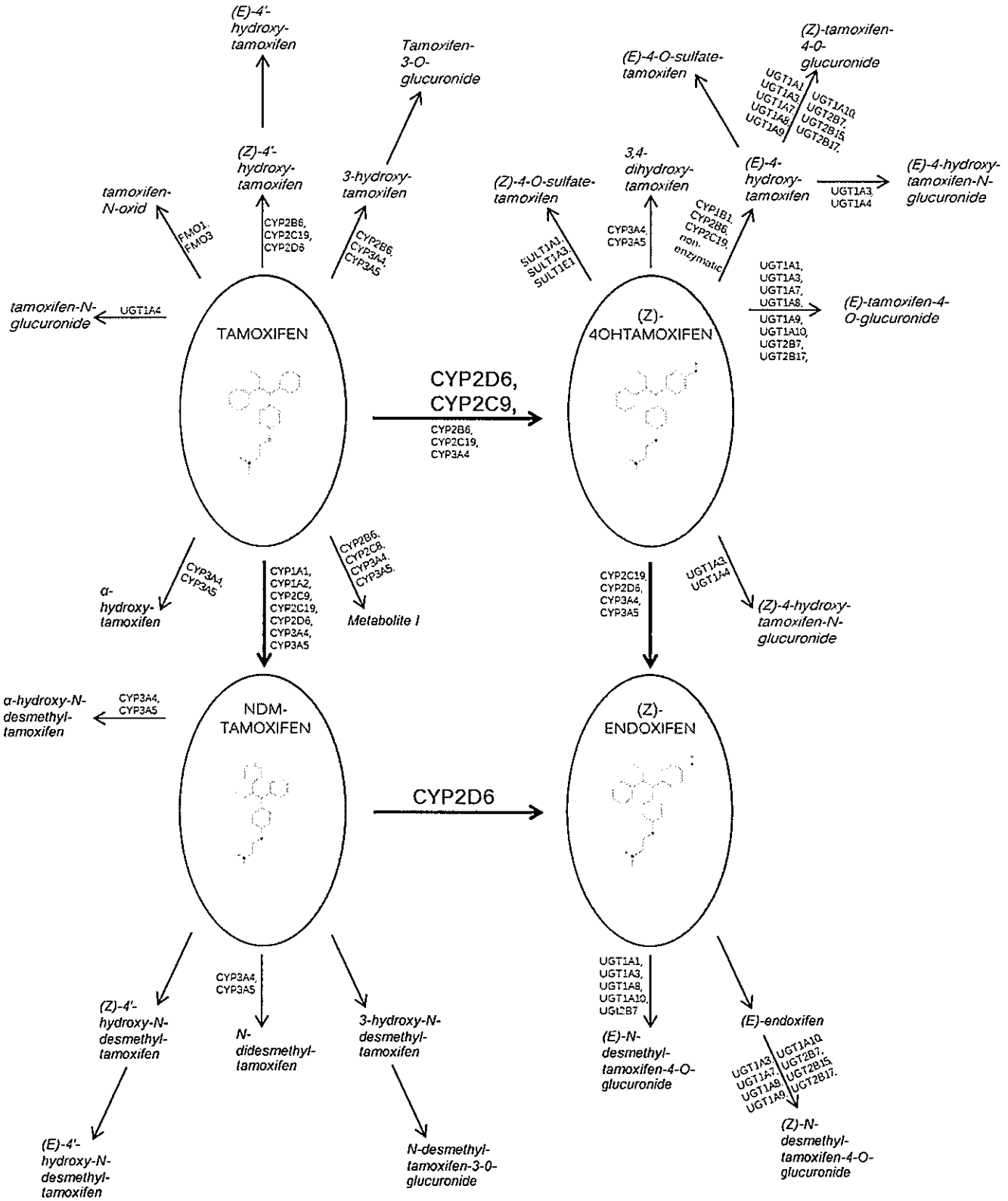

(E)-4'-hydroxy-tamoxifen
Tamoxifen-3-O-glucuronide
(Z)-4'-hydroxy-tamoxifen
3-hydroxy-tamoxifen
tamoxifen-N-oxid
FMO1, FMO3
CYP2B6, CYP2C19, CYP2D6
CYP2B6, CYP3A4, CYP3A5
tamoxifen-N-glucuronide
UGT1A4
TAMOXIFEN
CYP2D6, CYP2C9,
CYP2B6, CYP2C19, CYP3A4
(Z)-4OHTAMOXIFEN
(E)-4-O-sulfate-tamoxifen
(Z)-tamoxifen-4-O-glucuronide
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
α-hydroxy-tamoxifen
CYP3A4, CYP3A5
CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5
CYP2B6, CYP2C8, 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
(Z)-4'-hydroxy-N-desmethyl-tamoxifen
CYP3A4, CYP3A5
N-didesmethyl-tamoxifen
3-hydroxy-N-desmethyl-tamoxifen
UGT1A1, UGT1A3, UGT1A8, UGT1A10, UGT2B7
(E)-N-desmethyl-tamoxifen-4-O-glucuronide
(E)-endoxifen
UGT1A3, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B7, UGT2B15, UGT2B17
(E)-4'-hydroxy-N-desmethyl-tamoxifen
N-desmethyl-tamoxifen-3-0-glucuronide
(Z)-N-desmethyl-tamoxifen-4-O-glucuronide

**Figure 1**

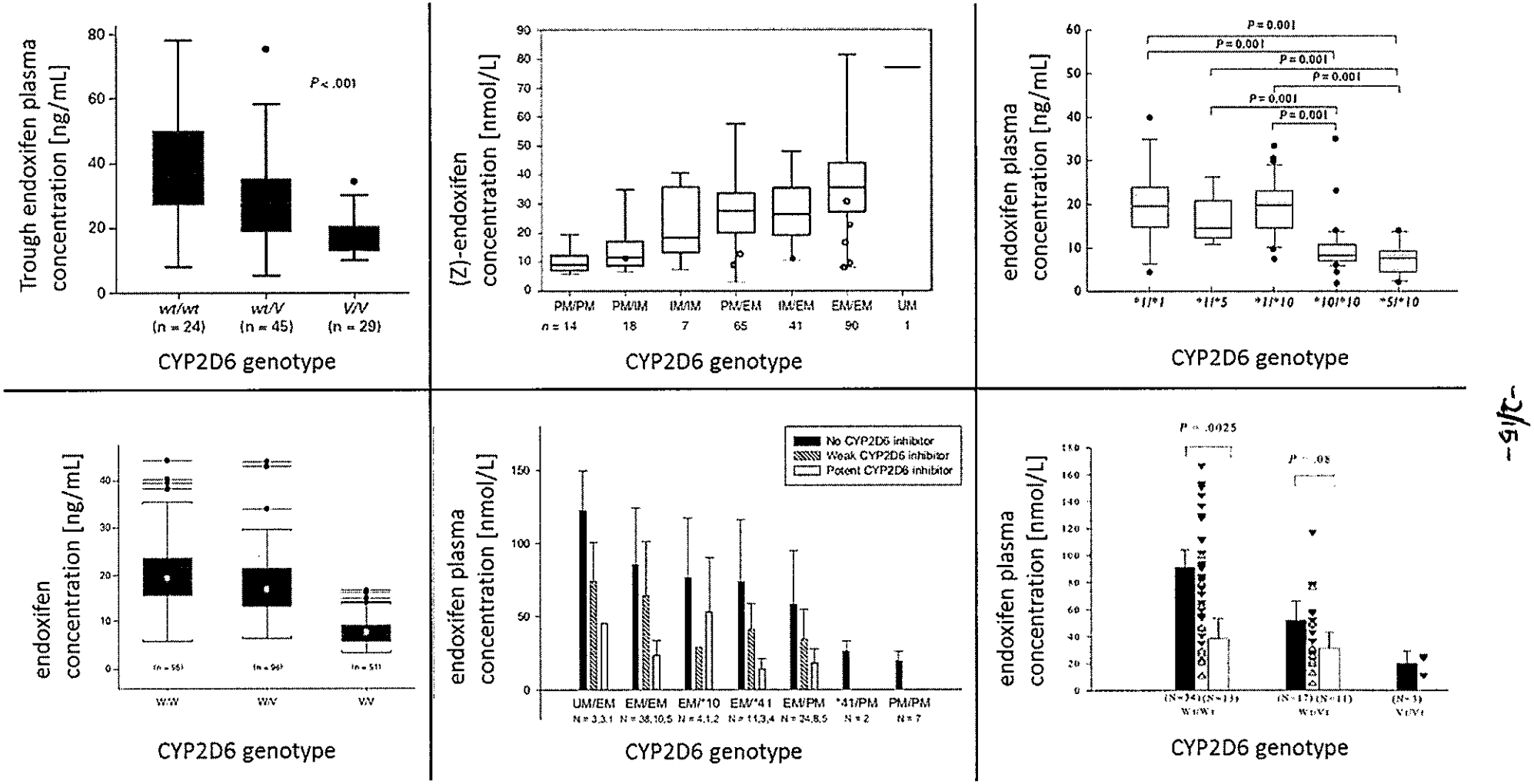

Trough endoxifen plasma concentration [ng/mL]
P < .001
wt/wt (n = 24)
wt/V (n = 45)
V/V (n = 29)
CYP2D6 genotype
(Z)-endoxifen concentration [nmol/L]
PM/PM n = 14
PM/IM 18
IM/IM 7
PM/EM 65
IM/EM 41
EM/EM 90
UM 1
CYP2D6 genotype
endoxifen plasma concentration [ng/mL]
P = 0.001
*1/*1
*1/*5
*1/*10
*10/*10
*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

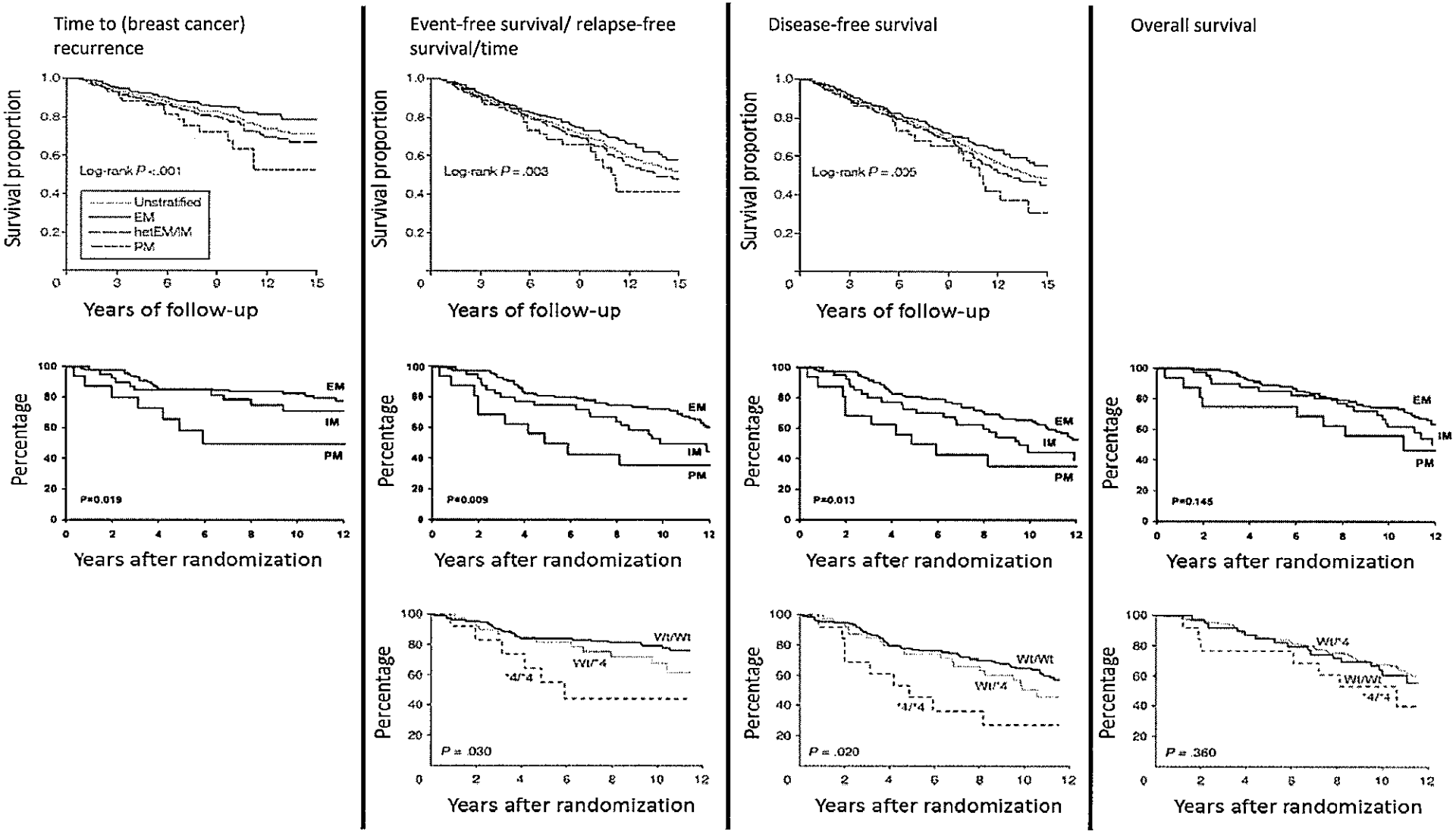
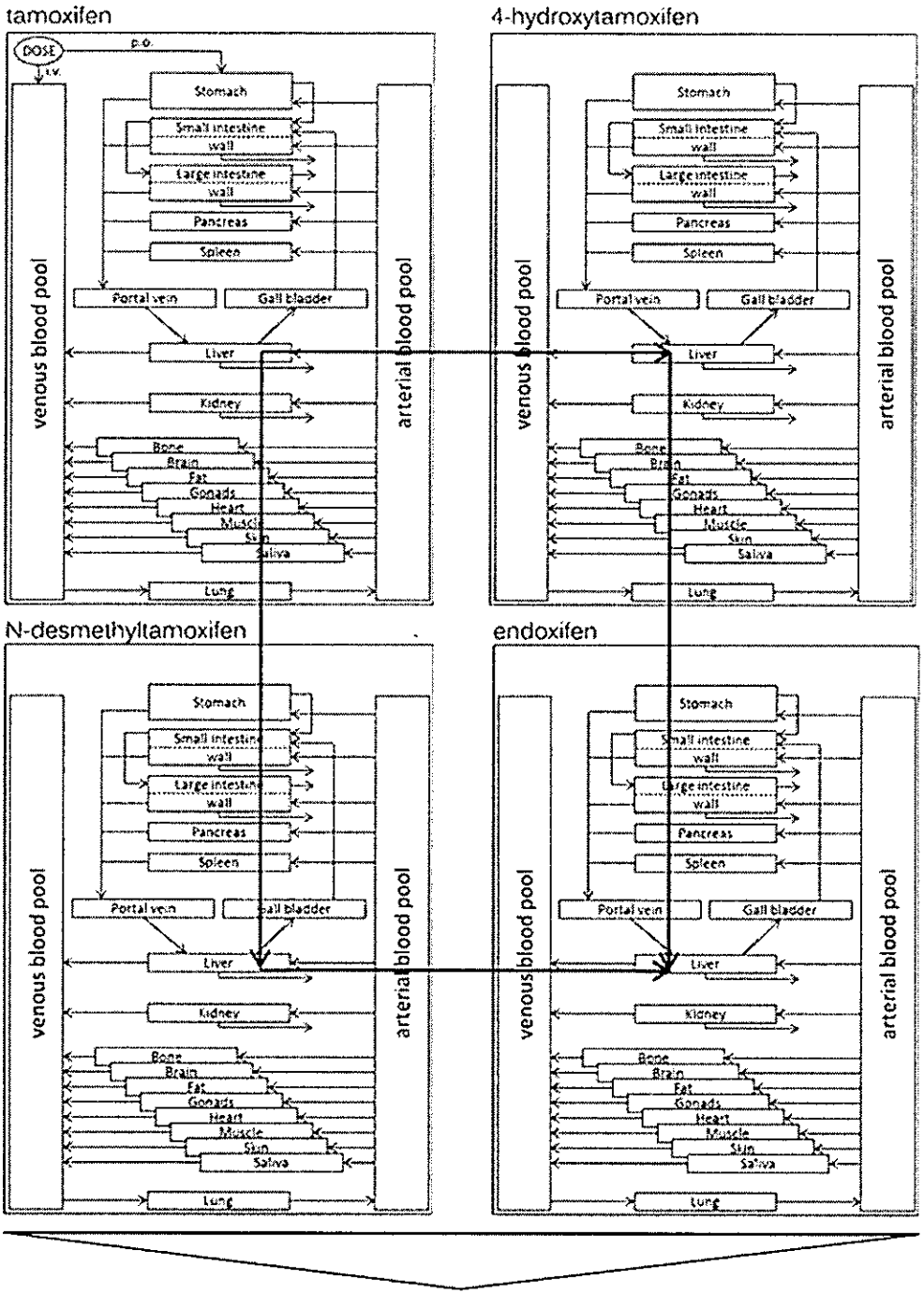

Time to (breast cancer) recurrence
Event-free survival/ relapse-free survival/time
Disease-free survival
Overall survival
Survival proportion
Log-rank P <.001
Unstratified
EM
hetEM/IM
PM
Log-rank P = .003
Log-rank P = .005
Years of follow-up
Percentage
EM
IM
PM
P=0.019
P=0.009
P=0.013
P=0.145
Years after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

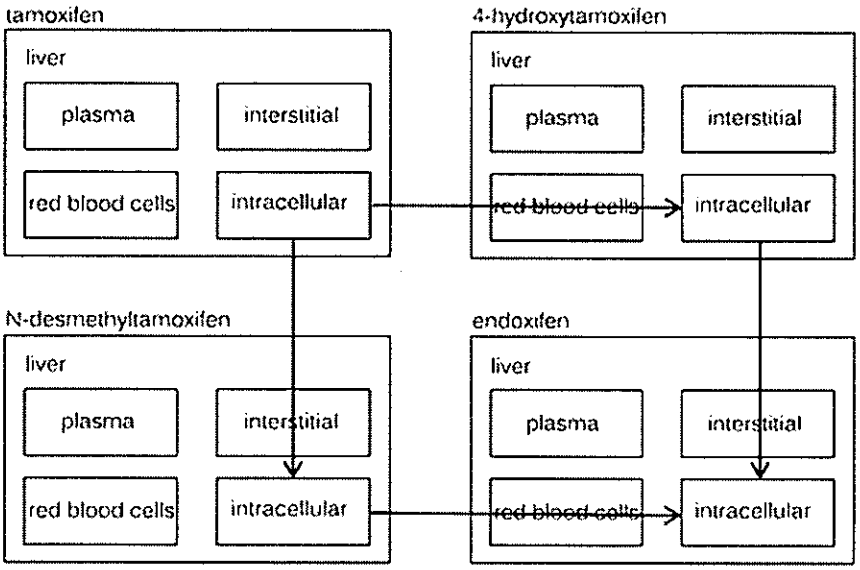

tamoxifen
4-hydroxytamoxifen
N-desmethyltamoxifen
endoxifen
liver
plasma
interstitial
red blood cells
intracellular

**Figure 4**

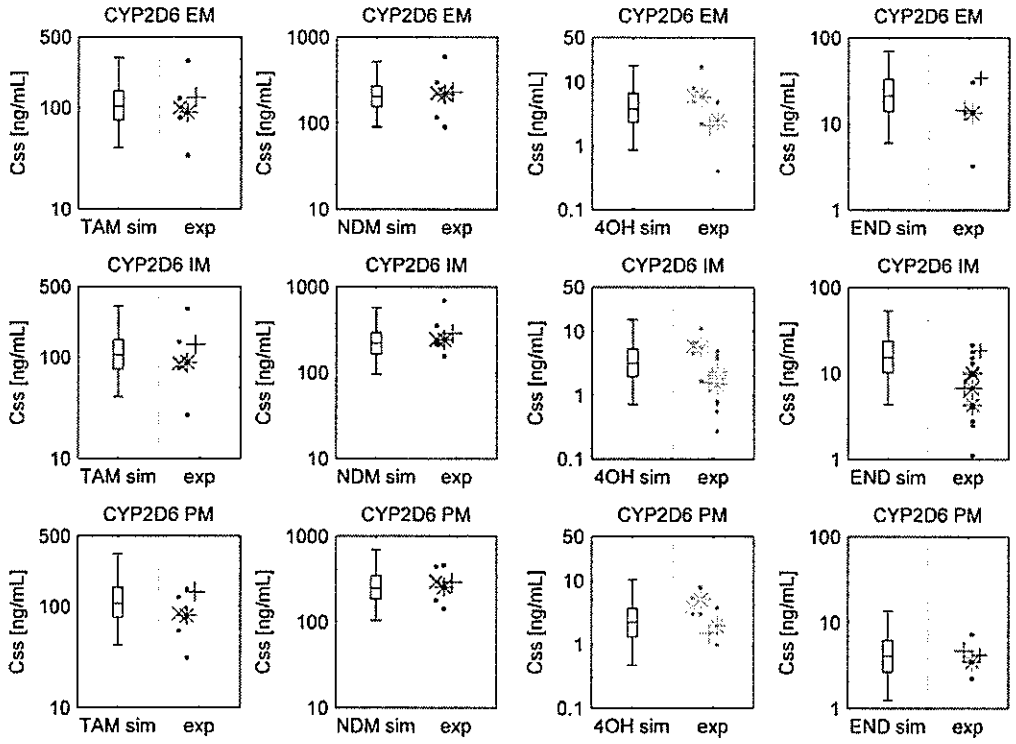



Figure 5A

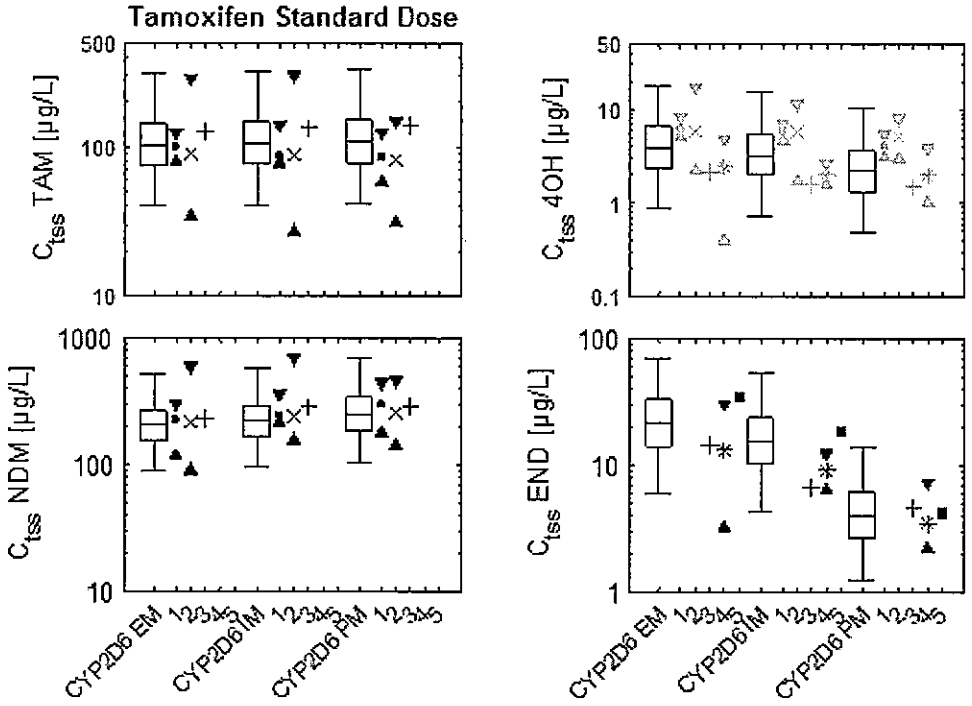



Figure 5B

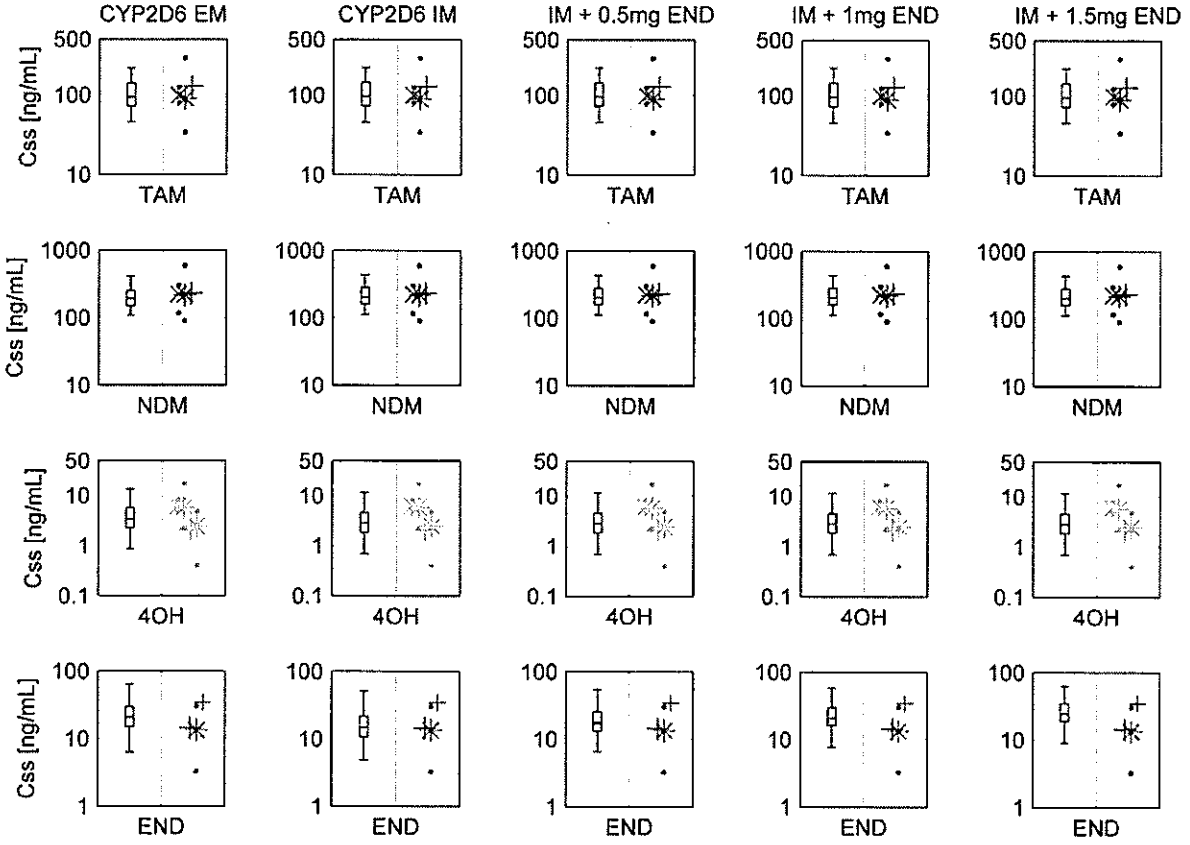



Figure 6A

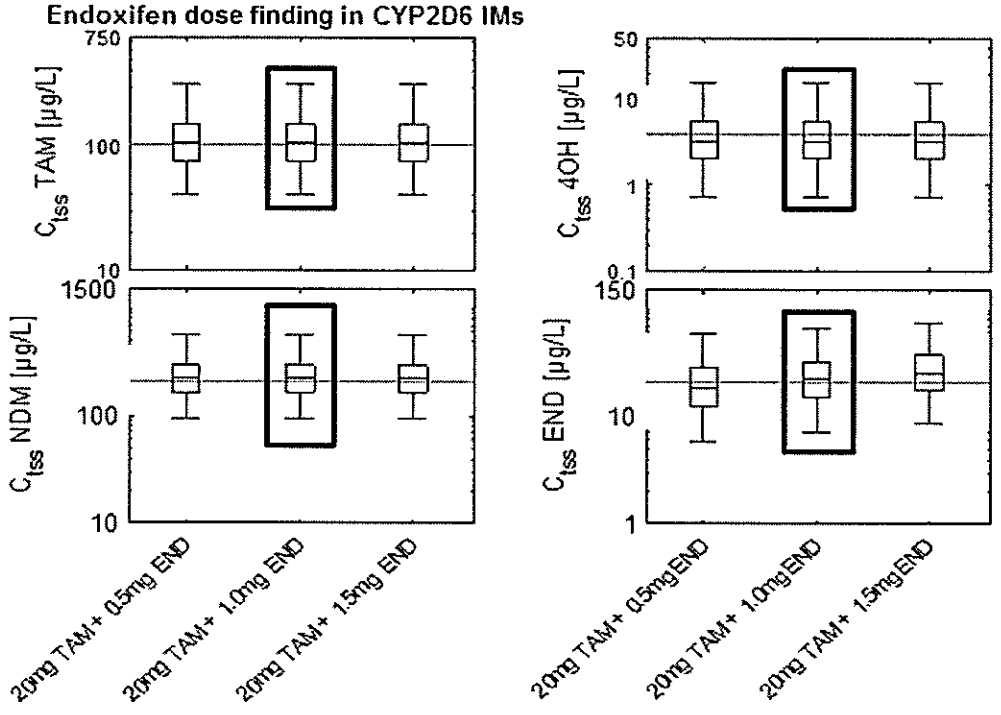



Figure 6B

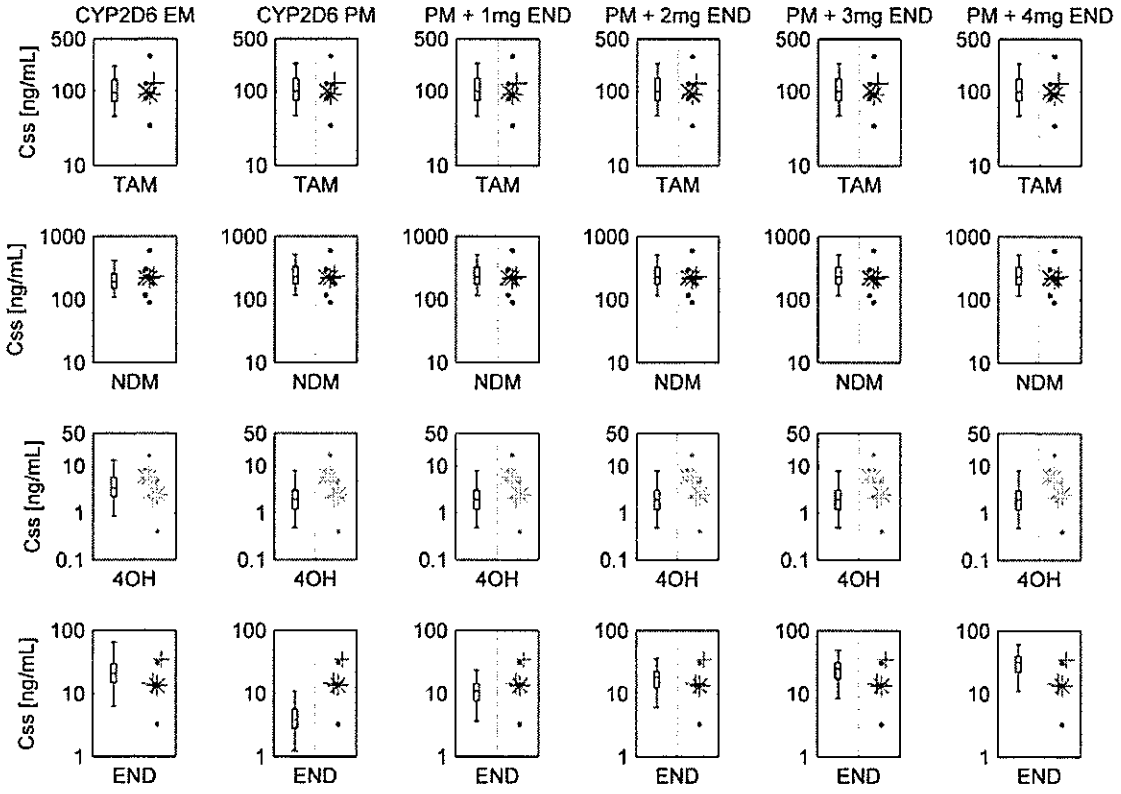



Figure 7A

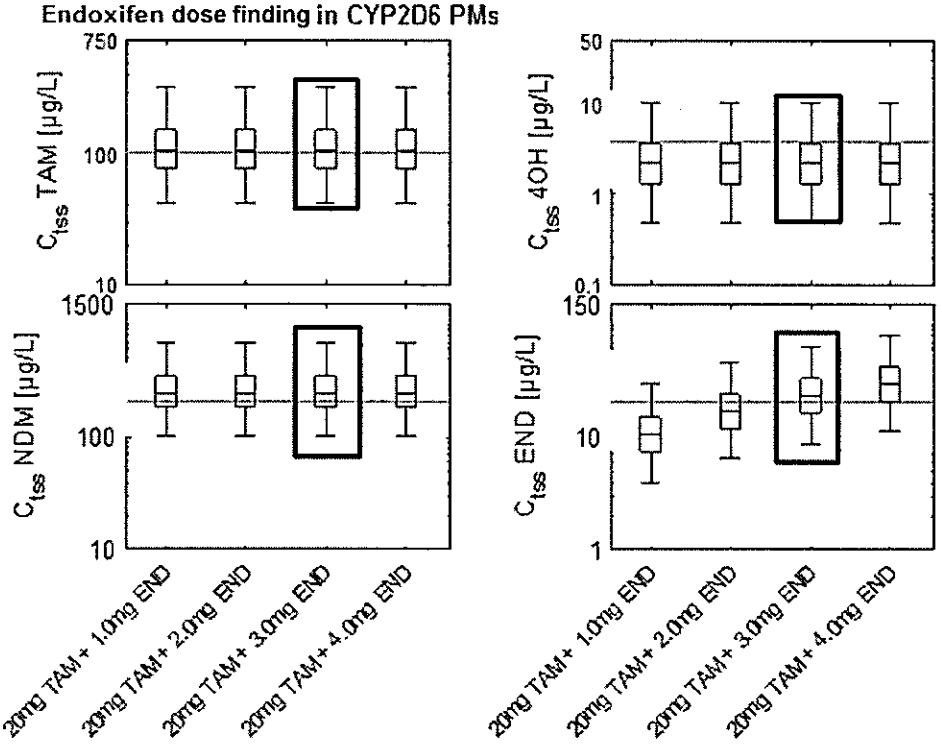



Figure 7B

**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

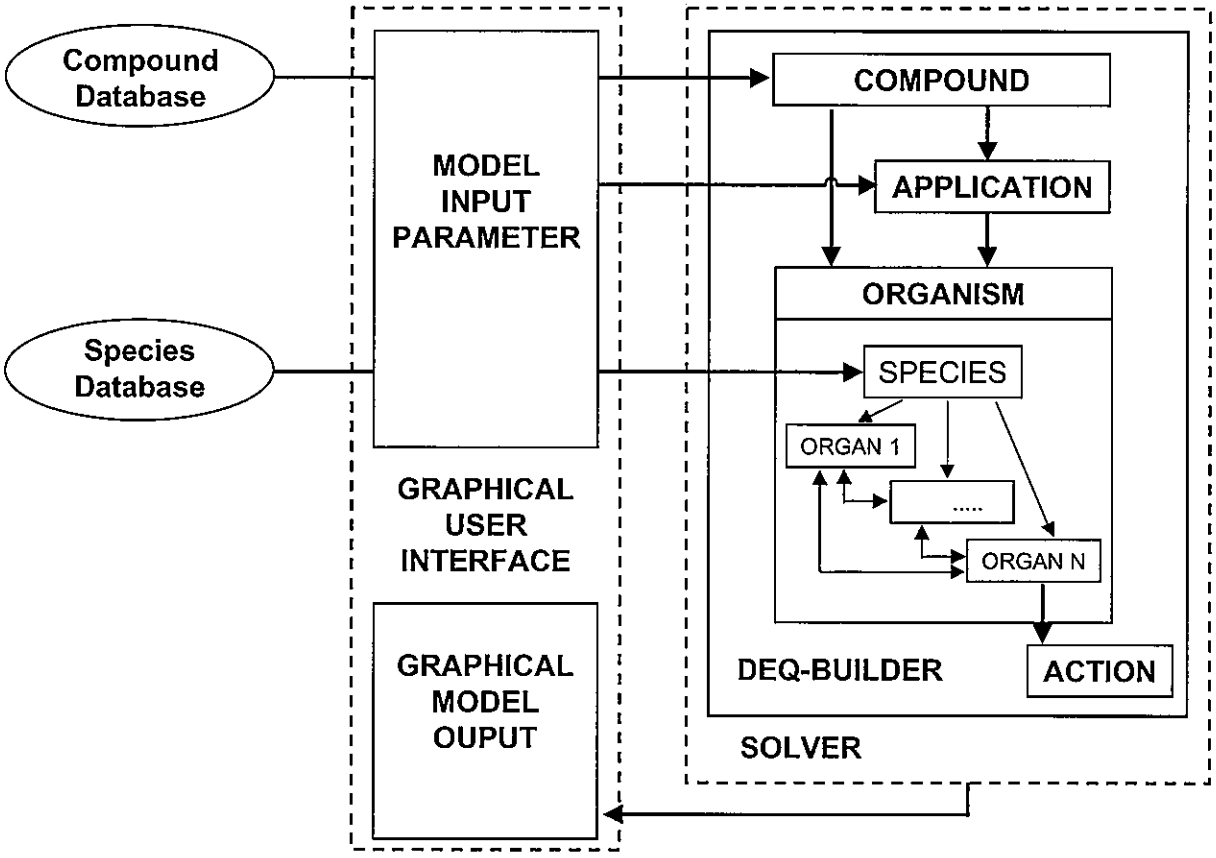

Compound Database
Species Database
MODEL INPUT PARAMETER
GRAPHICAL USER INTERFACE
GRAPHICAL MODEL OUPUT
COMPOUND
APPLICATION
ORGANISM
SPECIES
ORGAN 1
.....
ORGAN N
ACTION
DEQ-BUILDER
SOLVER

Figure 9

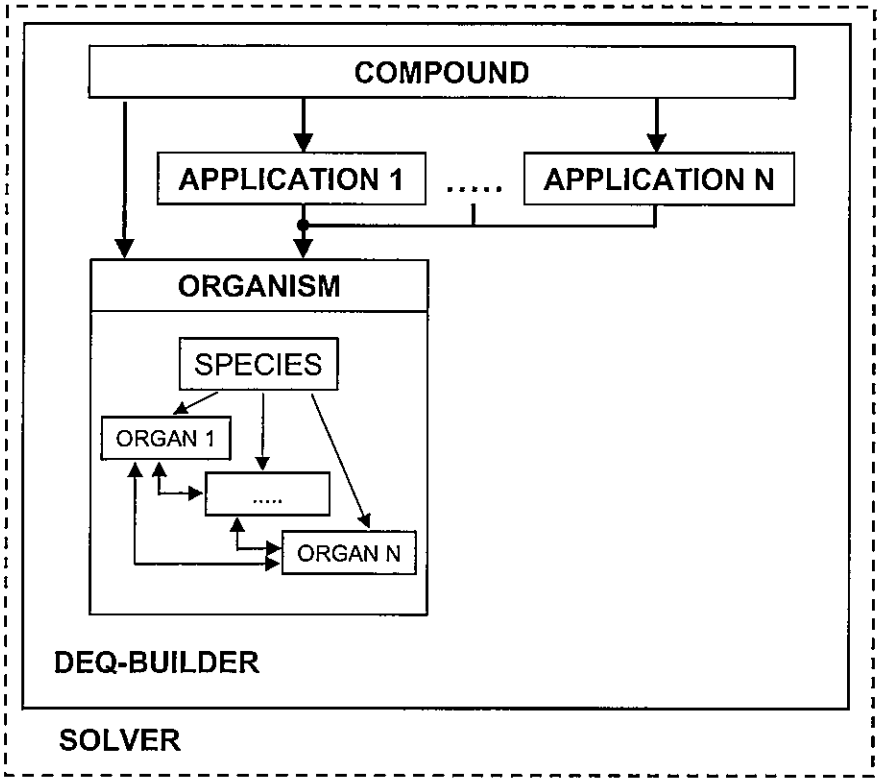



Figure 10

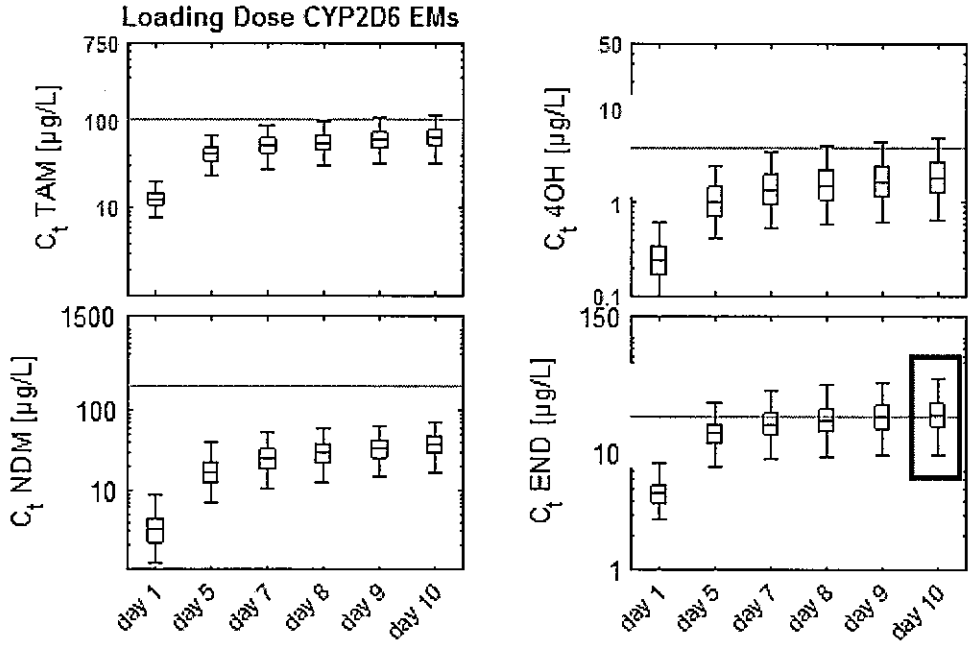



Figure 11

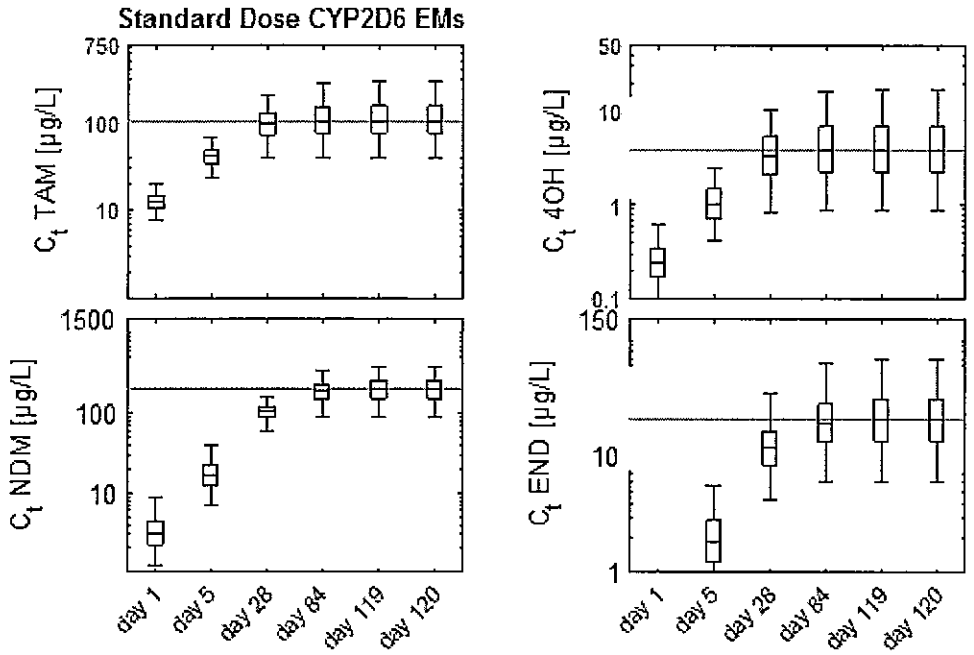



Figure 12

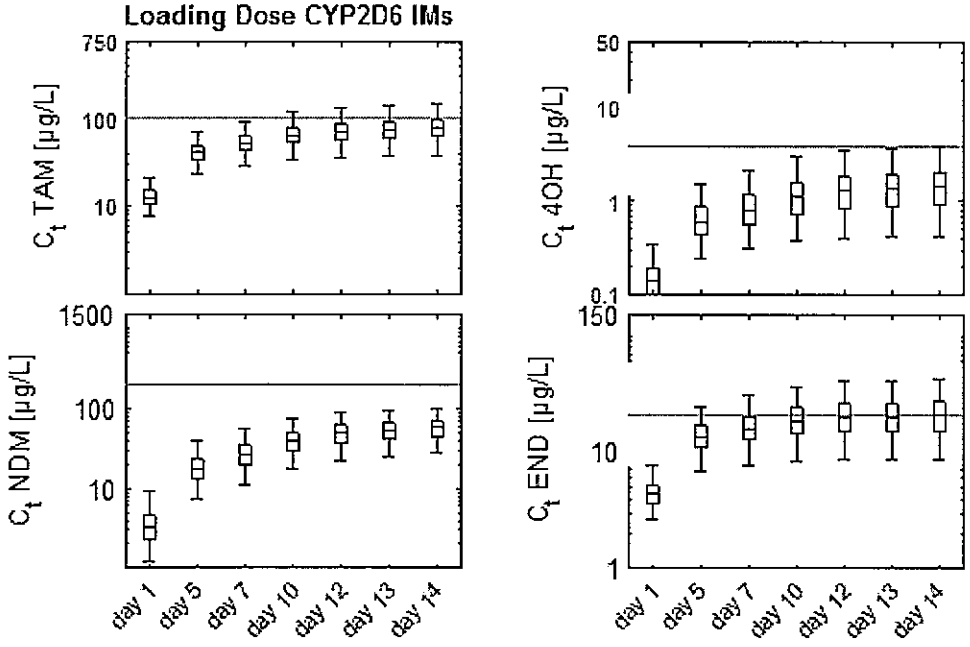



Figure 13

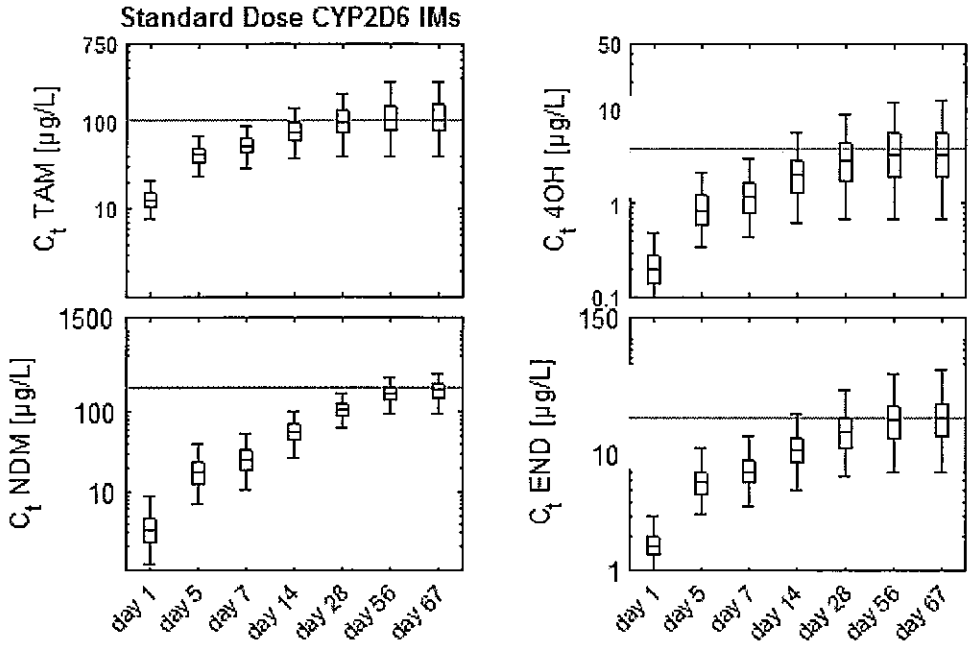



Figure 14

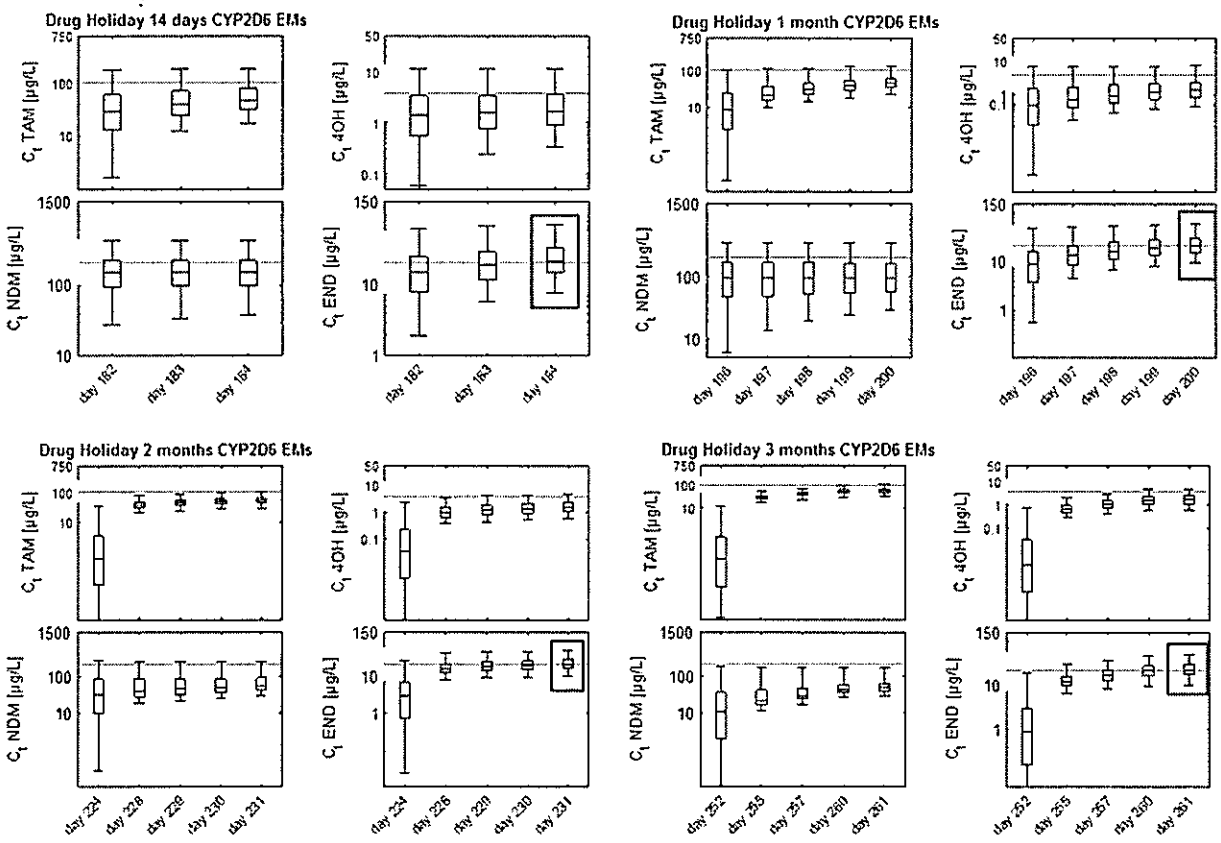



Figure 15

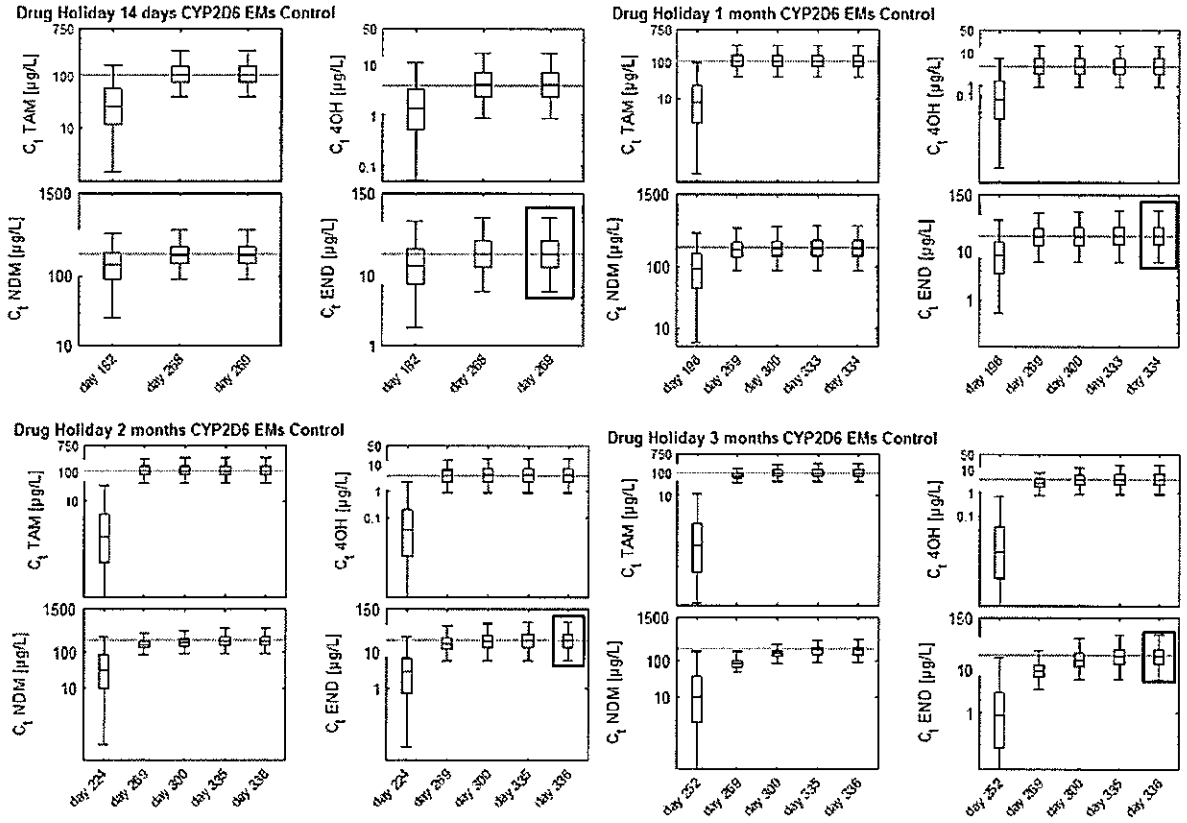

Drug Holiday 14 days CYP2D6 EMs Control
Drug Holiday 1 month CYP2D6 EMs Control
Drug Holiday 2 months CYP2D6 EMs Control
Drug Holiday 3 months CYP2D6 EMs Control
C_t TAM [µg/L]
C_t 4OH [µg/L]
C_t NDM [µg/L]
C_t END [µg/L]

**Figure 16**

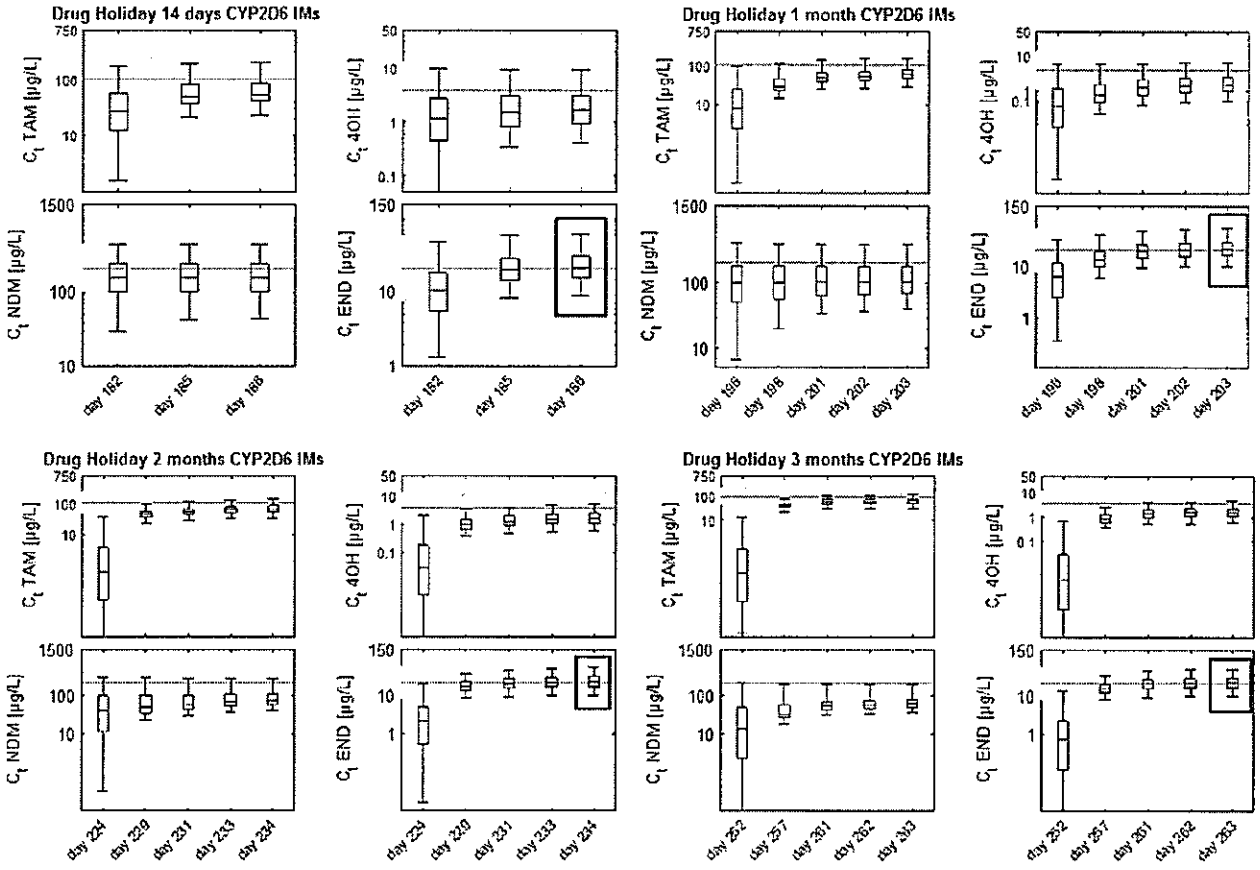

Drug Holiday 14 days CYP2D6 IMs
Drug Holiday 1 month CYP2D6 IMs
Drug Holiday 2 months CYP2D6 IMs
Drug Holiday 3 months CYP2D6 IMs
C_t TAM [µg/L]
C_t 4OH [µg/L]
C_t NDM [µg/L]
C_t END [µg/L]

**Figure 17**

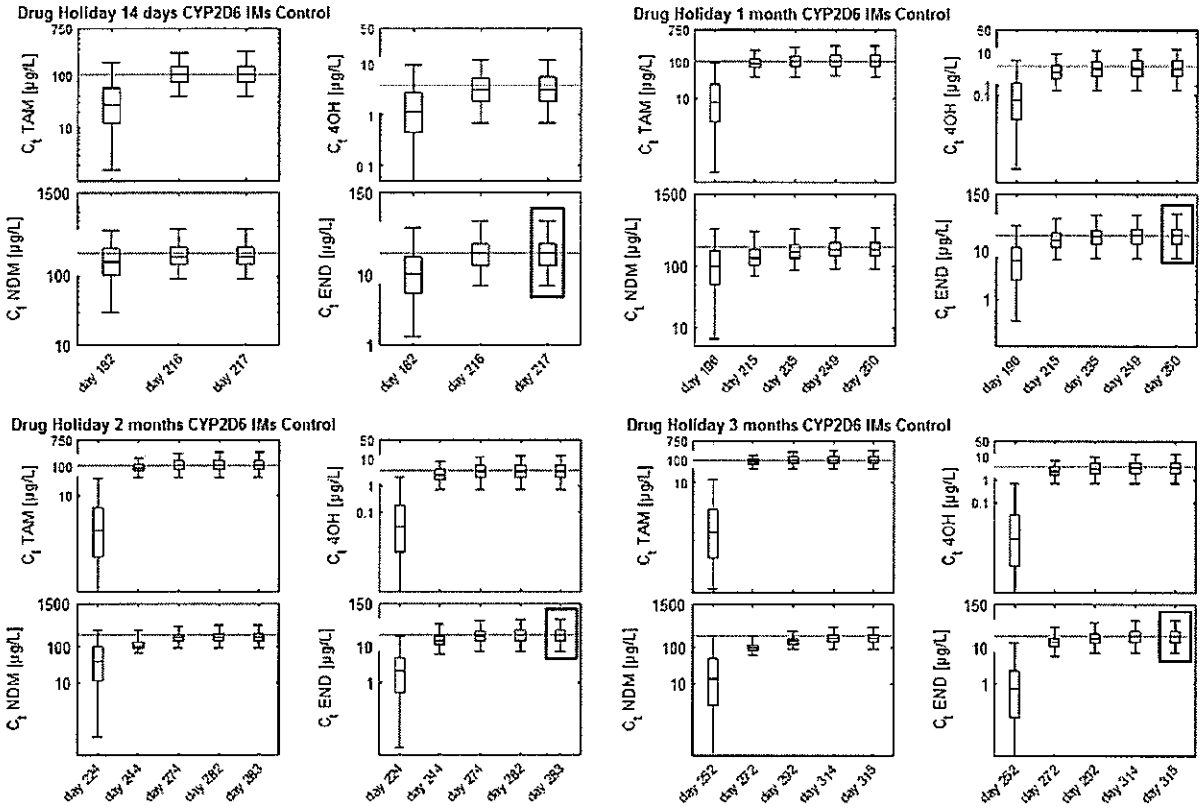

Drug Holiday 14 days CYP2D6 IMs Control
Drug Holiday 1 month CYP2D6 IMs Control
Drug Holiday 2 months CYP2D6 IMs Control
Drug Holiday 3 months CYP2D6 IMs Control
C_t TAM [µg/L]
C_t 4OH [µg/L]
C_t NDM [µg/L]
C_t END [µg/L]

**Figure 18**