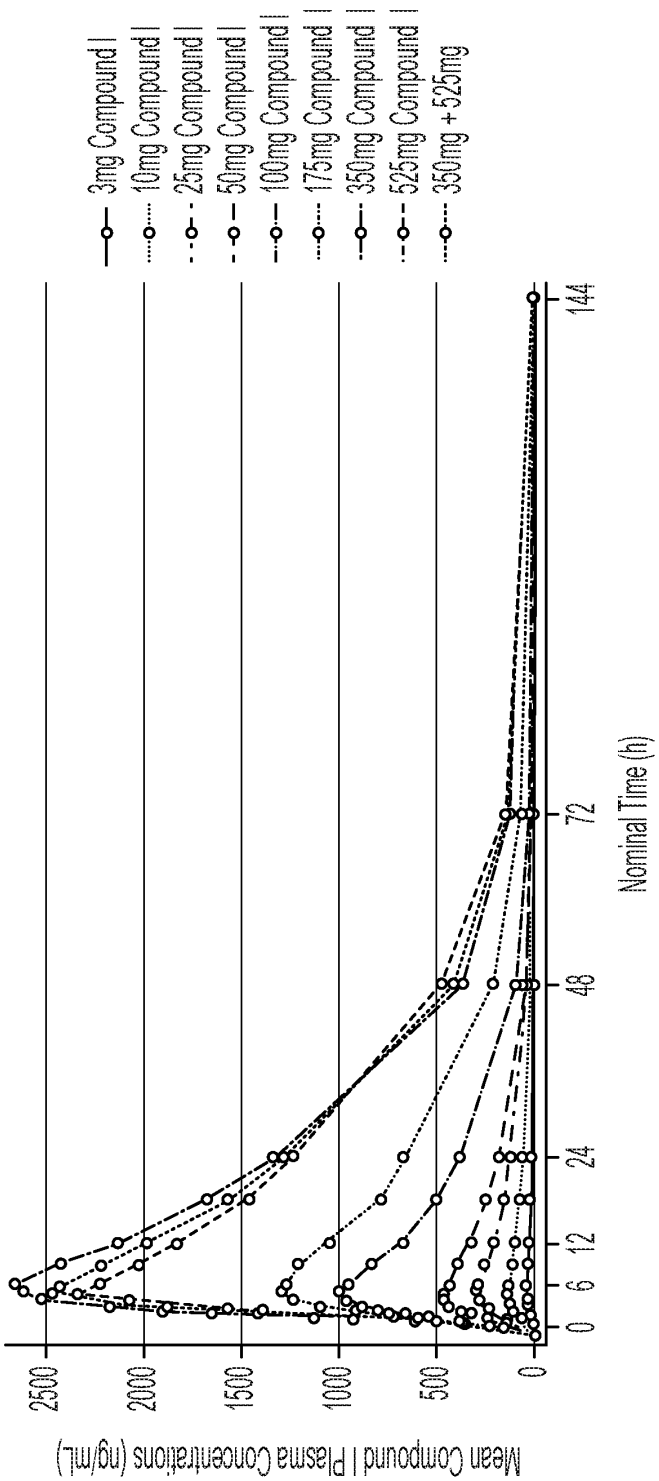

3mg Compound I
10mg Compound I
25mg Compound I
50mg Compound I
100mg Compound I
175mg Compound I
350mg Compound I
525mg Compound I
350mg +525mg
Mean Compound I Plasma Concentrations (ng/mL)
2500
2000
1500
1000
500
0
0
6
12
24
48
72
144
Nominal Time (h)

FIG. 1

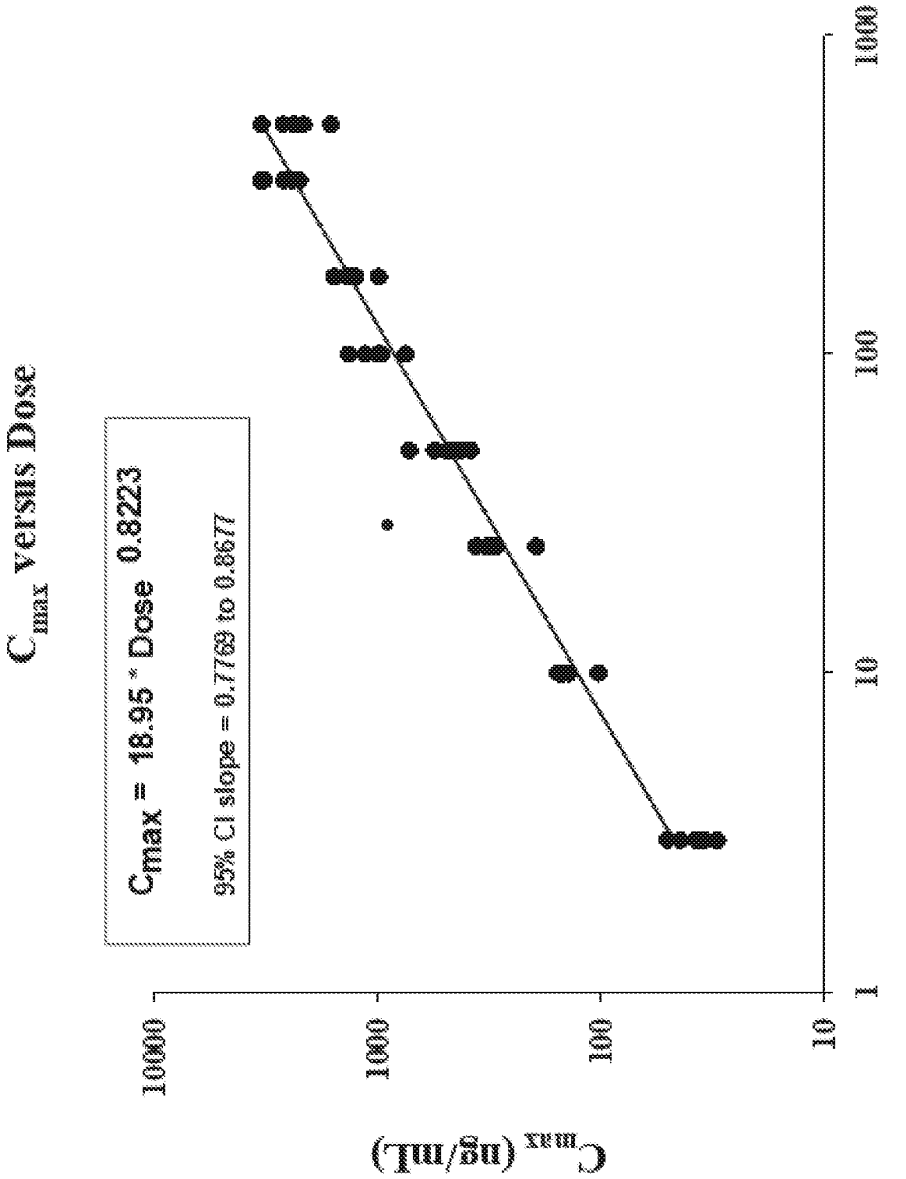

C_{max} versus Dose
C_{max} = 18.95 * Dose $^{0.8223}$
95% CI slope = 0.7769 to 0.8677
C_{max} (ng/mL)
10000
1000
100
10
1
10
100
1000
Dose (mg)

FIG. 2

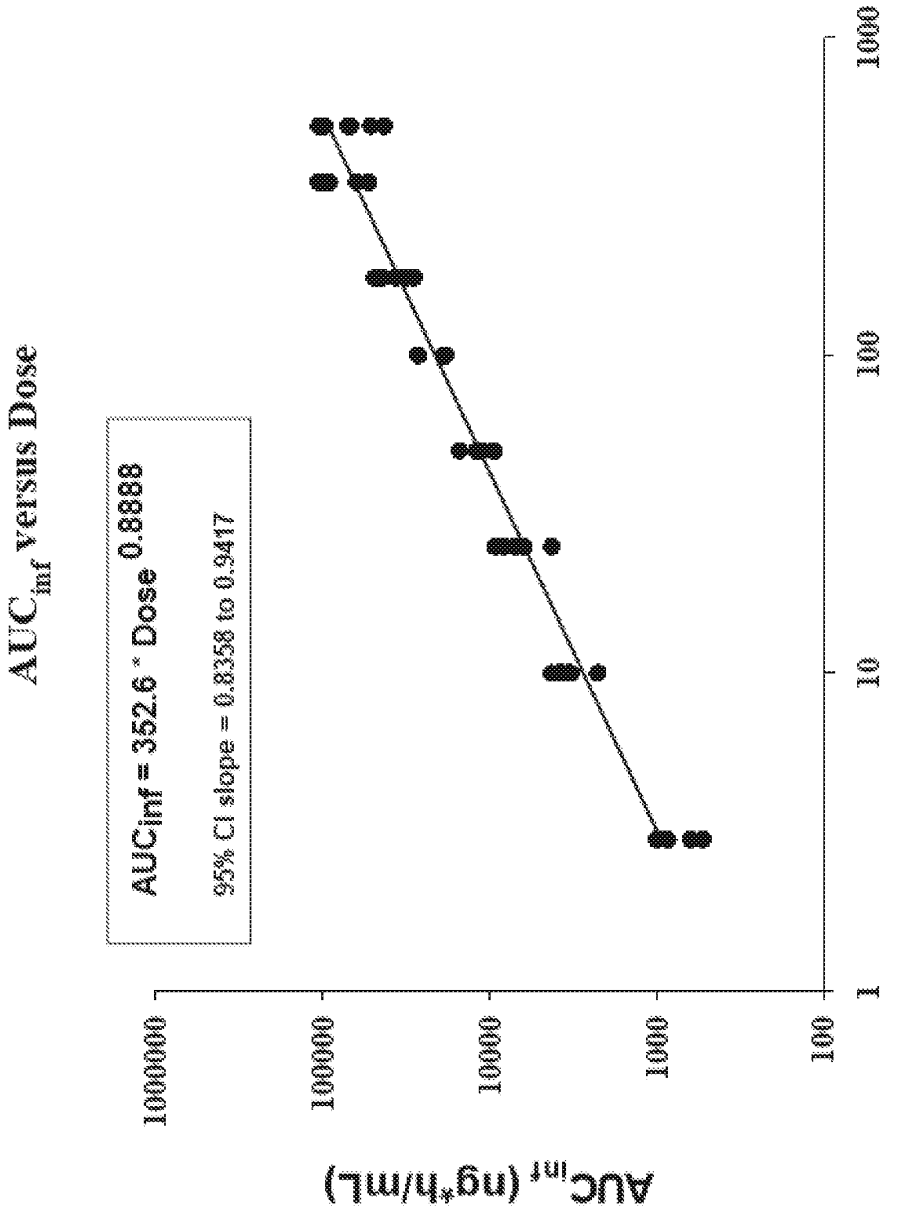

AUCinf versus Dose
AUCinf = 352.6 * Dose 0.8888
95% CI slope = 0.8358 to 0.9417
AUCinf (ng*h/mL)
1000000
100000
10000
1000
100
Dose (mg)
1
10
100
1000

FIG. 3

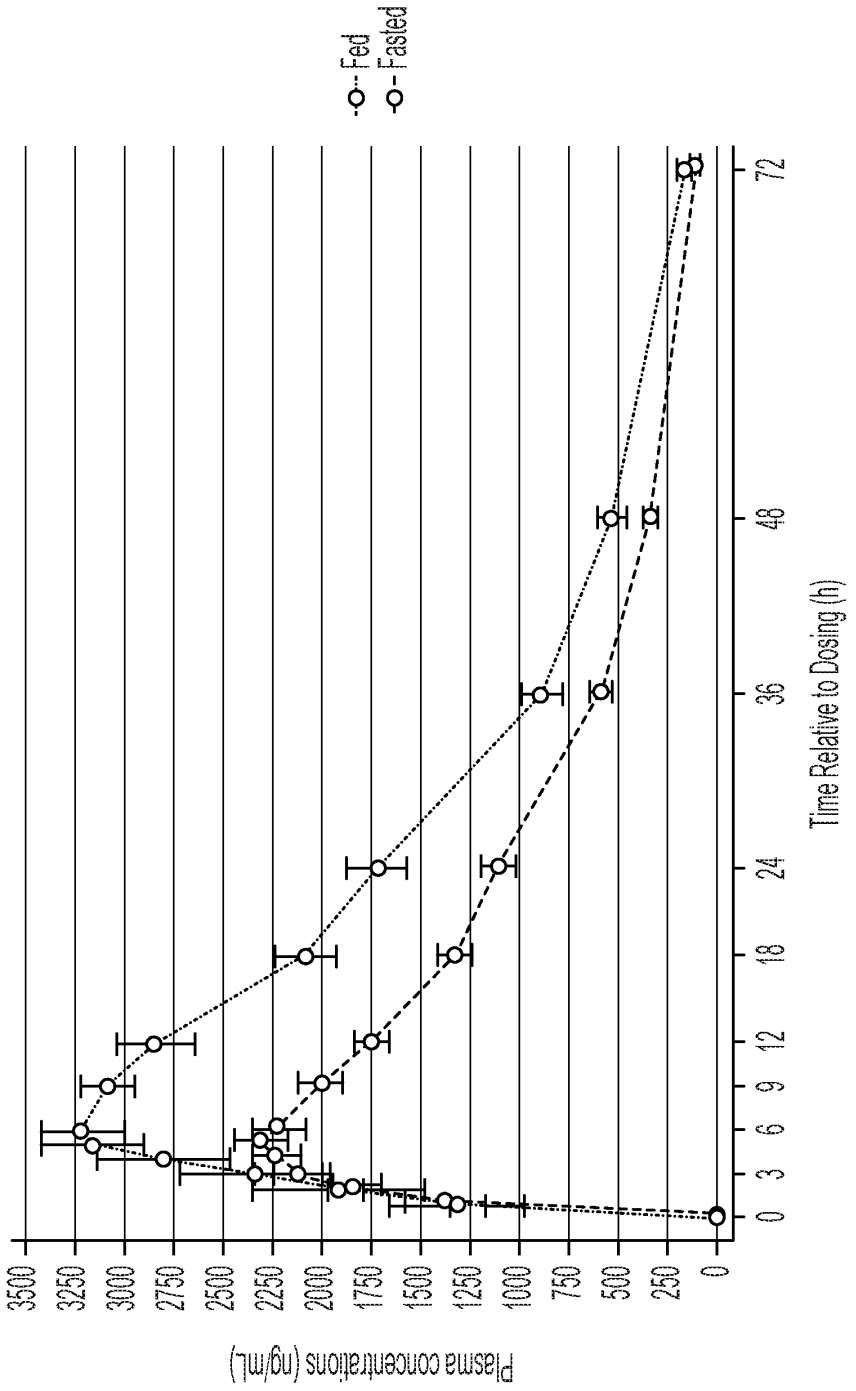

Fed
Fasted
Plasma concentrations (ng/mL)
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
0
3
6
9
12
18
24
36
48
72
Time Relative to Dosing (h)

FIG. 4

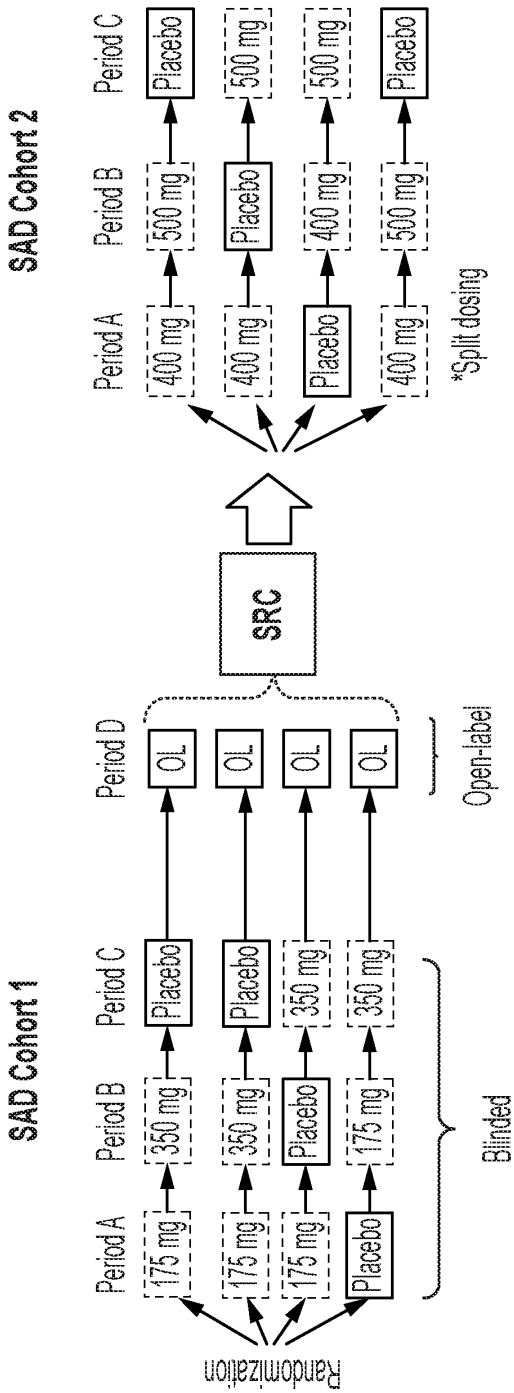

SAD Cohort 1
Period A
Period B
Period C
Period D
175 mg
350 mg
Placebo
OL
Blinded
Open-label
Randomization
SRC
SAD Cohort 2
400 mg
500 mg
*Split dosing

FIG. 5A

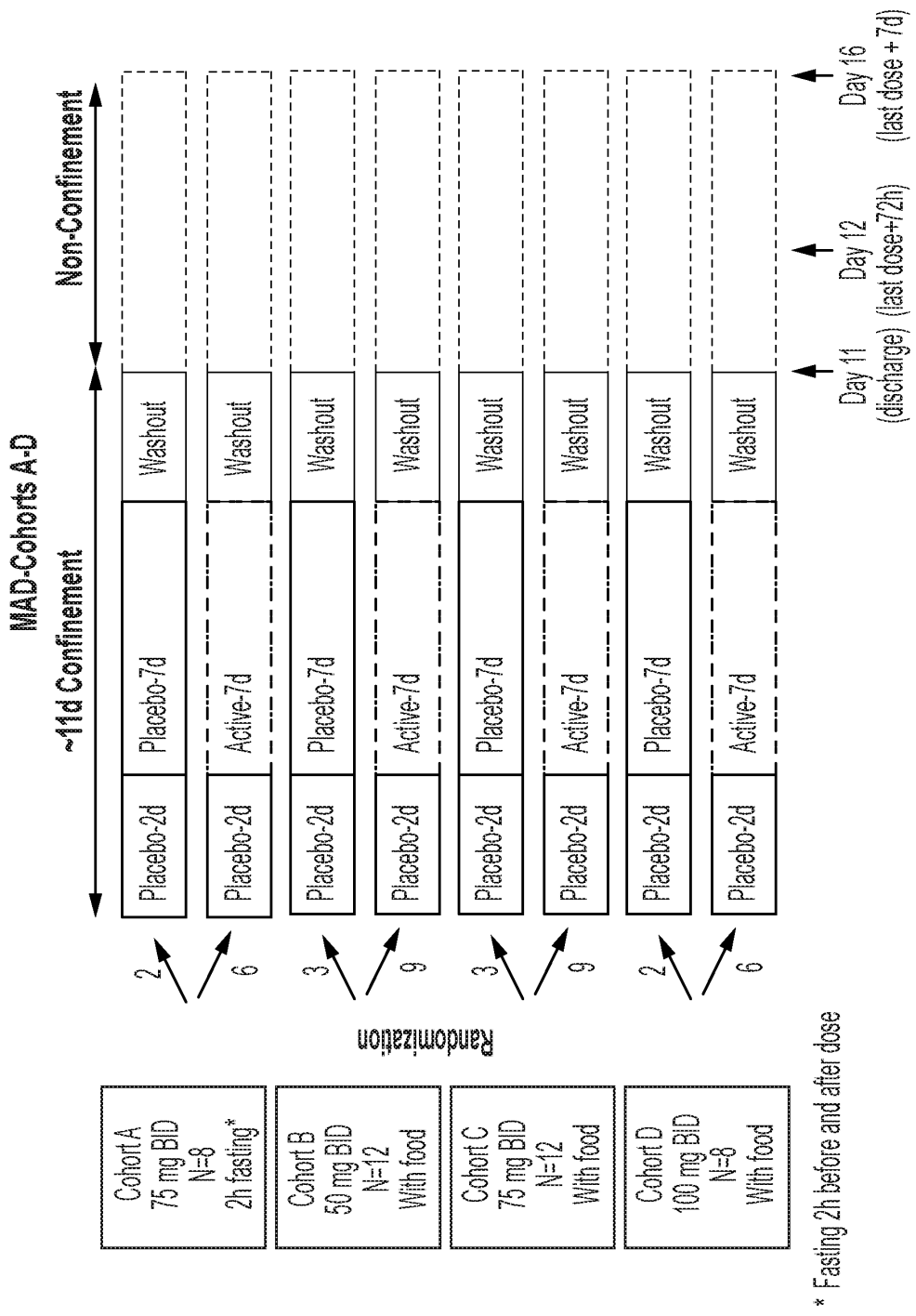

MAD-Cohorts A-D
~11d Confinement
Non-Confinement
Placebo-2d
Placebo-7d
Active-7d
Washout
Randomization
2
6
3
9
3
9
2
6
Day 11 (discharge)
Day 12 (last dose+72h)
Day 16 (last dose + 7d)
Cohort A 75 mg BID N=8 2h fasting*
Cohort B 50 mg BID N=12 With food
Cohort C 75 mg BID N=12 With food
Cohort D 100 mg BID N=8 With food
* Fasting 2h before and after dose

FIG. 5B

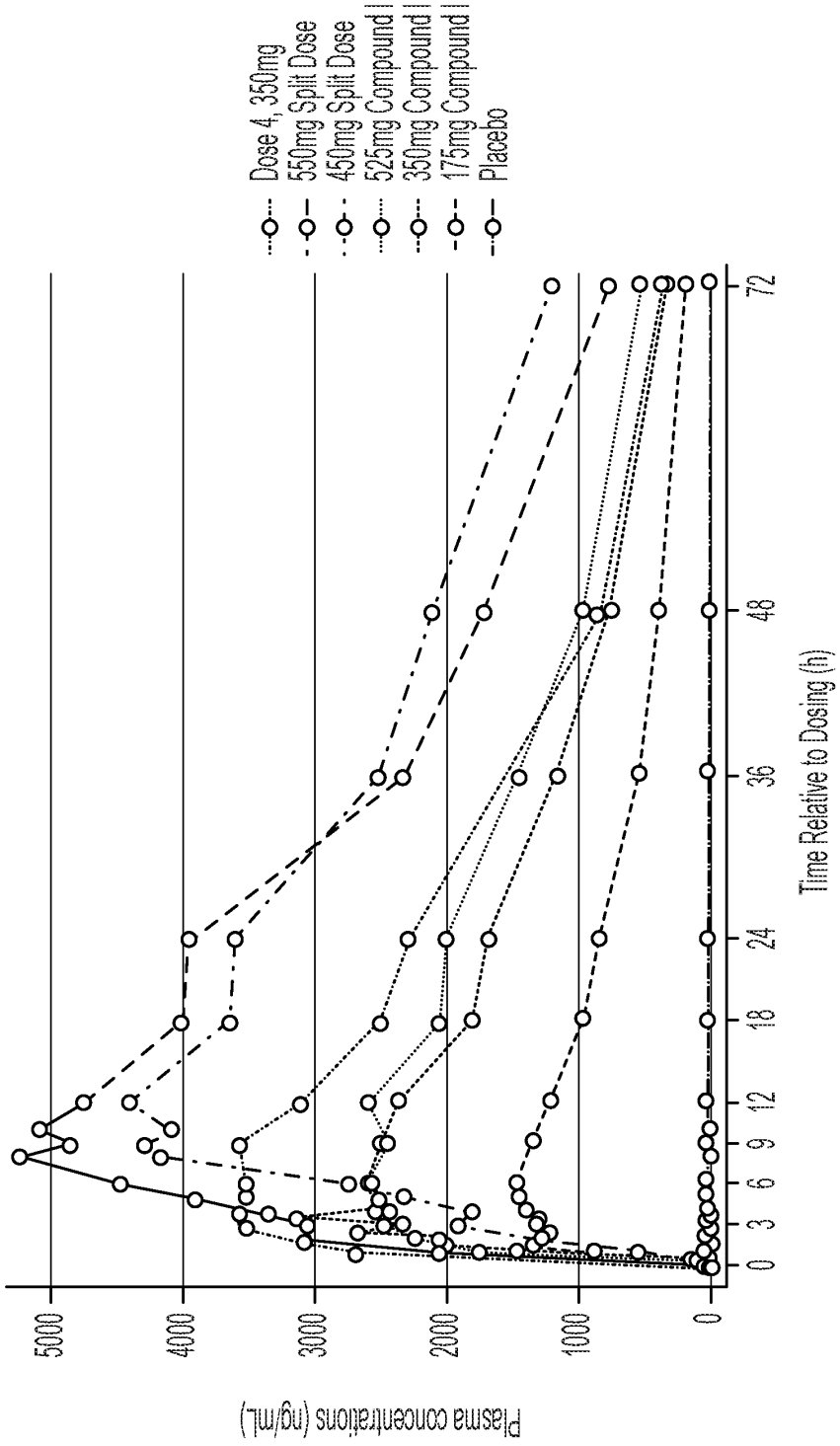

Dose 4, 350mg
550mg Split Dose
450mg Split Dose
525mg Compound I
350mg Compound I
175mg Compound I
Placebo
Plasma concentrations (ng/mL)
5000
4000
3000
2000
1000
0
0 3 6 9 12 18 24 36 48 72
Time Relative to Dosing (h)

FIG. 6

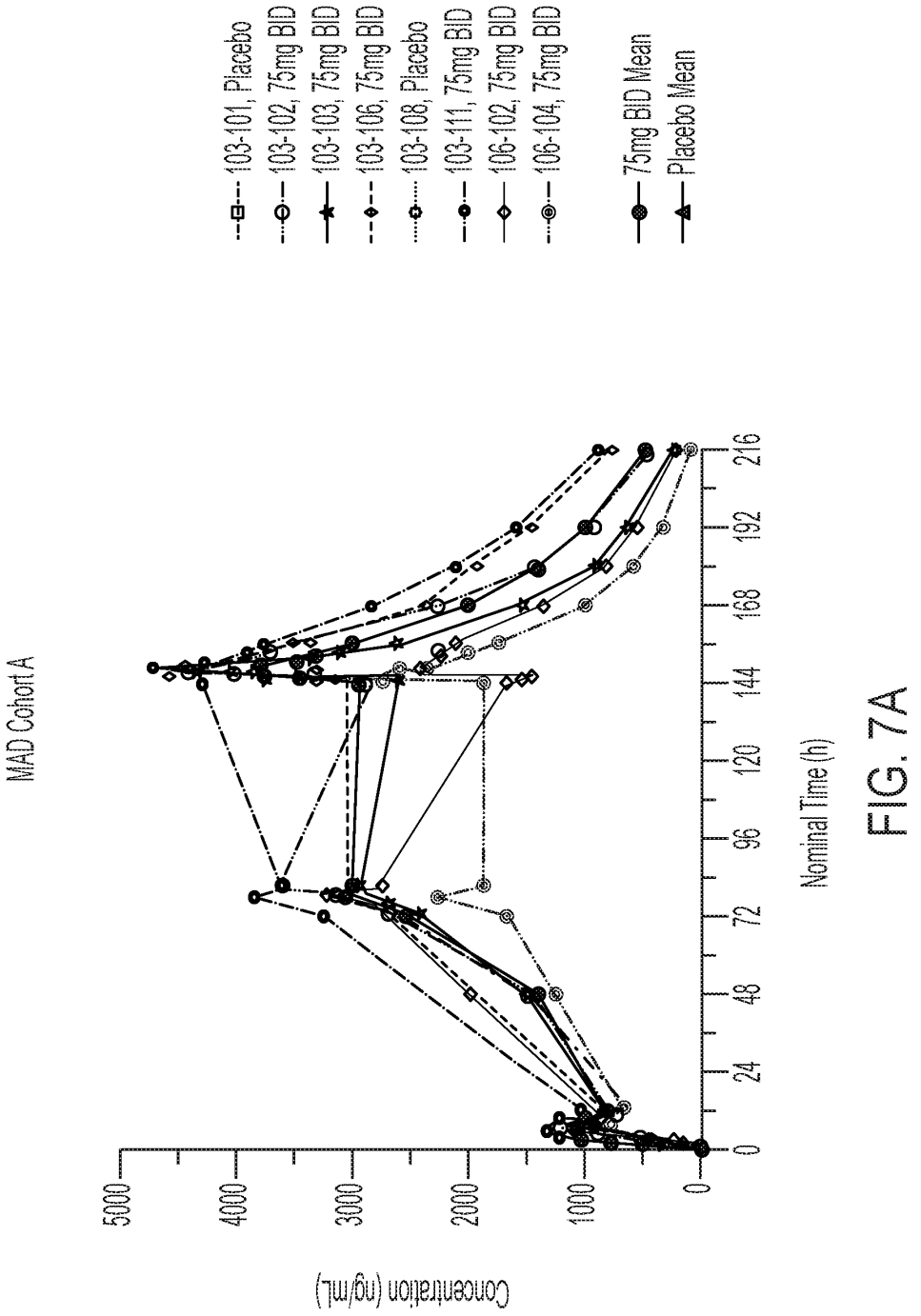

103-101, Placebo
103-102, 75mg BID
103-103, 75mg BID
103-106, 75mg BID
103-108, Placebo
103-111, 75mg BID
106-102, 75mg BID
106-104, 75mg BID
75mg BID Mean
Placebo Mean
MAD Cohort A
Concentration (ng/mL)
5000
4000
3000
2000
1000
0
0
24
48
72
96
120
144
168
192
216
Nominal Time (h)

FIG. 7A

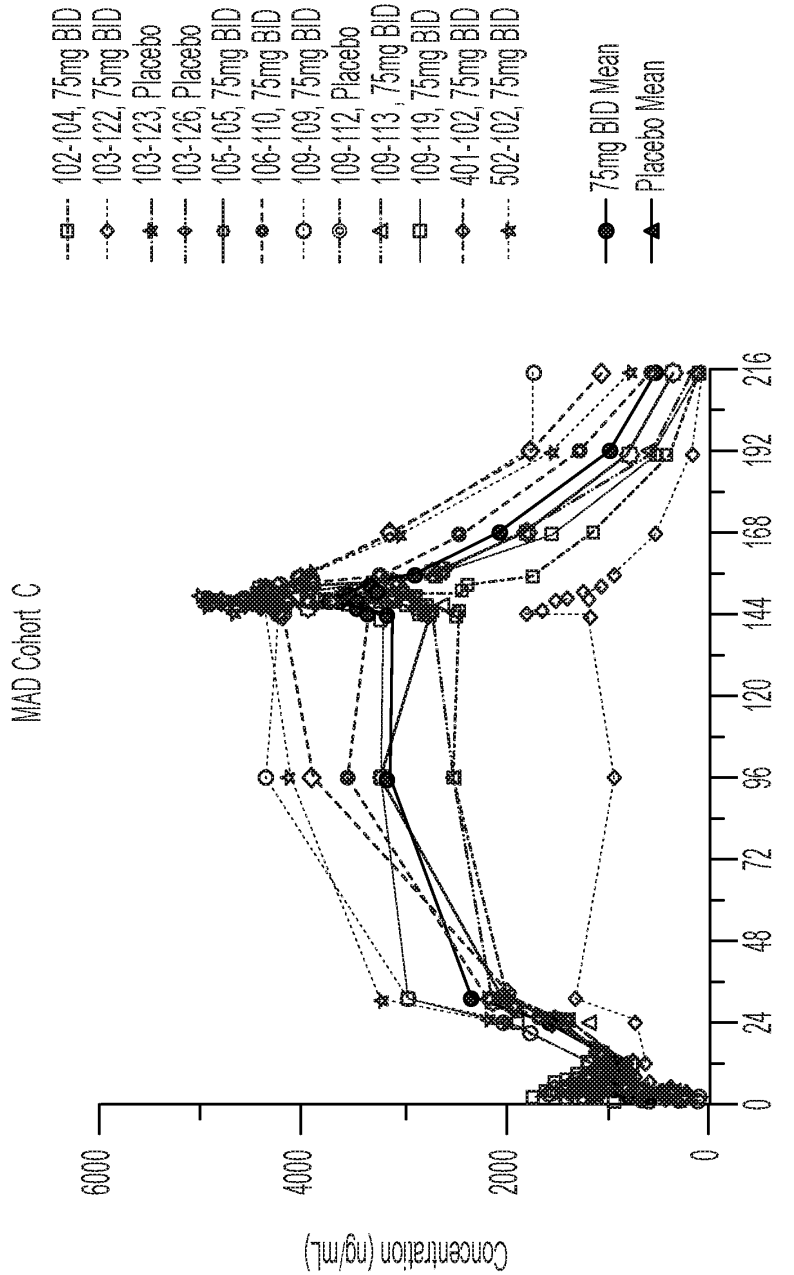

102-104, 75mg BID
103-122, 75mg BID
103-123, Placebo
103-126, Placebo
105-105, 75mg BID
106-110, 75mg BID
109-109, 75mg BID
109-112, Placebo
109-113 , 75mg BID
109-119, 75mg BID
401-102, 75mg BID
502-102, 75mg BID
75mg BID Mean
Placebo Mean
MAD Cohort C
Concentration (ng/mL)
6000
4000
2000
0
0
24
48
72
96
120
144
168
192
216
Nominal Time (h)

FIG. 7B

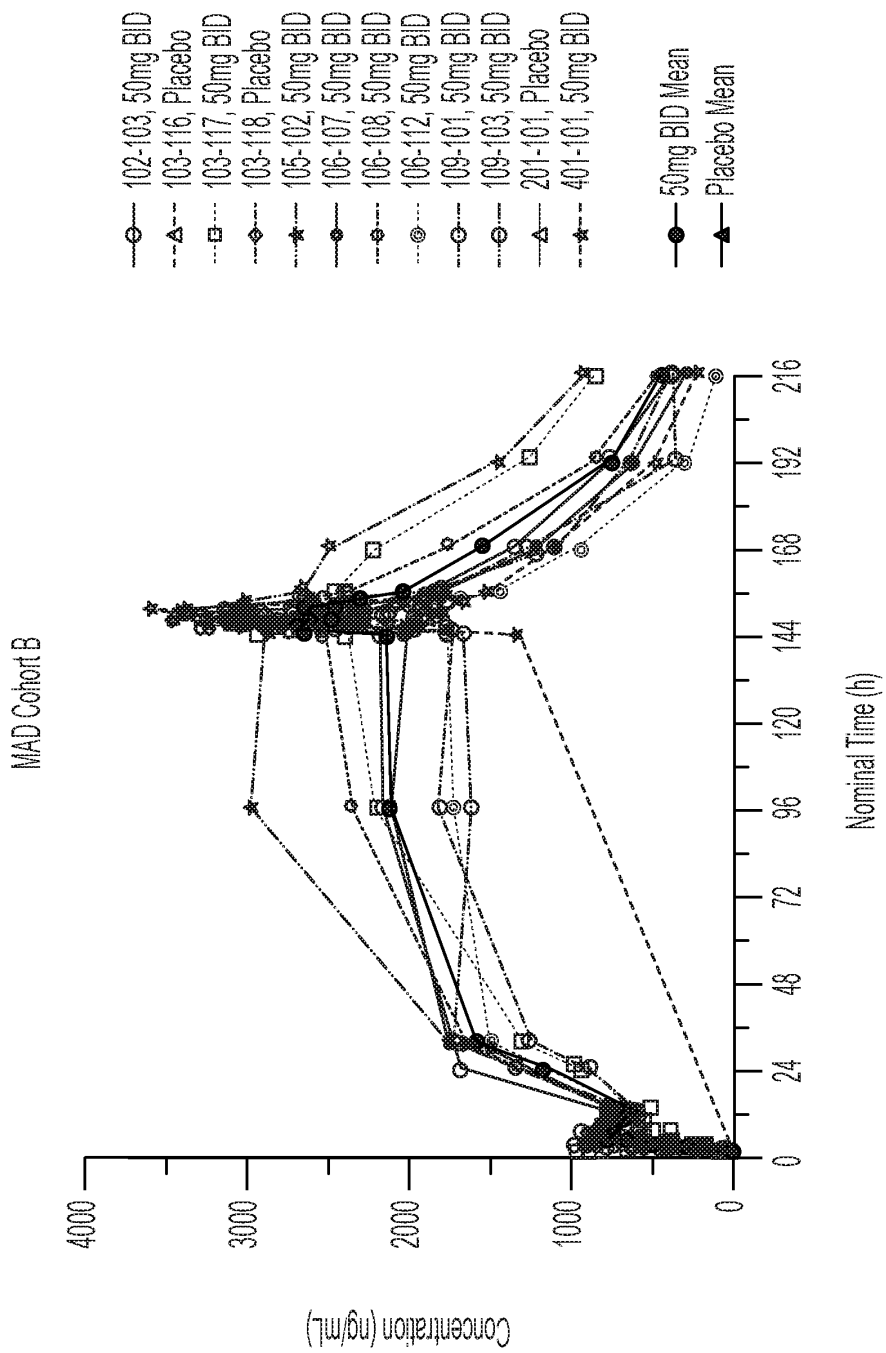

102-103, 50mg BID
103-116, Placebo
103-117, 50mg BID
103-118, Placebo
105-102, 50mg BID
106-107, 50mg BID
106-108, 50mg BID
106-112, 50mg BID
109-101, 50mg BID
109-103, 50mg BID
201-101, Placebo
401-101, 50mg BID
50mg BID Mean
Placebo Mean
MAD Cohort B
Concentration (ng/mL)
4000
3000
2000
1000
0
0
24
48
72
96
120
144
168
192
216
Nominal Time (h)

FIG. 8A

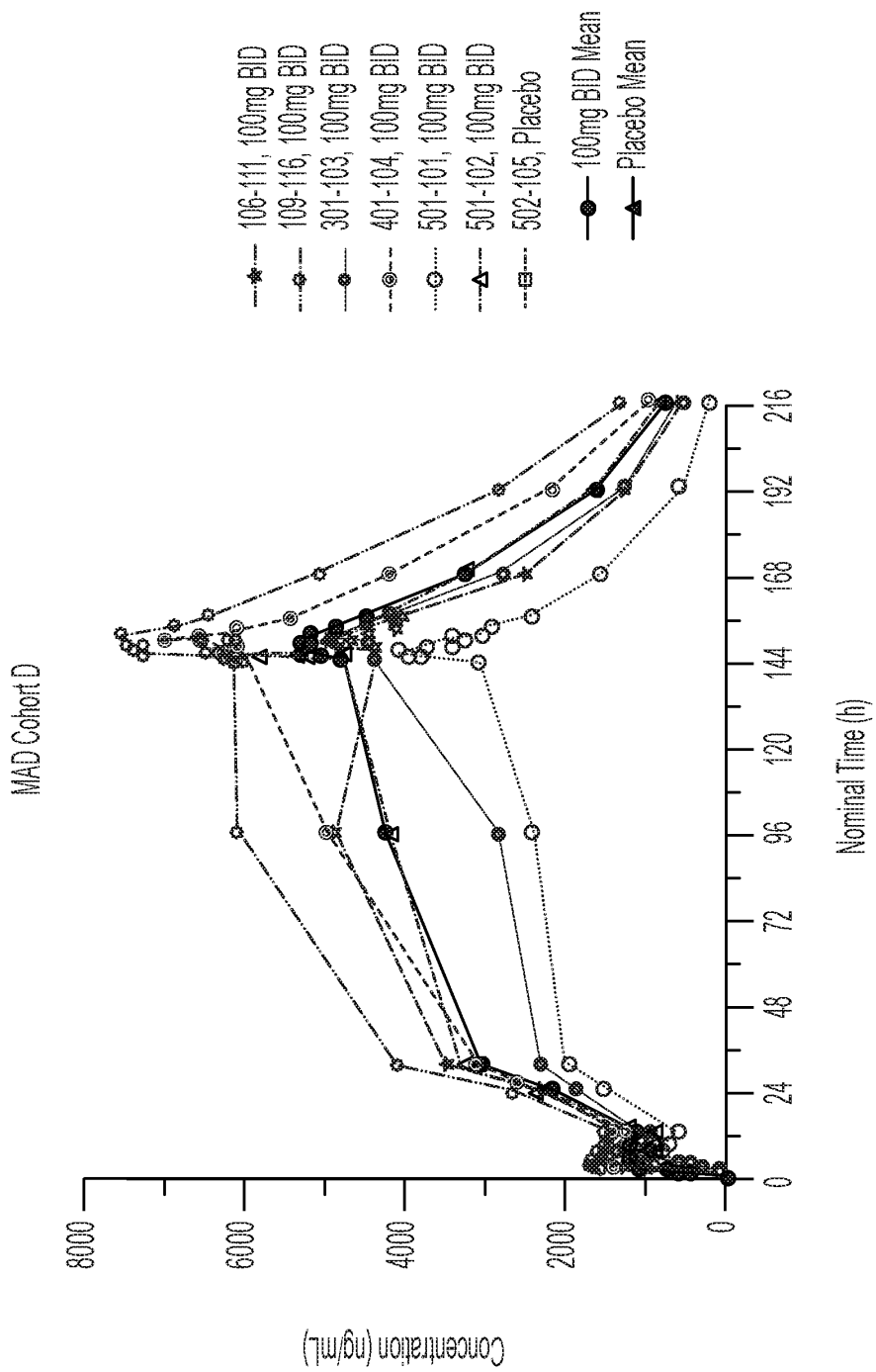

106-111, 100mg BID
109-116, 100mg BID
301-103, 100mg BID
401-104, 100mg BID
501-101, 100mg BID
501-102, 100mg BID
502-105, Placebo
100mg BID Mean
Placebo Mean
MAD Cohort D
Concentration (ng/mL)
8000
6000
4000
2000
0
0
24
48
72
96
120
144
168
192
216
Nominal Time (h)

FIG. 8B

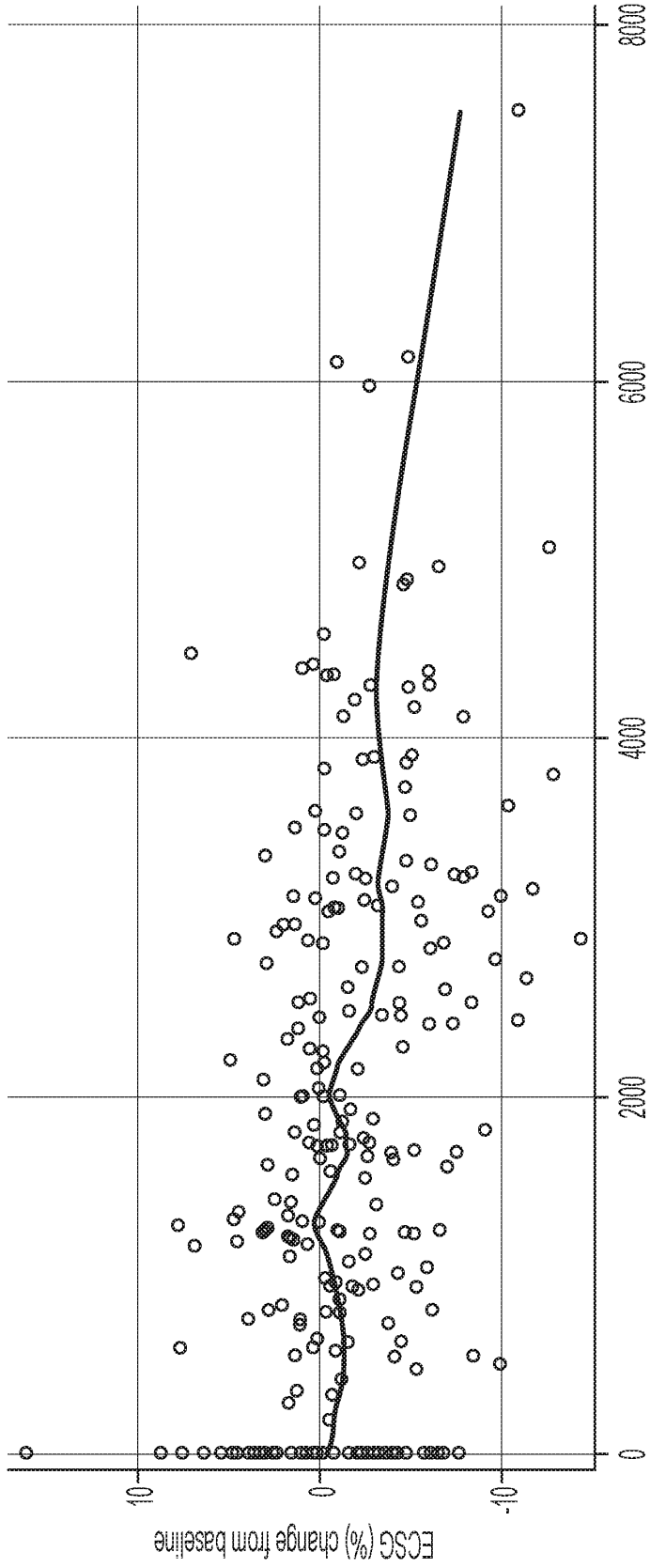

ECSG (%) change from baseline
10
0
-10
0
2000
4000
6000
8000
Plasma (ng/mL)
LOESS Fitted Line

FIG. 9A

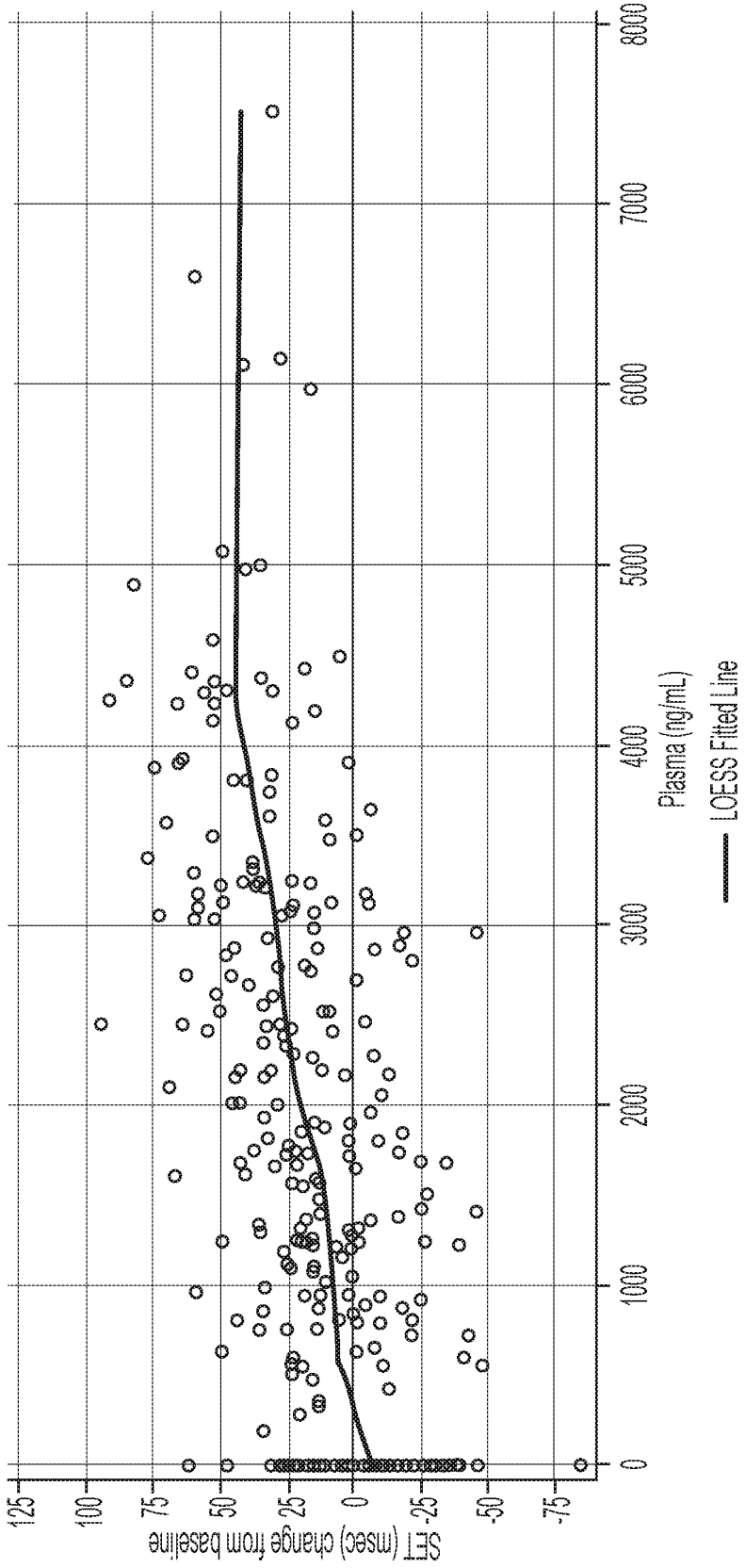

SFT (msec) change from baseline
125
100
75
50
25
0
-25
-50
-75
0
1000
2000
3000
4000
5000
6000
7000
8000
Plasma (ng/mL)
LOESS Fitted Line

FIG. 9B

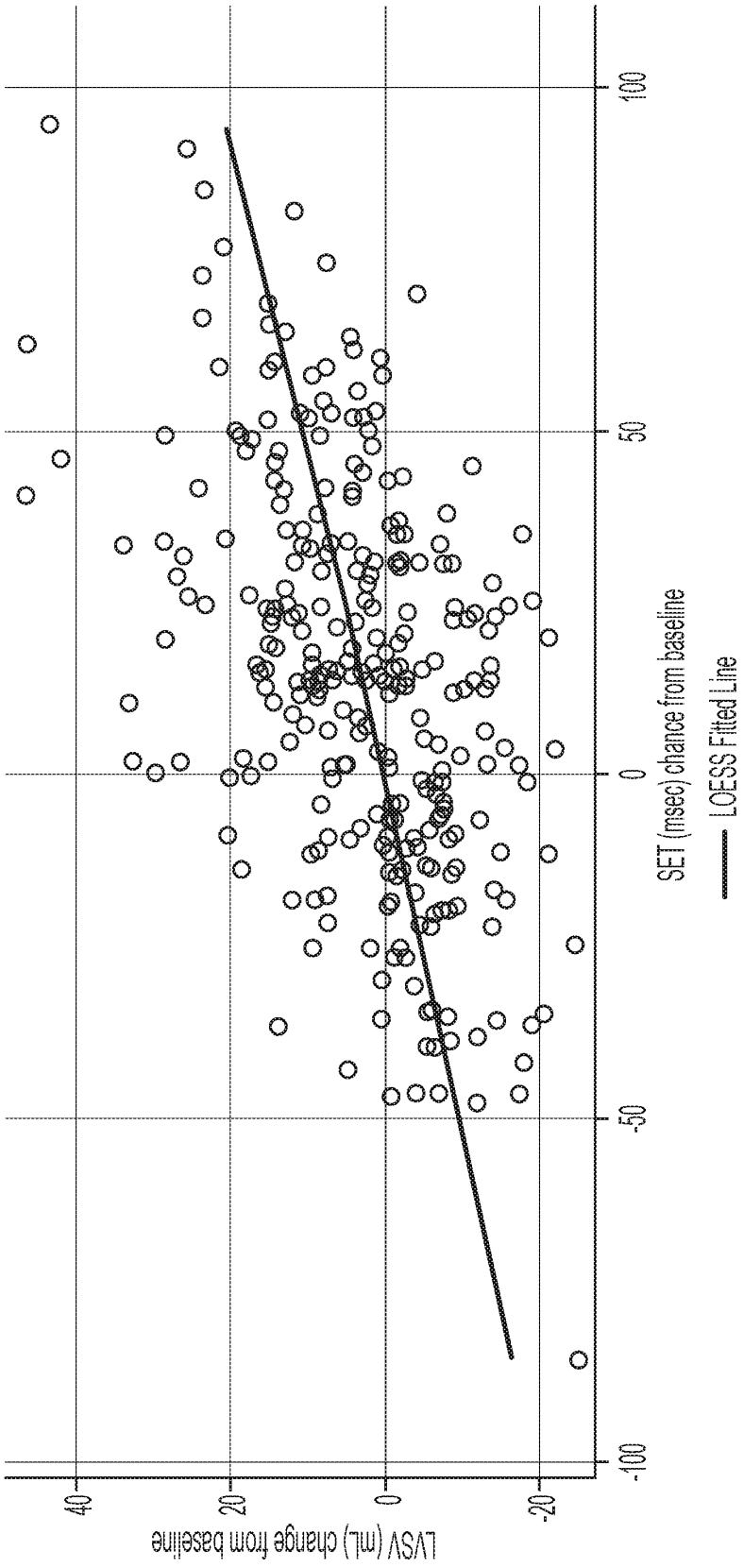

LVSV (mL) change from baseline
40
20
0
-20
SET (msec) change from baseline
100
50
0
-50
-100
LOESS Fitted Line

FIG. 9C

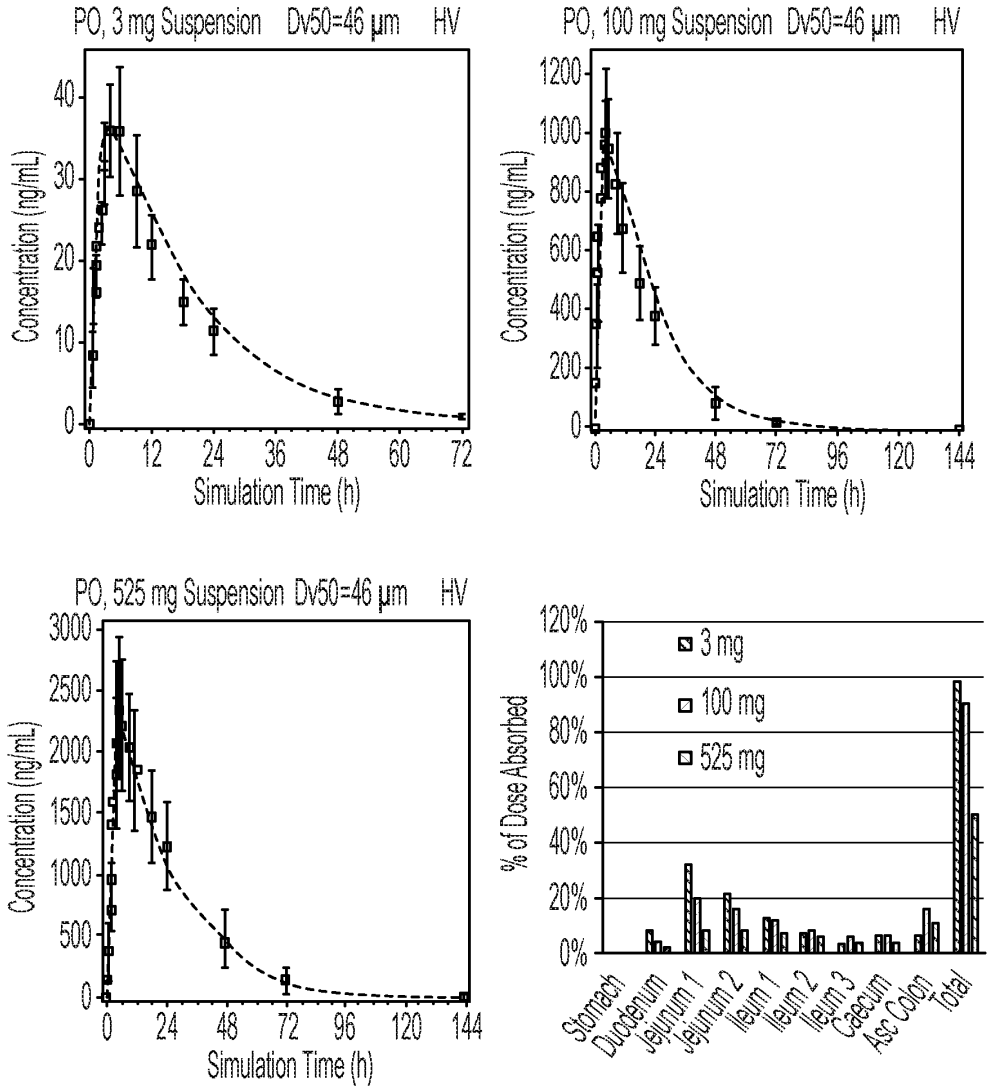

PO, 3 mg Suspension Dv50=46 µm HV
Concentration (ng/mL)
Simulation Time (h)
PO, 100 mg Suspension Dv50=46 µm HV
Concentration (ng/mL)
Simulation Time (h)
PO, 525 mg Suspension Dv50=46 µm HV
Concentration (ng/mL)
Simulation Time (h)
% of Dose Absorbed
3 mg
100 mg
525 mg
Stomach
Duodenum
Jejunum 1
Jejunum 2
Ileum 1
Ileum 2
Ileum 3
Caecum
Asc Colon
Total

FIG. 10

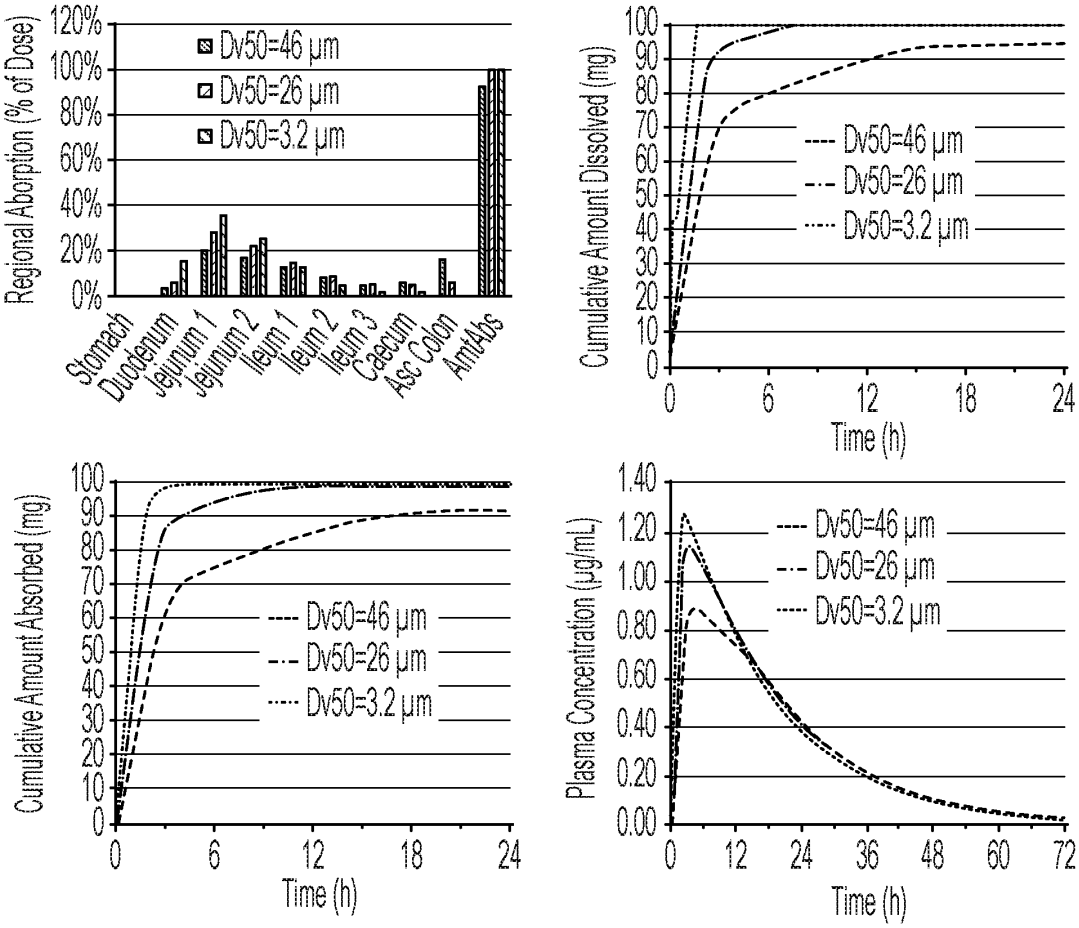

Regional Absorption (% of Dose)
120%
100%
80%
60%
40%
20%
0%
Dv50=46 µm
Dv50=26 µm
Dv50=3.2 µm
Stomach
Duodenum
Jejunum 1
Jejunum 2
Ileum 1
Ileum 2
Ileum 3
Caecum
Asc Colon
AmtAbs
Cumulative Amount Dissolved (mg)
Time (h)
Cumulative Amount Absorbed (mg)
Time (h)
Plasma Concentration (µg/mL)
Time (h)

FIG. 11

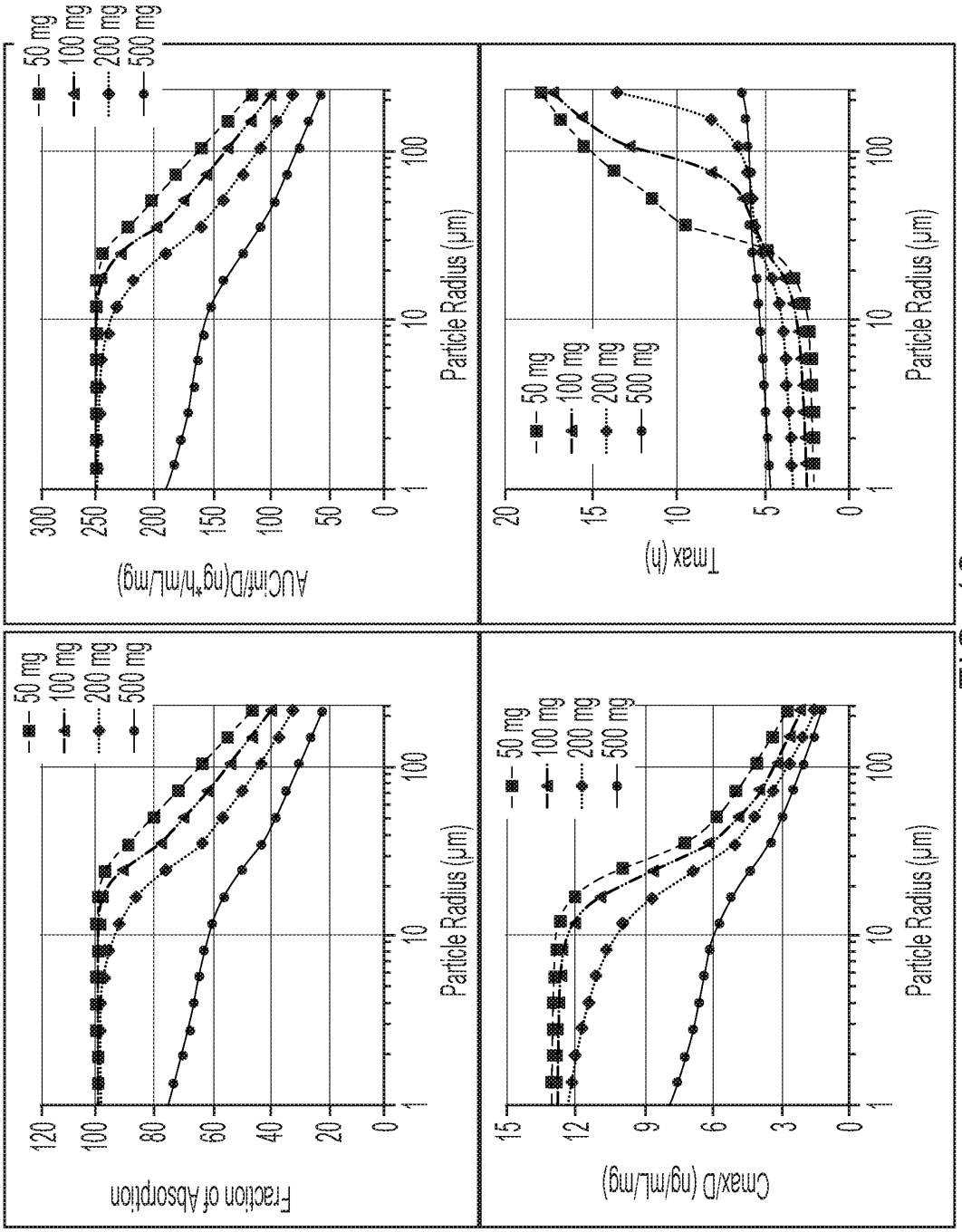

AUCinf/D(ng*h/mL/mg)
Tmax (h)
Fraction of Absorption
Cmax/D (ng/mL/mg)
Particle Radius (µm)
50 mg
100 mg
200 mg
500 mg

FIG. 12

Predicted and Observed Systemic Exposure Parameters Following Administration of Compound I to Dogs

Study	Particle Size Distribution	Formulation	Species	Dose Route	Dose	F (%)	Dose Normalized Exposure		
	Dv10/Dv50/Dv90						C_{max}/D	AUC_{last}/D	AUC_{inf}/D
1	NA	Solution	Beagle dog	IV Bolus	0.25 mg/kg	NA	NA	10.5	10.6
Predicted						NA	NA	10.4	10.5
Prediction error (%)								0.335	0.611
2	NA	Suspension	Beagle dog	PO	0.5 mg/kg	108	564	11.1	11.5
Predicted						100	497	10.9	11.4
Prediction error (%)						-7.85	-11.9	-1.50	-1.30
3	8.1/26/50	Suspension	Beagle dog	PO	25 mg	108	600	11.4	11.5
Predicted						96.3	493	9.78	9.93
Prediction error (%)						-11.2	-17.8	-14.2	-13.6
4	1.9/3.2/5.6	Suspension	Beagle dog	PO	1 mg/kg	107	582	10.8	11.3
Predicted						100	572	11.1	11.4
Prediction error (%)						-6.19	-1.72	2.78	0.442
5	1.9/3.2/5.6	Suspension	Beagle dog	PO	10 mg/kg	129	595	12.1	13.7
Predicted						95.3	524	10.6	10.8
Prediction error (%)						-26.3	-12.0	-12.4	-21.2
6	19/46/89	Suspension	Beagle dog	PO	0.1 mg/kg	116	588	11.9	12.3
Predicted						100	571	11.1	11.3
Prediction error (%)						-13.8	-2.91	-6.72	-7.80
7	19/46/89	Suspension	Beagle dog	PO	1 mg/kg	86.1	514	9.03	9.13
Predicted						100	447	9.80	10.0
Prediction error (%)						16.1	-13.1	8.55	9.10
8	19/46/89	Suspension	Beagle dog	PO	100 mg	39.7	164	3.75	4.21
Predicted						40.4	180	3.79	4.17
Prediction error (%)						1.69	9.53	1.09	-1.03

Abbreviations: AUCinf/D (ng*h/mL/mg), dose normalized area under the plasma drug concentration-time curve from time zero to time infinity; AUClast/D, dose normalized AUC from time 0 to the last time point with a measurable concentration or simulation length; Cmax/D (ng/mL/mg), dose normalized maximum plasma concentration; F, bioavailability; IV, intravenous; PO, per oral; Dv10/Dv50/Dv90, the maximum particle diameter(μm) below which 10%/50%/90% of the sample volume exists; NA, not available or not applicable.

FIG. 13

Predicted and Observed Systemic Exposure Parameters Following Administration of Compound I to Healthy Volunteers

	Particle Size Distribution	Formulation	Dose Route	Dose	F (%)	Dose Normalized Exposure		
	Dv10/Dv50/Dv90					C_{max}/D	AUC_{last}/D	AUC_{inf}/D
	19/46/89	Suspension	PO	3 mg	NA	12.0	245	257
Predicted					99.0	12.1	262	267
Prediction error (%)						-0.611	-6.94	-4.15
	19/46/89	Suspension	PO	100 mg	NA	10.00	237	237
Predicted					90.9	9.47	245	245
Prediction error (%)						5.32	-3.68	-3.63
	19/46/89	Suspension	PO	525 mg	NA	4.43	137	138
Predicted					50.7	4.42	124	124
Prediction error (%)						0.318	9.76	10.1

Abbreviations: AUCinf/D (ng*h/mL/mg), dose normalized area under the plasma drug concentration-time curve from time zero to time infinity; AUClast/D, dose normalized AUC from time 0 to the last time point with a measurable concentration or simulation length; Cmax/D (ng/mL/mg), dose normalized maximum plasma concentration; F, bioavailability; IV, intravenous; PO, per oral; Dv10/Dv50/Dv90, the maximum particle diameter(μm) below which 10%/50%/90% of the sample volume exists; NA, not available or not applicable.

FIG. 14

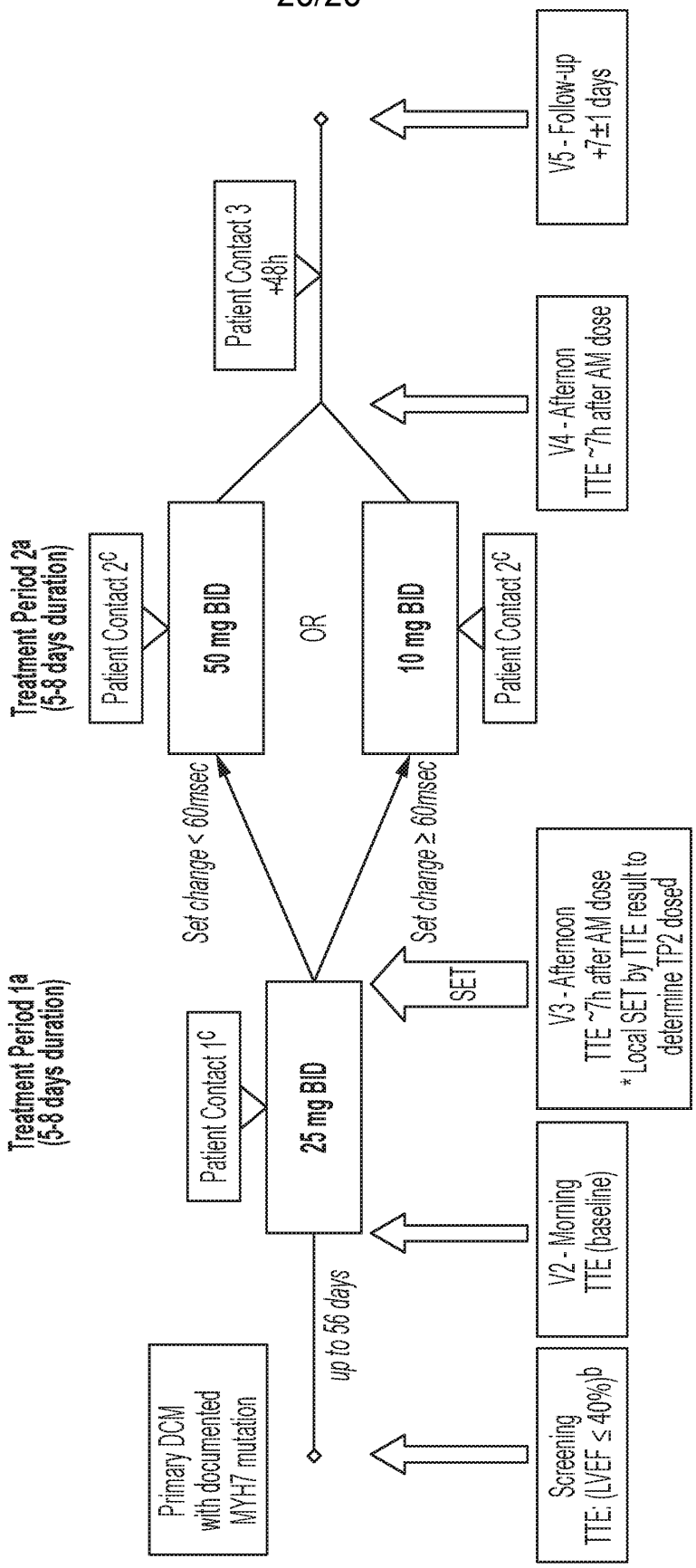

Primary DCM with documented MYH7 mutation
Screening TTE: (LVEF ≤ 40%)b
V2 - Morning TTE (baseline)
up to 56 days
Treatment Period 1a (5-8 days duration)
Patient Contact 1c
25 mg BID
SET
V3 - Afternoon TTE ~7h after AM dose * Local SET by TTE result to determine TP2 dosed
Set change < 60msec
Set change ≥ 60msec
Treatment Period 2a (5-8 days duration)
Patient Contact 2c
50 mg BID
OR
10 mg BID
Patient Contact 2c
V4 - Afternon TTE ~7h after AM dose
Patient Contact 3 +48h
V5 - Follow-up +7±1 days

FIG. 15