

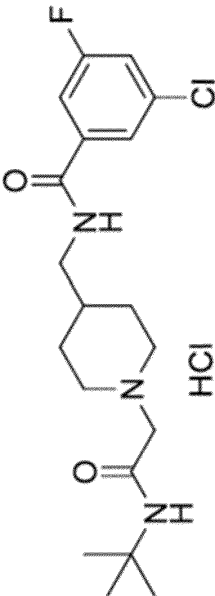
International nomenclature	N-((1-(2-(tert-butylamino)-2-oxoethyl)piperidin-4-yl)methyl)-3-chloro-5-fluorobenzamide hydrochloride
Sponsor name	PRAX-944
Other name	NP169944, PRX0001782, Z944
CAS number	1797986-84-5 (HCl salt); 1199236-64-0 (freebase)
Structure	
Molecular formula	C ₁₉ H ₂₇ ClFN ₃ O ₂ HCl
Molecular weight	420.35 (HCl salt); 383.89 (free base)

FIG. 1

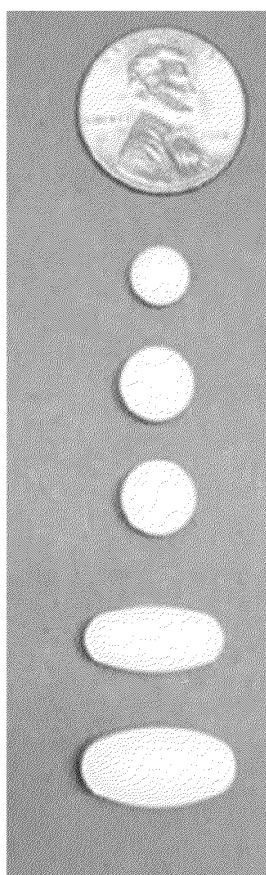


FIG. 2A

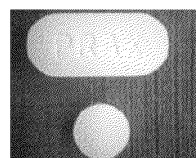


FIG. 2B

Mixed Parallel and Cross-Over Design
PRAX-944-107 Study Schema

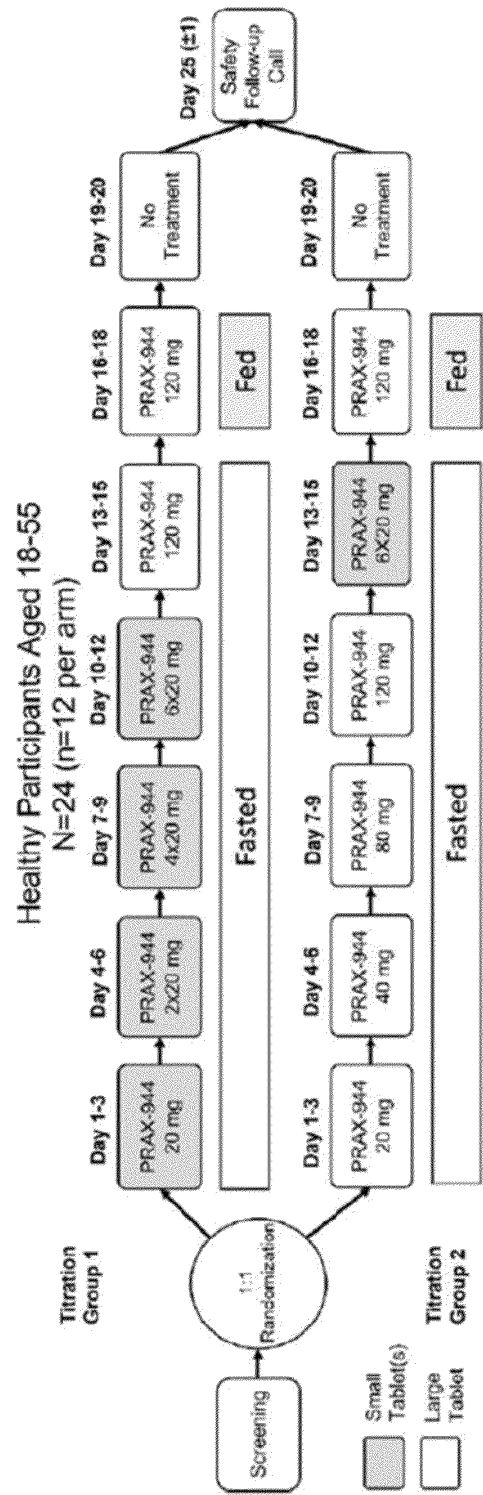


FIG. 3A

ARM Name	Titration Group 1	Titration Group 2
Intervention Name	PRAX-944	
Type	Drug	
Dose Formulation	Modified-release tablet	
Unit Dose Strength(s)	20 and 120 mg	20, 40, 80, and 120 mg
Dosage Level(s)	titrated from 20 mg to 120 mg	titrated from 20 mg to 120 mg
Day 1-3	1×20-mg small tablet fasting	1×20-mg large tablet fasting
Day 4-6	2×20-mg small tablet fasting	1×40-mg tablet fasting
Day 7-9	4×20-mg small tablet fasting	1×80-mg tablet fasting
Day 10-12	6×20-mg small tablet fasting	1×120-mg tablet fasting
Day 13-15	1×120-mg tablet fasting	6×20-mg tablet fasting
Day 16-18	1×120-mg tablet fed	1×120-mg tablet fed
Route of Administration	Oral	
Active Pharmaceutical Ingredient	N-((1-(2-(tert-butylamino)-2-oxoethyl)piperidin-4-yl)methyl)-3-chloro-5-fluorobenzamide hydrochloride	
Sourcing	Provided centrally by the sponsor	
Packaging and Labeling	Study drug will be provided in pre-packaged containers. Each container will be labeled as required per country requirements.	

FIG. 3B

Quantitative Composition of PRAX-944 MR Tablet, 20, 40, 80 and 120 mg										
Component	Quality	Function	20 mg		40 mg		80 mg		120 mg	
			% w/w	mg/tablet	% w/w	mg/tablet	% w/w	mg/tablet	% w/w	mg/tablet
PRAX-944 HCl	In-house	Active	4.87	21.90 ^a	9.73	43.80 ^b	19.47	87.60 ^c	29.20	131.40 ^d
Silicified microcrystalline cellulose ^e	NF	Filler	44.63	200.85	39.77	178.95	30.03	135.15	20.30	91.35
Mannitol	USP-NF, Ph. Eur.	Filler	8.00	36.00	8.00	36.00	8.00	36.00	8.00	36.00
Hypromellose	USP, Ph. Eur.	Matrix polymer	40.00	180.00	40.00	180.00	40.00	180.00	40.00	180.00
Colloidal silicon dioxide	USP-NF, Ph. Eur.	Glidant	1.50	6.75	1.50	6.75	1.50	6.75	1.50	6.75
Magnesium stearate	USP-NF, Ph. Eur.	Lubricant	1.00	4.50	1.00	4.50	1.00	4.50	1.00	4.50
Film Coating										
Opadry® II white 85F18422 ^f	In-house	Film coating agent	3.00	13.50	3.00	13.50	3.00	13.50	3.00	13.50
Purified water ^g	USP, Ph. Eur.	Processing aid	NA	NA	NA	NA	NA	NA	NA	NA
Total weight of film-coated tablet				463.5		463.5		463.5		463.5
HCl=hydrochloric acid; NA=not applicable; MR=modified release; NF=National Formulary; Ph. Eur.=European Pharmacopoeia; USP=United States Pharmacopeia.										
^a Equivalent to 20.0 mg PRAX-944 free base per tablet.										
^b Equivalent to 40.0 mg PRAX-944 free base per tablet										
^c Equivalent to 80.0 mg PRAX-944 free base per tablet										
^d Equivalent to 120.0 mg PRAX-944 free base per tablet										
^e Quantity of silicified microcrystalline cellulose is adjusted based on exact quantity of PRAX-944 HCl added after adjusting for purity.										
^f Opadry® II white 85F18422 is comprised of compendial grade polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, and talc.										
^g Water removed during processing and not present in final formulation.										

FIG. 3C

Exemplary Phase 3 Study Design			
Dose	Purpose	With Existing Tablet Strengths	Ideally with New Tablet Strengths
Placebo	Efficacy	Pbo Pbo Pbo Pbo Pbo	Pbo
5 mg	Titration	Pbo Pbo Pbo Pbo 5mg	5mg
10 mg	Titration	Pbo Pbo Pbo Pbo 5mg	10mg
20 mg	Titration	Pbo Pbo Pbo Pbo 20mg	20mg
40 mg	Titration	Pbo Pbo Pbo Pbo 20mg	40mg
60 mg	Titration	Pbo Pbo Pbo Pbo 20mg	60mg
80 mg	Titration	Pbo 20mg 20mg 20mg 20mg	80mg
100 mg	Efficacy	20mg 20mg 20mg 20mg 20mg	100mg

FIG. 3D

7/20

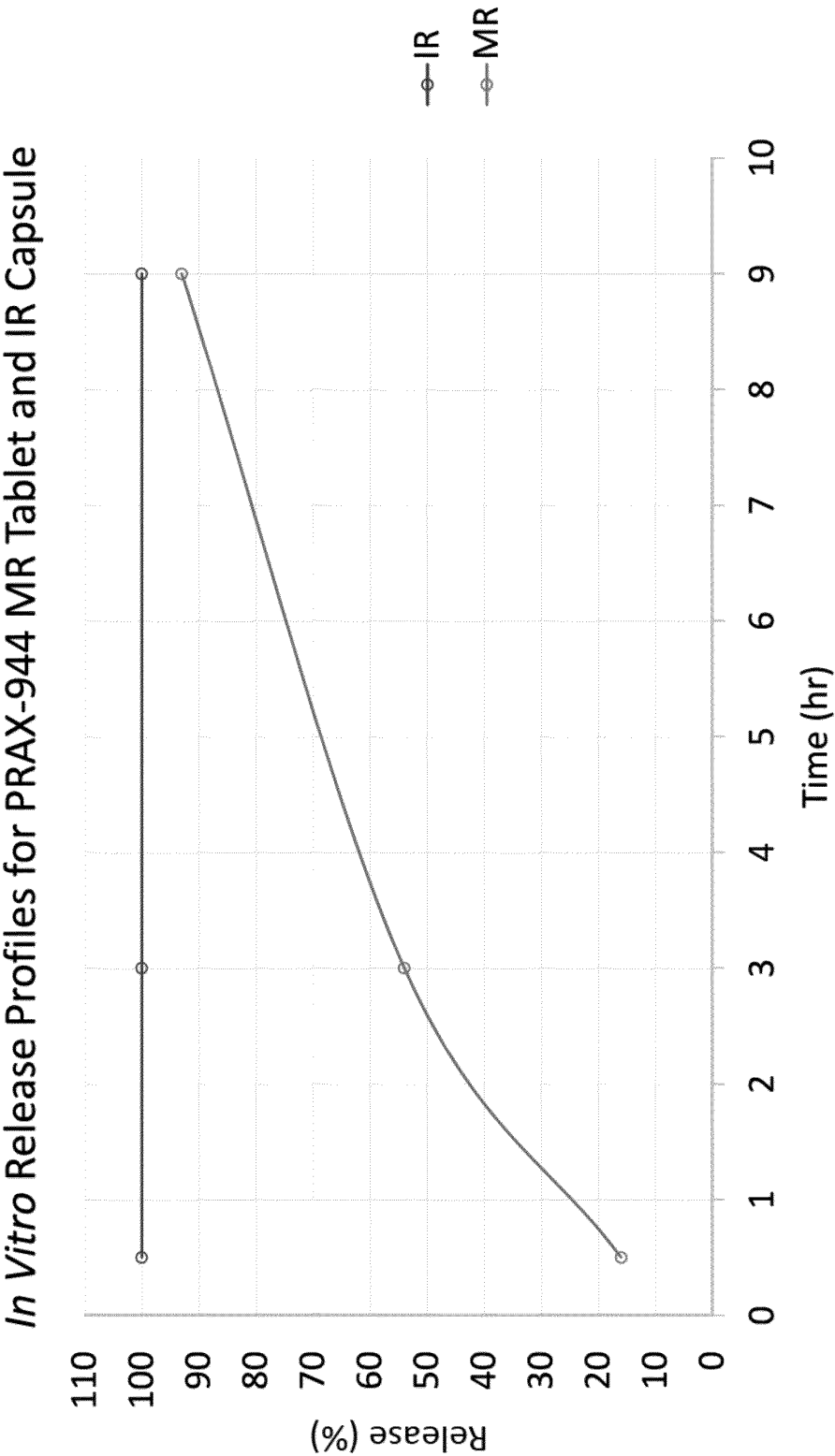
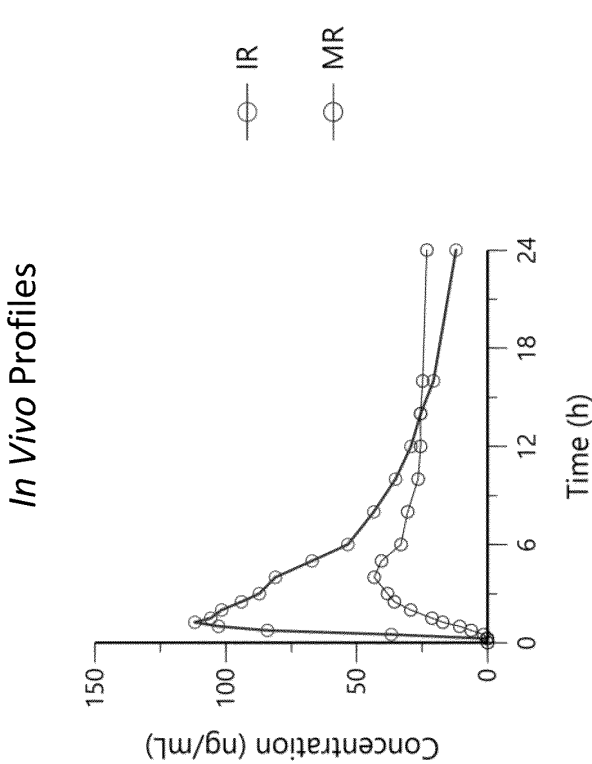


FIG. 4A



Formulation	C _{max} (ng/mL) (CV%)	AUC _∞ (ng.hr/mL) (CV%)
IR	131 (25.6)	1090 (24.4)
MR	47.1 (34.3)	1010 (34.2)

FIG. 4B

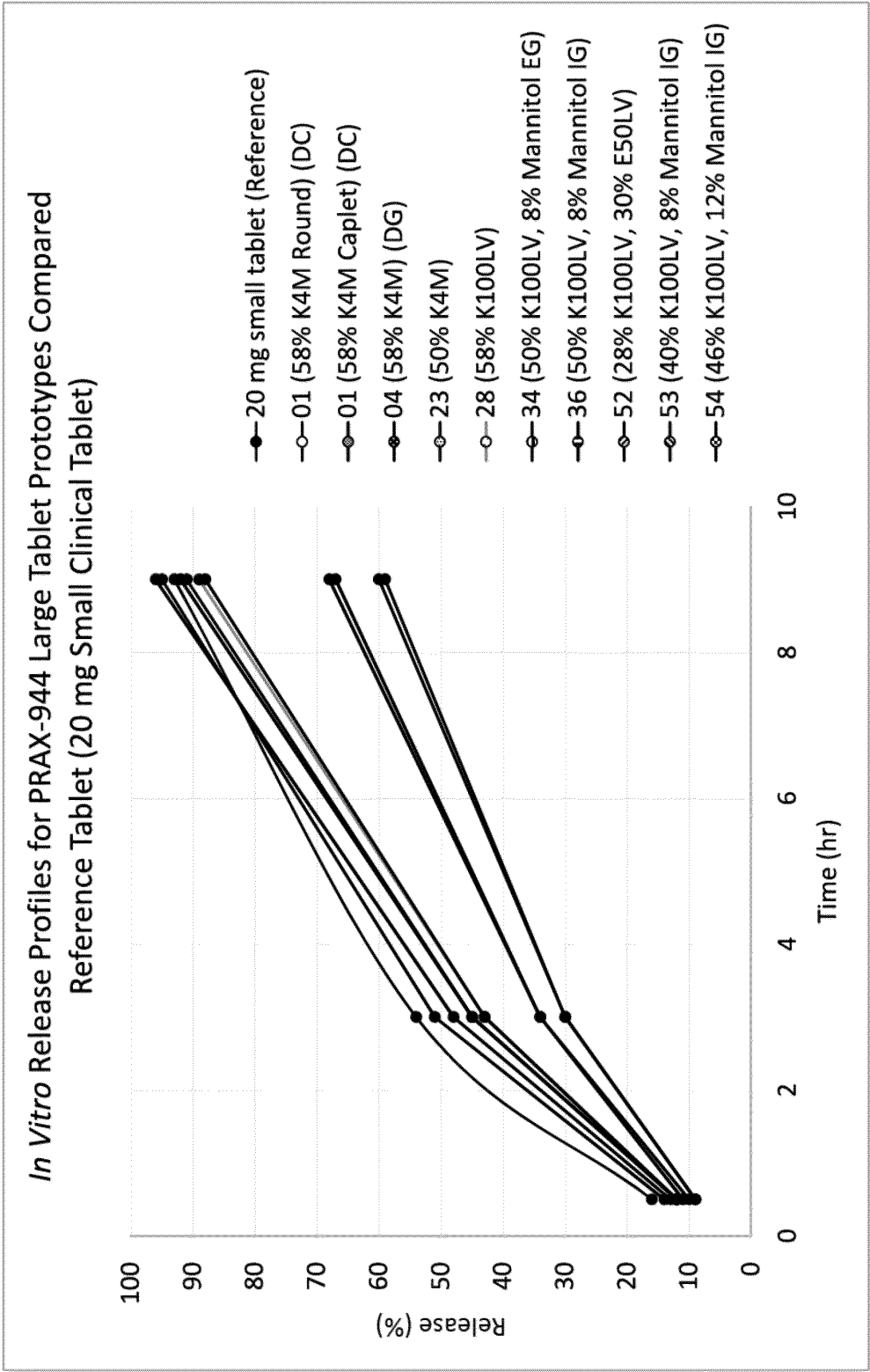


FIG. 5A

10/20

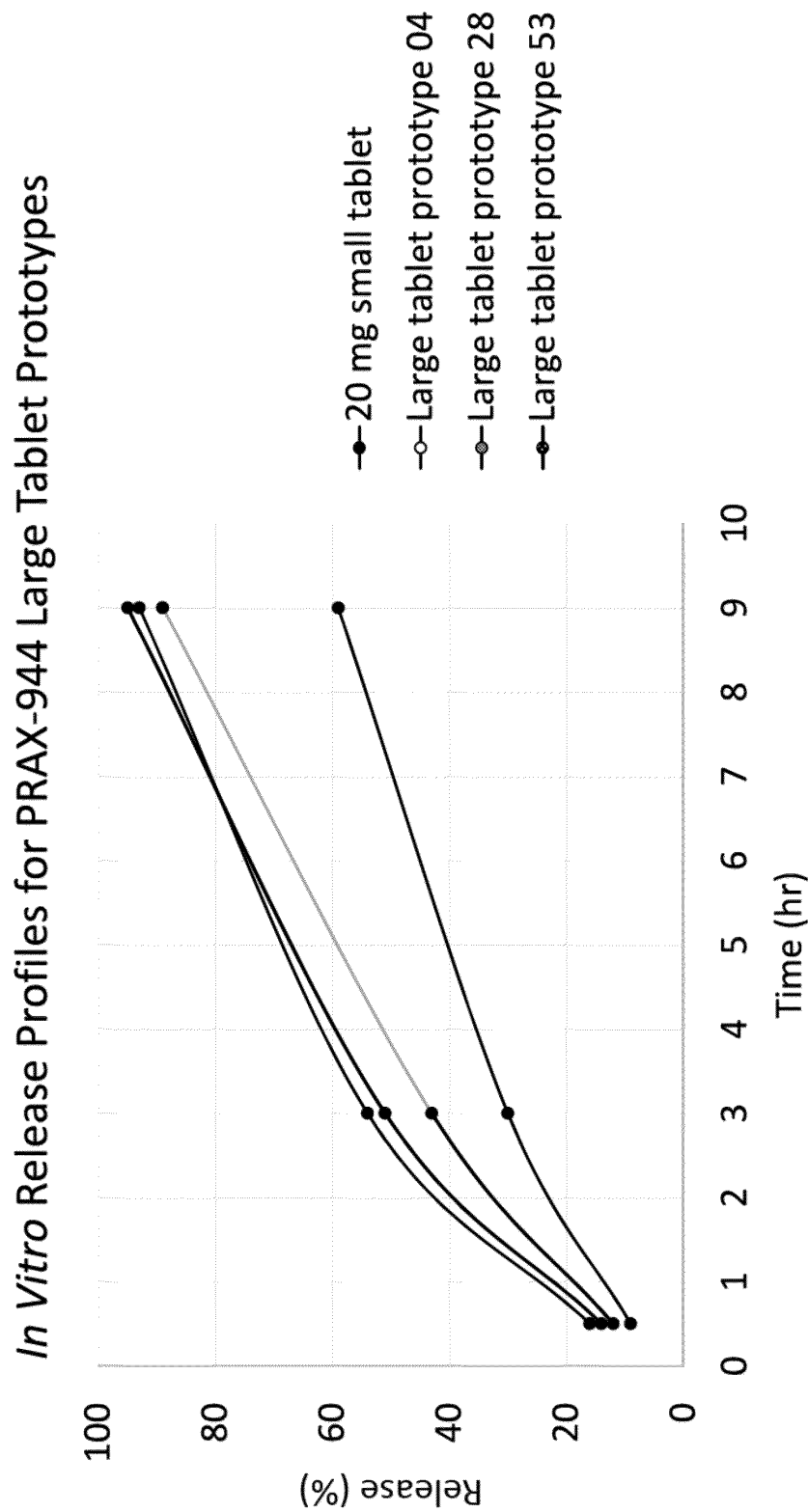


FIG. 5B

11/20

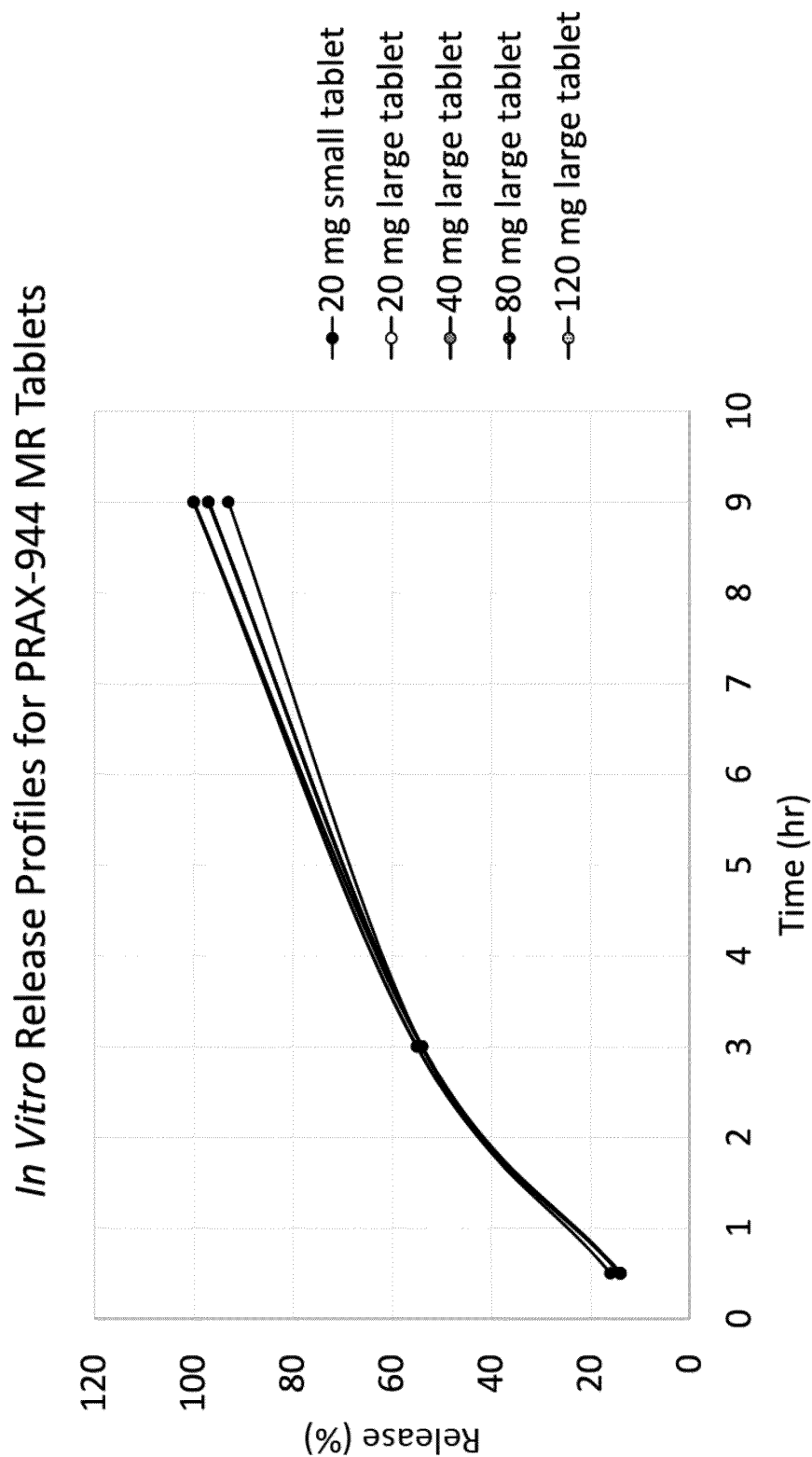


FIG. 5C

12/20

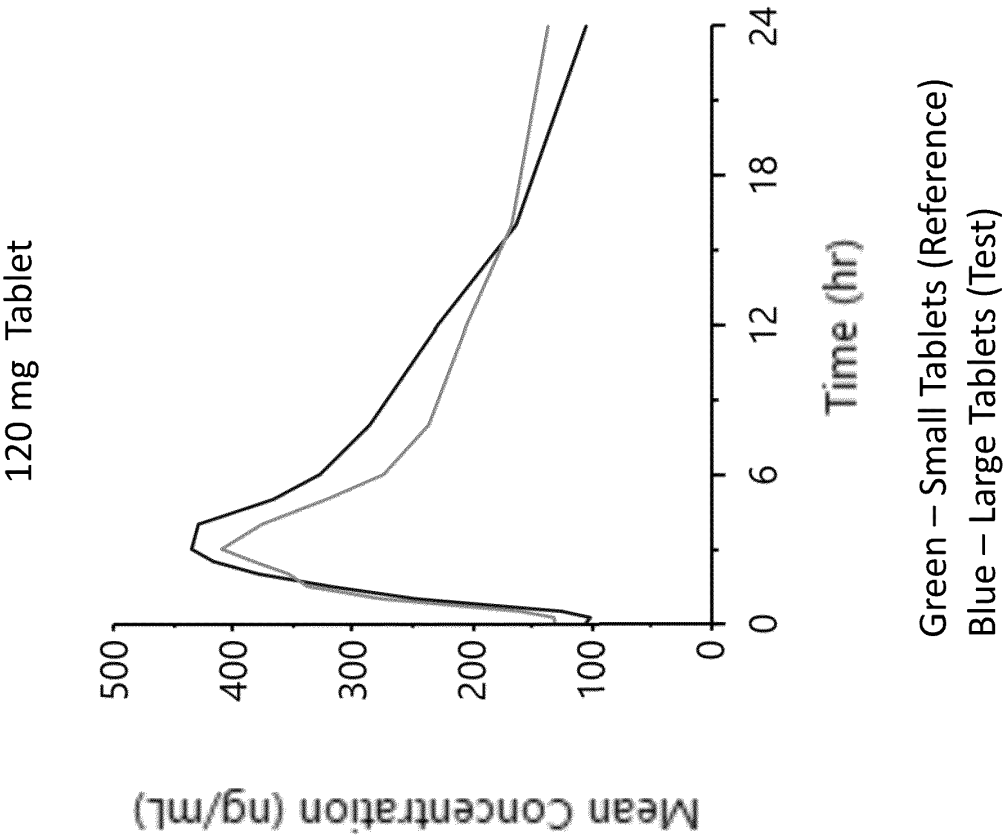


FIG. 6A

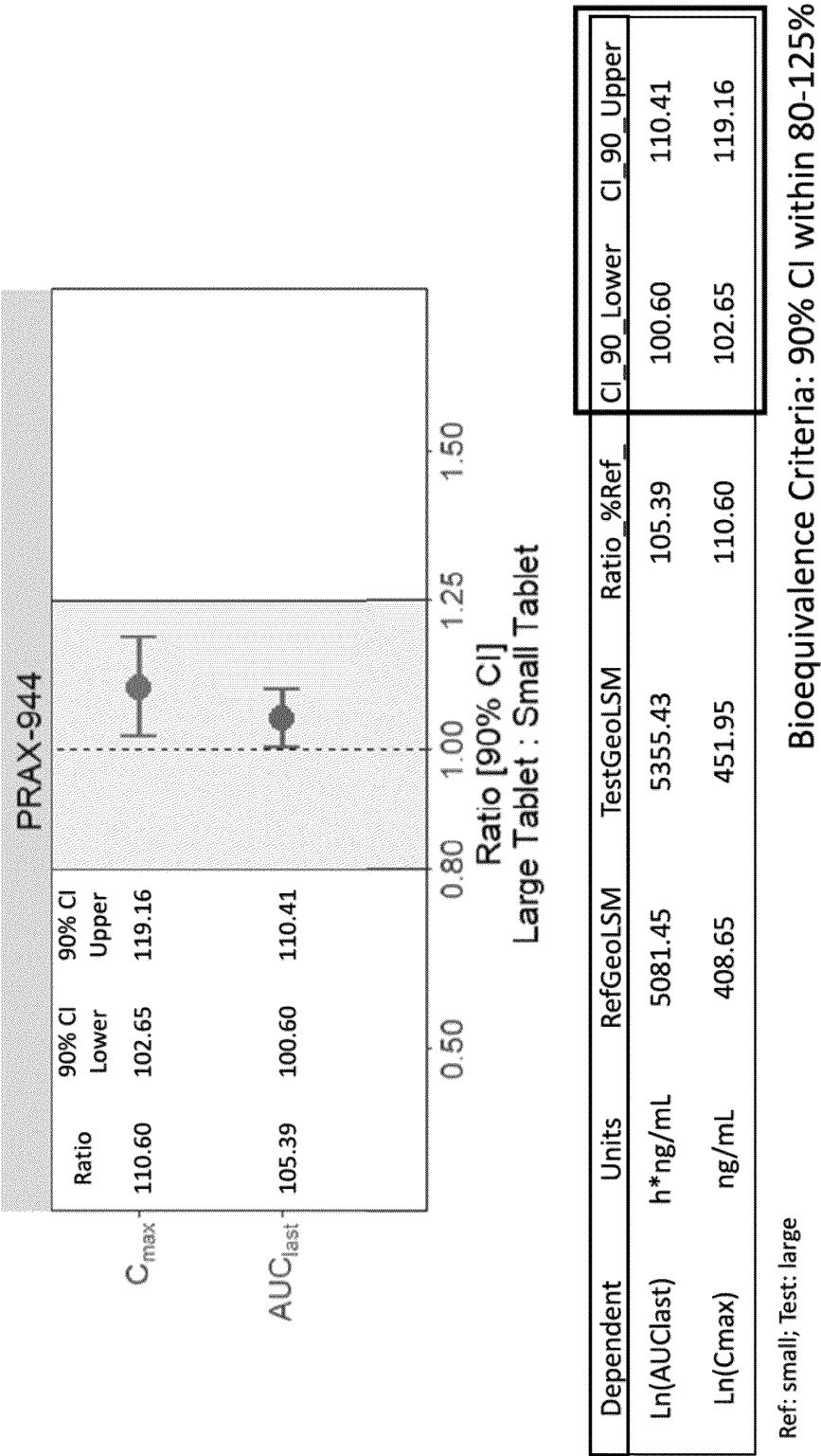


FIG. 6B

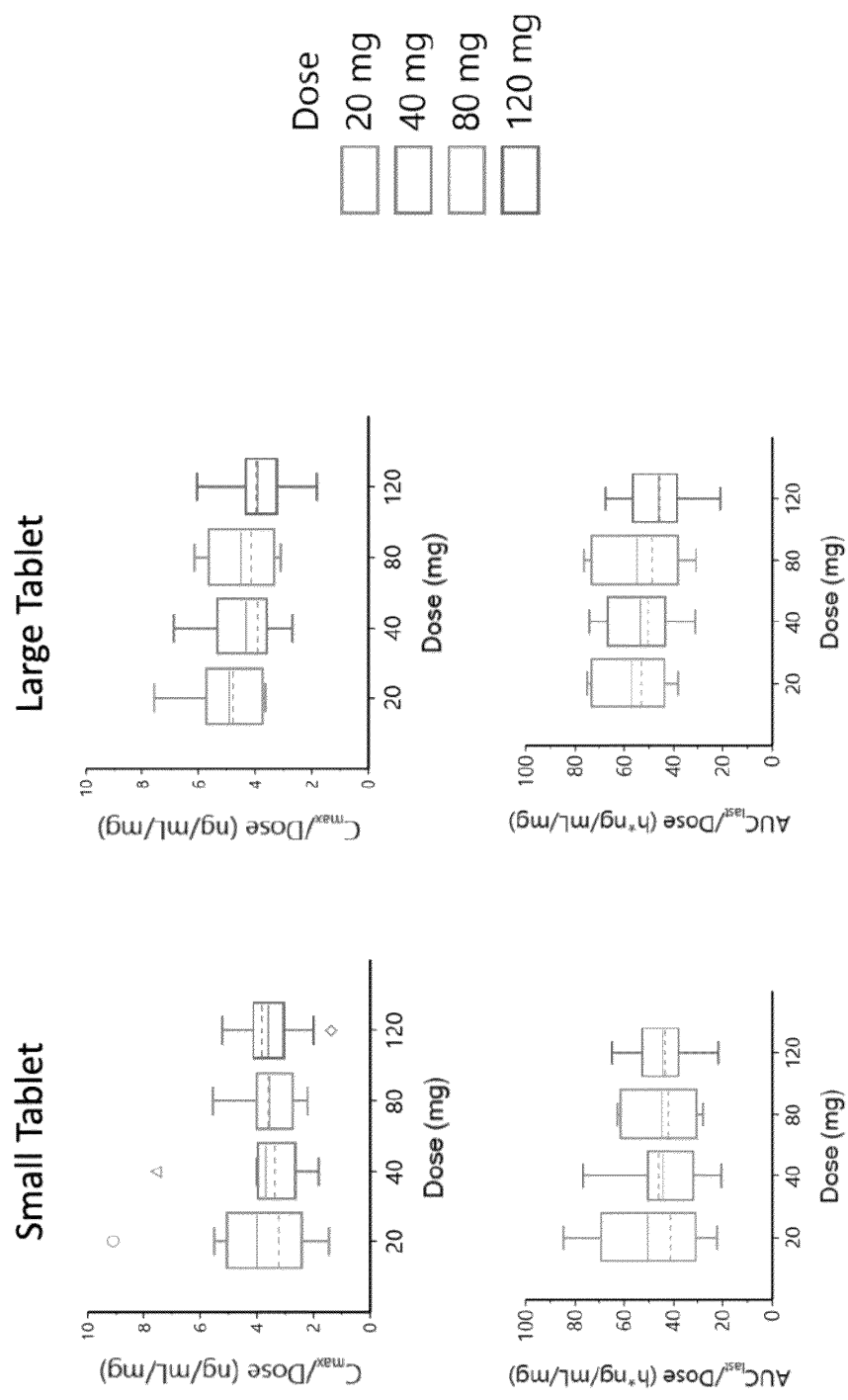


FIG. 7

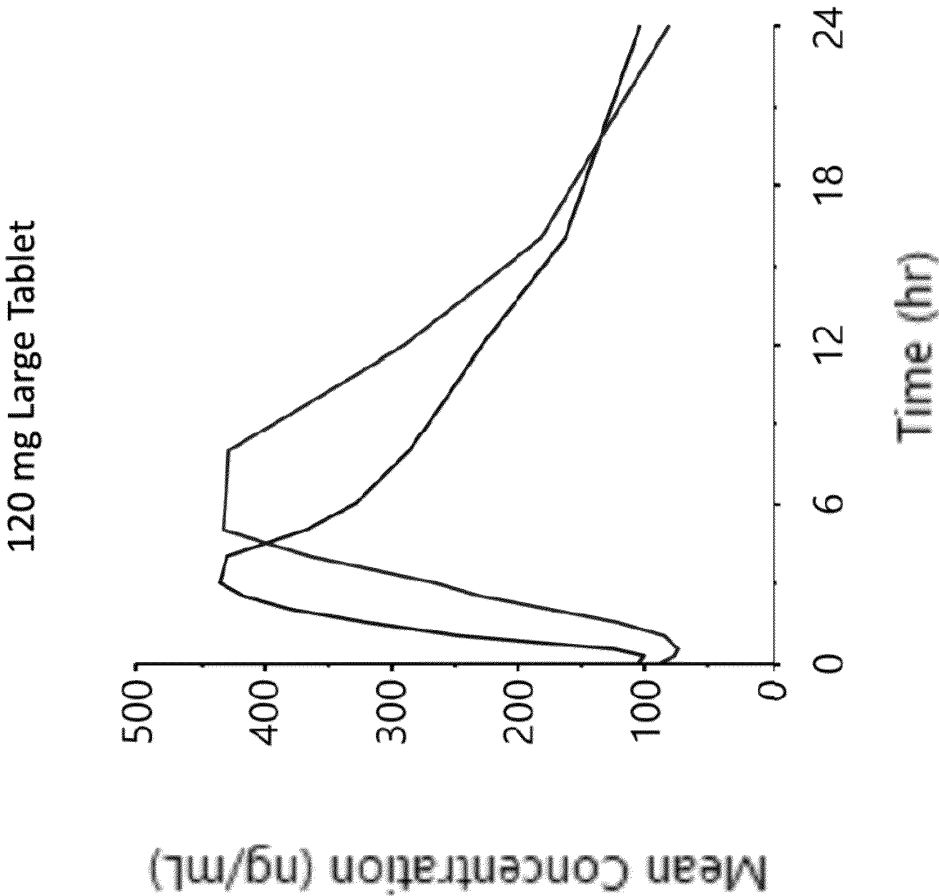


FIG. 8A

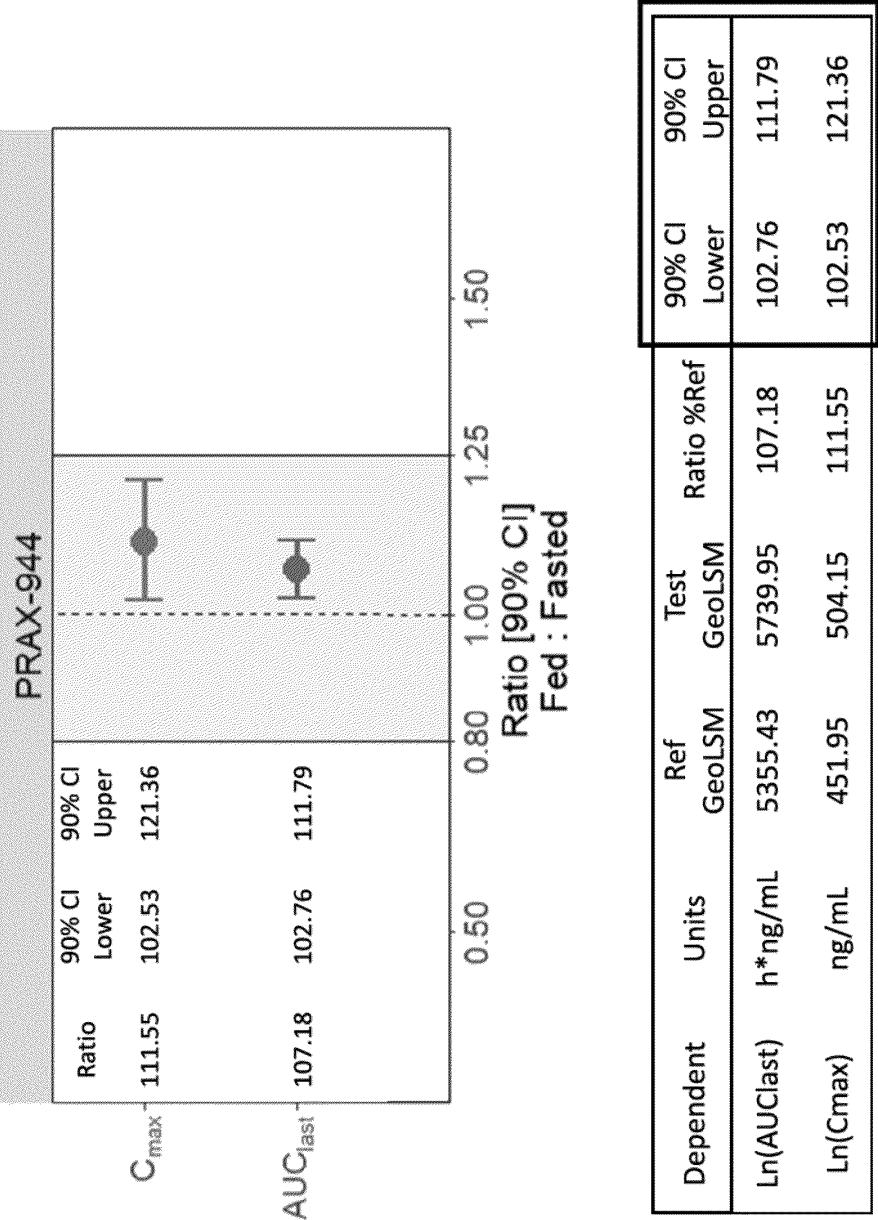
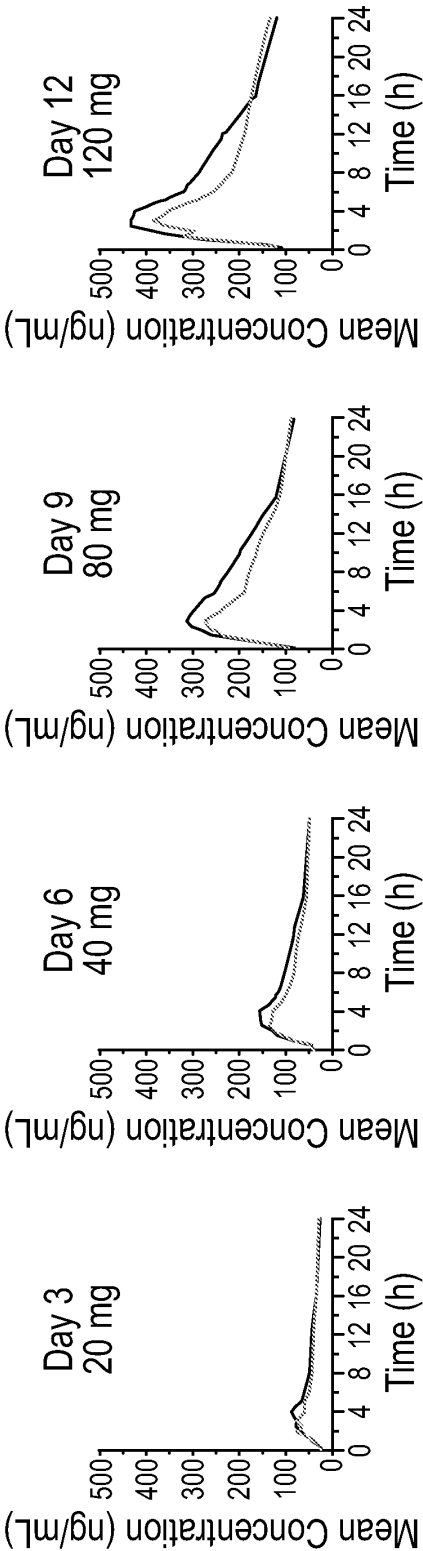


FIG. 8B



Green - Small Tablets
Blue - Large Tablets

FIG. 9A

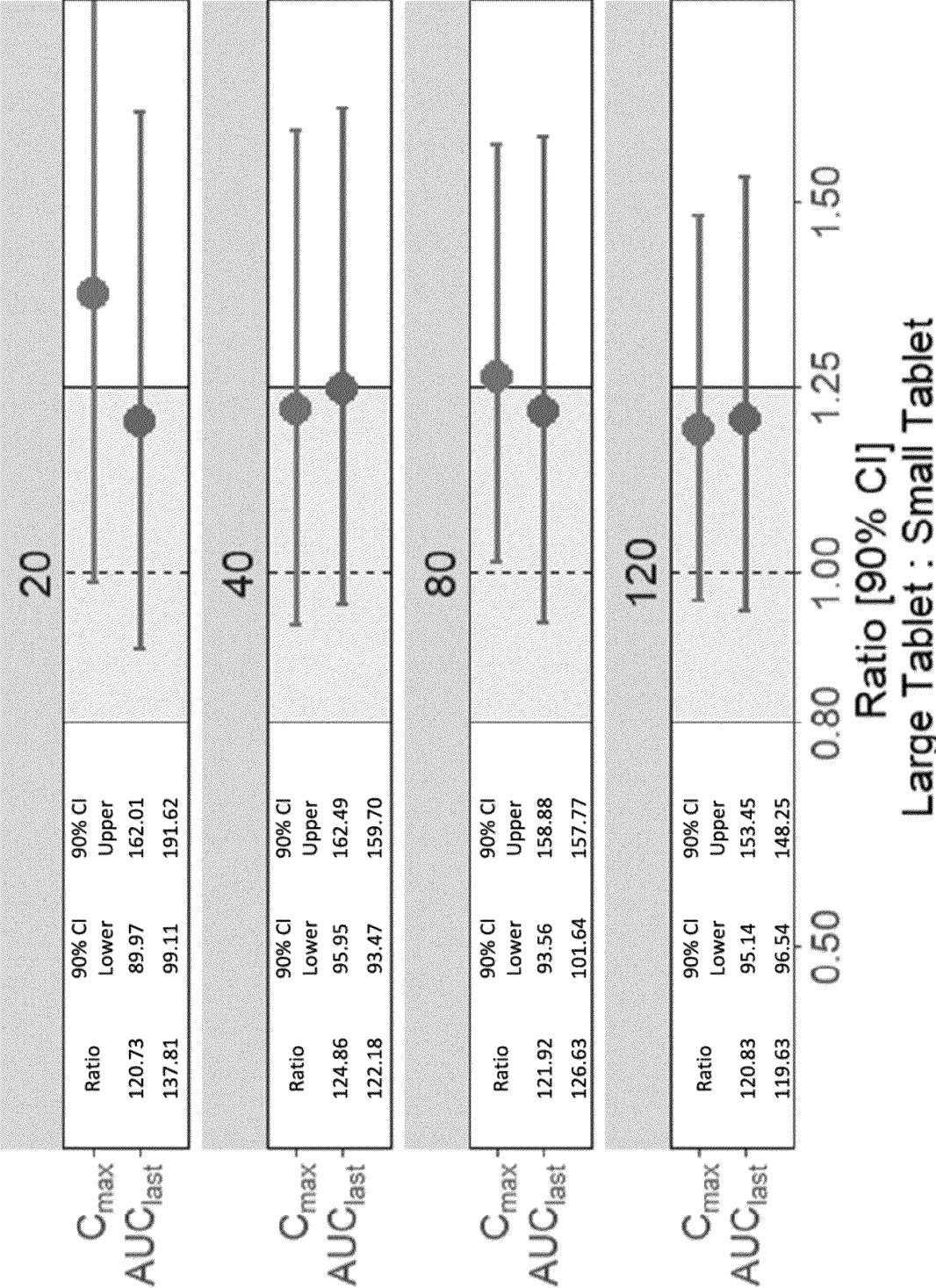


FIG. 9B

Dose	Dependent	Units	RefGeoLSM	TestGeoLSM	Ratio_%Ref_	CI_90_Lower	CI_90_Upper
20.00	Ln(AUClast)	h*ng/mL	912.14	1101.22	120.73	89.97	162.01
	Ln(Cmax)	ng/mL	69.41	95.66	137.81	99.11	191.62
40.00	Ln(AUClast)	h*ng/mL	1662.75	2076.16	124.86	95.95	162.49
	Ln(Cmax)	ng/mL	136.26	166.48	122.18	93.47	159.70
80.00	Ln(AUClast)	h*ng/mL	3432.11	4184.42	121.92	93.56	158.88
	Ln(Cmax)	ng/mL	274.26	347.31	126.63	101.64	157.77
120.00	Ln(AUClast)	h*ng/mL	4666.13	5637.90	120.83	95.14	153.45
	Ln(Cmax)	ng/mL	393.62	470.89	119.63	96.54	148.25

Ref: small; Test: large

Bioequivalence Criteria: 90% CI within 80-125%

FIG. 9C

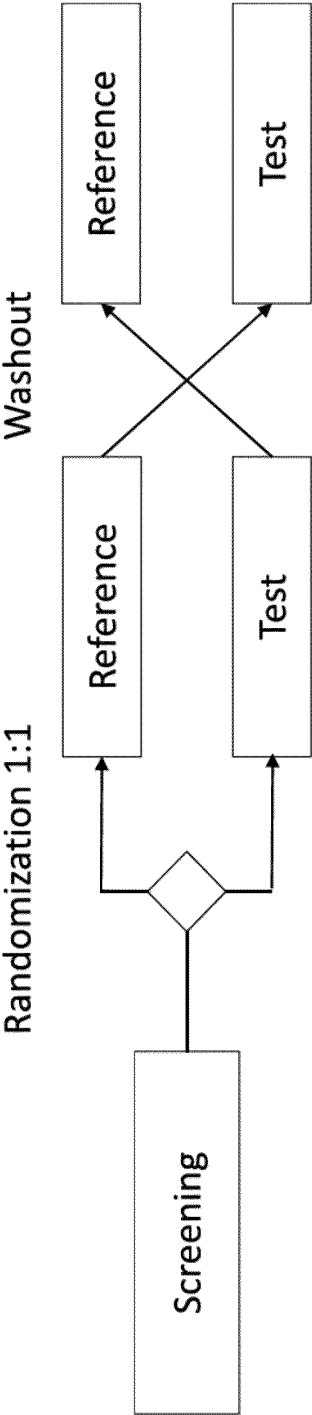


FIG. 10A