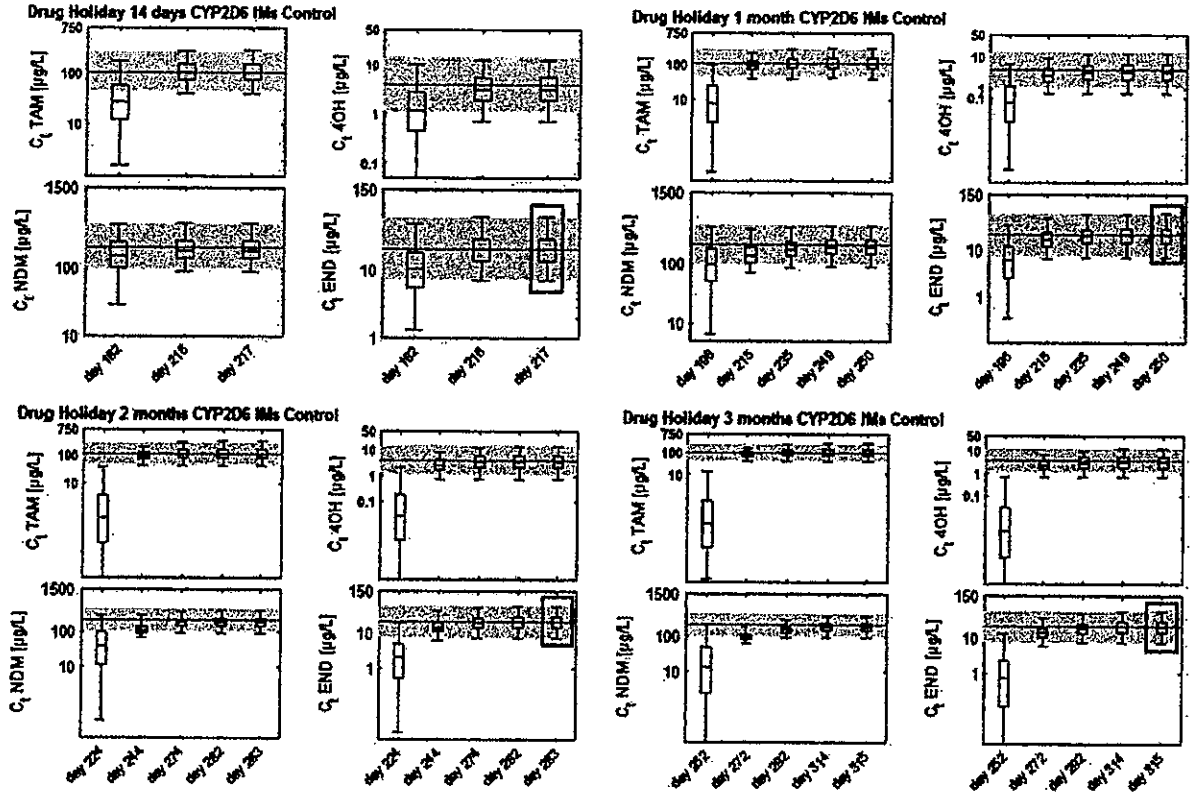

Drug Holiday 14 days CYP2D6 Mis Control
Drug Holiday 1 month CYP2D6 Mis Control
Drug Holiday 2 months CYP2D6 Mis Control
Drug Holiday 3 months CYP2D6 Mis Control
C_t TAM [µg/L]
C_t 4OH [µg/L]
C_t NDM [µg/L]
C_t END [µg/L]

Figure 18