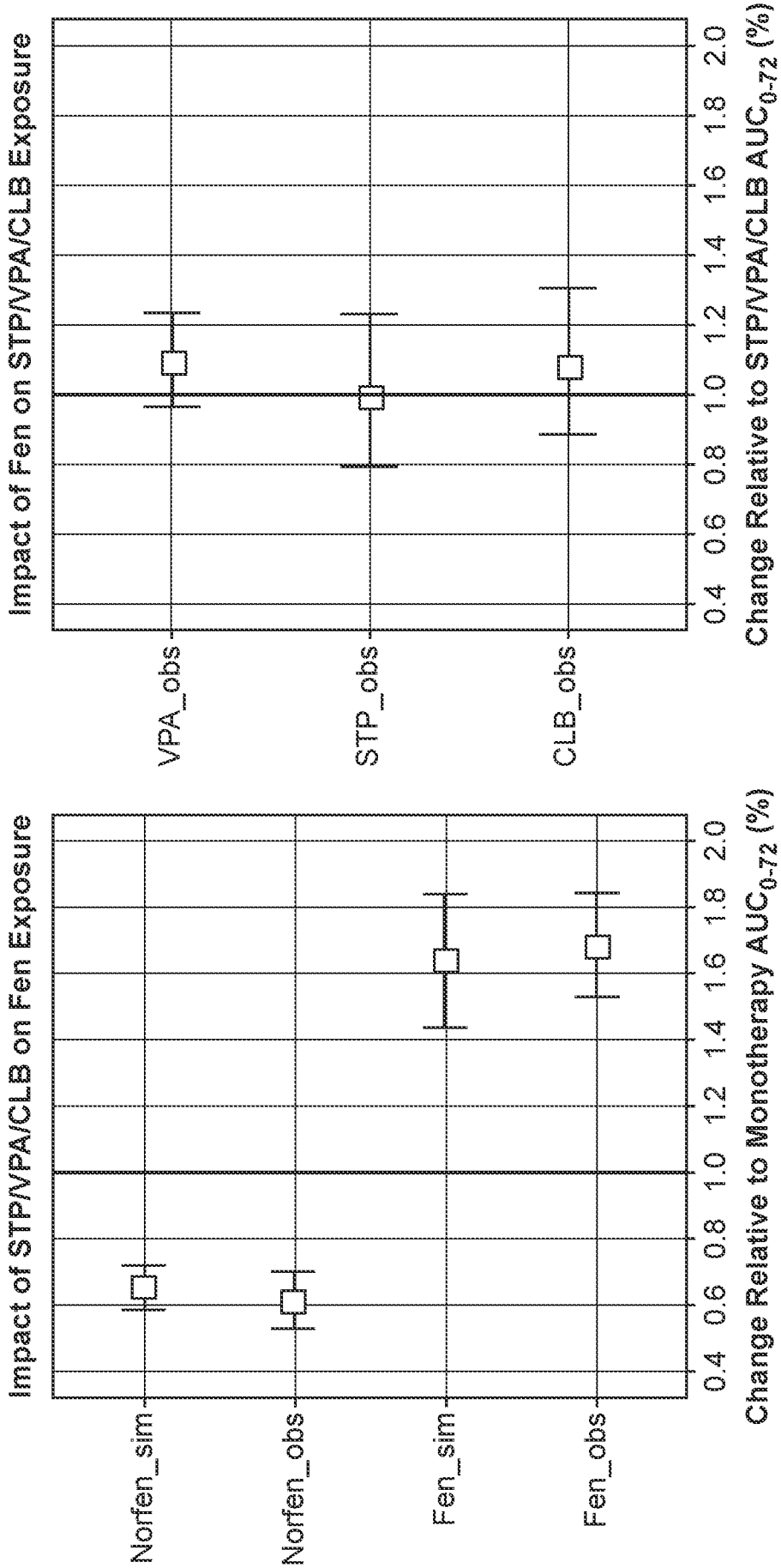
Study Day	-28 to -2	-1	1															2		3	4	
					Times After Dosing (h)																	
	Screening	Admission	Pre-dose	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	9	12	24	36	48	72	Follow-up Call
General Assessments																						
Informed Consent	X																					
Inclusion/Exclusion	X	X																				
Medical History	X	X																				
Weight, Height and BMI	X	X																				
Vein Assessment	X																					
Carbon Monoxide Breath Test	X	X																				
Drug Screen	X	X																				
Alcohol breath Test	X	X																				
FSH Test (Post-Menopausal Women)	X																					
CYP2D6 Genotyping (Period 1 only)			X																			
IMP Administration				X																		
Safety Assessments																						
Urine Pregnancy Test	X	X																				
Physical Examination	X	X																				
Safety Labs	X		X																	X		
C-SSRS	X																			X		
Urinalysis	X	X																				
ECG	X																					
Vital Signs	X	X	X		X	X		X					X		X		X	X				
Adverse Events	←																					→
Concomitant Medications	X	←																				X
PK Assessments																						
Plasma Samples			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

FIG. 1



$AUC_{0\text{-}72,obs}$ for all analytes was calculated using R (Version 3.3.1)

FIG. 2

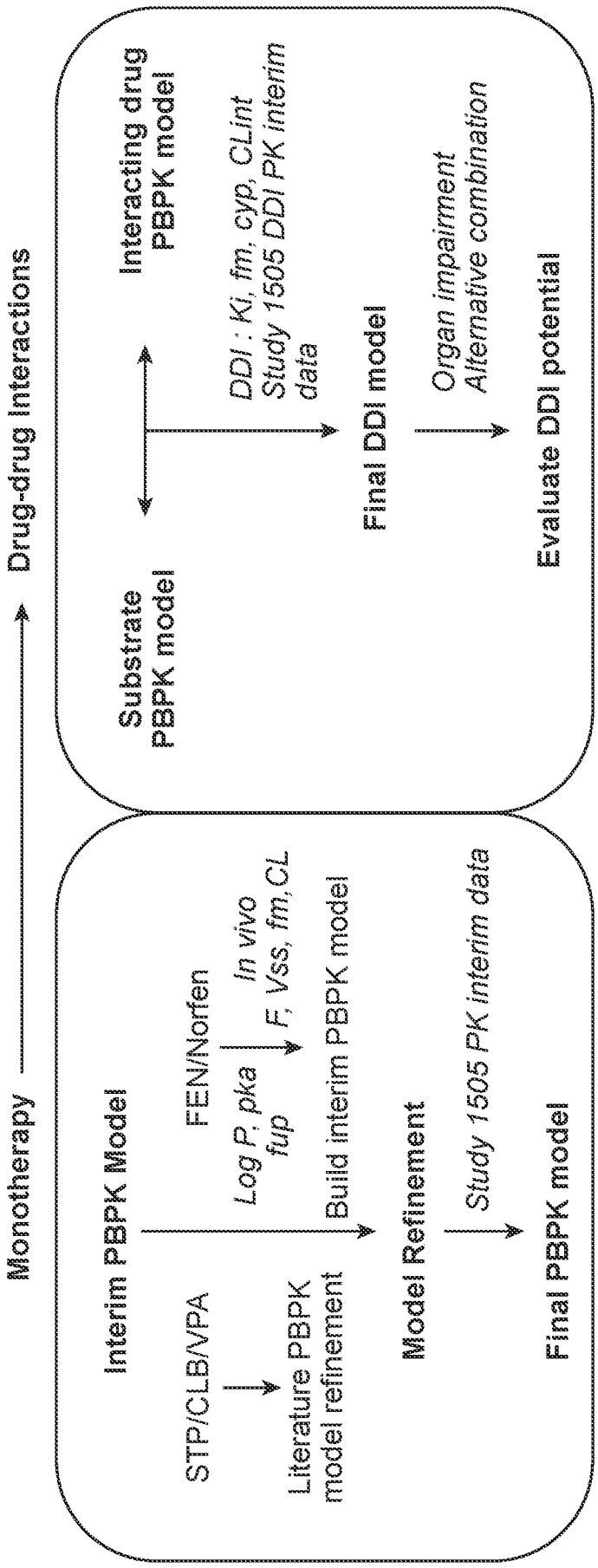

Monotherapy
Drug-drug Interactions
Interim PBPK Model
STP/CLB/VPA
Literature PBPK model refinement
FEN/Norfen
Log P, pka
fup
In vivo
F, Vss, fm, CL
Build interim PBPK model
Model Refinement
Study 1505 PK interim data
Final PBPK model
Substrate PBPK model
Interacting drug PBPK model
DDI : Ki, fm, cyp, CLint
Study 1505 DDI PK interim data
Final DDI model
Organ impairment
Alternative combination
Evaluate DDI potential

FIG. 3

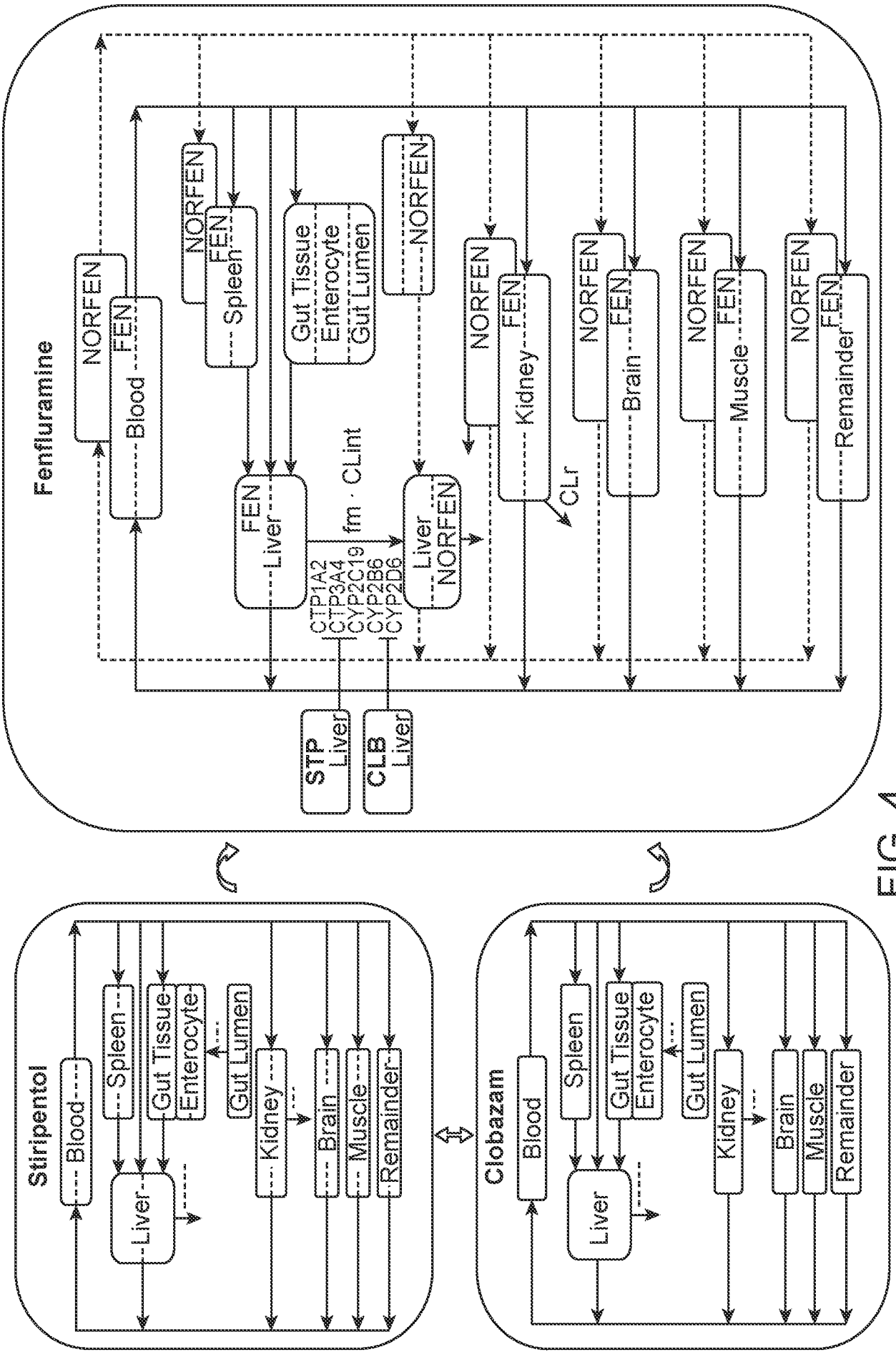

Fenfluramine
NORFEN
FEN
Blood
NORFEN
FEN
Spleen
Gut Tissue
Enterocyte
Gut Lumen
NORFEN
FEN
Liver
fm · CLint
CYP1A2
CYP3A4
CYP2C19
CYP2B6
CYP2D6
Liver
NORFEN
NORFEN
FEN
Kidney
CLr
NORFEN
FEN
Brain
NORFEN
FEN
Muscle
NORFEN
FEN
Remainder
STP
Liver
CLB
Liver
Stiripentol
Blood
Spleen
Gut Tissue
Enterocyte
Gut Lumen
Liver
Kidney
Brain
Muscle
Remainder
Clobazam
Blood
Spleen
Gut Tissue
Enterocyte
Gut Lumen
Liver
Kidney
Brain
Muscle
Remainder

FIG. 4

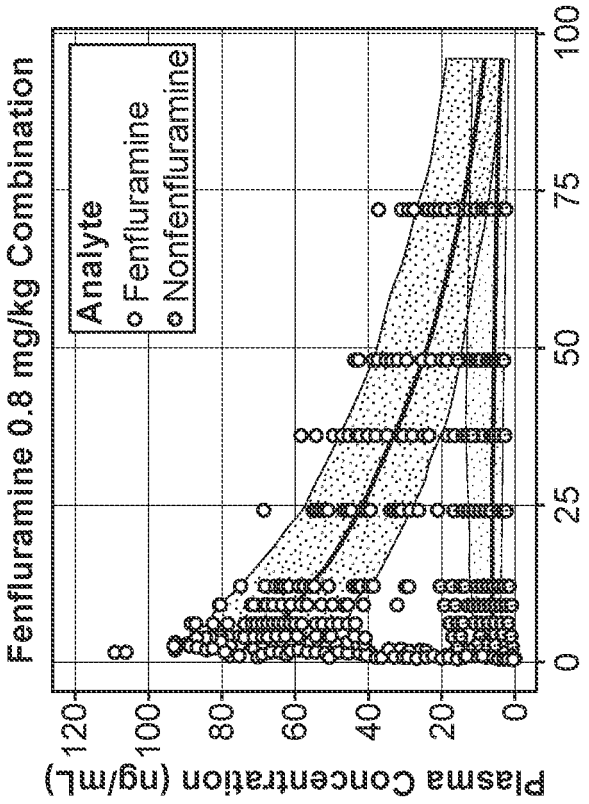


FIG. 5A

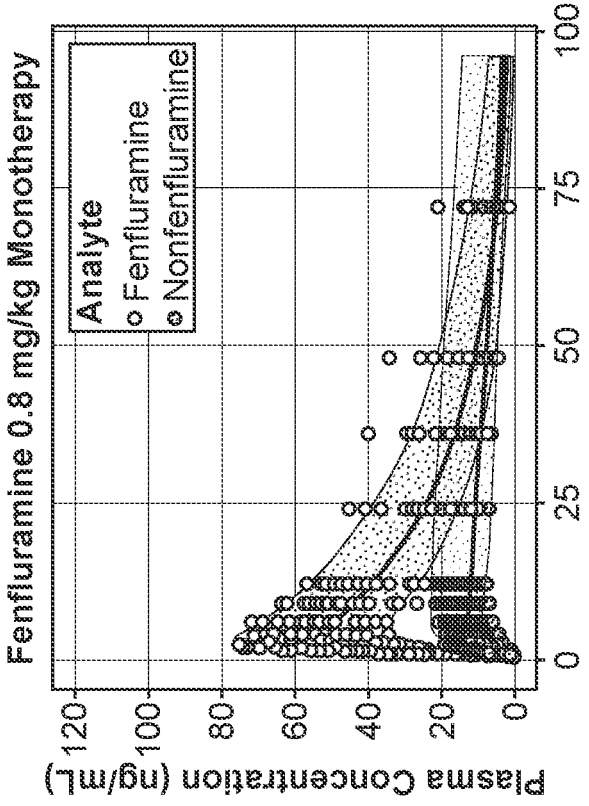


FIG. 5B

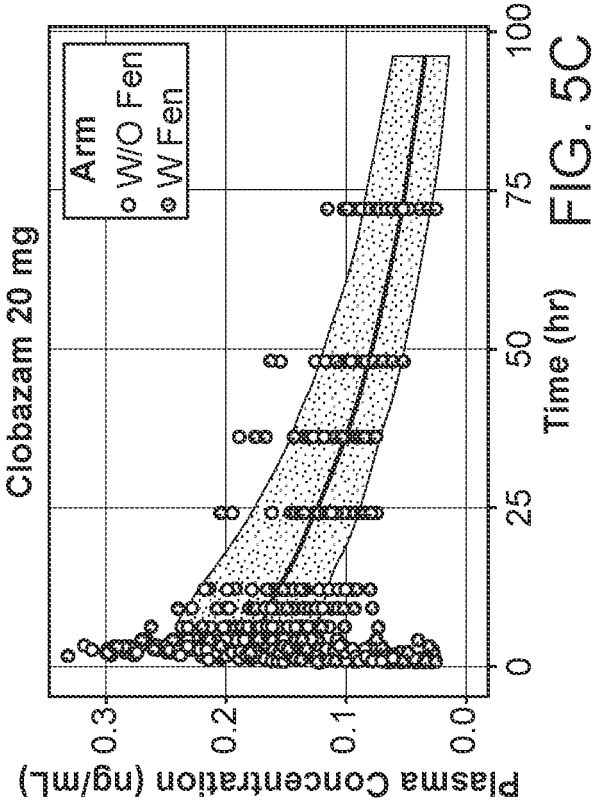


FIG. 5C

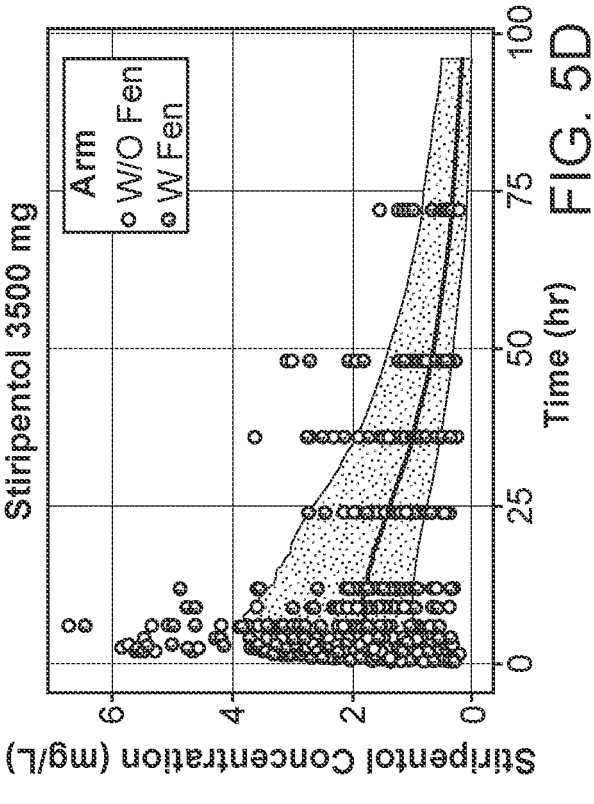


FIG. 5D

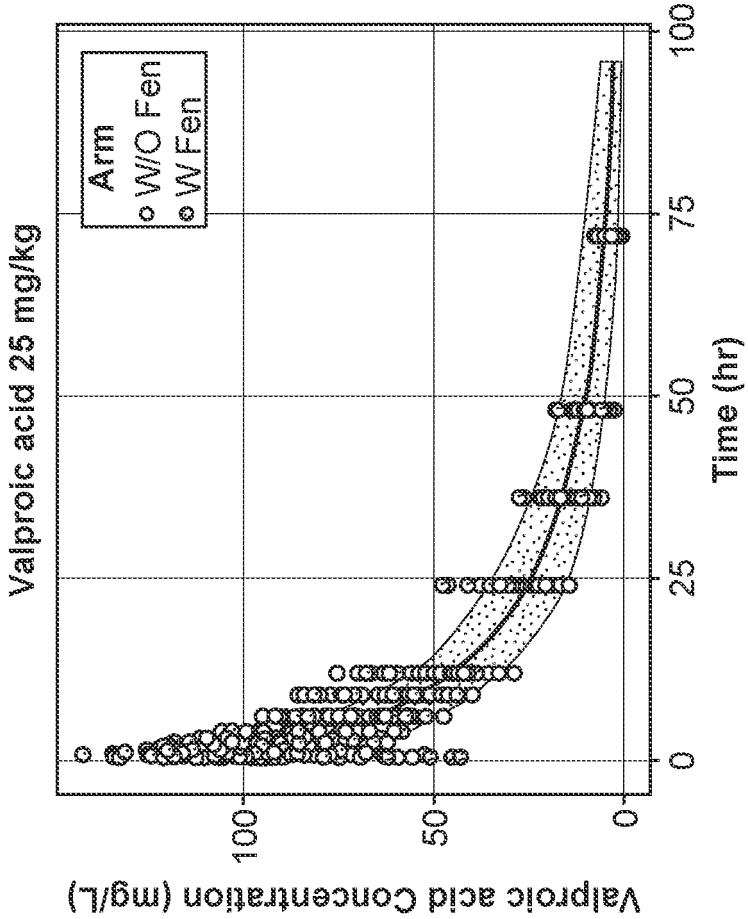

Valproic acid 25 mg/kg
Arm
W/O Fen
W Fen
Valproic acid Concentration (mg/L)
100
50
0
0
25
50
75
100
Time (hr)

FIG. 5E

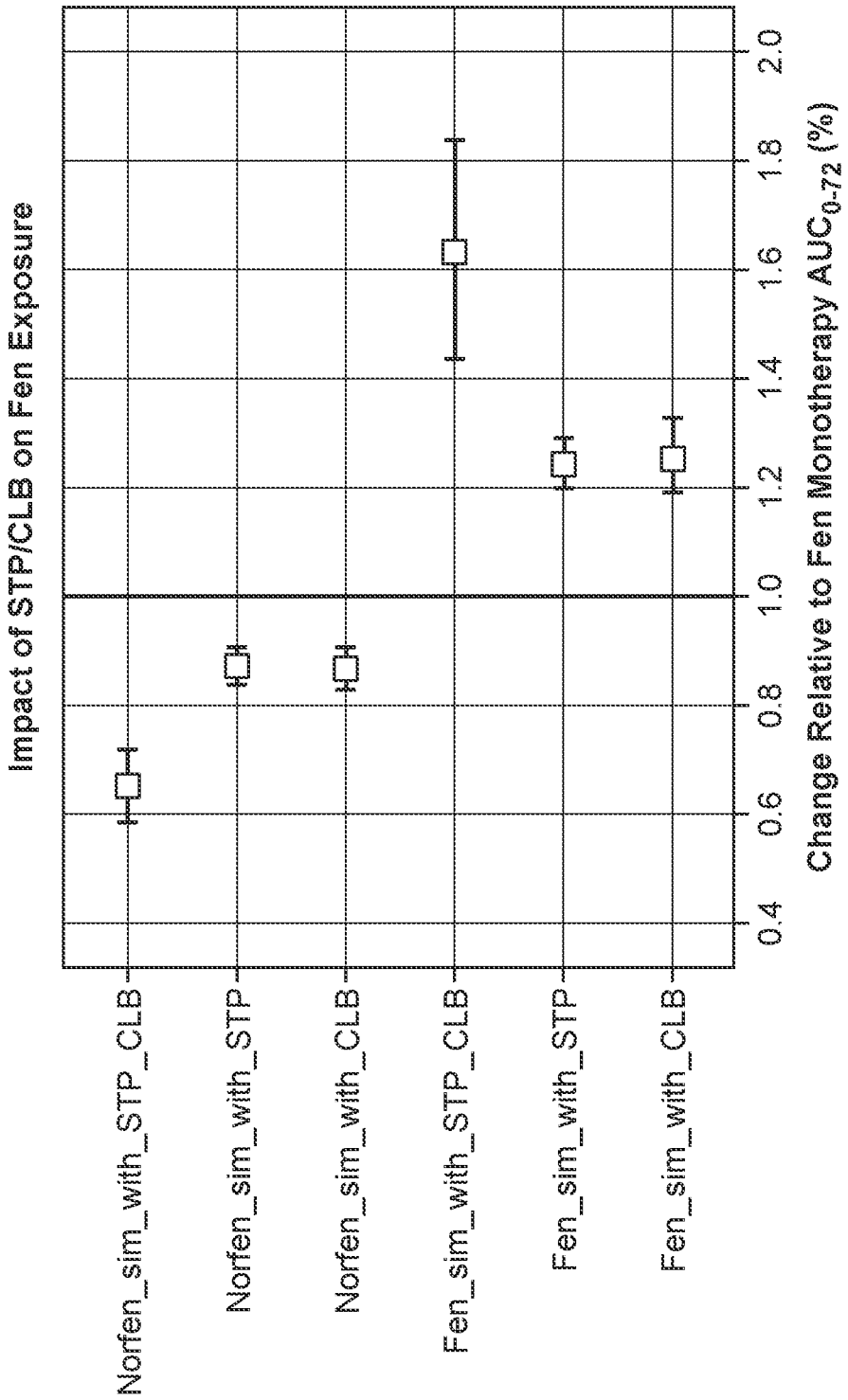

Impact of STP/CLB on Fen Exposure
Norfen_sim_with_STP_CLB
Norfen_sim_with_STP
Norfen_sim_with_CLB
Fen_sim_with_STP_CLB
Fen_sim_with_STP
Fen_sim_with_CLB
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
Change Relative to Fen Monotherapy AUC0-72 (%)

FIG. 6

Fenfluramine

Pathway	Clearance	Inhibition	Induction
CYP1A2	++		
CYP2B6	++		1
CYP2C9	+		
CYP2C19	+		
CYP2D6	++	1	
CYP3A4	+		1
Renal	++		

FIG. 7A

Norfenfluramine

Pathway	Clearance	Inhibition	Induction
CYP2B6			1
CYP2D6		1	
CYP3A4			1

FIG. 7B

Stiripentol clearance pathway profile

Pathway	Clearance	Inhibition	Induction
CYP1A2	+	2	Unknown
CYP2B6		2	
CYP2C9		1	
CYP2C19	+ (invivo)	1	
CYP2D6		2	
CYP3A4		2	1
Renal and glucuronides	++ (invivo)		

FIG. 7C

Clobazam

Pathway	Clearance	Inhibition	Induction
CYP2B6	+		
CYP2C19	+		
CYP2D6		2	
CYP3A4	++		1
Renal	++		

FIG. 7D

N-desmethylclobazam

Pathway	Clearance	Inhibition	Induction
CYP2C9		1	
CYP2C19	++		
CYP3A4			1
UGT1A4		1	
UGT1A6		1	
UGT2B4		1	
Renal	++		

FIG. 7E

Cannabidiol clearance pathway profile

Pathway	Clearance	Inhibition	Induction
CYP1A2		2 (time dependent)	None (upto 1 µM)
CYP2B6		2	
CYP2C8		1	
CYP2C9	+	1	
CYP2C19	+	1	
CYP2D6		1	
CYP3A4	++	2	

FIG. 7F