

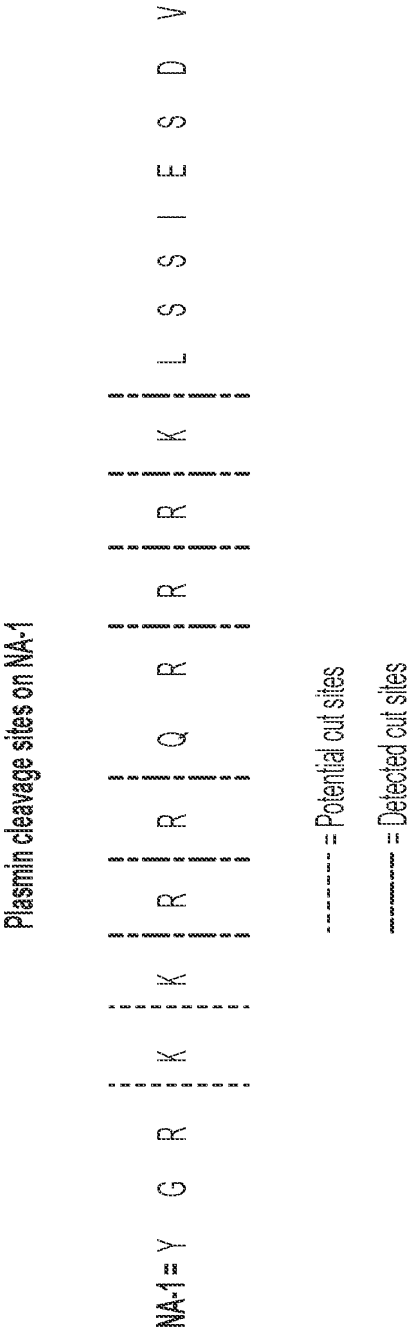


FIG. 1

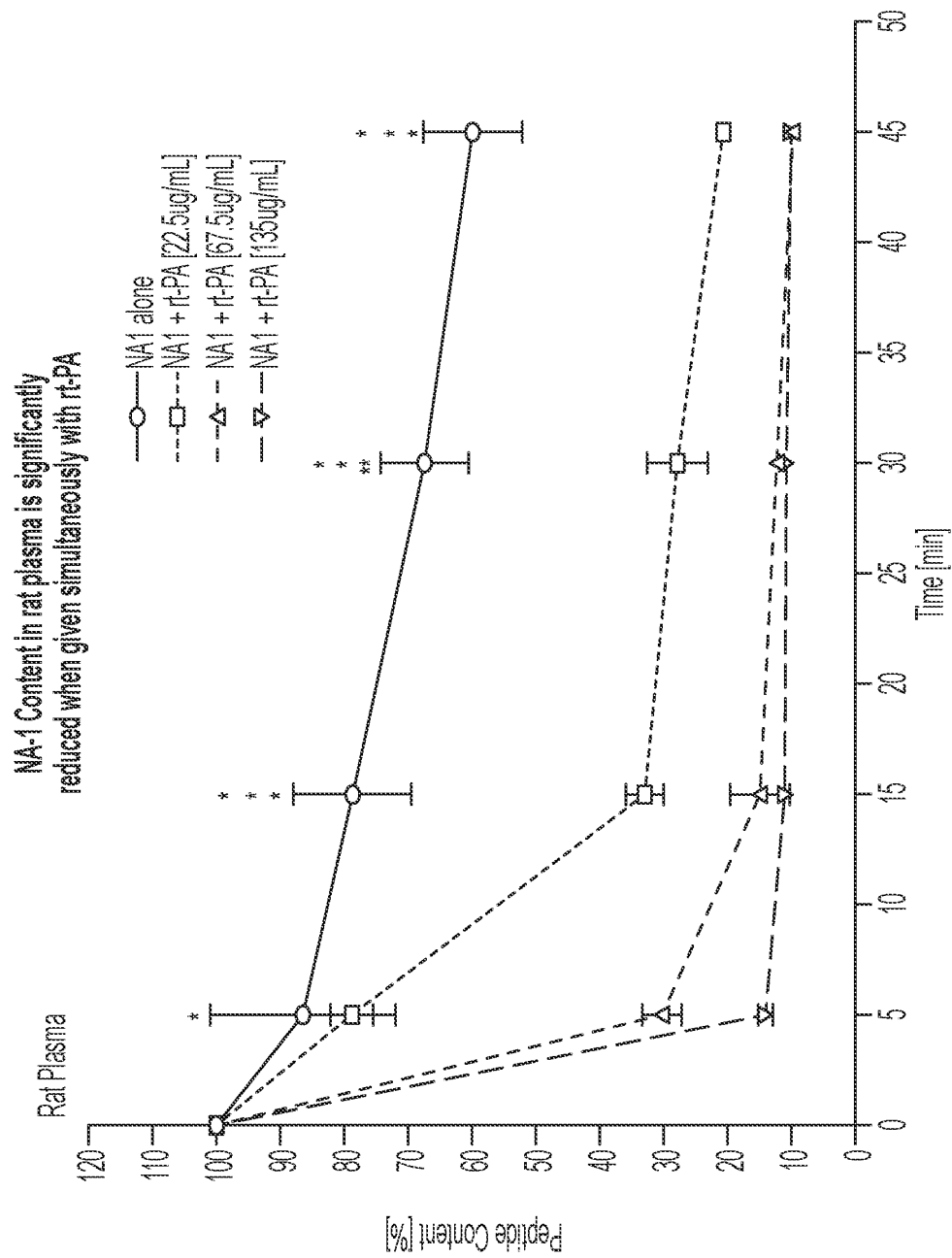


FIG. 2

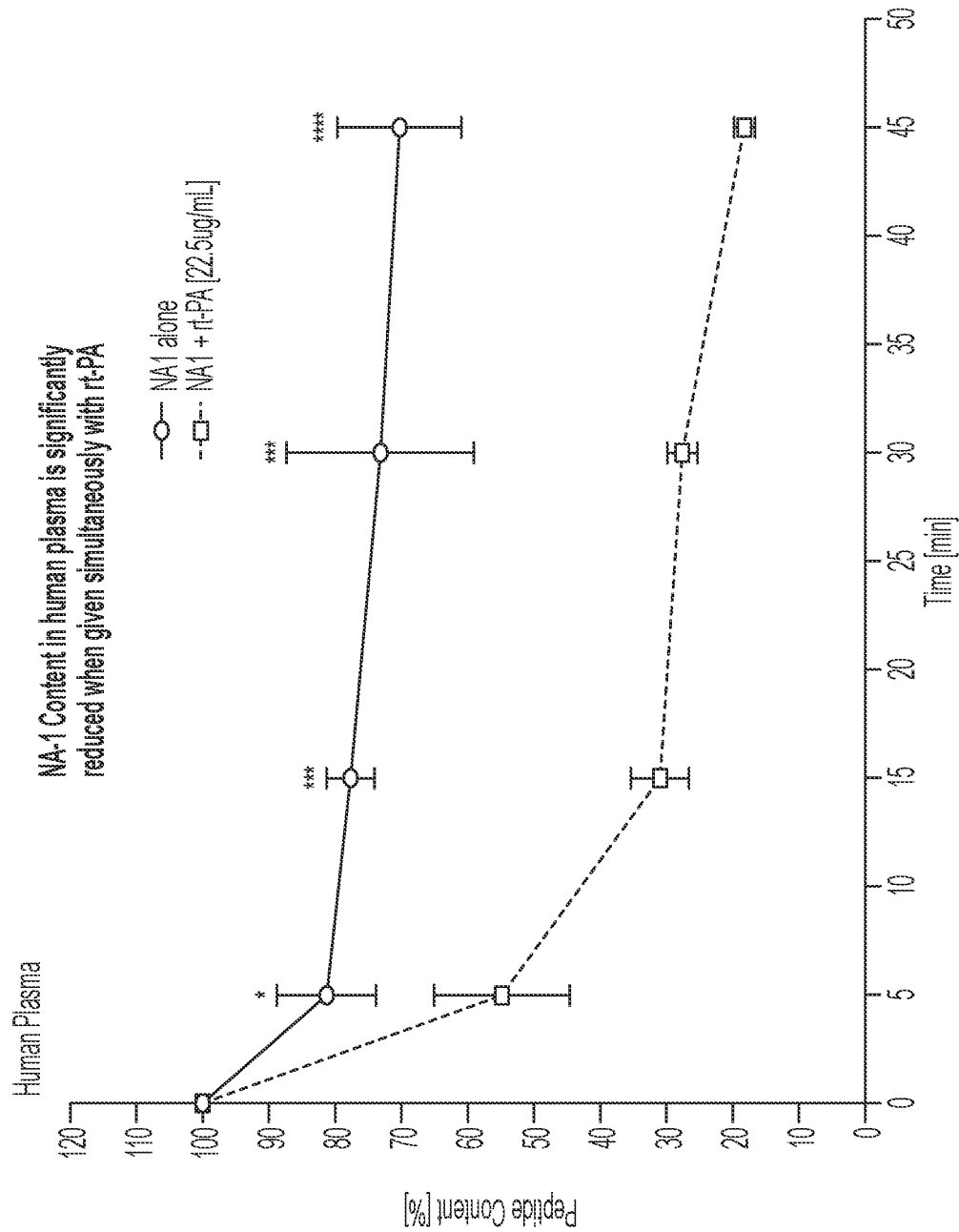


FIG. 3

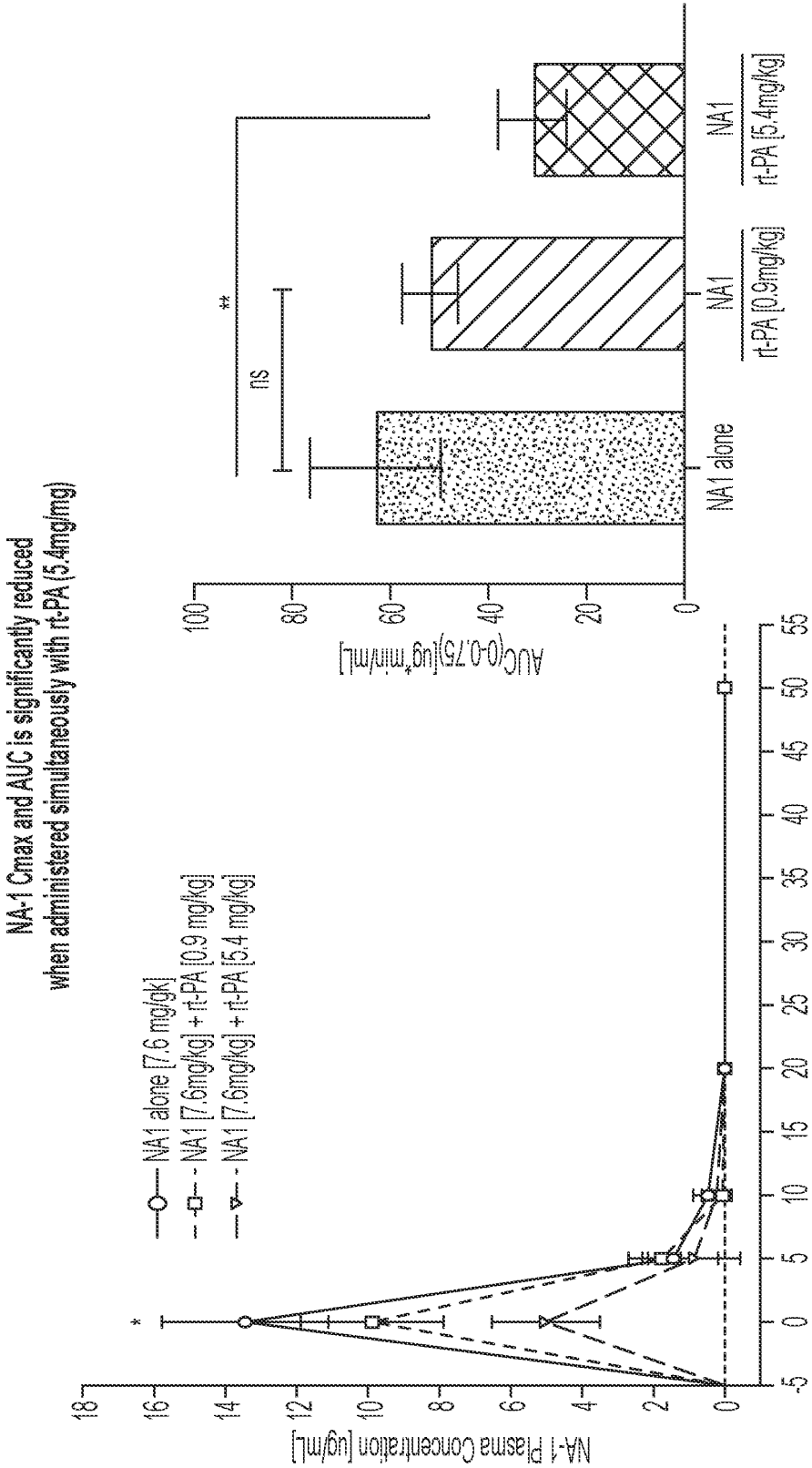


FIG. 4

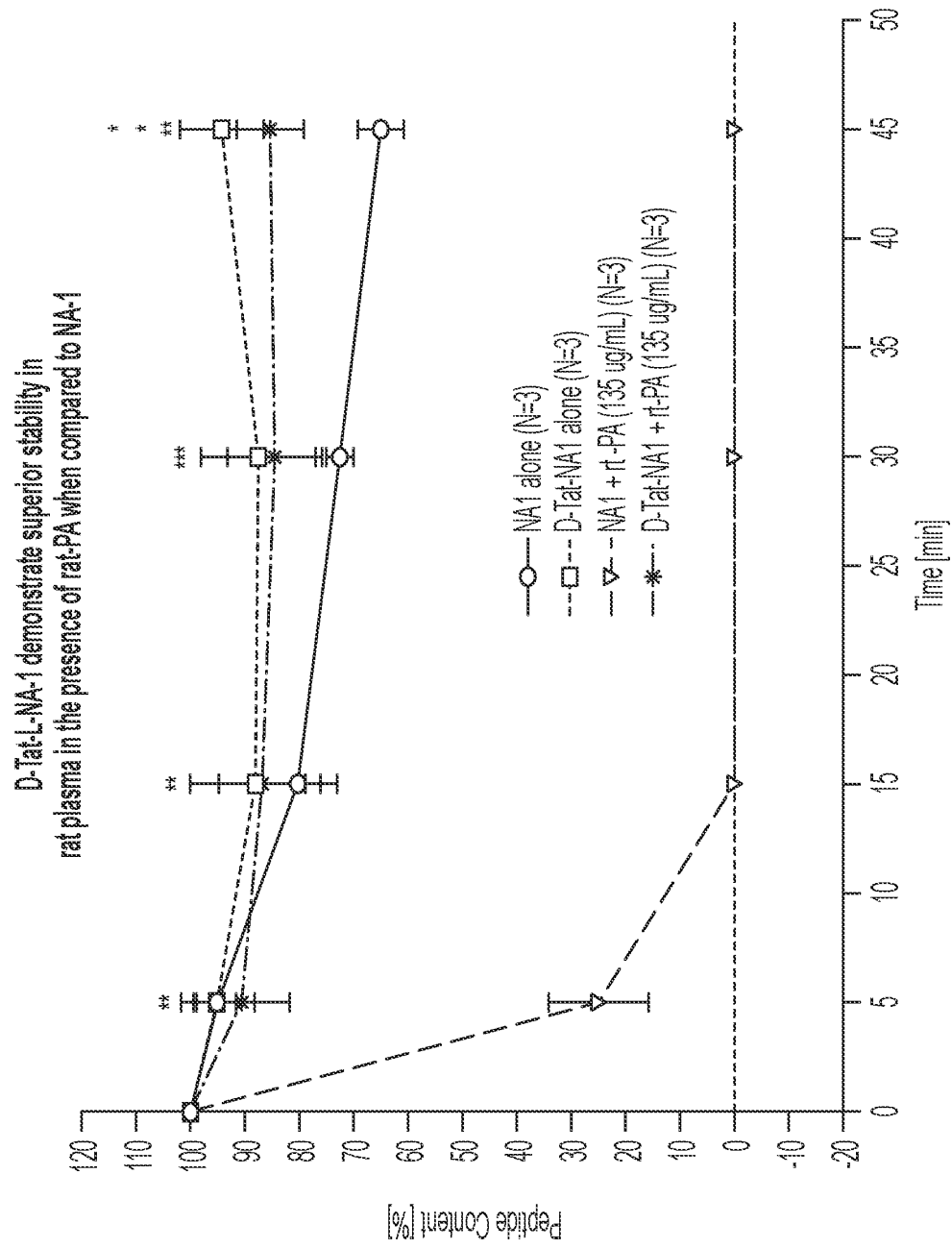


FIG. 5

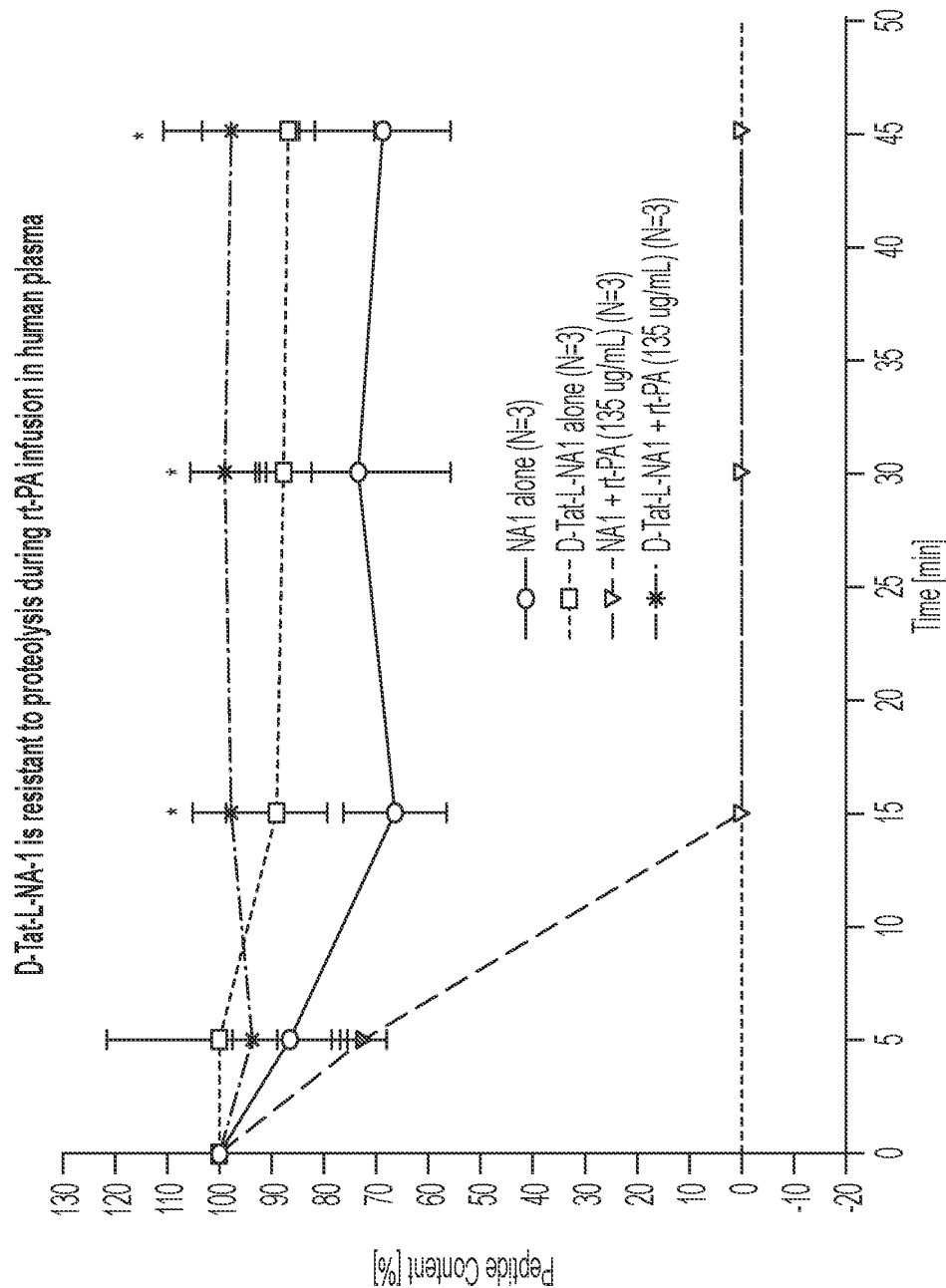


FIG. 6

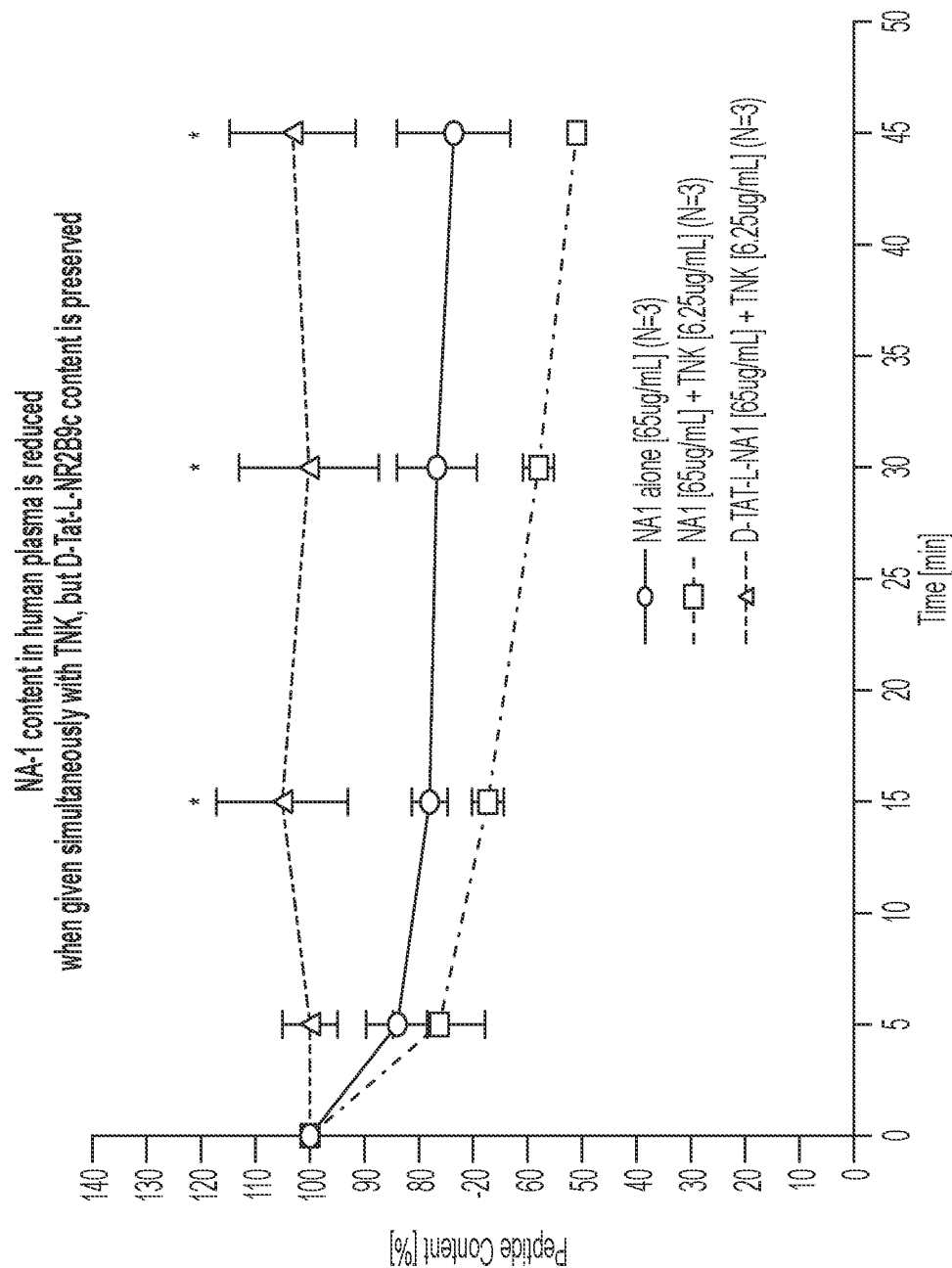


FIG. 7

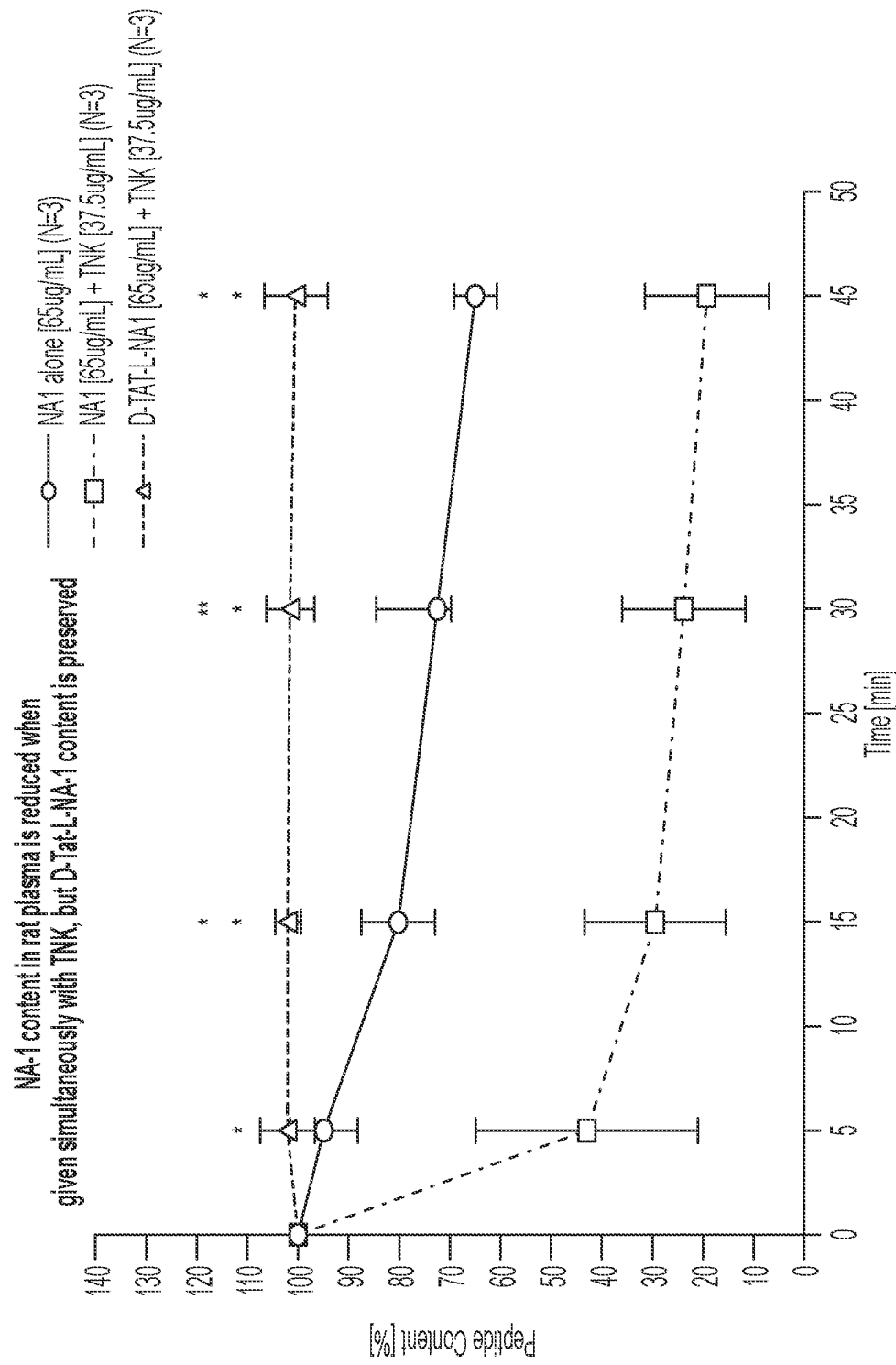


FIG. 8

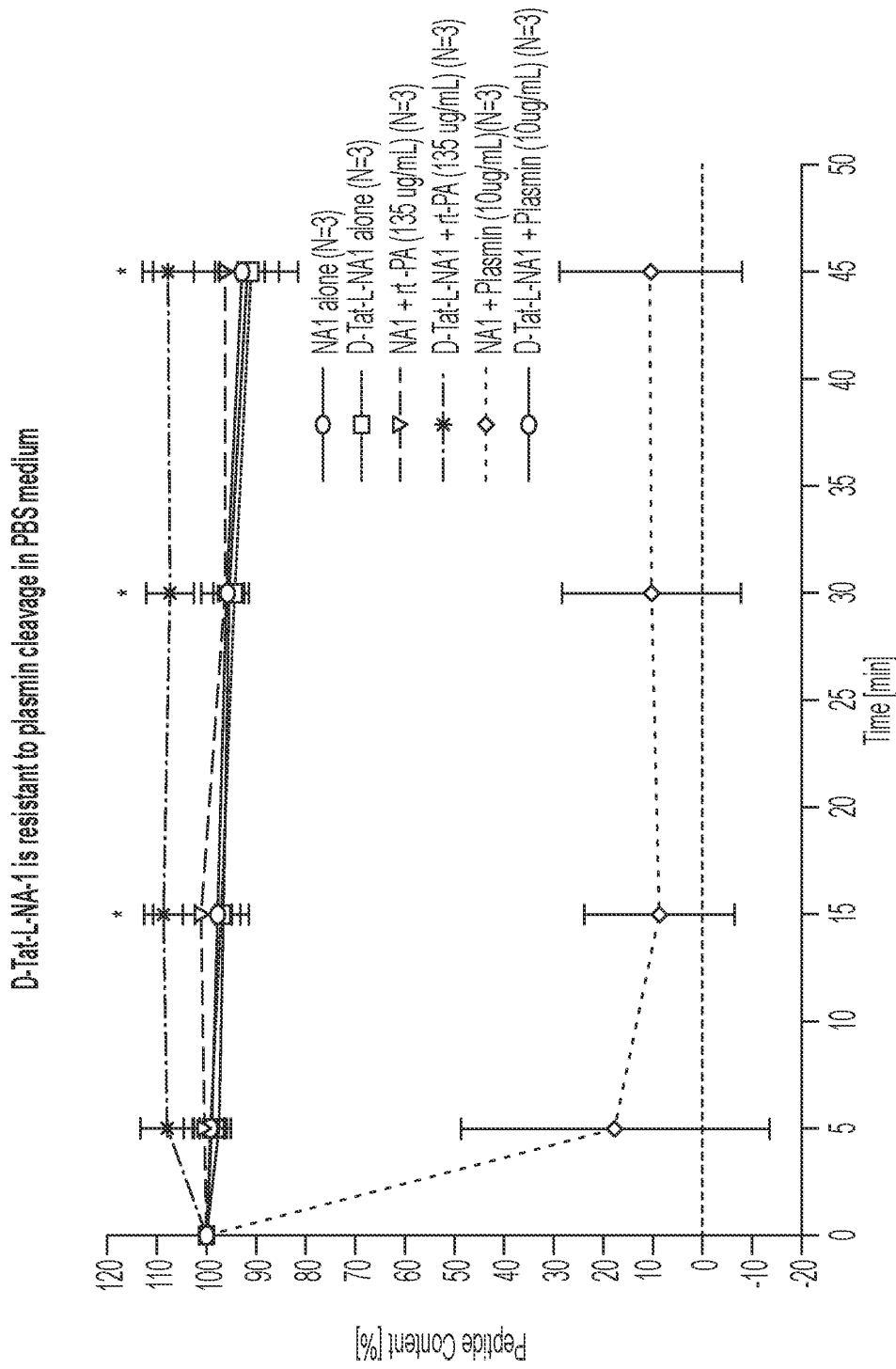


FIG. 9

Results: D-Tat-L-NA-1 dissociates pre-formed NR2B/PSD95 complexes in rat brain lysates

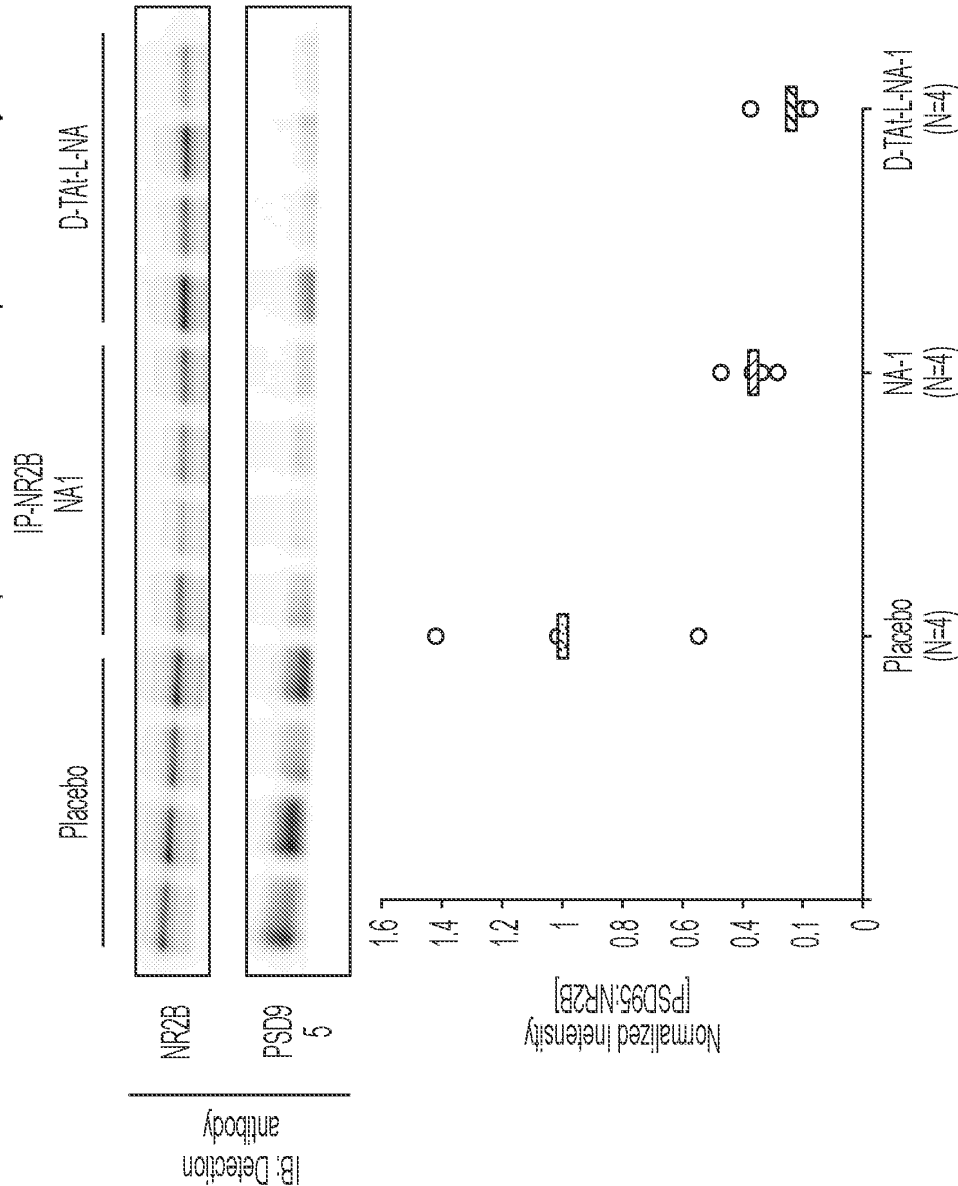


FIG. 10

D-Tat-L-NA1 and D-Tat-L-IESDV effectively bind the target protein PSD95-PDZ2

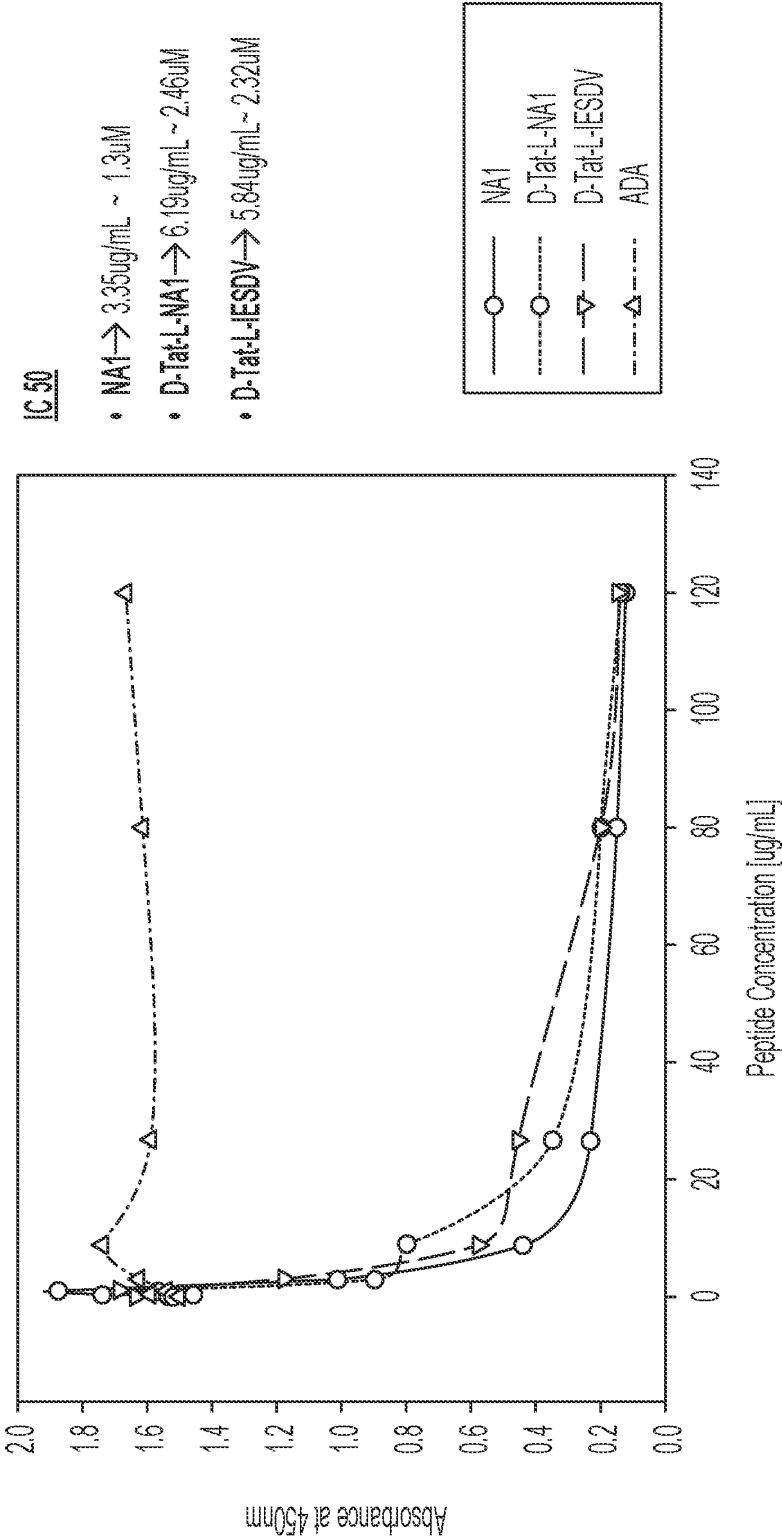


FIG. 11

Result: NA-1 and D-Tat-L-NA1 have a high binding affinity PSD95-PDZ2 domain

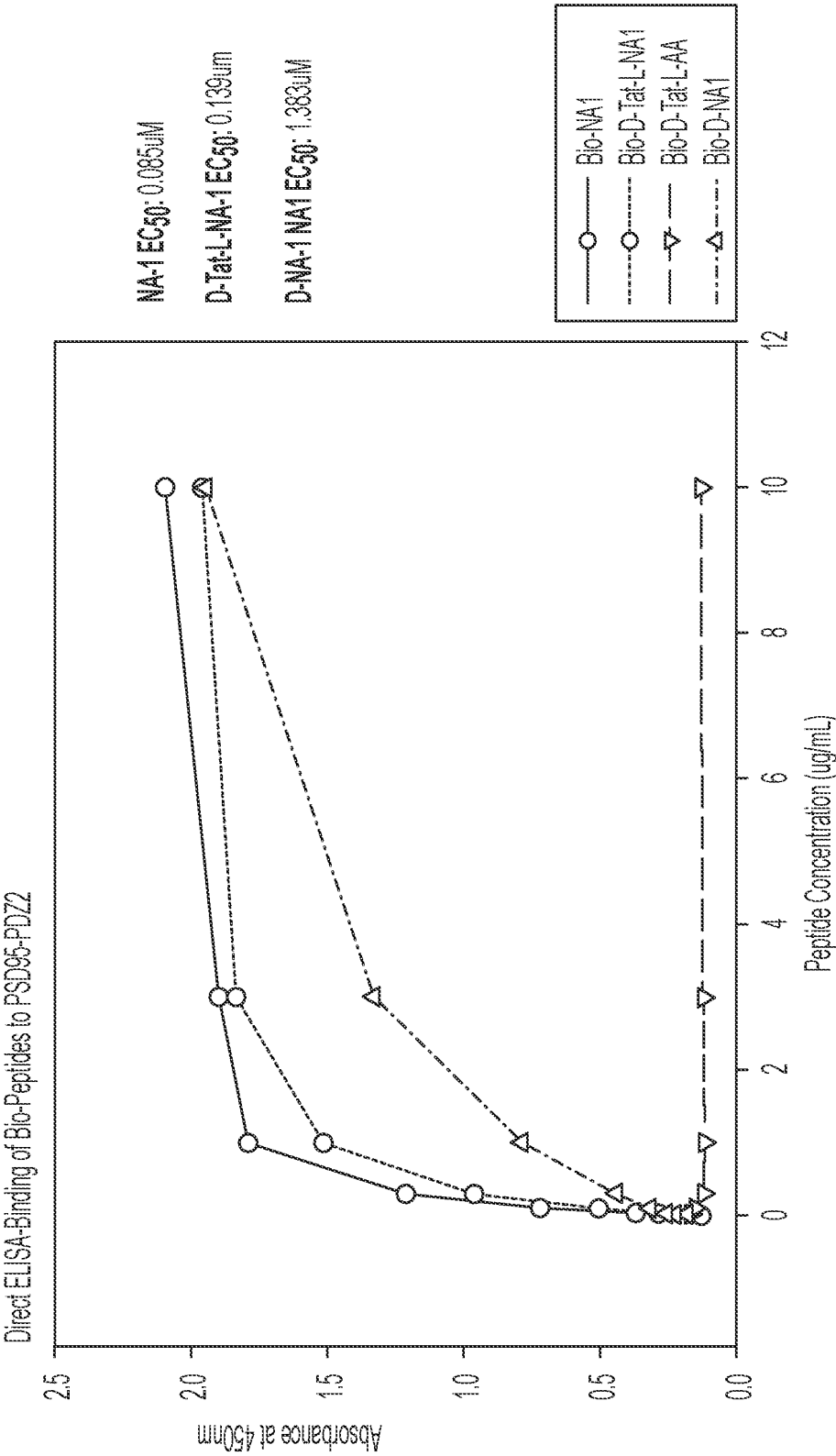


FIG. 12

Subcutaneous NA-1 achieved similar plasma exposure relative to IV NA-1

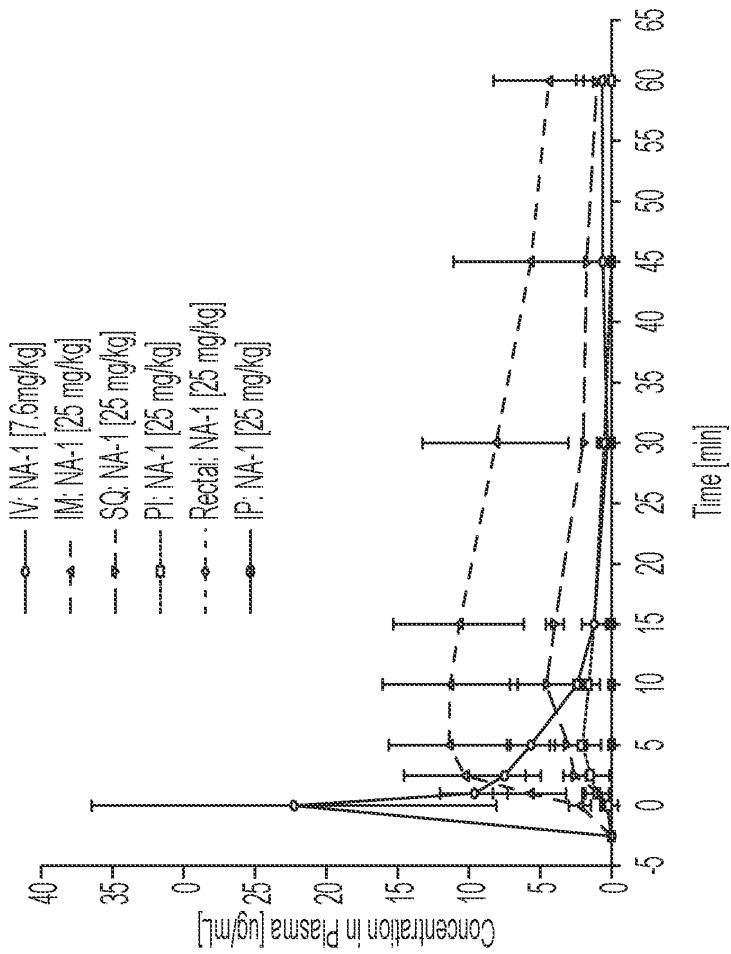


FIG. 13

Pharmacokinetic Parameter	NA-1 IV (7.6mg/kg)	NA-1 IV (25mg/kg)	NA-1 IM (25mg/kg)	NA-1 SQ (25mg/kg)
Cmax(ug/ml)	22.27	54.28	11.37	4.93
Tmax(min)	1	1	5	15
T1/2(min)	12.40	17.10	34.40	22.85
AUC(0-last) (ug/ml*min)	130.59	266.94	467.21	165.00
AUC(0-inf) (ug/ml*min)	142.26	308.39	685.19	205.01
Cl(ml/min/kg)	0.05	0.08	0.04	0.12

Subcutaneous D-Tat-L-IESDV achieved higher plasma concentration and a greater plasma exposure relative to subcutaneous NA-1

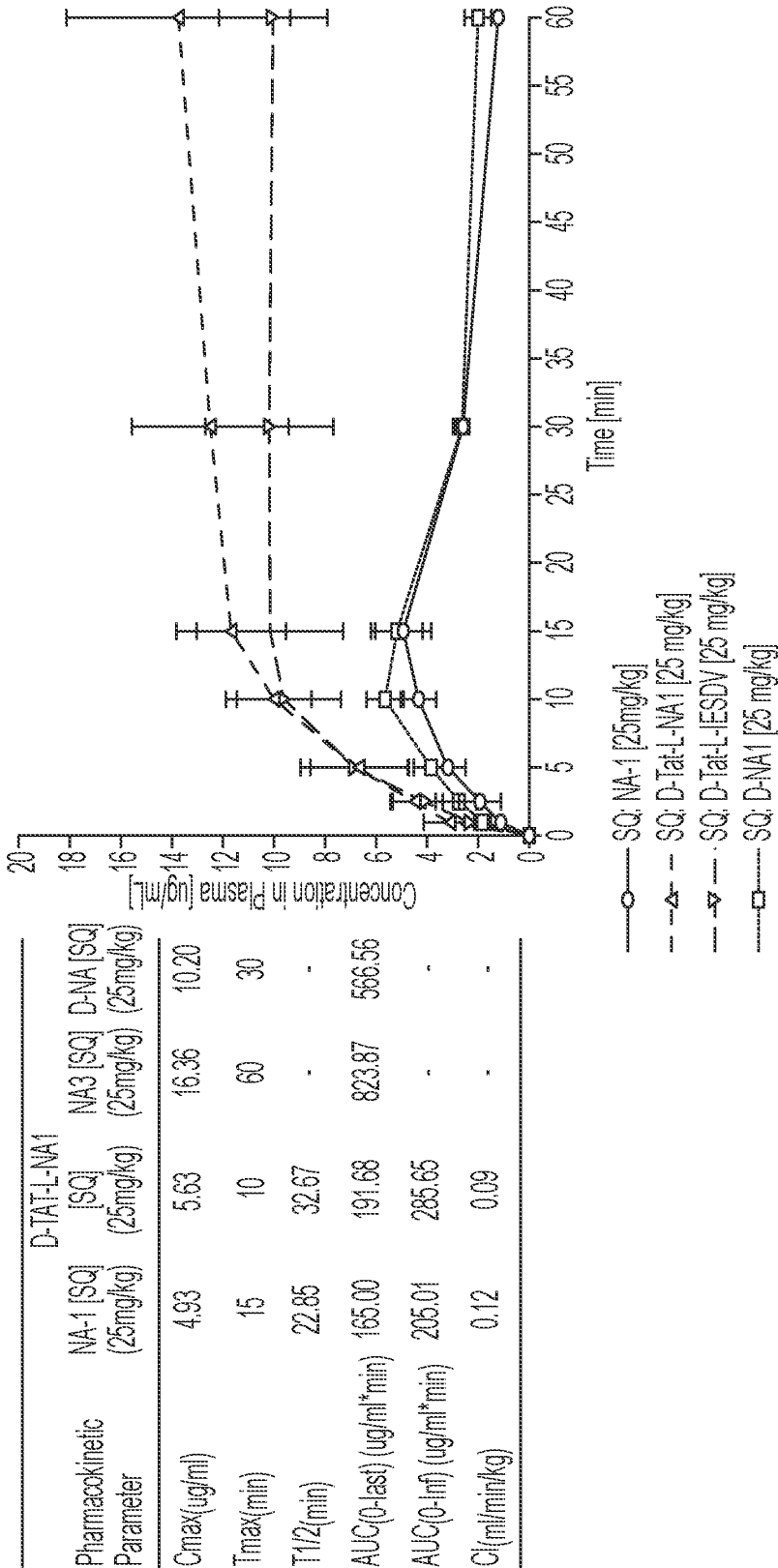


FIG. 14

Pharmacokinetic Parameter	NA-1 SQ (25mg/kg)	NA-3 SQ (25mg/kg)	NA-3 SQ (8.3mg/kg)	NA-3 SQ (2.8mg/kg)
C _{max} (ug/ml)	4.93	11.16	6.89	3.42
T _{max} (min)	15	60	60	60
T _{1/2} (min)	22.85	267.08	300.24	200.62
AUC _(0-last) (ug/ml*min)	165.00	5134.09	1862.66	503.79
AUC _(0-inf) (ug/ml*min)	205.01	6142.35	3355.93	684.26
Cl _(ml) (ml/kg)	0.12	0.004	0.002	

FIG. 15A

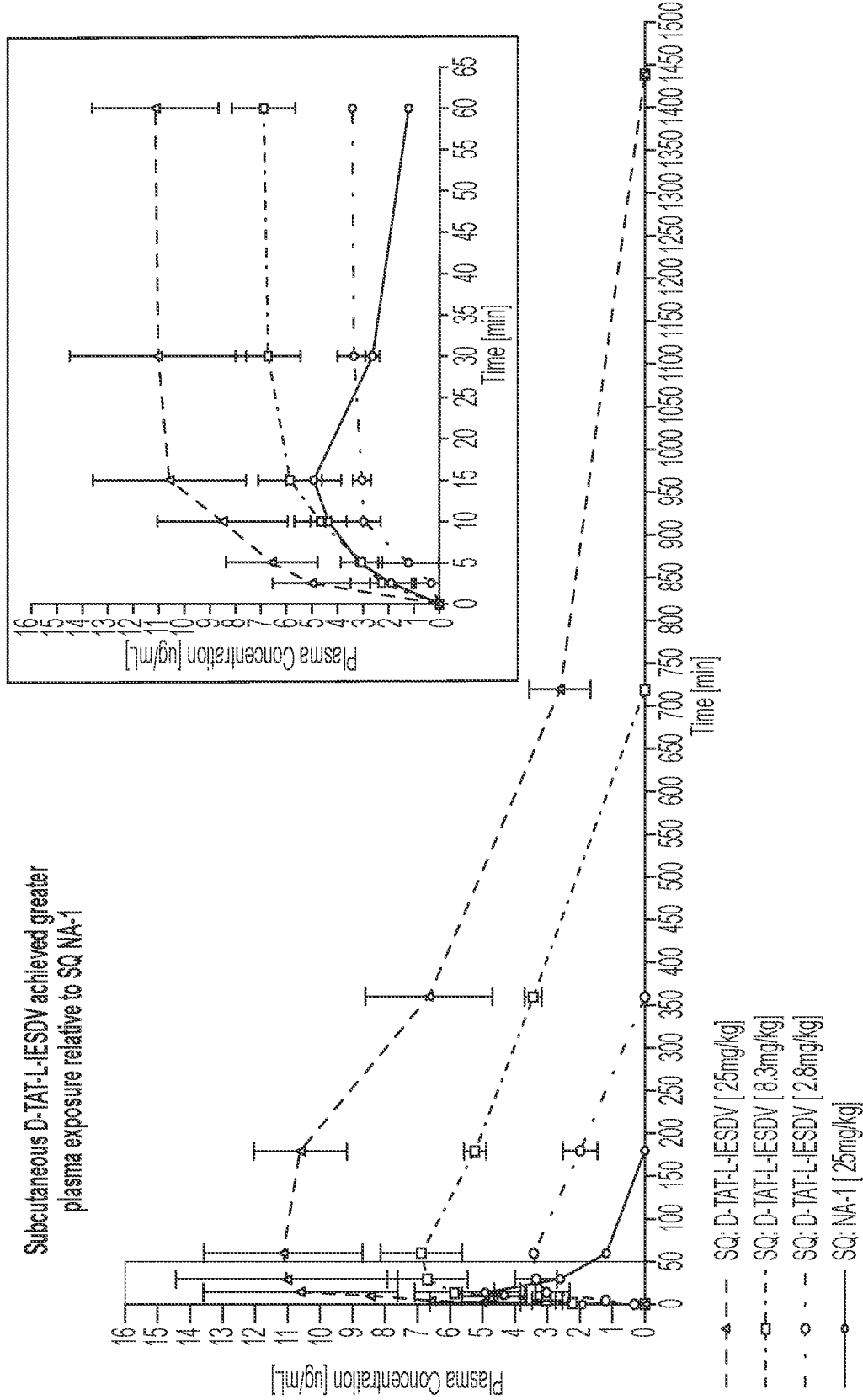


FIG. 15B

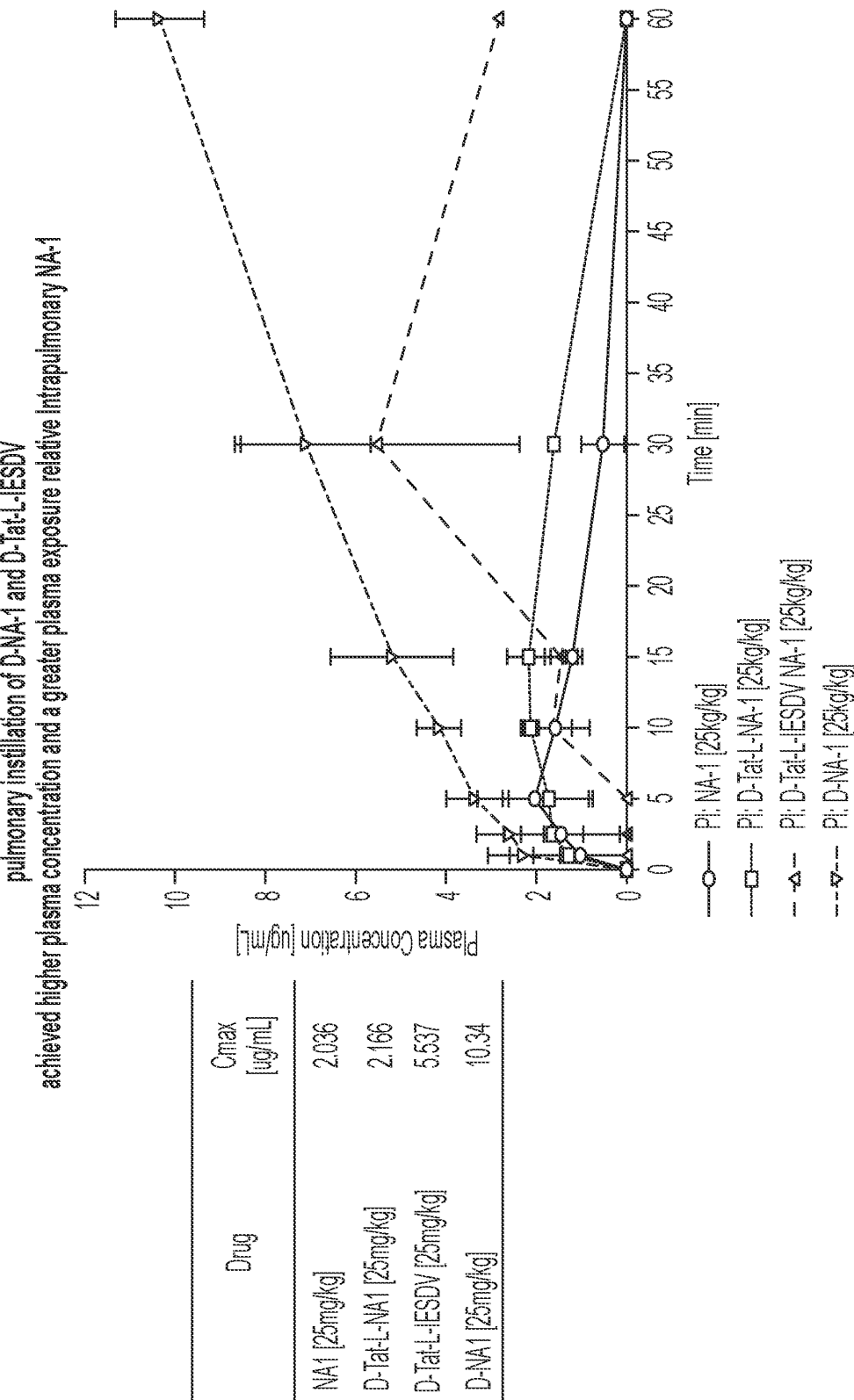


FIG. 16

There is not significant histamine release after
subcutaneous administration of D-Tat-L-FSDV at a dose of 8.3 mg/kg or 2.8 mg/kg dose

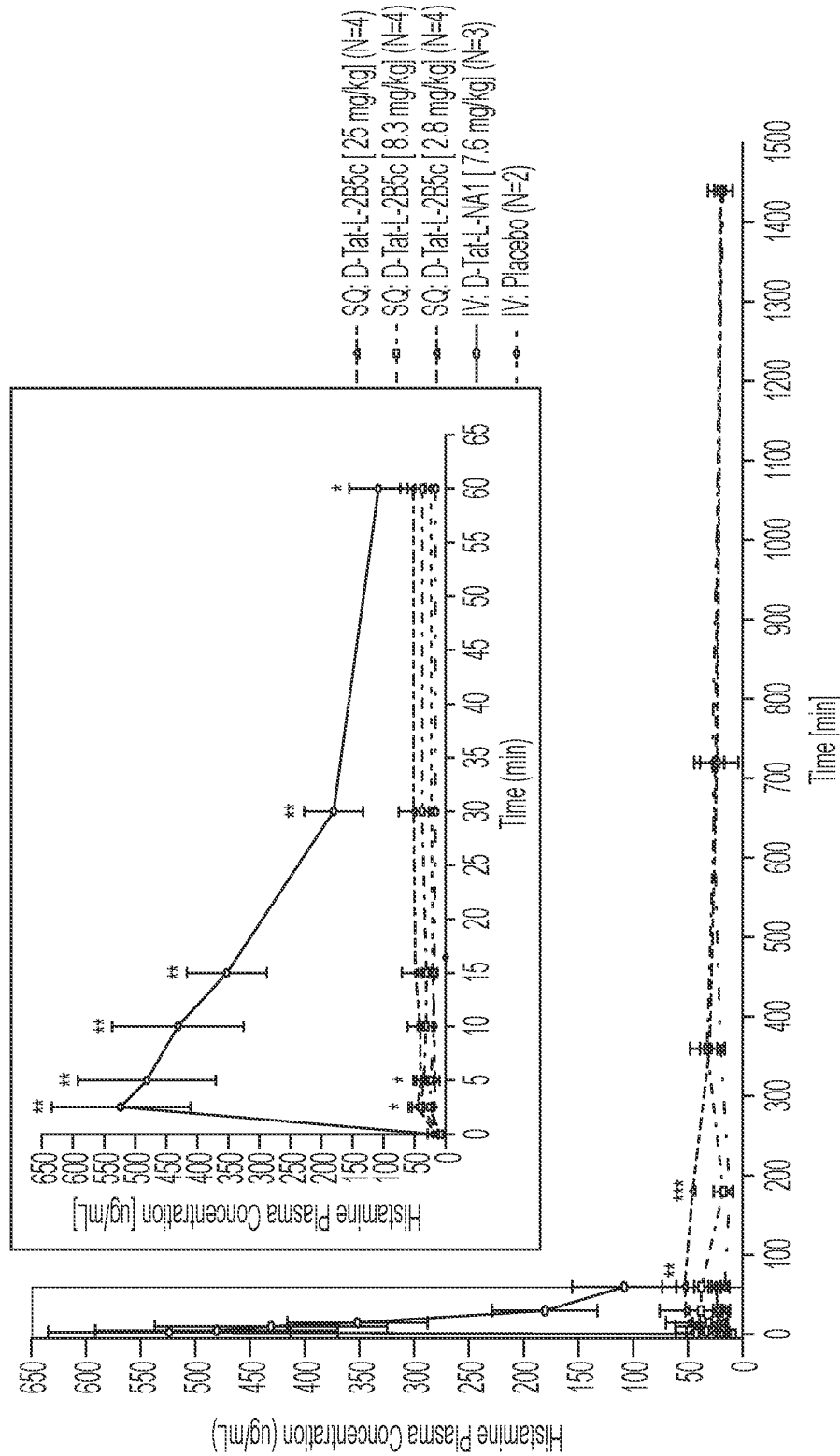


FIG. 17

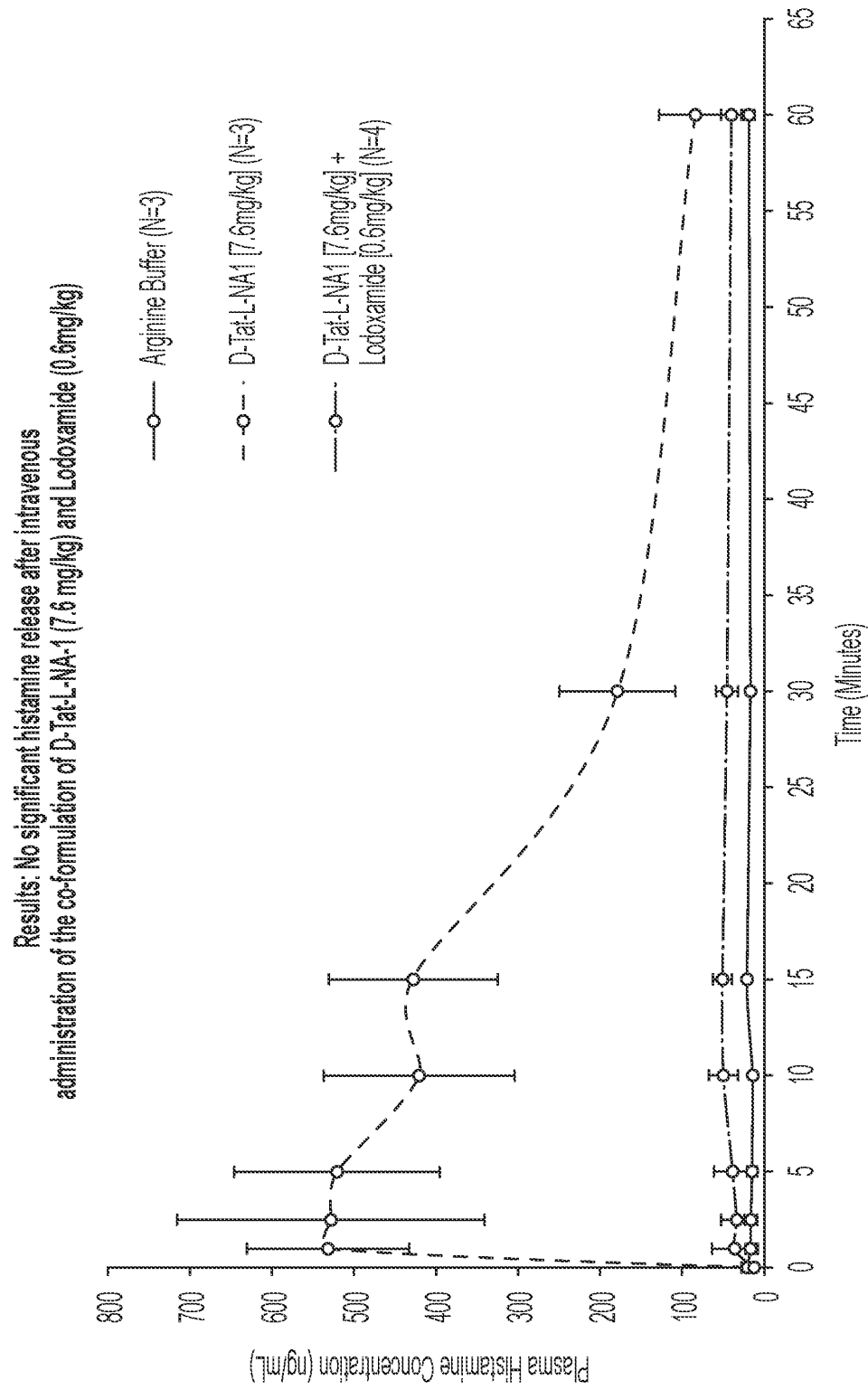


FIG. 18

Intravenous administration of D-Tat-L-NA¹-Lodo 1 hour
after stroke onset reduced infarct volume and hemispheric swelling in animals subjected to an mCAo model

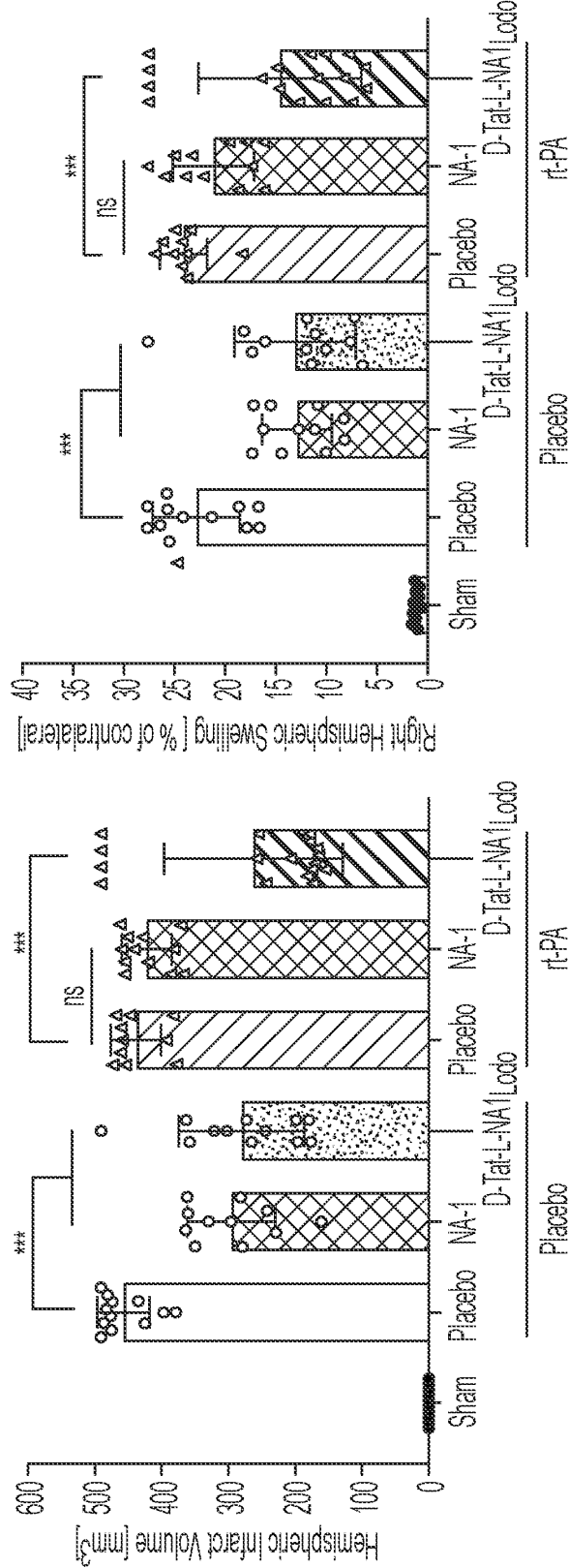


FIG. 19

D-Tat-L-NA-1_{Lodo} administration resulted in an improved neurological outcome 24 hours after stroke onset

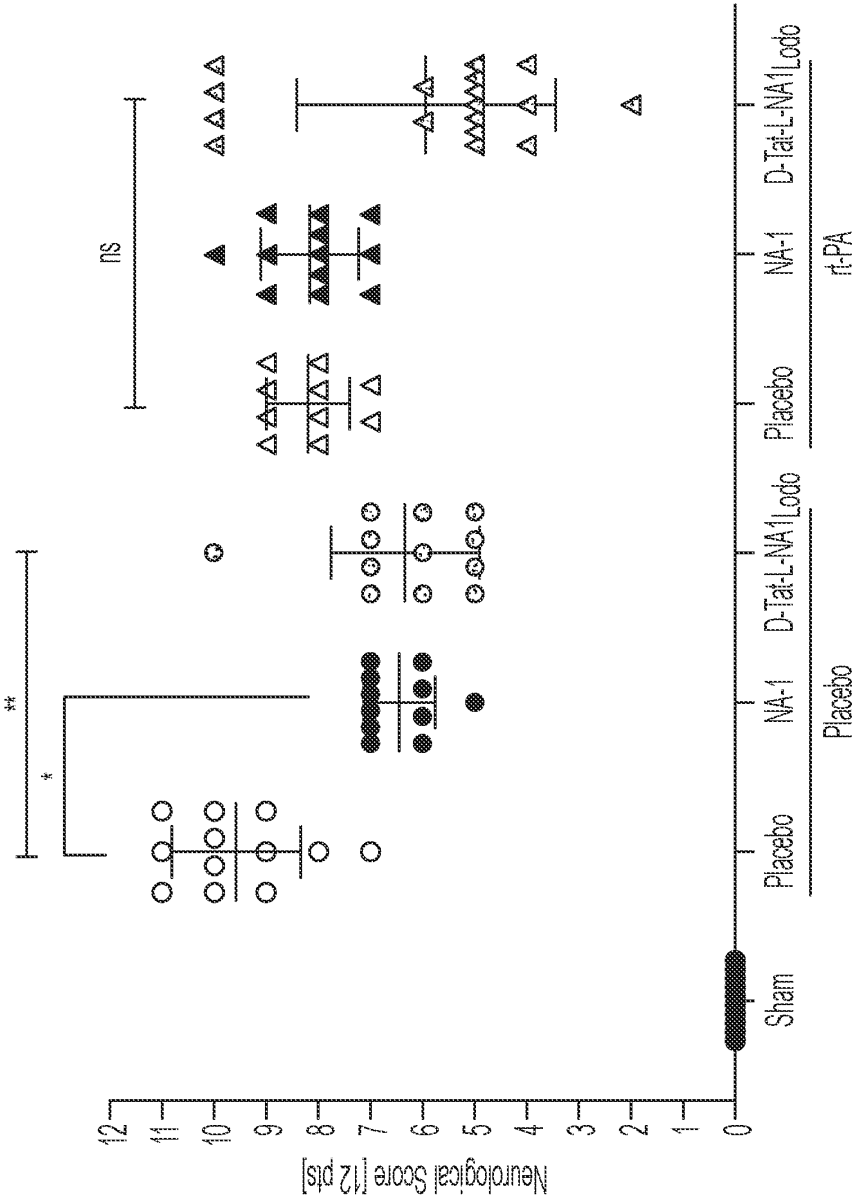


FIG. 20

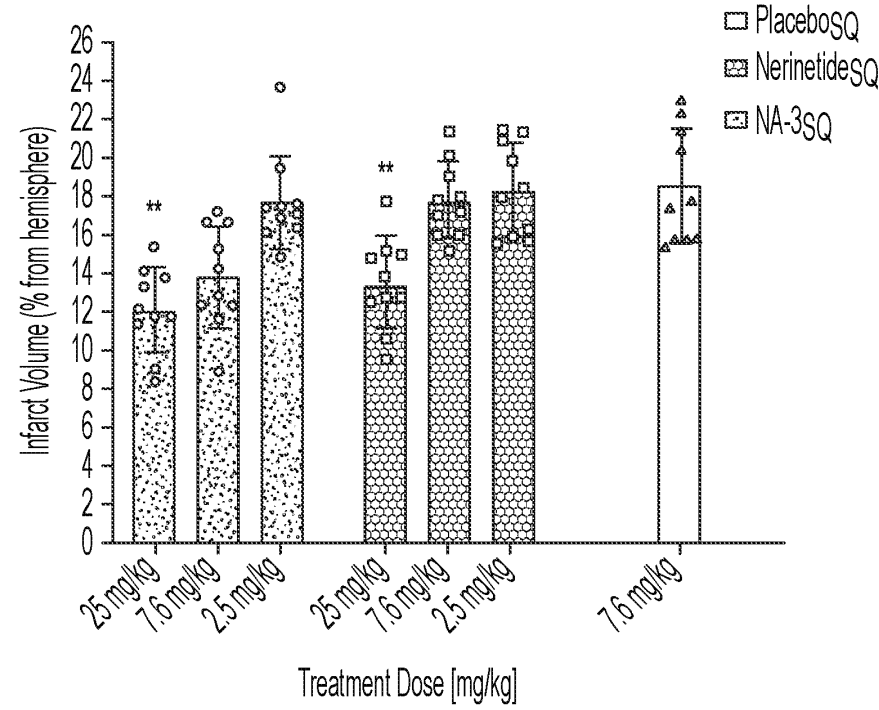


FIG. 21

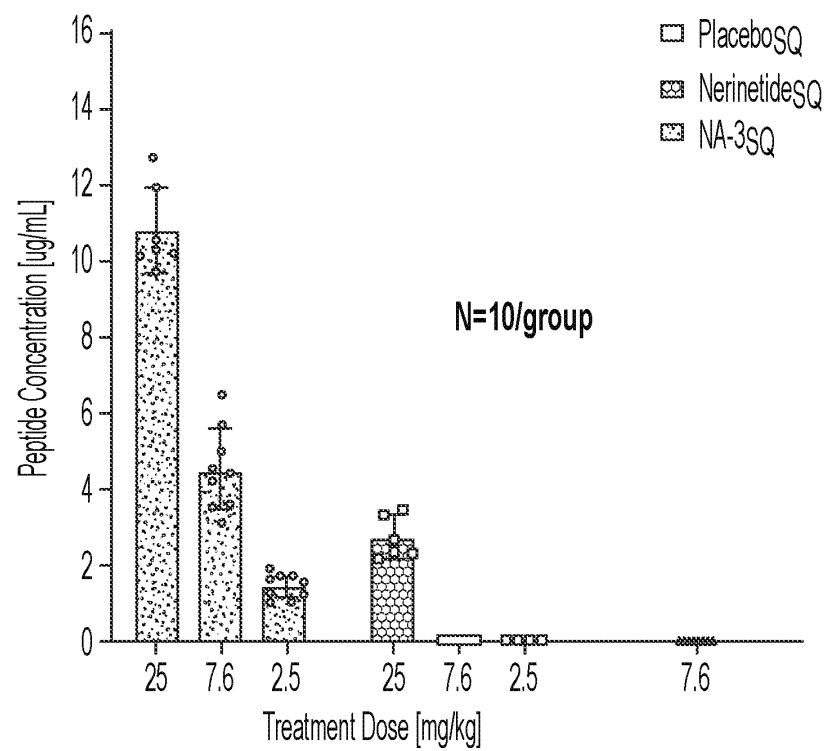


FIG. 22

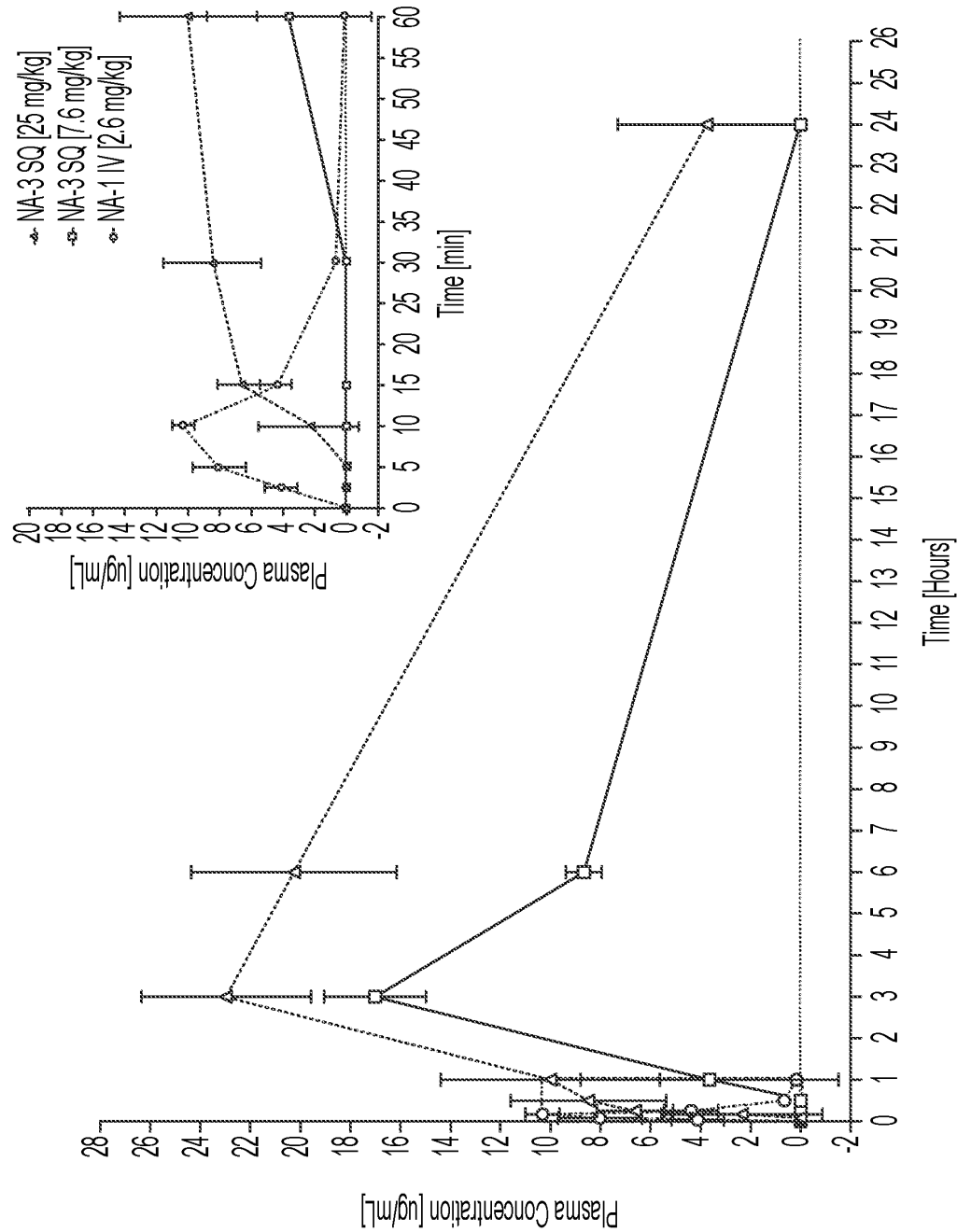


FIG. 23

Pharmacokinetic Parameters	Nerinetide Alone (N=3)	NA-3 25mg/kg (N=5)	NA-3 7.6mg/kg (N=2)	NA-3 2.6mg/kg (N=3)
C _{max} (ug/ml)	10.30 ± 0.69	24.06* ± 1.96	17.02 ± 2.05	-
t _{max} (h)	0.17 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	-
t _{1/2} (h)	0.15 ± 0.03	10.84 ± 1.66	-	-
AUC _(0-last) (ug/ml*h)	2.59 ± 0.14	342.19* ± 31.01	65.66* ± 4.97	-
AUC _(0-inf) (ug/ml*h)	2.63 ± 0.15	442.96 ± 53.60	-	-
Cl (ml/h/kg)	0.99 ± 0.06	0.05 ± 0.01	-	-

FIG. 24

Parameters	Baseline				30 min after Nerinetide administration		
	Nerinetide IV 2.6 mg/kg (N=3)	NA-3 SQ 25mg/kg (N=5)	NA-3 SQ 7.6mg/kg (N=4)	NA-3 SQ 2.6mg/kg (N=3)	Nerinetide IV 2.6 mg/kg (N=3)	NA-3 SQ 25mg/kg (N=5)	NA-3 SQ 7.6mg/kg (N=4)
Temperature (C°)	36.60 ± 0.40	36.86 ± 0.61	37.18 ± 0.79	36.57 ± 0.55	-	-	-
Heart Rate (bpm)	130.33 ± 22.03	122.80 ± 9.01	124.00 ± 12.19	109.33 ± 17.10	120.67 ± 20.60	120.00 ± 6.67	119.25 ± 10.24
Respiratory Rate (bpm)	29.33 ± 10.07	22.20 ± 2.95	23.75 ± 2.22	26.67 ± 13.80	28.67 ± 6.43	21.80 ± 2.49	24.50 ± 3.51
Systolic Blood Pressure (mmHg)	81.00 ± 5.20	71.60 ± 17.83	84.25 ± 31.19	76.00 ± 12.12	67.00 ± 3.46	69.20 ± 6.18	68.50 ± 4.95
Diastolic Blood Pressure (mmHg)	33.33 ± 3.21	31.60 ± 5.77	53.50 ± 29.33	36.67 ± 8.74	36.00 ± 12.49	27.20 ± 4.87	26.50 ± 0.71
Mean Arterial Blood Pressure (mmHg)	49.33 ± 0.58	45.00 ± 7.04	64.25 ± 30.90	49.67 ± 9.71	46.67 ± 7.57	41.20 ± 2.28	40.50 ± 0.71
O ₂ Saturation (%)	93.67 ± 1.53	94.00 ± 3.54	96.50 ± 2.52	95.67 ± 4.16	96.00 ± 2.00	94.40 ± 2.30	93.25 ± 4.65
ET CO ₂ (mmHg)	42.00 ± 2.00	41.20 ± 2.05	44.75 ± 2.06	42.67 ± 5.69	42.00 ± 2.65	41.00 ± 2.12	44.50 ± 3.32

FIG. 25

		60 min after Nerinetide administration			
Parameters	NA-3 SQ 2.6mg/kg (N=3)	Nerinetide IV 2.6 mg/kg (N=3)	NA-3 SQ 25mg/kg (N=5)	NA-3 SQ 7.6mg/kg (N=4)	NA-3 SQ 2.6mg/kg (N=3)
Temperature (C°)	-	-	-	-	-
Heart Rate (bpm)	103.67 ± 14.22	125.67 ± 14.22	123.40 ± 16.86	129.75 ± 20.27	110.67 ± 12.86
Respiratory Rate (bpm)	23.67 ± 10.41	32.67 ± 10.41	24.40 ± 4.62	26.25 ± 4.27	24.67 ± 11.15
Systolic Blood Pressure (mmHg)	70.67 ± 17.04	76.33 ± 17.04	75.60 ± 14.94	89.67 ± 18.90	70.67 ± 18.88
Diastolic Blood Pressure (mmHg)	38.67 ± 11.93	33.00 ± 11.93	33.60 ± 11.30	36.33 ± 9.07	34.00 ± 11.14
Mean Arterial Blood Pressure (mmHg)	49.00 ± 13.08	47.33 ± 13.08	47.60 ± 11.63	54.00 ± 12.17	46.00 ± 13.75
O ₂ Saturation (%)	97.00 ± 0.00	93.67 ± 0.00	92.00 ± 3.67	95.00 ± 2.94	97.33 ± 0.58
ET CO ₂ (mmHg)	39.67 ± 4.73	42.67 ± 4.73	41.00 ± 2.12	43.75 ± 1.89	40.67 ± 4.73

FIG. 25
CONTINUED

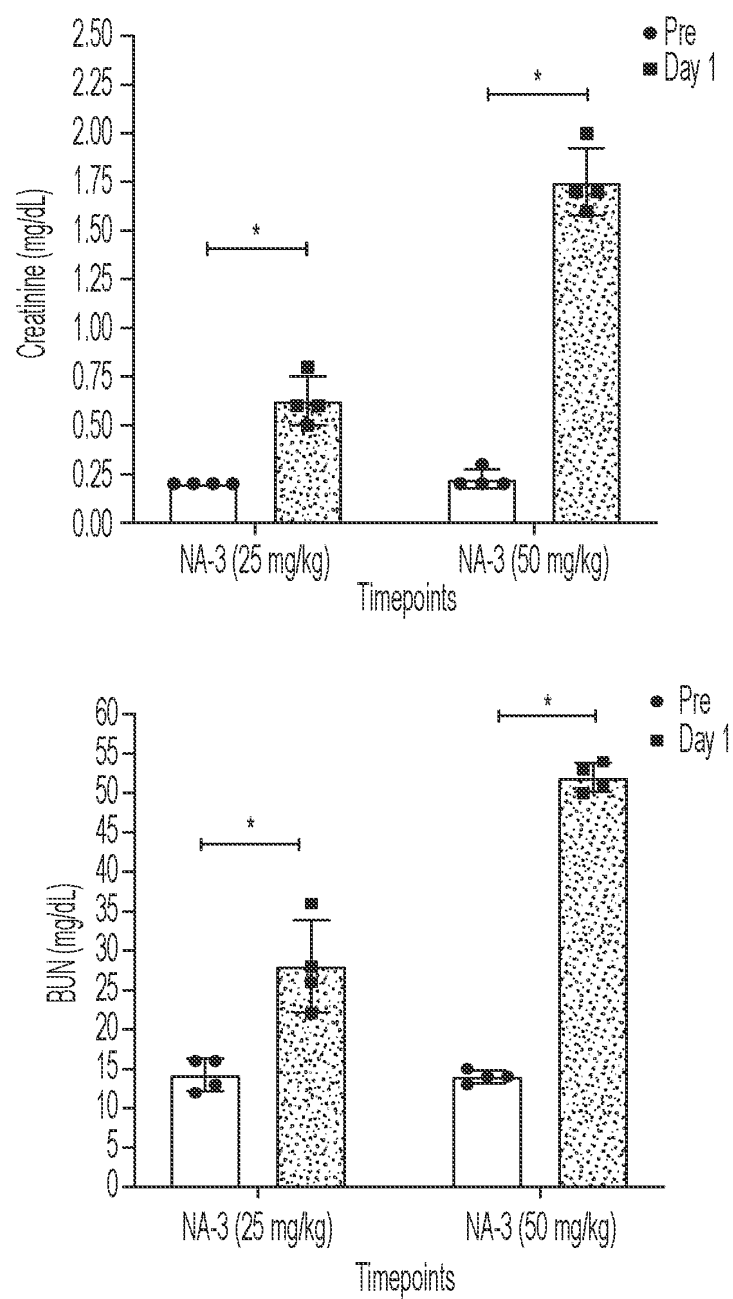


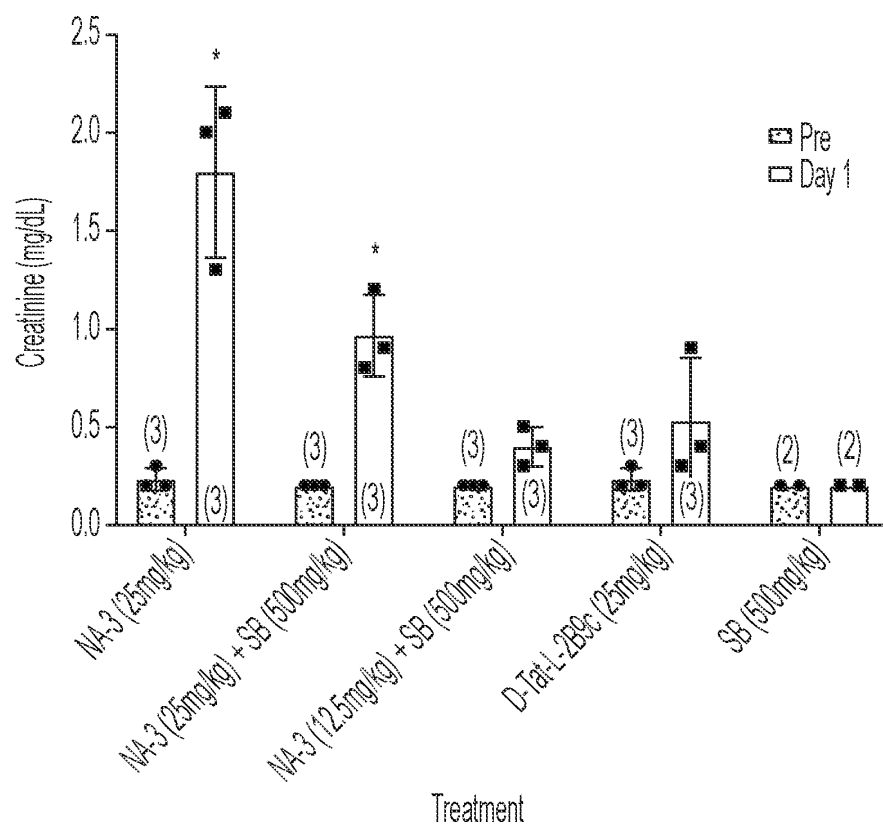
FIG. 26A

Parameters	Reference Range	NA-3SQ 25 mg/kg (N=4)		NA-3SQ 7.6 mg/kg (N=4)	NA-3SQ 2.6 mg/kg (N=3)	NA-1IV 2.6 mg/kg (N=3)
		Day 7	Day 14	Day 7	Day 7	Day 7
Electrolytes						
Sodium (Na ⁺)(mmol/L)	147 - 155	137.5 ± 2.65	144.5 ± 5.0	159.8 ± 0.96	144.0 ± 0.00	145.3 ± 0.58
Potassium (K ⁺)(mmol/L)	4.7 - 5.7	5.9 ± 0.48	4.6 ± 0.15	8.5 ± 0.00	3.9 ± 0.47	4.0 ± 0.36
Total Calcium (CA)(mg/dL)	9.9 - 10.9	11.9 ± 0.21	10.2 ± 0.42	4.0 ± 0.00	10.1 ± 0.26	10.0 ± 0.10
Phosphorus (Phos)(mg/dL)	3.8 - 5.6	9.1 ± 3.26 *	3.2 ± 2.01	2.05 ± 0.51	2.97 ± 0.38	3.5 ± 0.55

FIG. 26B

Parameters	Reference Range	NA-3SQ 25 mg/kg (N=4)		NA-3SQ 7.6 mg/kg (N=4)	NA-3SQ 2.6 mg/kg (N=3)		NA-1IV 2.6 mg/kg (N=3)
		Day 7	Day 14	Day 7	Day 7	Day 7	Day 7
Chemistry							
Alanine Aminotransferase (ALT)(U/L)	24 - 78	89.3 ± 7.80	43.8 ± 7.80	53.0 ± 18.28	39.67 ± 3.06		35.0 ± 13.53
Alkaline Phosphatase (ALP)(U/L)	55 - 237	109.5 ± 16.30	129.5 ± 17.71	30.75 ± 9.91	74.33 ± 22.81		108.7 ± 19.63
Albumin (ALB)(g/dL)	3.8 - 4.8	3.95 ± 0.42	4.05 ± 0.45	4.28 ± 0.25	4.70 ± 0.26		4.27 ± 0.15
Amylase (AMY)(U/L)	117 - 389	773.5 ± 208.31 *	296.0 ± 53.96	279.25 ± 26.27	191.33 ± 38.21		242.3 ± 20.31
Total Protein (TP)(mg/dL)	7.3 - 8.3	8.3 ± 0.35	7.1 ± 0.35	7.0 ± 0.08	7.5 ± 0.45		7.4 ± 0.21
Total Bilirubin (TBL)(U/L)	0.0 - 0.3	0.23 ± 0.05	0.25 ± 0.10	0.30 ± 0.0	0.40 ± 0.0		0.30 ± 0.1
Globulin (GLOB)(g/dL)	2.8 - 3.4	4.4 ± 0.57	3.0 ± 0.67	2.73 ± 0.24	2.87± 0.47		3.1 ± 0.12
Glucose (GLU)(mg/dL)	55 - 89	85.8 ± 7.23	68.8 ± 8.66	67.0 ± 7.75	71.0 ± 7.81		76.3 ± 10.69
Creatinine (CRE)(mg/dL)	1.0 - 1.4	19.9 ± 0.15 *	1.3 ± 0.19	1.1 ± 0.28	1.0 ± 0.06		0.8 ± 0.21
Blood Urea Nitrogen (BUN)(mg/dL)	22 - 30	151.3 ± 27.57 *	18.0 ± 2.0	19.25 ± 1.26	18.33 ± 2.31		20.0 ± 3.61

FIG. 26B
CONTINUED



Significant differences are indicated with an asterisk when compared to the control group/(SB Alone)
(Two-way ANOVA post hoc Tukey's correction for multiple comparisons test, * $P < 0.01$)

FIG. 27

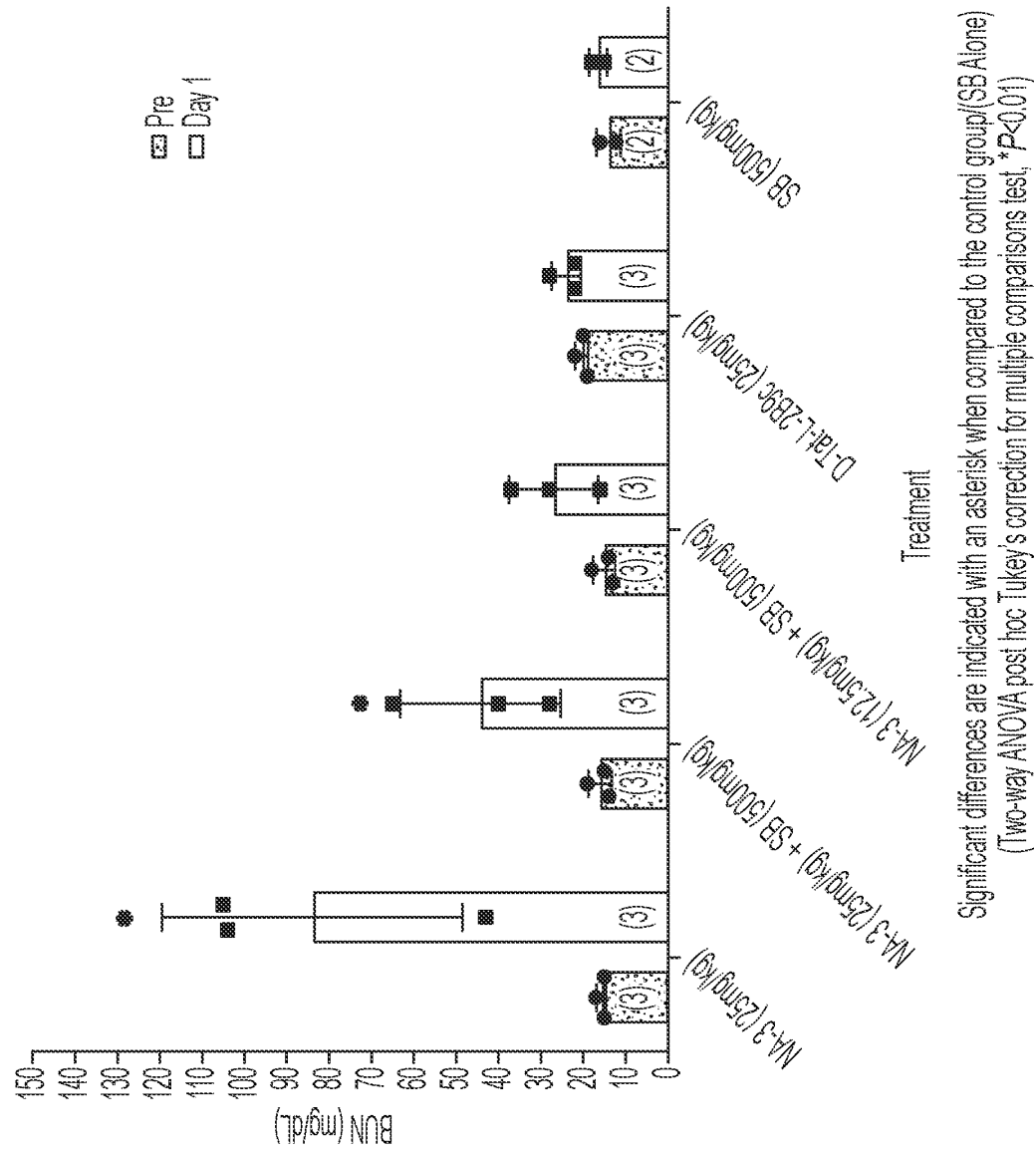


FIG. 28

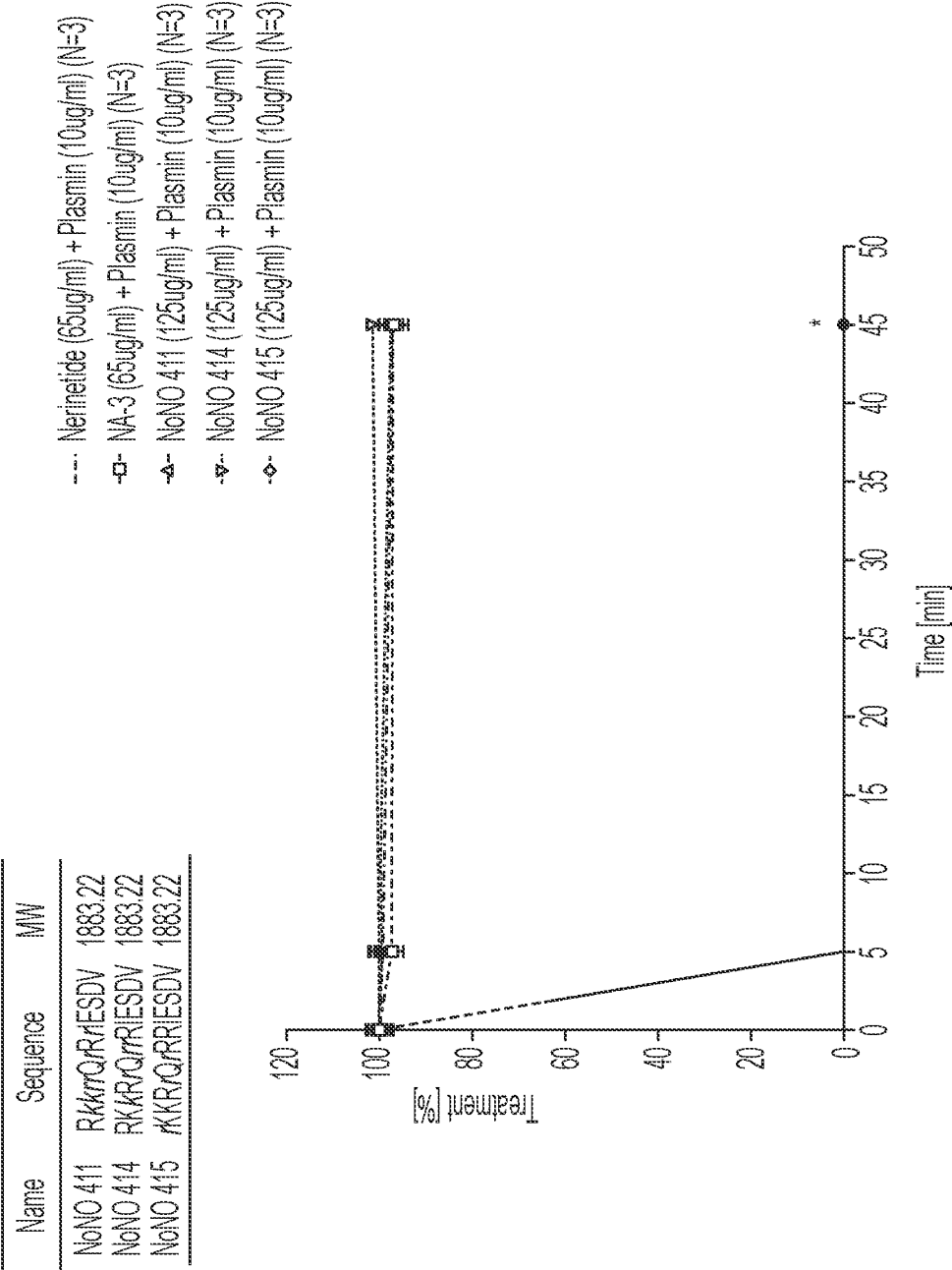


FIG. 29

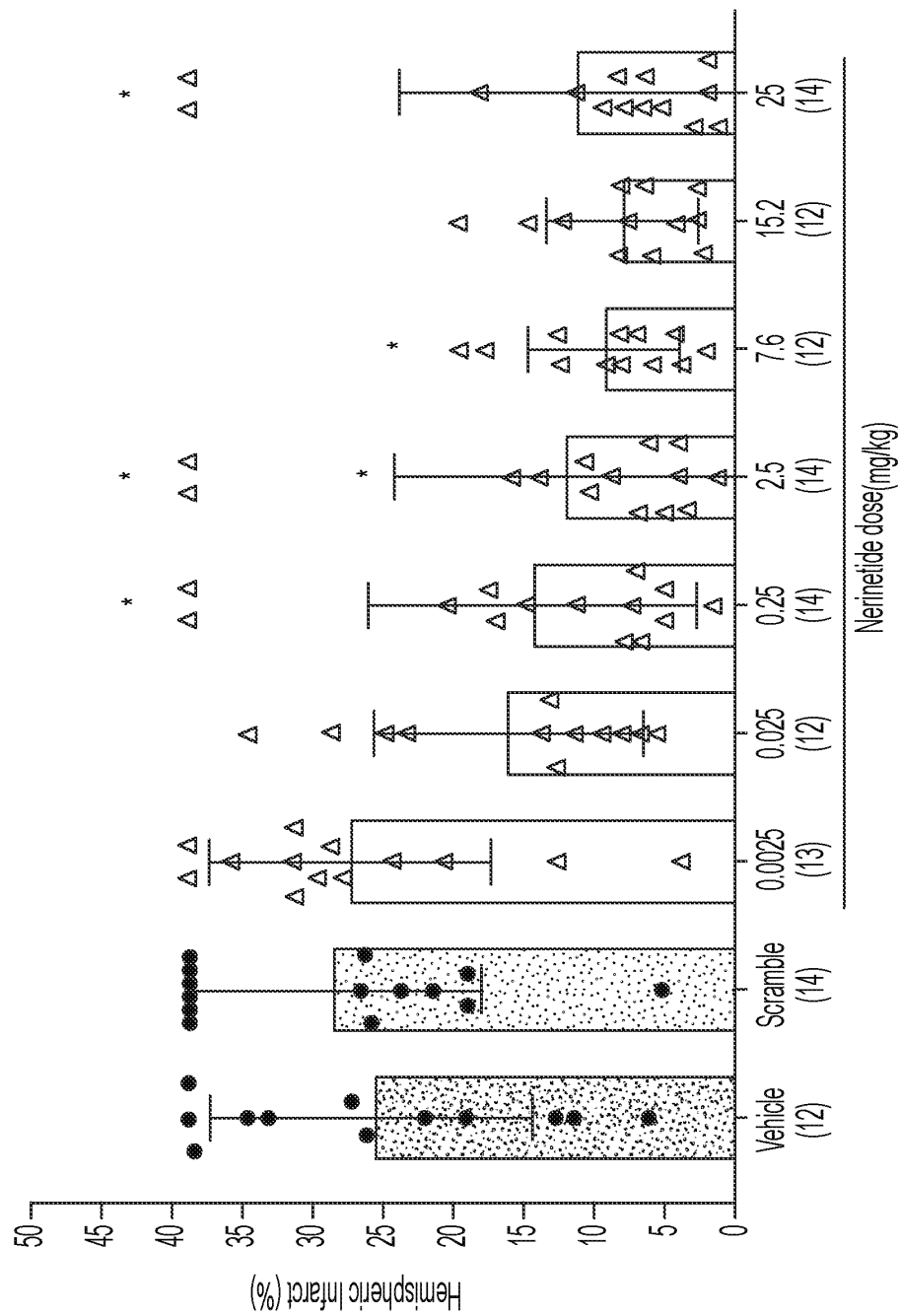


FIG. 30A

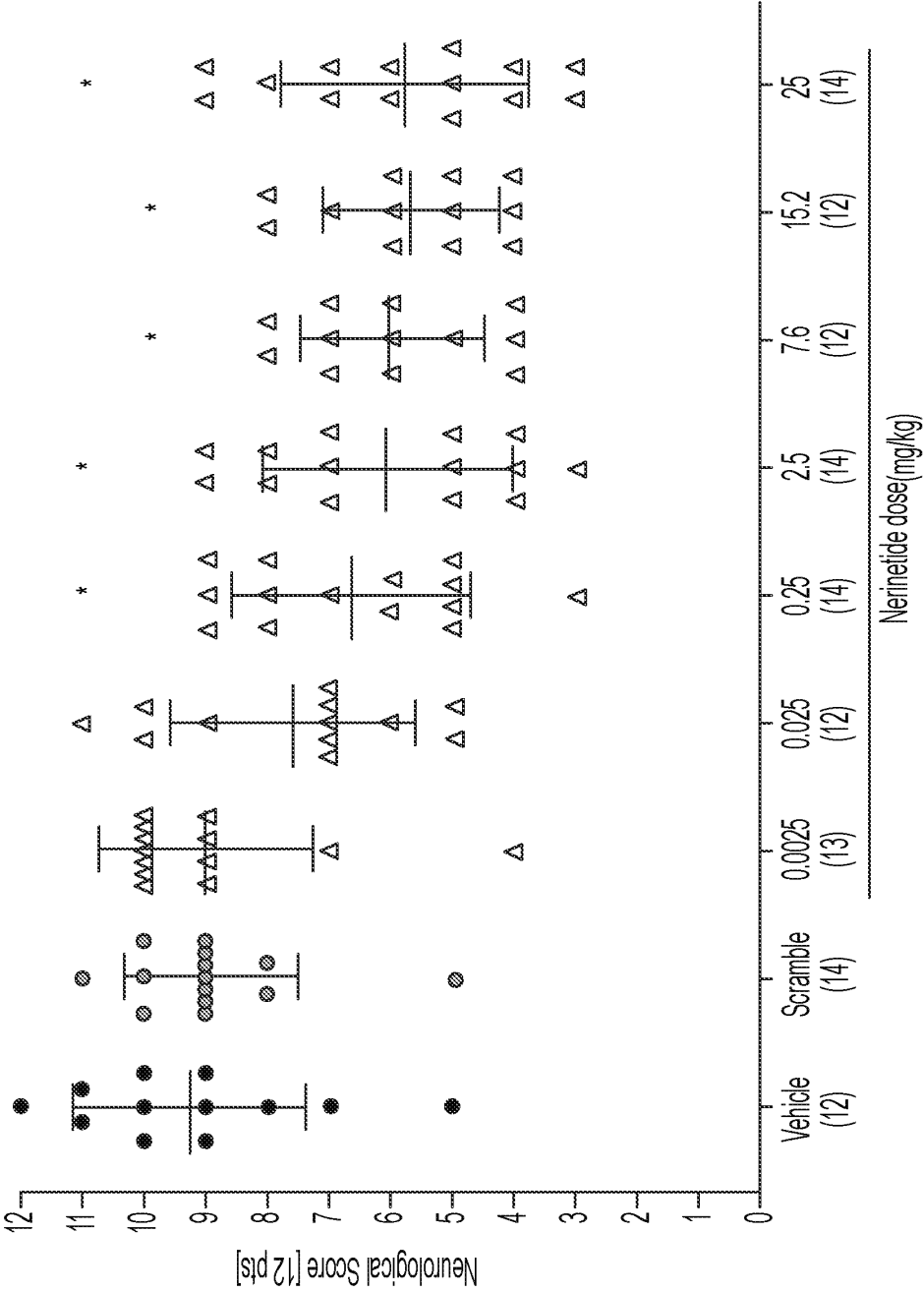


FIG. 30B

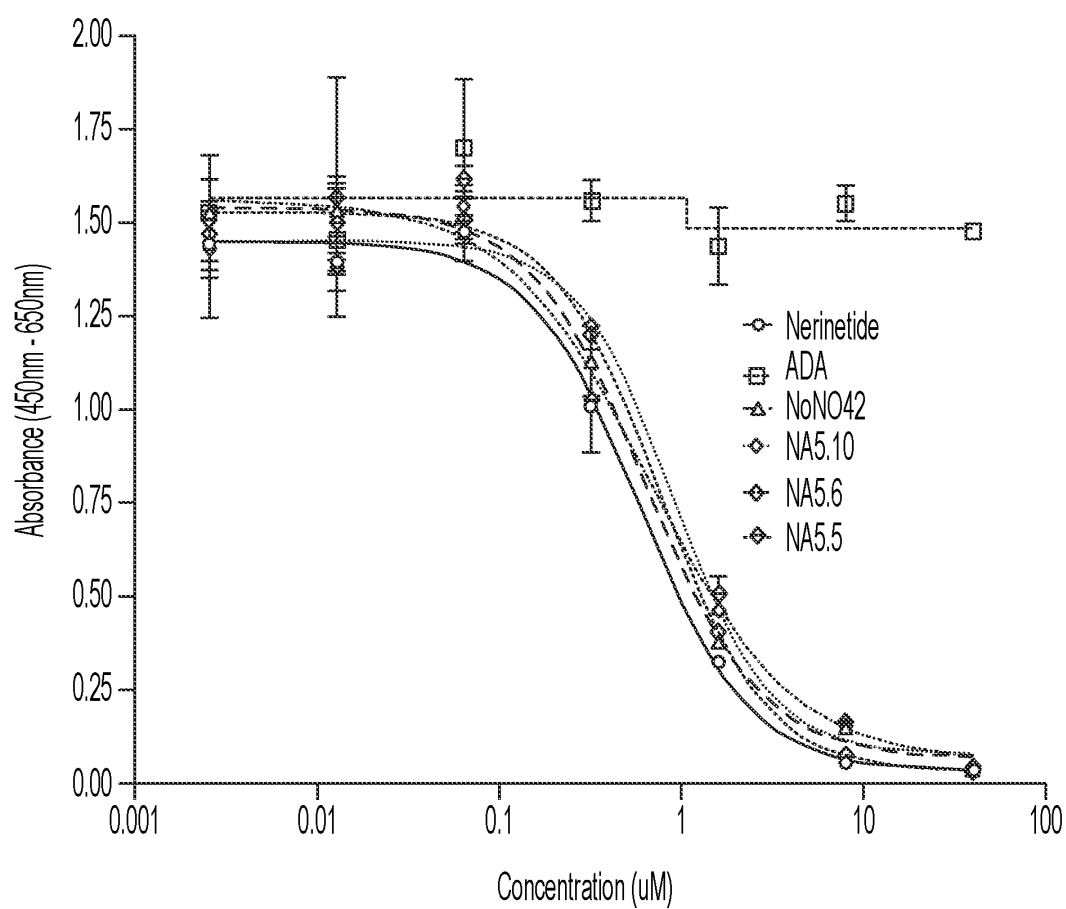


FIG. 31

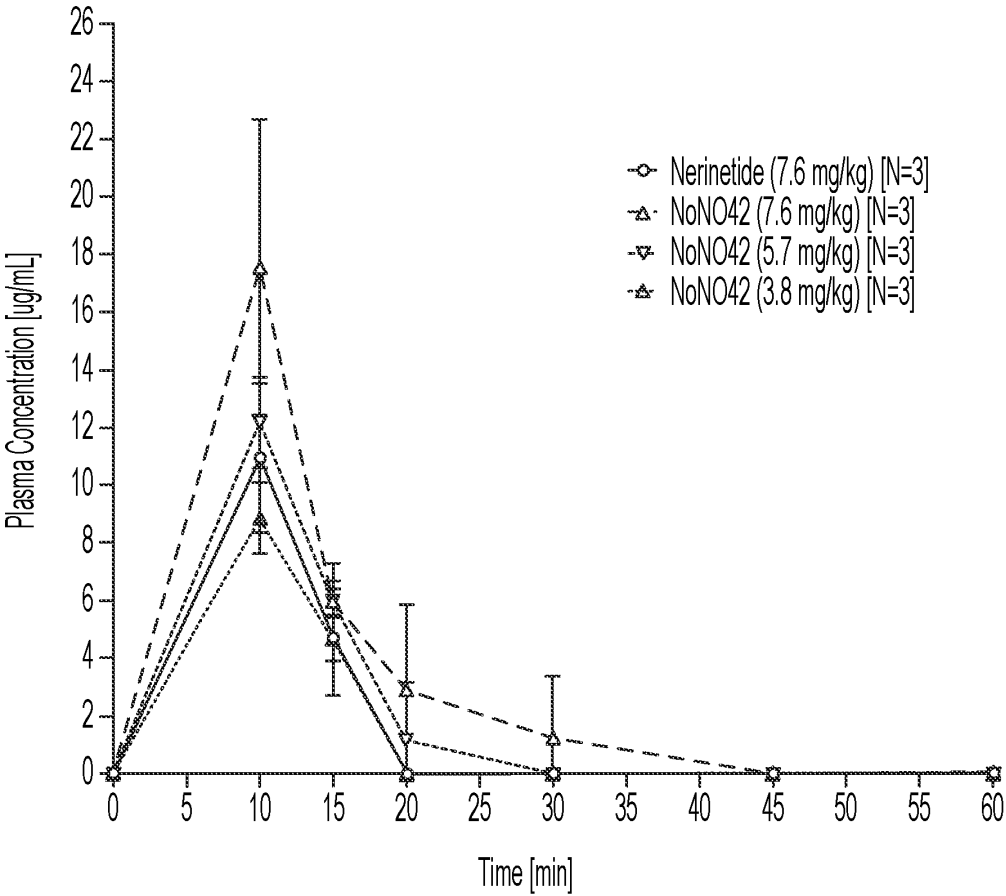


FIG. 32

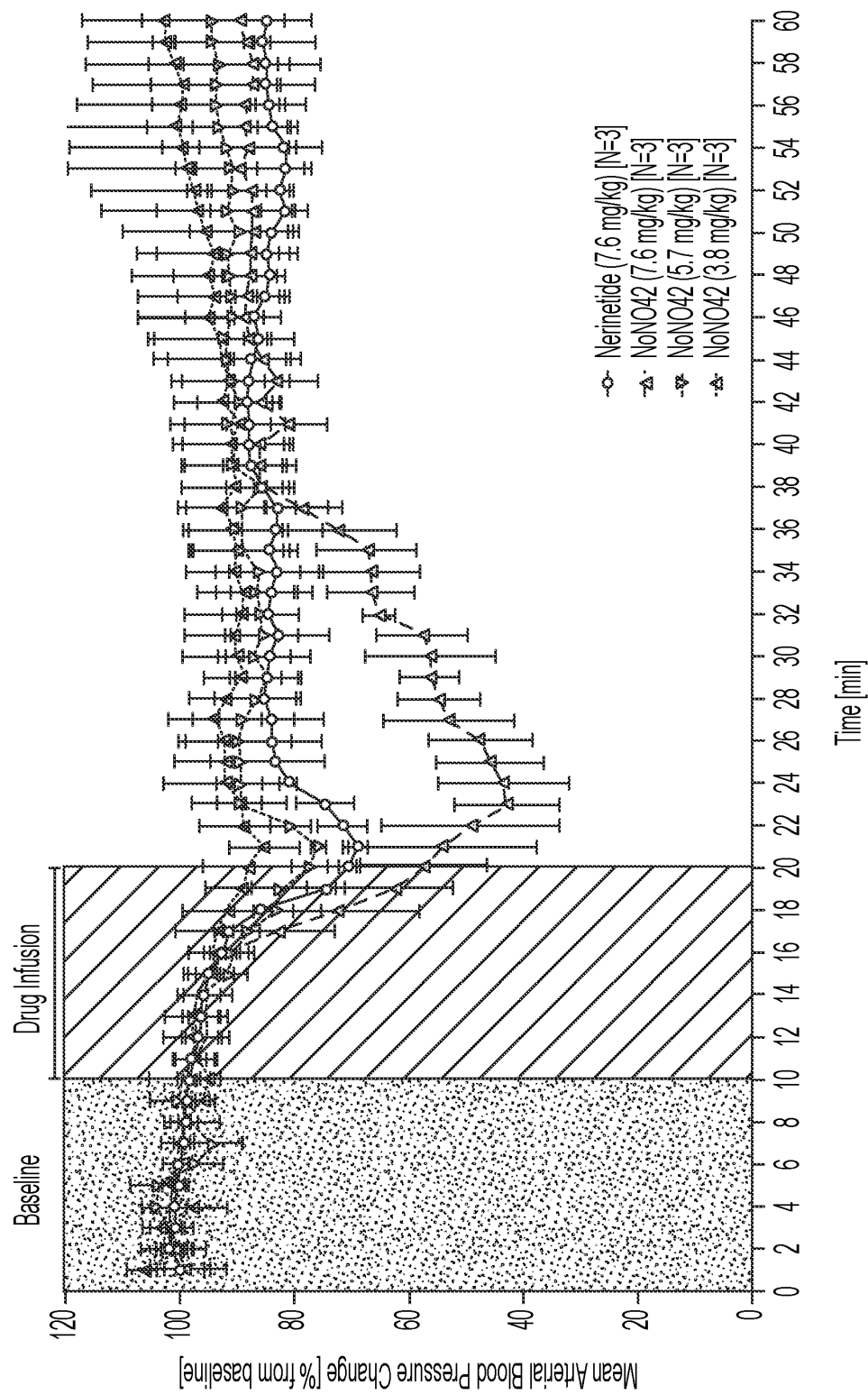


FIG. 33

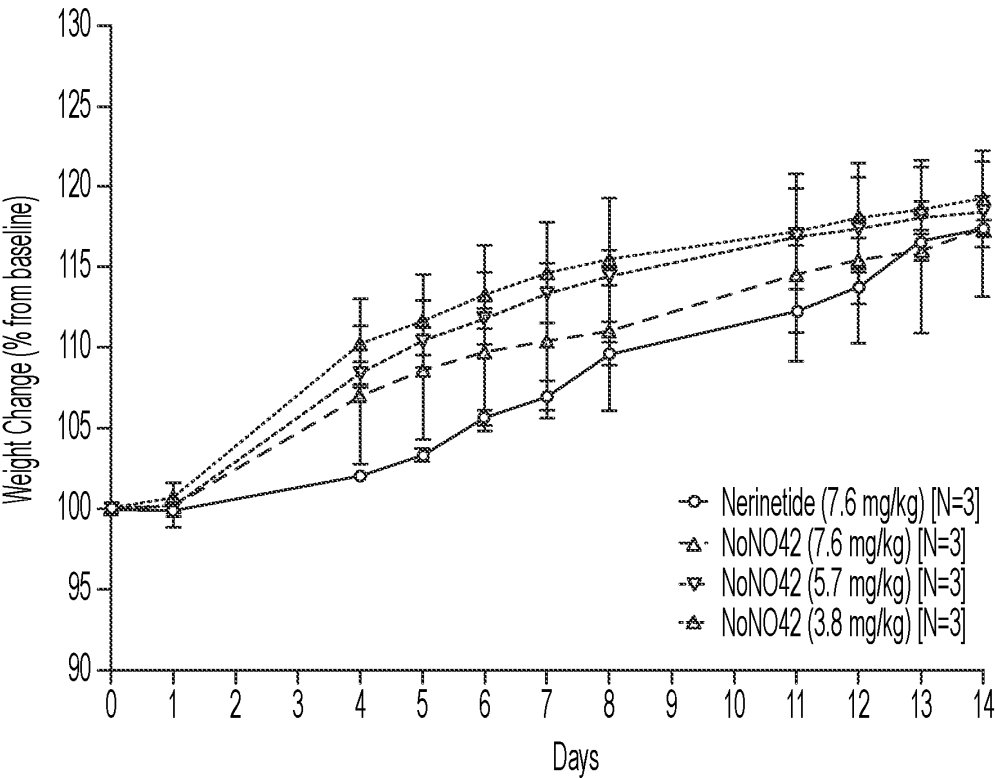


FIG. 34