

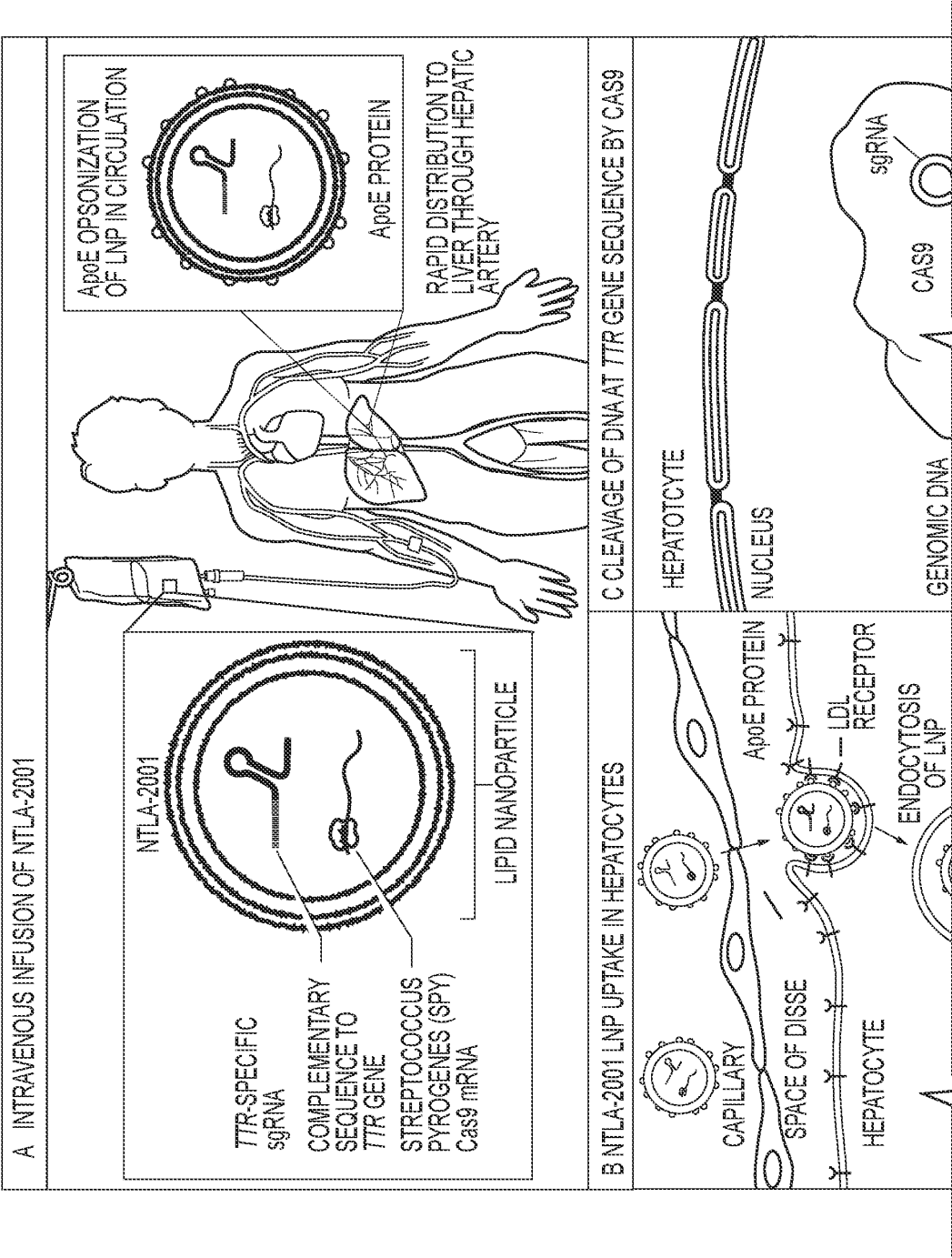


FIG. 1

TO FIG. 1 (CONT)

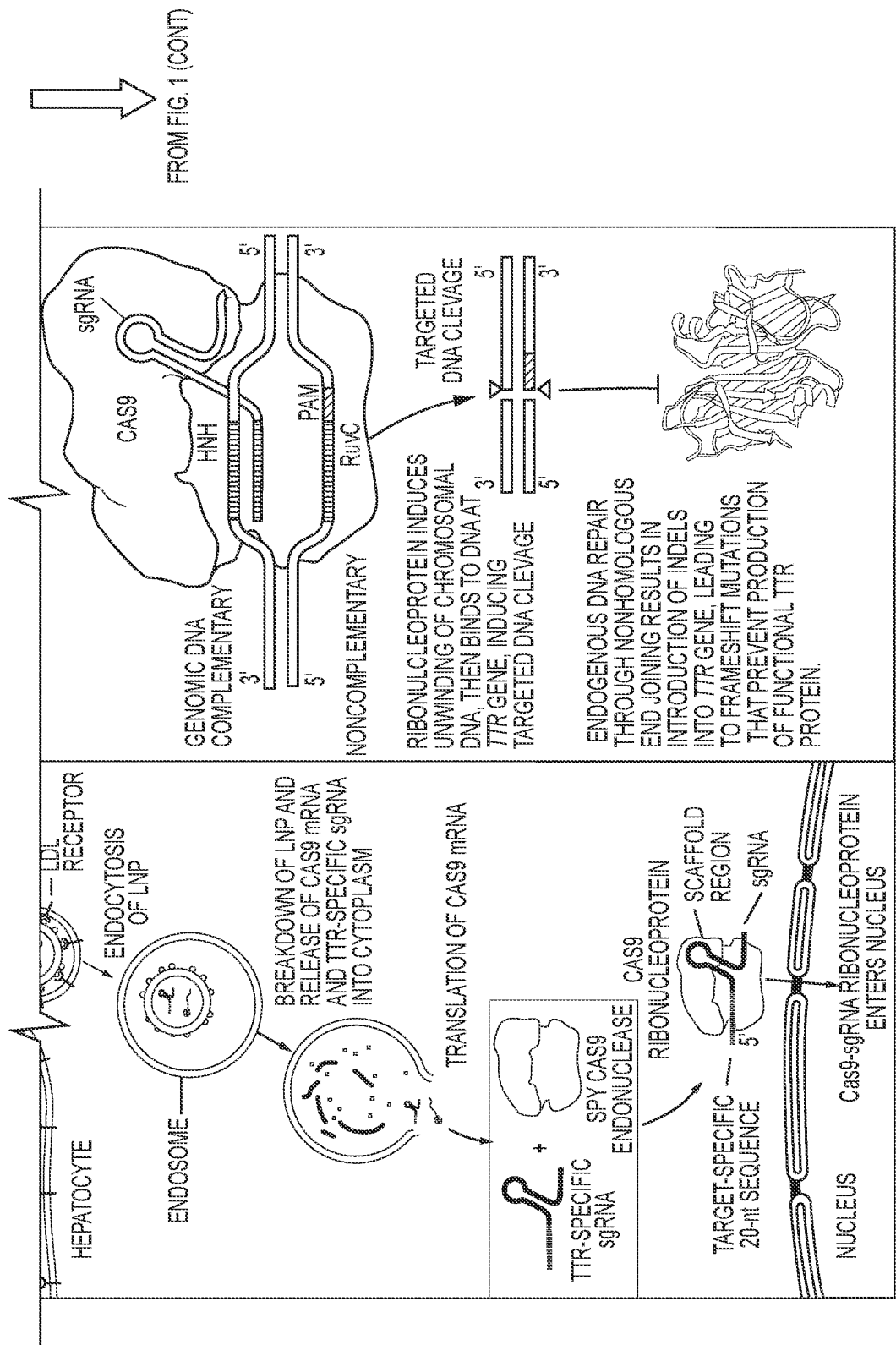


FIG. 1 (CONT.)

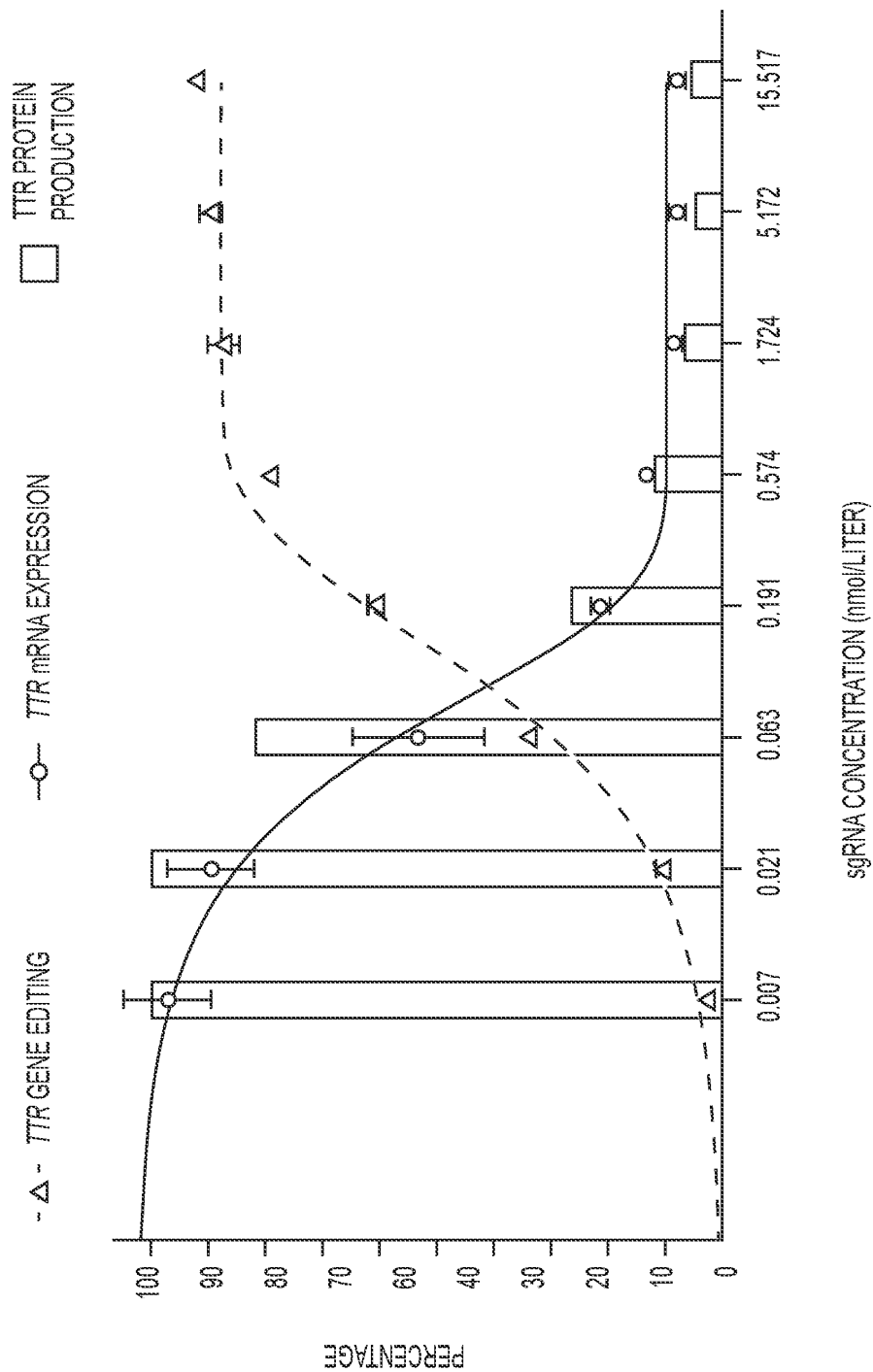


FIG. 2

FIG. 3A

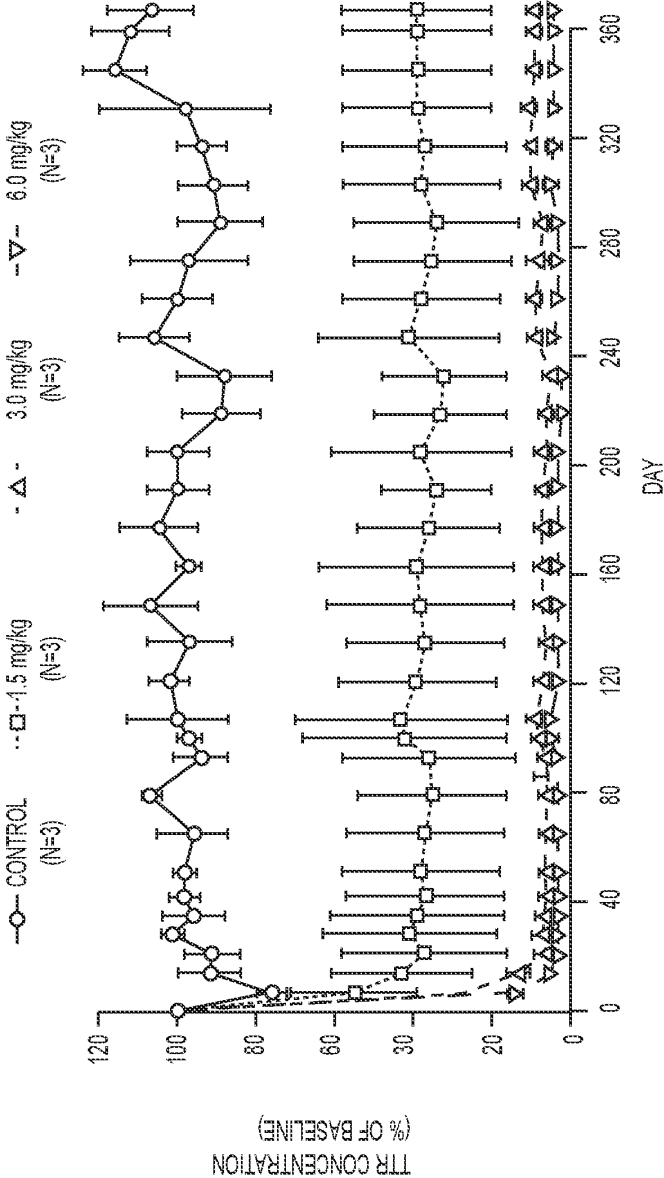


FIG. 3B

INDEL SIZE	SEQUENCE	INDEL FREQUENCY %
WILD TYPE	AGACACAAATACCAGTCCAGCGAGGCAGAG [G/A] AGGAGCAG	—
+1	AGACACAAATACCAGTCCAAGCGAGGCAGAG [G/A] AGGAGCAG	98.9
>+1	AGACACAAATACCAGTCCANCGCGAGGCAGAG [G/A] AGGAGCAG	1.03

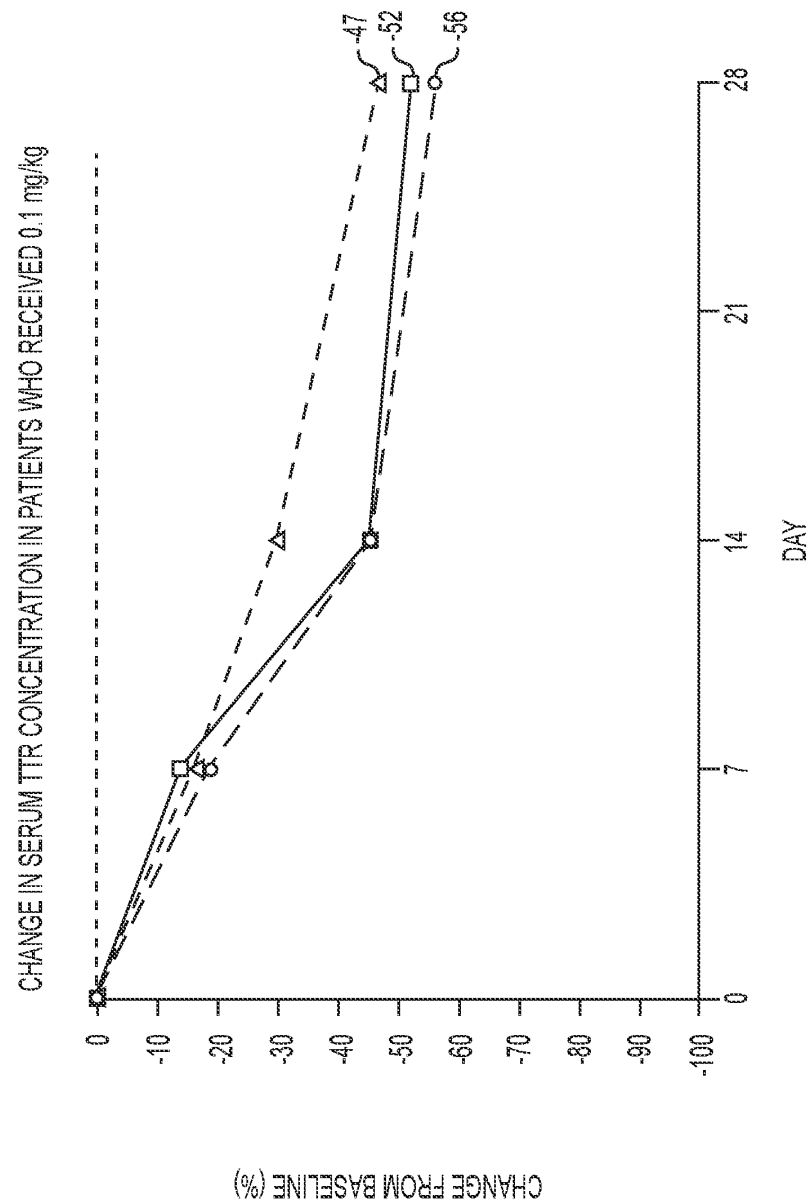


FIG. 4A

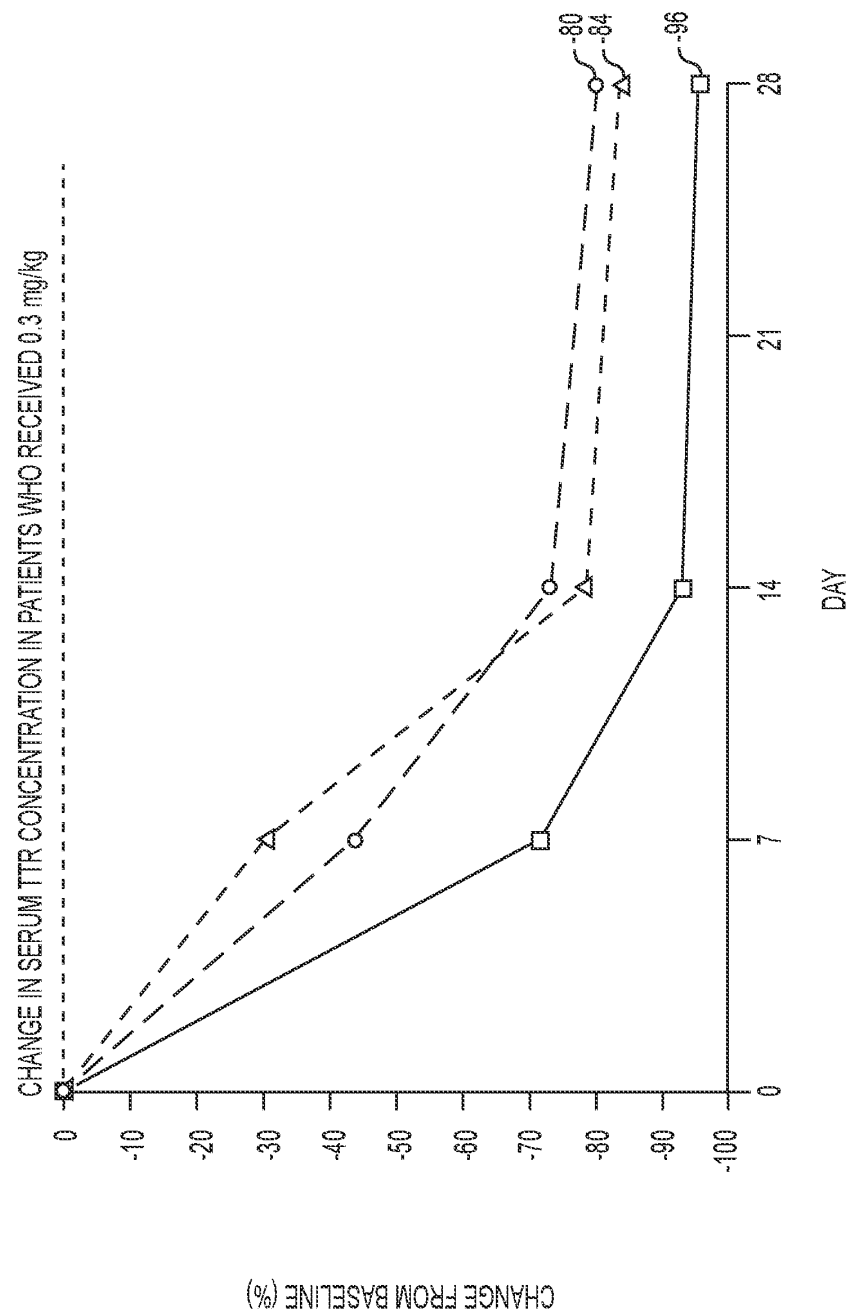


FIG. 4B

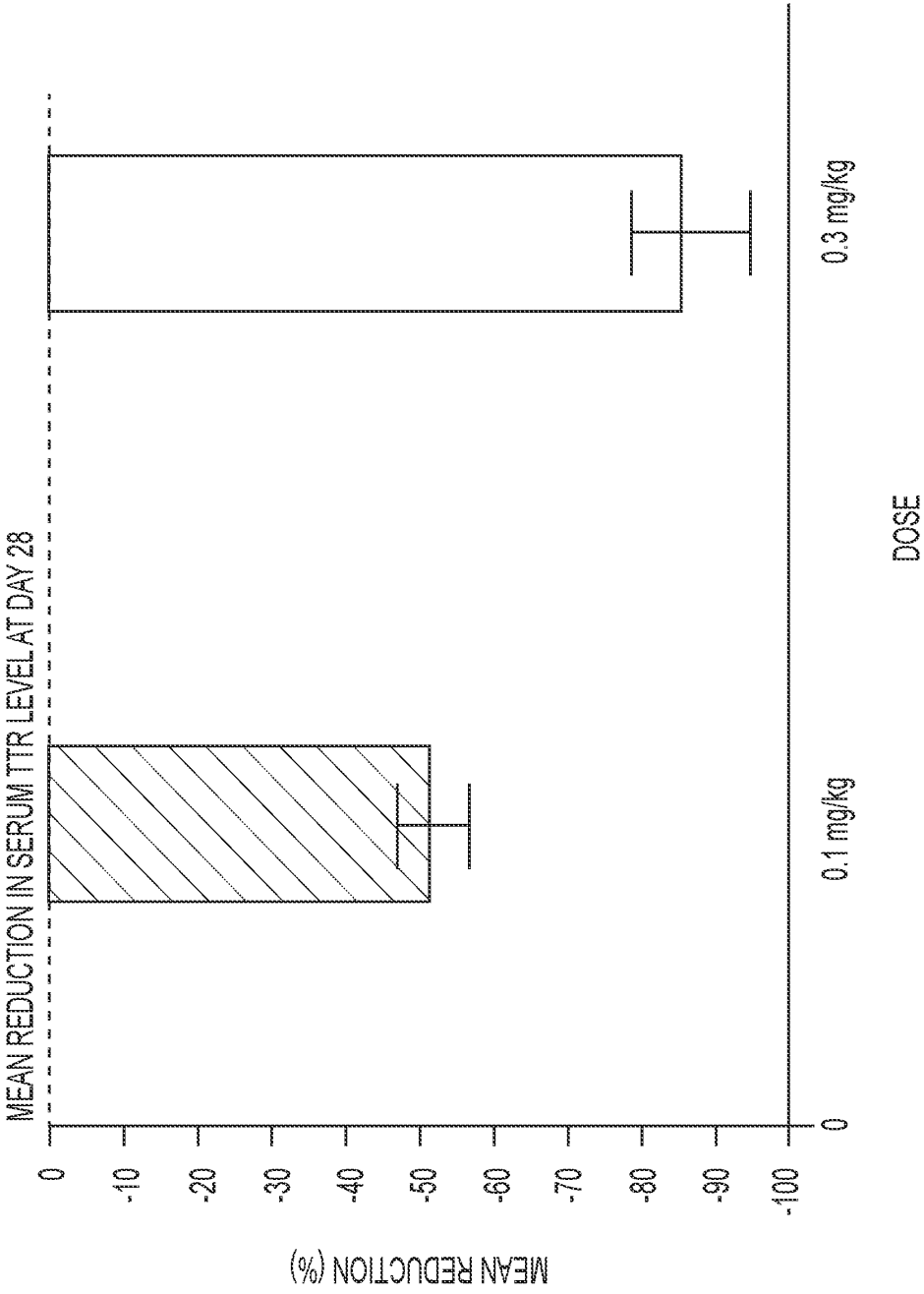


FIG. 4C

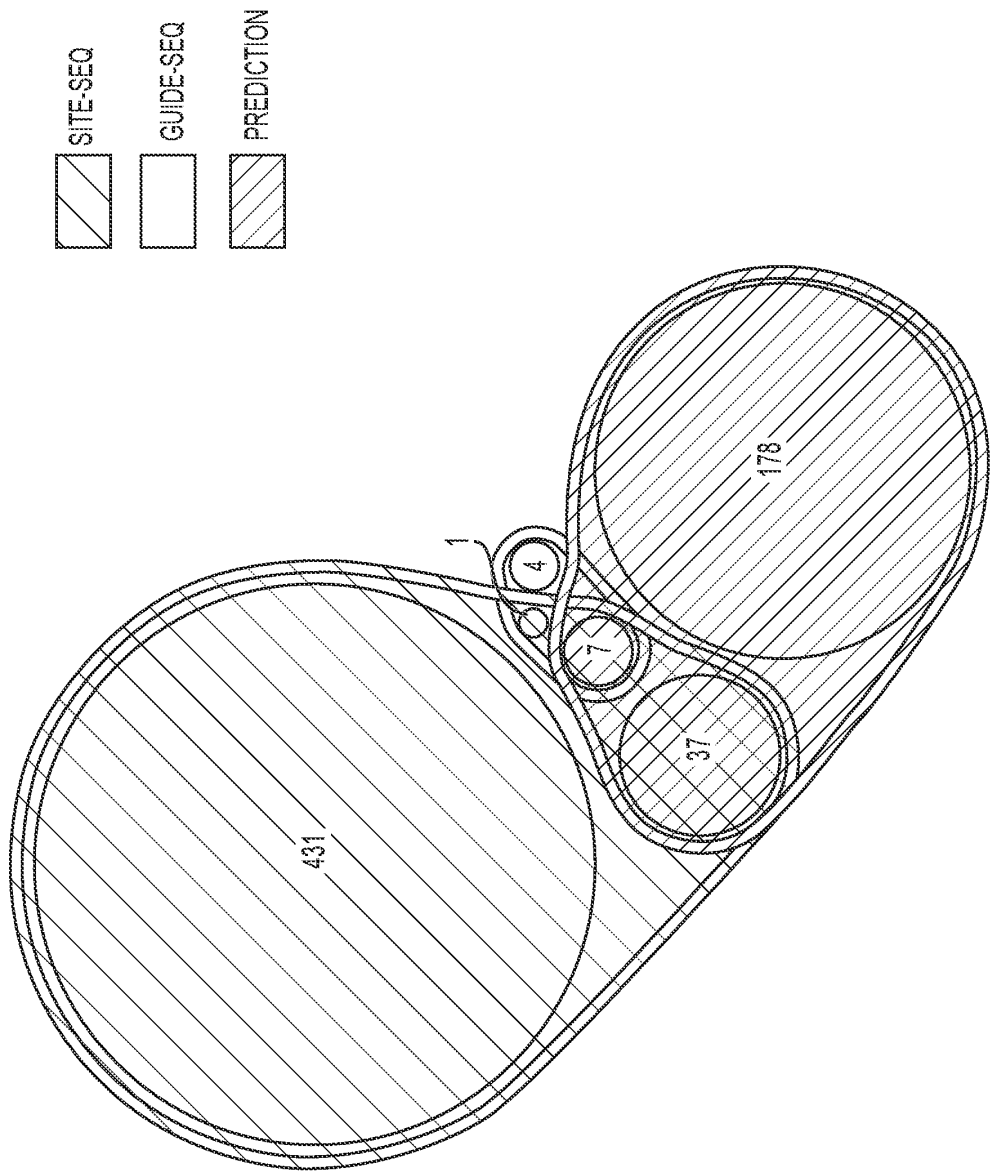


FIG. 5

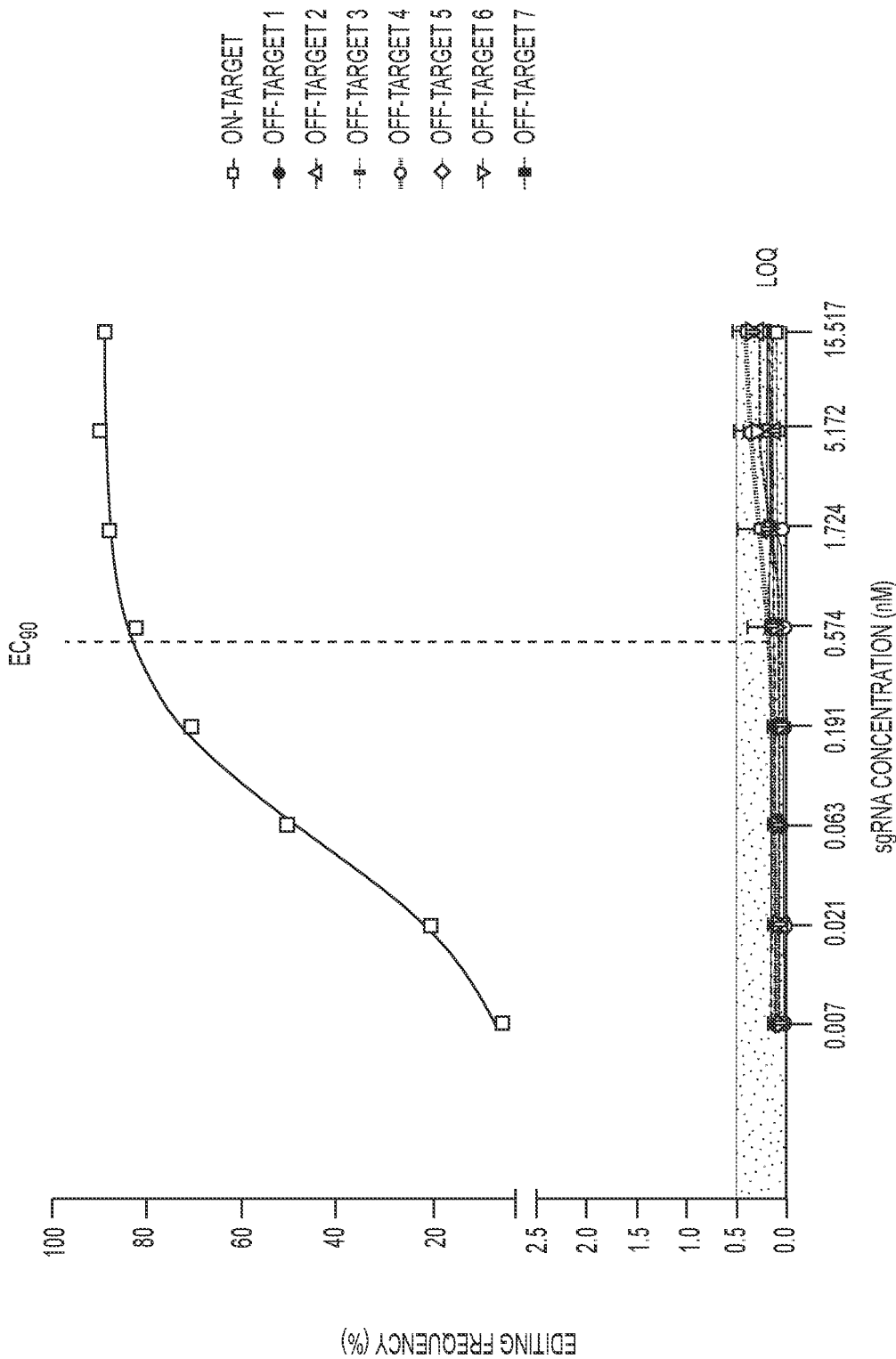


FIG. 6A

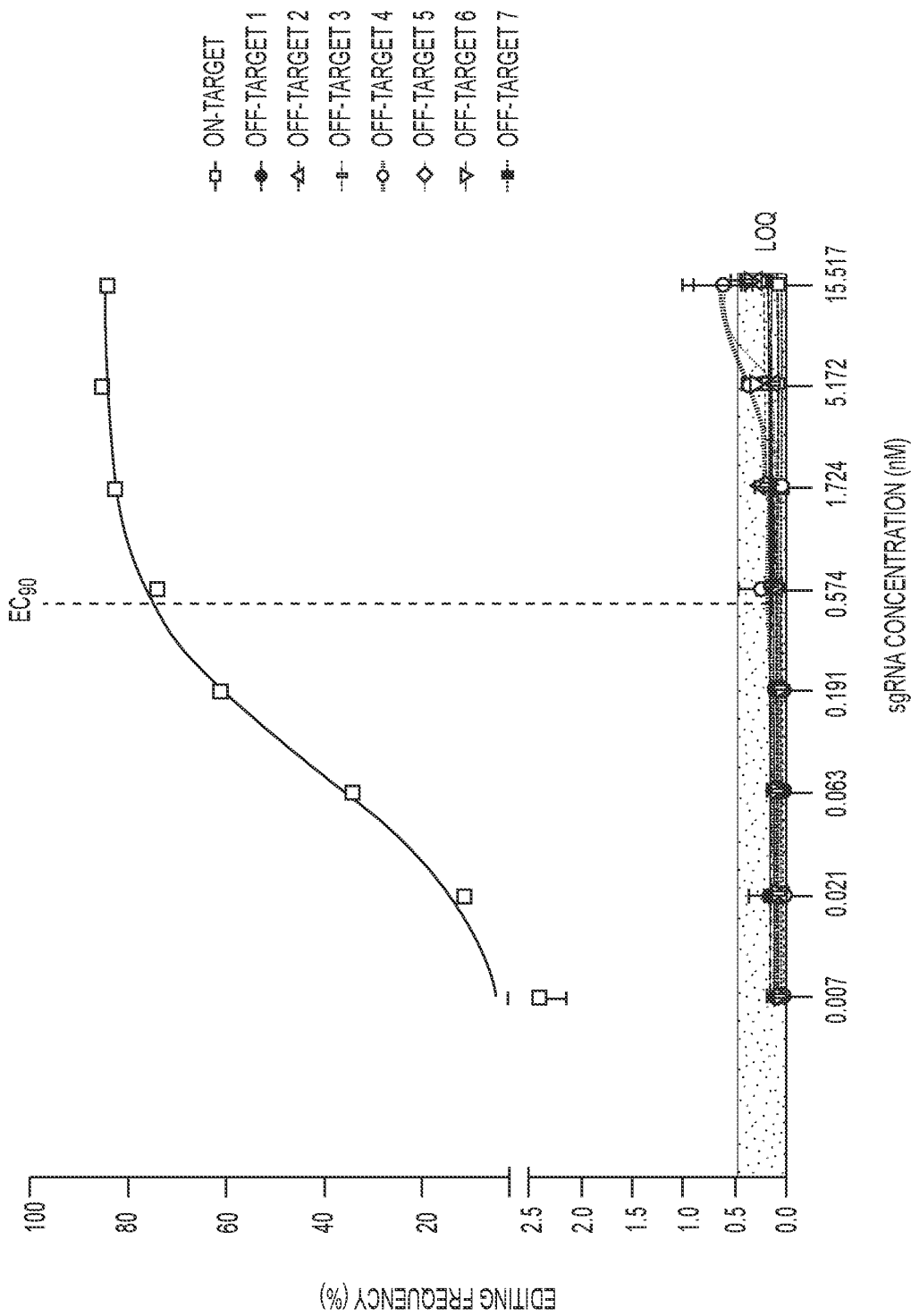


FIG. 6B

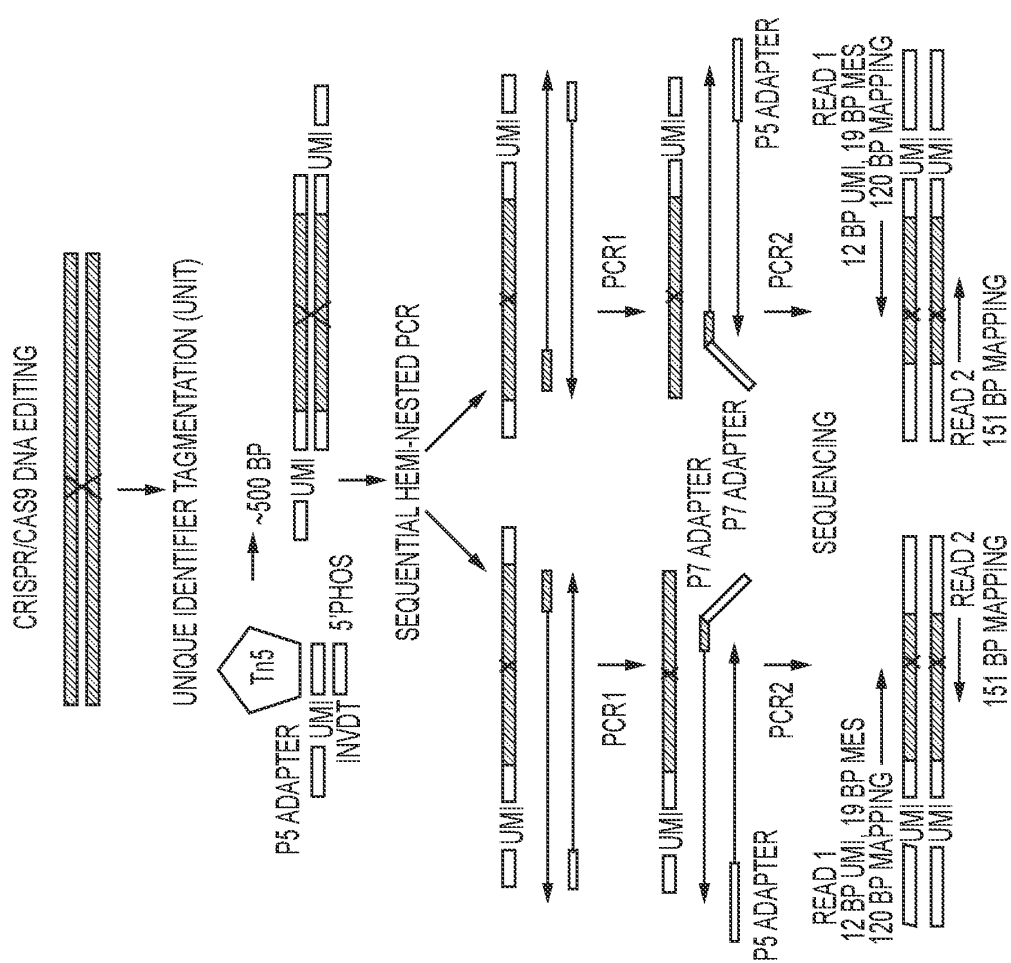


FIG. 7

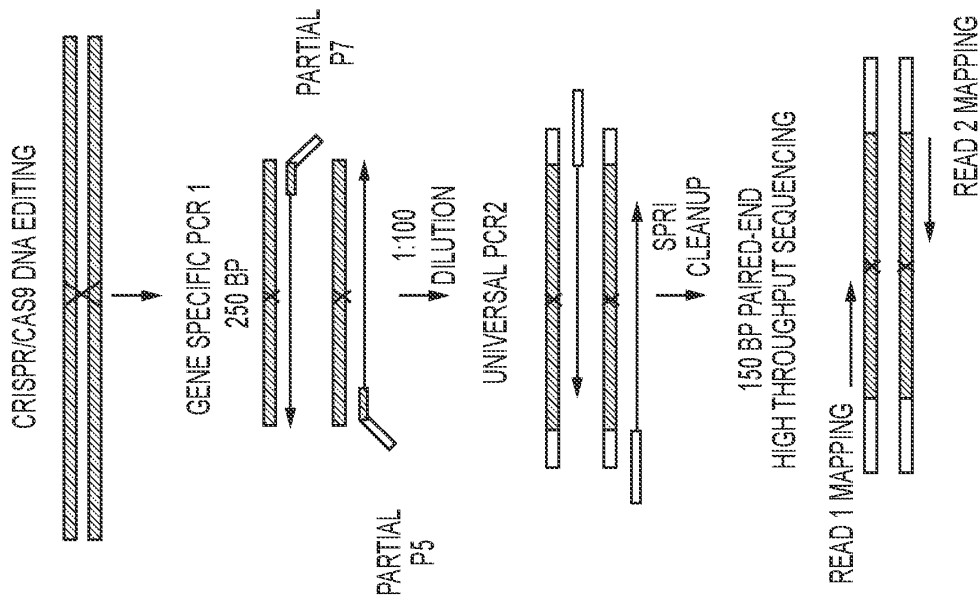


FIG. 8A

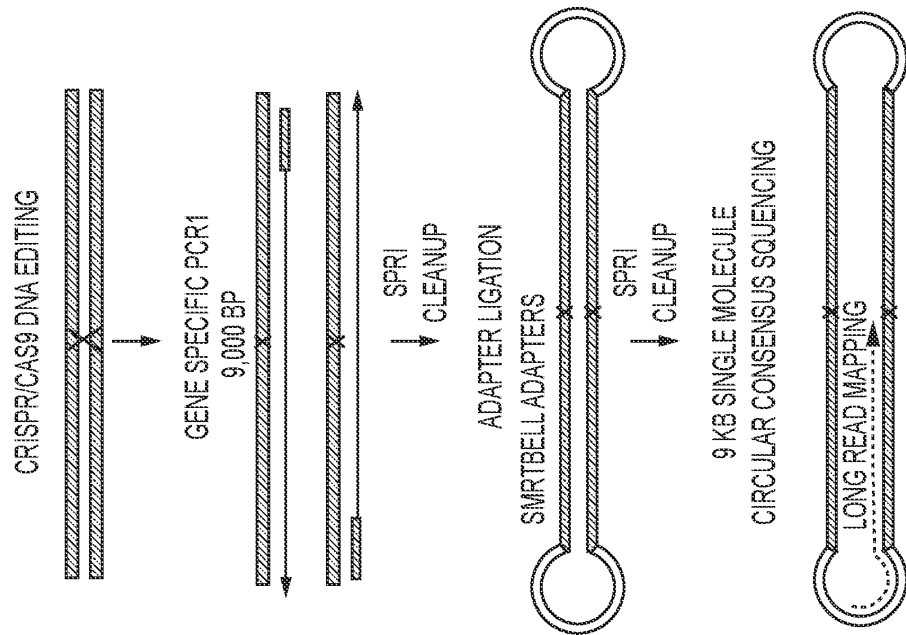


FIG. 8B

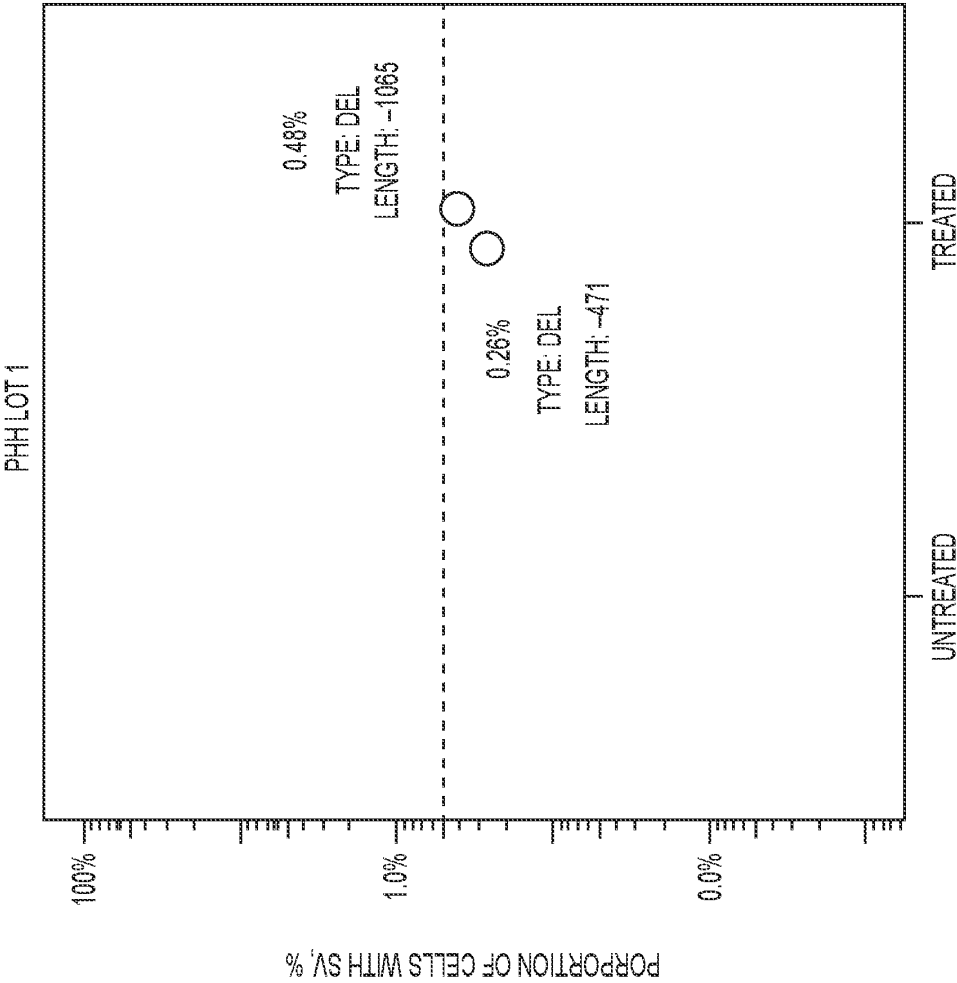


FIG. 9

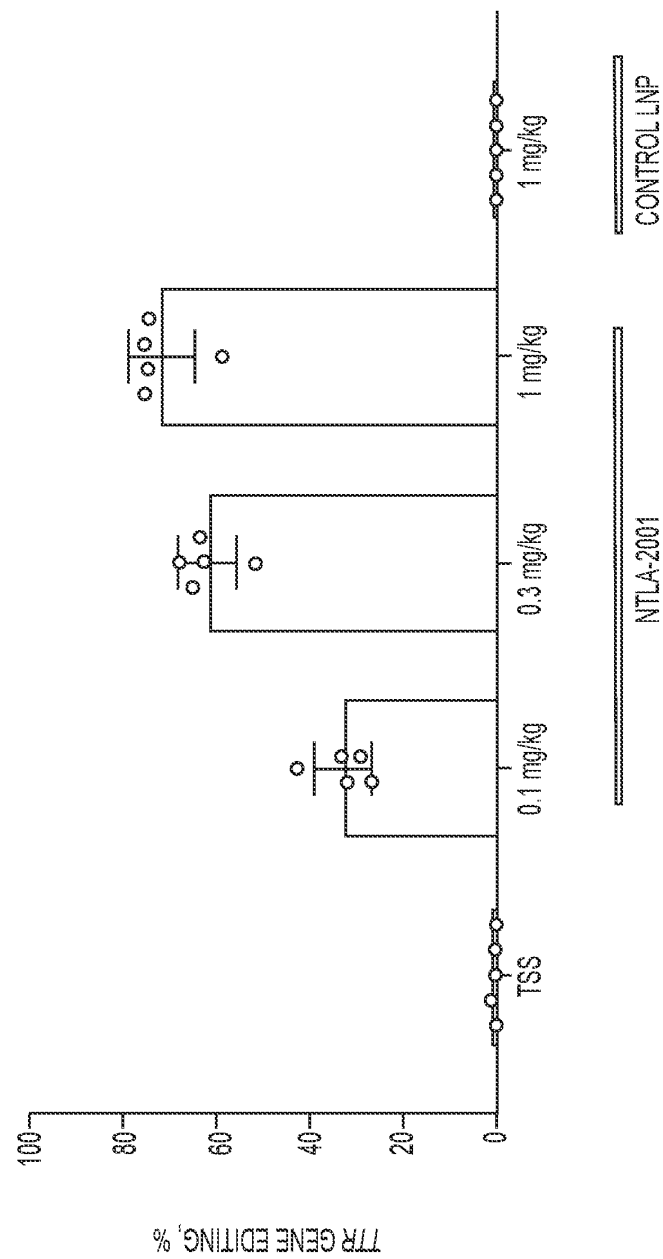


FIG. 10A

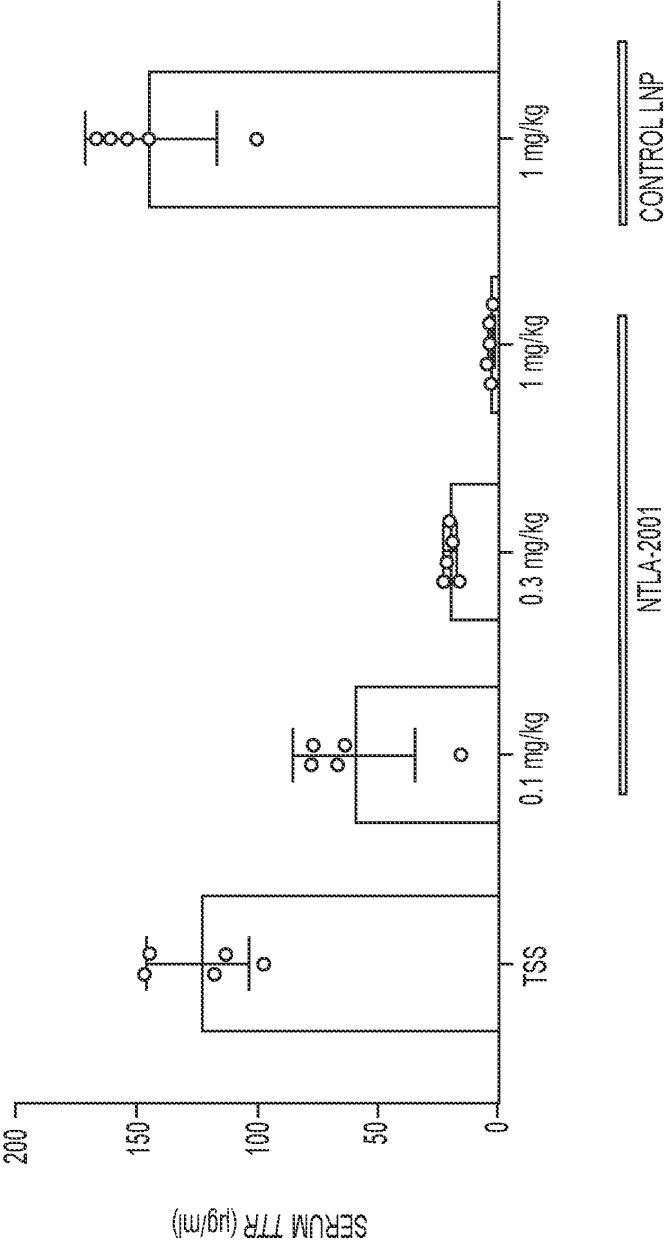


FIG. 10B

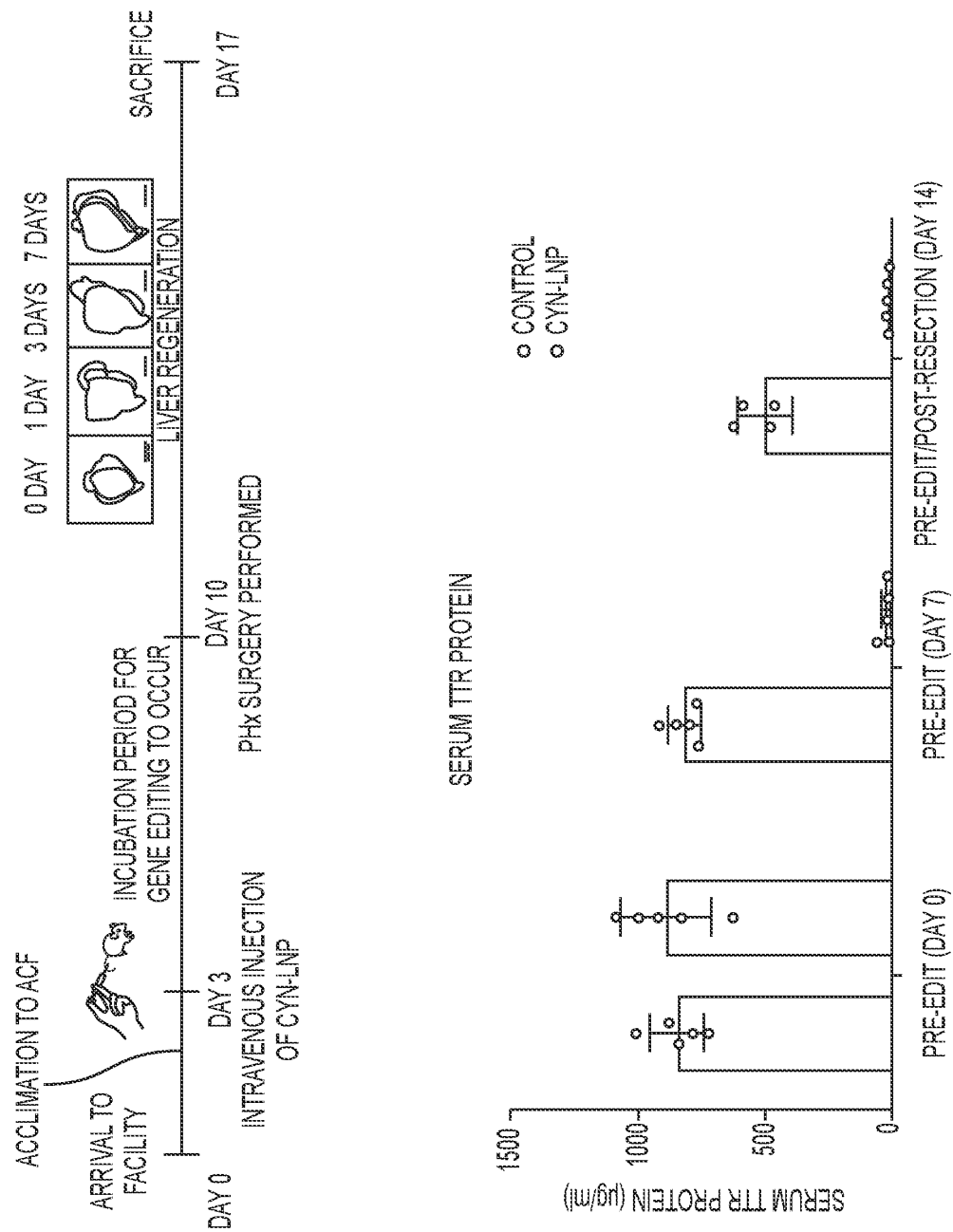


FIG. 11

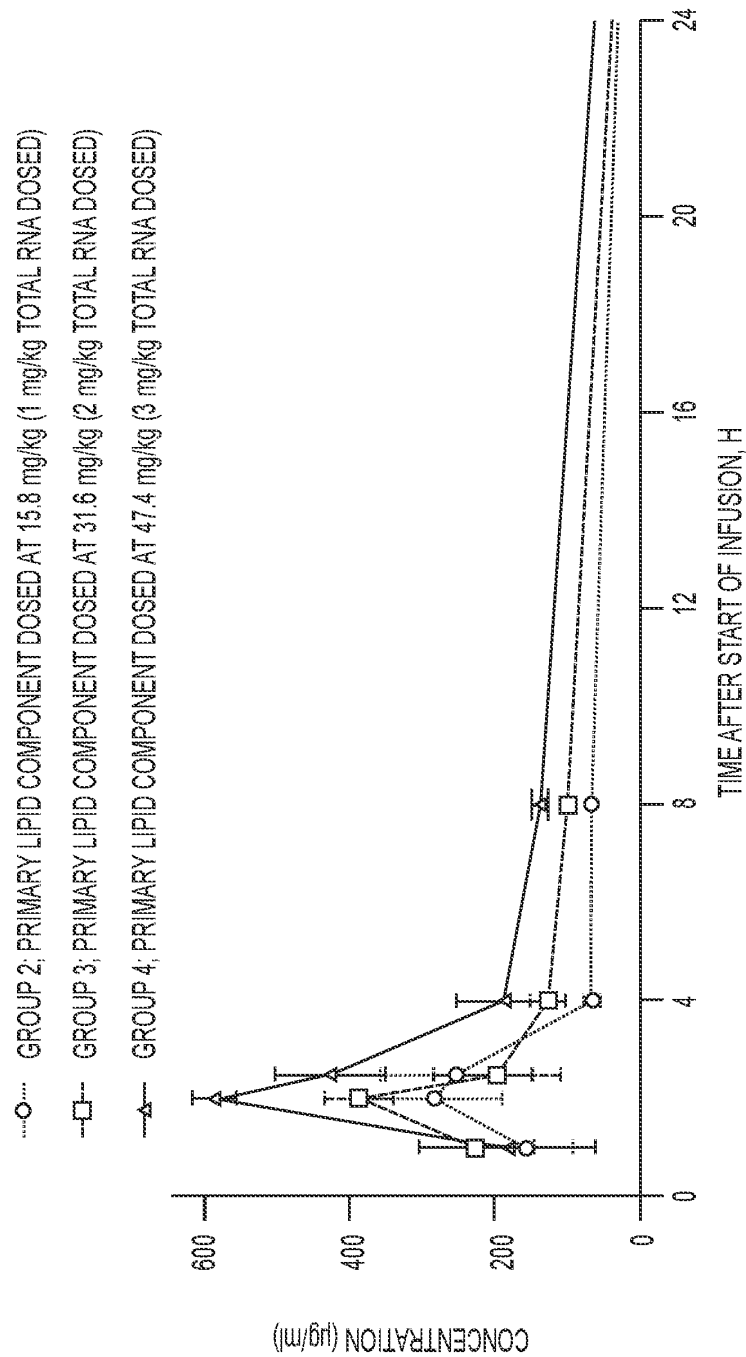


FIG. 12

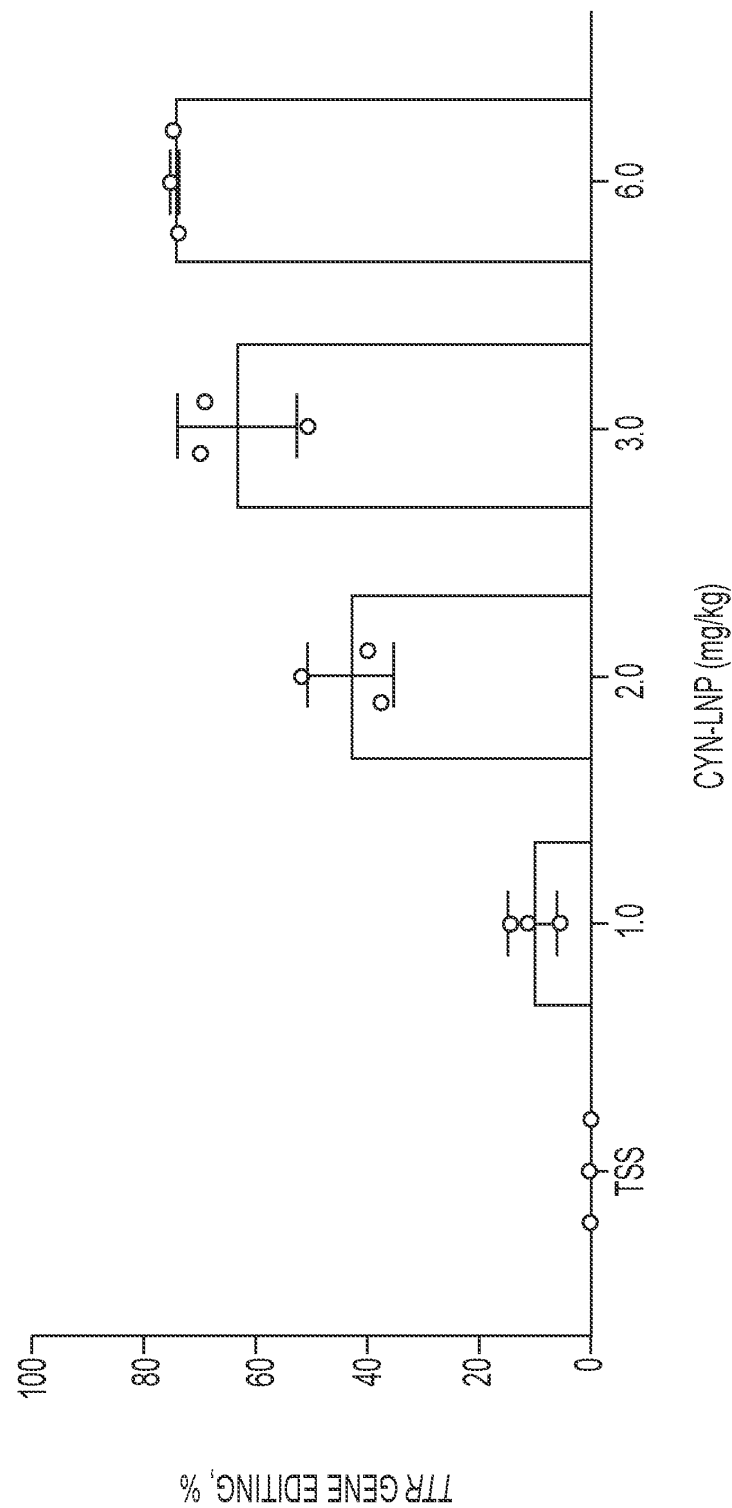


FIG. 13A

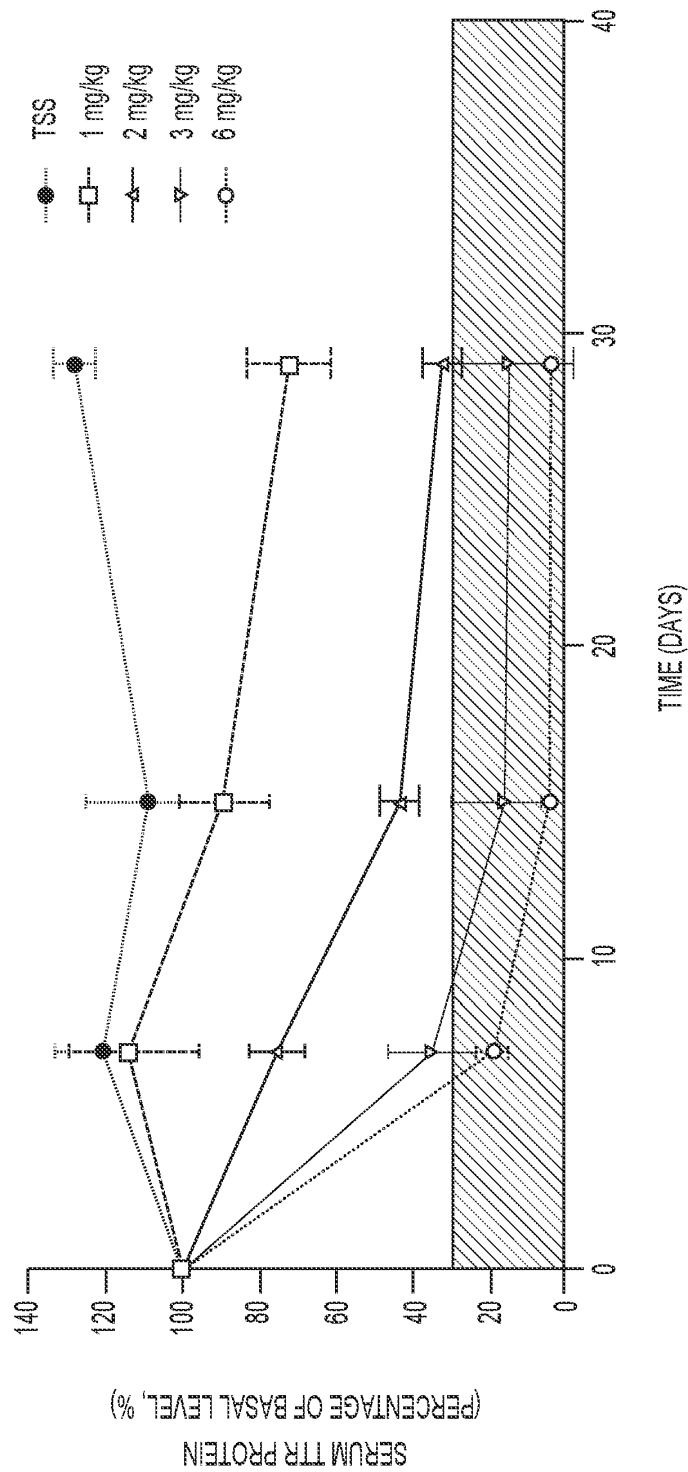


FIG. 13B

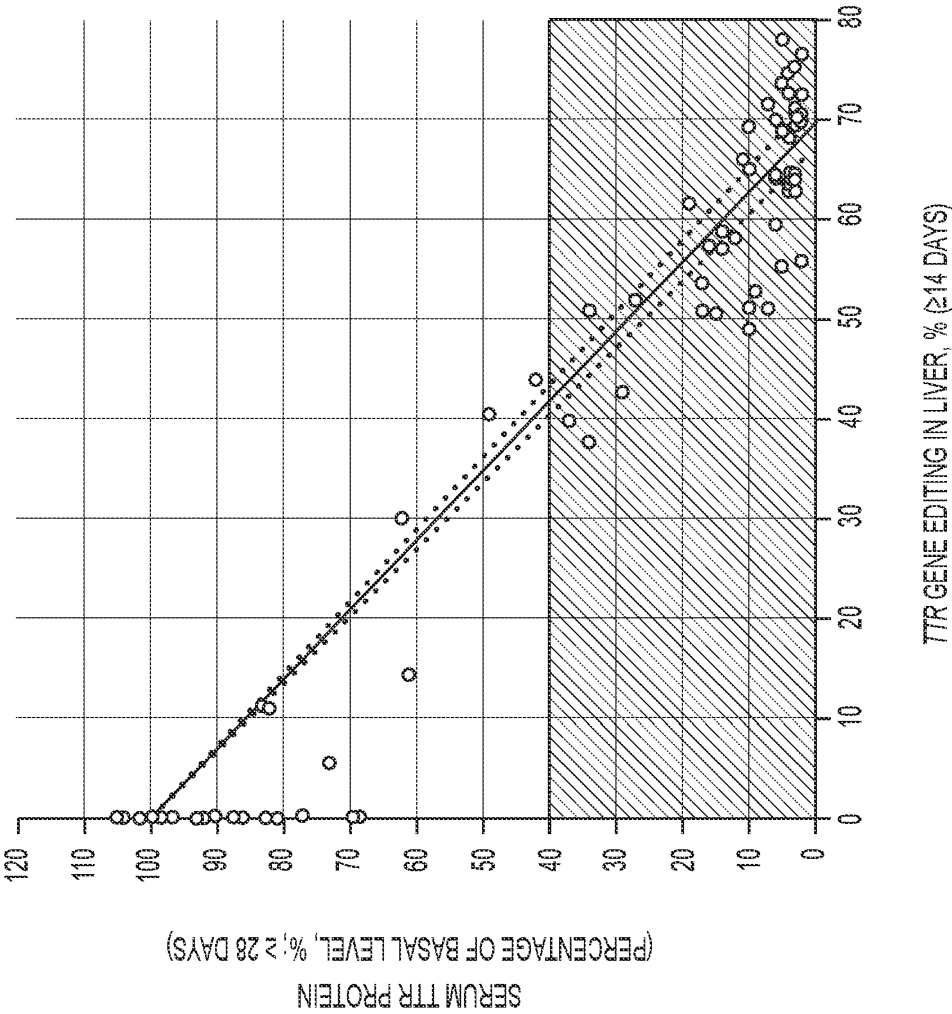


FIG. 14

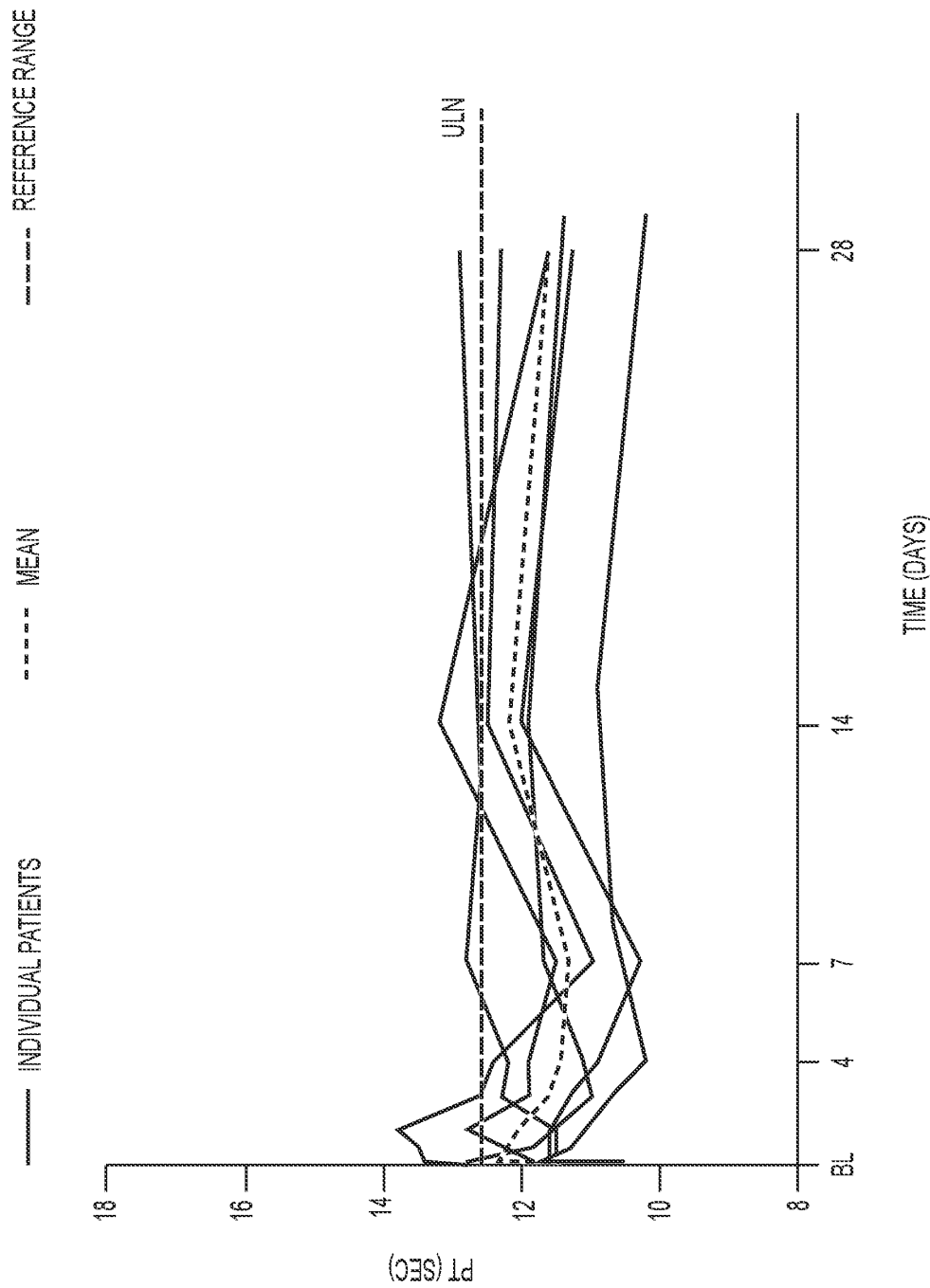


FIG. 15A

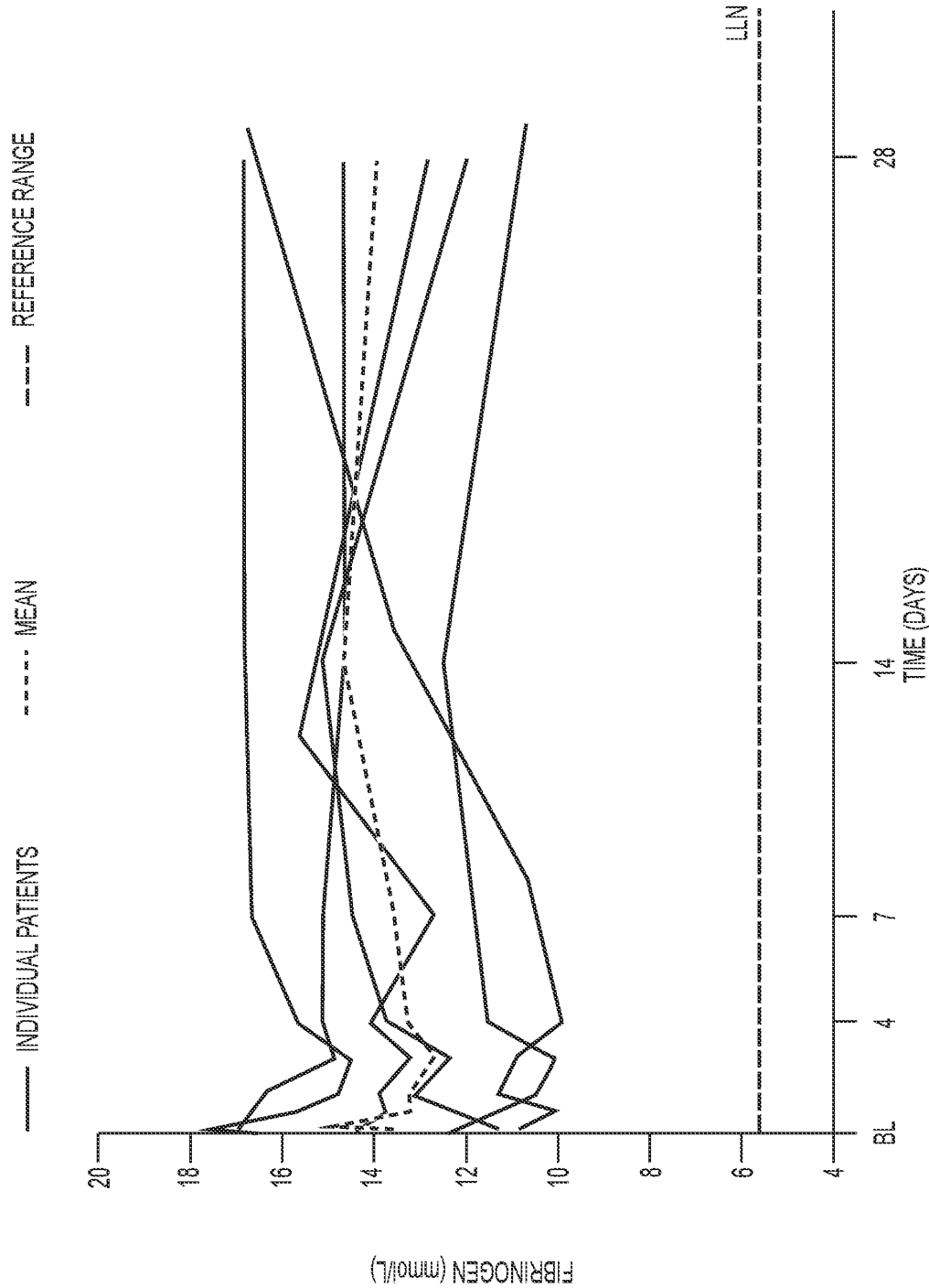


FIG. 15B

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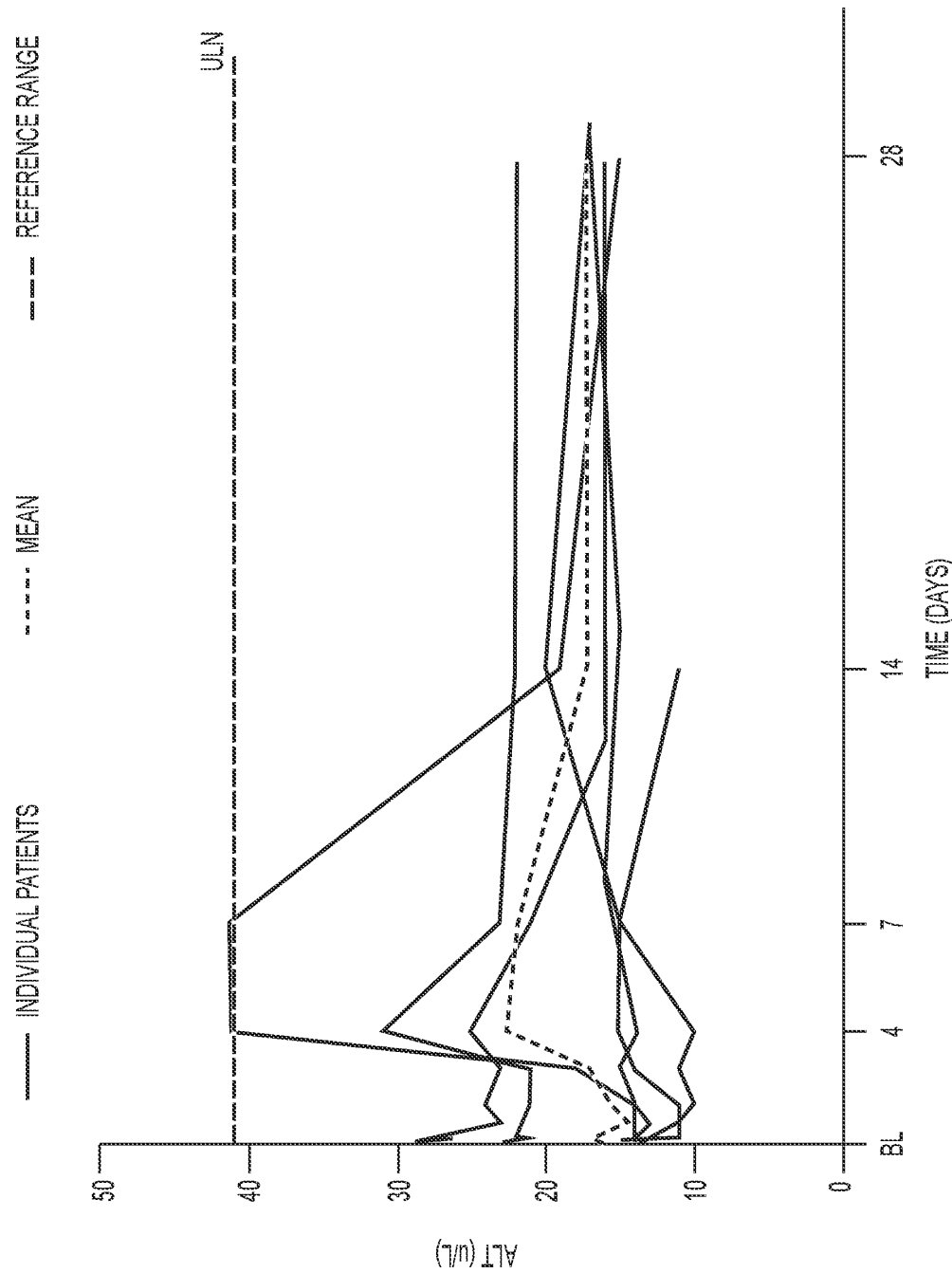


FIG. 15C

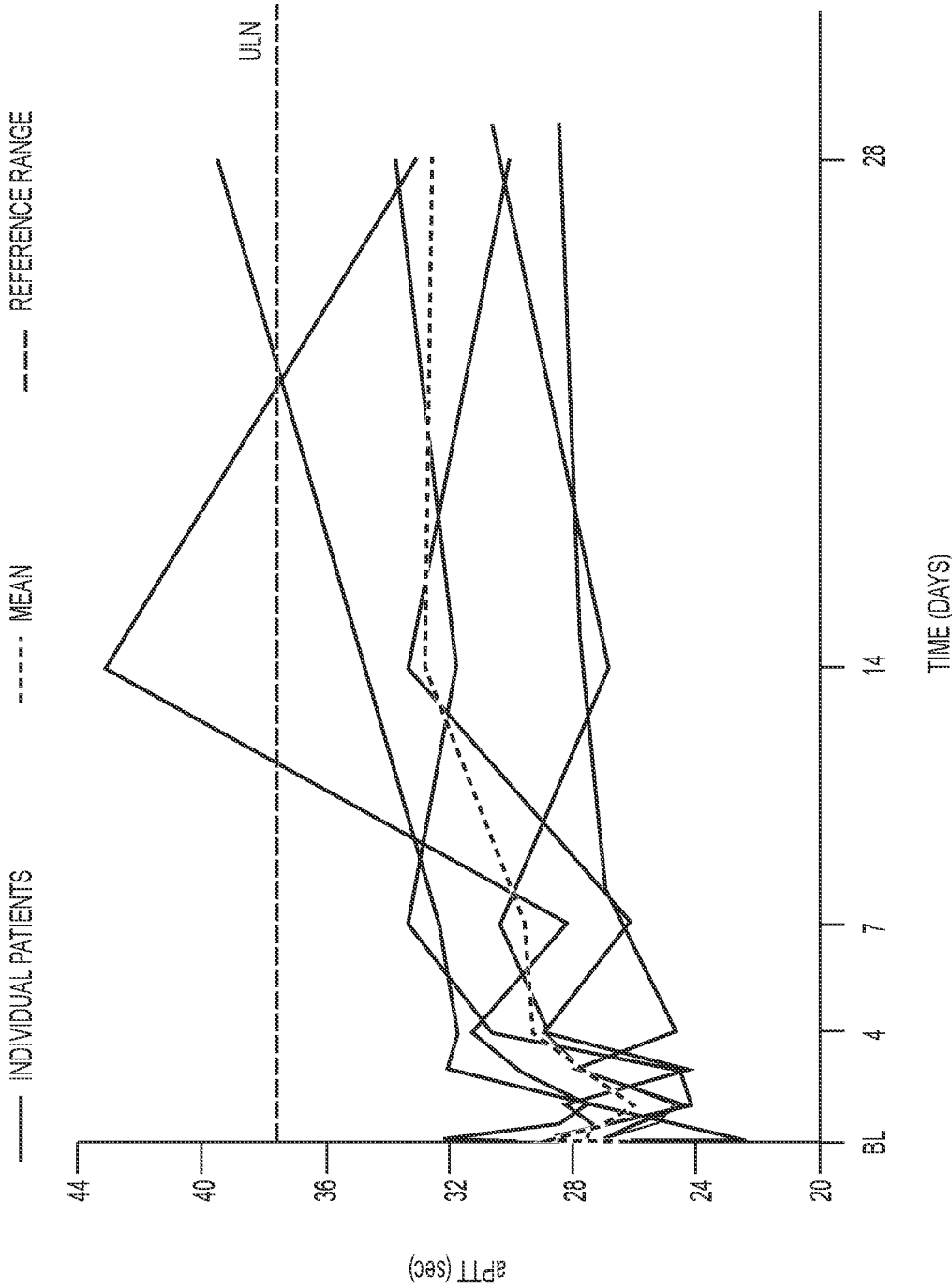


FIG. 15D

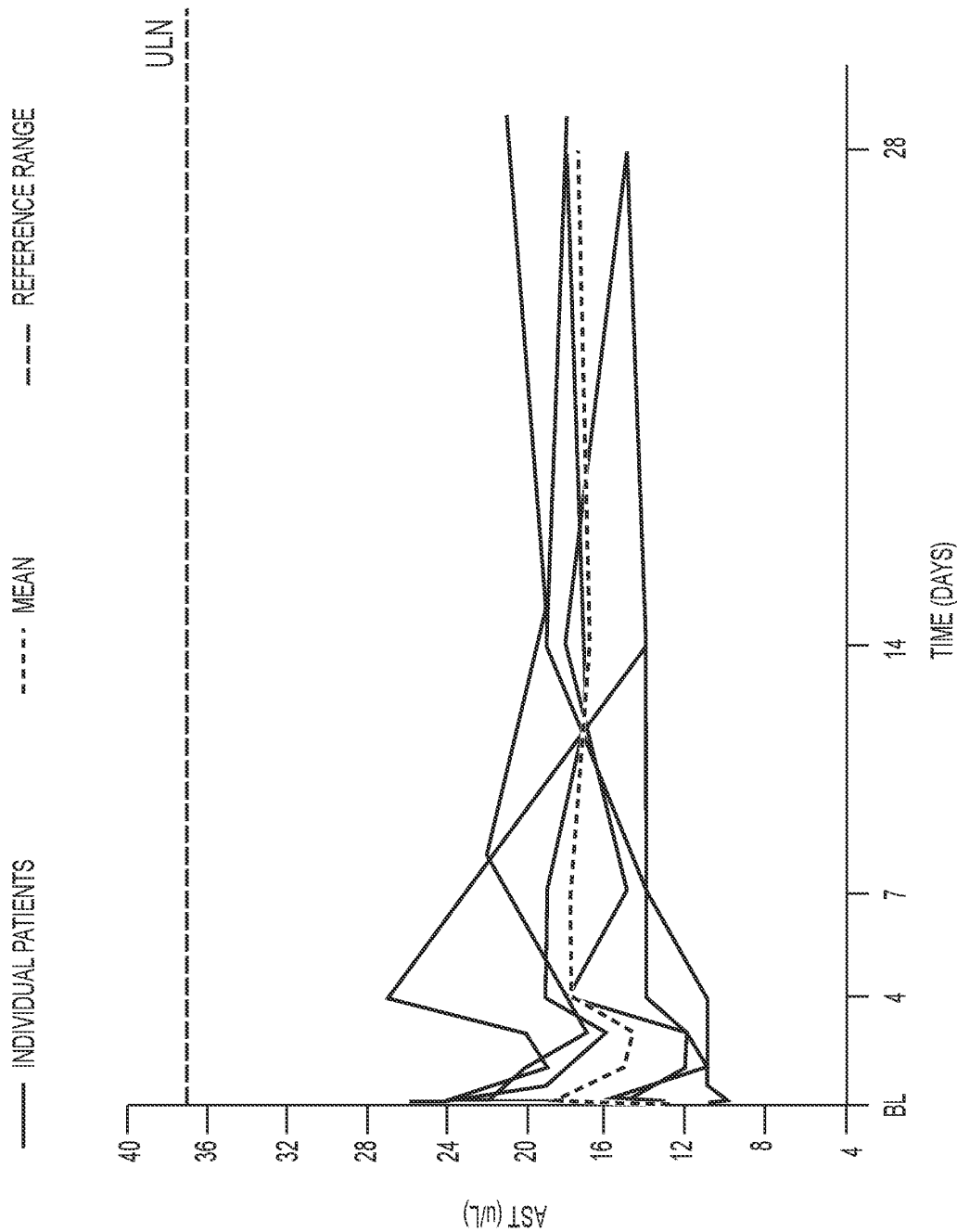


FIG. 15E

GROUP	TOTAL RNA DOSE (MG/KG)	ANALYTE	ANALYTE DOSE (MG/KG)	C _{MAX} (NG/ML)	T _{MAX} (HR)	AUC _{LAST} (HR*NG/ML)	AUC _{INF} (HR*NG/ML)	CI (ML/MIN/KG)	T _{1/2} (HR)	VZ (L/KG)
2	1	PRIMARY LIPID	15.8	346,000 (7.26)	2 (2.00-2.50)	2,100,000 (11.1)	2,100,000 (11.1)	0.127 (11.5)	13.6 (7.79)	0.15 (15.5)
		PEG2000	2.70	50,500 (16.9)	2 (2.00-2.50)	136,000 (15.7)	136,000 (15.7)	0.335 (15.6)	2.82 (22)	0.0811 (22.5)
		CYN-sgRNA	0.333	2,730 (38.7)	2.25 (2.00-2.50)	26,000 (13.5)	23,600 NC	0.235 NC	19.1 NC	0.388 NC
		CAS9 mRNA	0.667	4,400 (25.6)	2 (2.00-2.50)	32,300 (62.1)	32,300 (62.1)	0.535 (88.5)	13.9 (29.1)	0.592 (77.8)
3	2	PRIMARY LIPID	31.6	388,000 (12.1)	2 (2.00-2.00)	2,790,000 (13.4)	2,790,000 (13.4)	0.191 (13.2)	13.5 (6.43)	0.224 (19)
		PEG2000	5.40	71,900 (3.23)	2 (2.00-2.00)	216,000 (6.36)	216,000 (6.33)	0.418 (6.46)	3.26 (57.7)	0.121 (64.3)
		CYN-sgRNA	0.667	4,470 (16)	2 (2.00-2.00)	30,600 (7.08)	30,800 (7.24)	0.362 (7.44)	16.8 (7.2)	0.527 (8)
		CAS9 mRNA	1.33	6,670 (37.5)	2 (1.00-2.00)	47,700 (9.65)	47,700 (9.64)	0.468 (9.79)	15.1 (4.91)	0.614 (13.7)
4	3	PRIMARY LIPID	47.4	586,000 (5.26)	2 (2.00-2.00)	4,450,000 (7.79)	4,450,000 (7.79)	0.178 (8.03)	14.9 (5.45)	0.23 (10)
		PEG2000	8.10	94,600 (11.4)	2 (2.00-2.00)	312,000 (20)	313,000 (20.1)	0.444 (22.3)	5.17 (42.5)	0.187 (25.6)
		CYN-sgRNA	1.00	7,170 (3.61)	2 (2.00-2.00)	52,100 (53.9)	52,400 (53)	0.403 (62.1)	20.7 (25.9)	0.726 (71.6)
		CAS9 mRNA	2.00	14,400 (23.1)	2 (2.00-2.00)	130,000 (53)	130,000 (53)	0.305 (46.1)	14.9 (31)	0.367 (36.4)

GIVEN THE HUMAN-SPECIFIC PHARMACOLOGIC ACTIVITY OF NTLA-2001, A SURROGATE PRODUCT, CYN-LNP, DIFFERING ONLY IN THE NUCLEOTIDE SEQUENCE OF THE TARGETING REGION IN THE sgRNA, WAS USED FOR CYNOMOLGUS STUDIES.
DATA PRESENTED AS MEAN (CV%) EXCEPT T_{MAX} PRESENTED AS MEDIAN (MIN- MAX). ALL INFUSIONS WERE FOR 2 HOURS.
ANALYTE DOSE USED IN NON-COMPARTMENTAL ANALYSIS.

FIG. 16

PREFERRED TERM	ALL PATIENTS RECEIVING 0.1 MG/KG DOSE (N = 3)		ALL PATIENTS RECEIVING 0.3 MG/KG DOSE (N = 3)		ALL PATIENTS	
	RELATED	NOT RELATED	RELATED	NOT RELATED	RELATED	NOT RELATED
DIARRHEA	0	1 (33.3%)	0	0	0	1 (16.7%)
NAUSEA	1 (33.3%)	0	0	0	1 (16.7%)	0
INFUSION-RELATED REACTION	1 (33.3%)	0	0	0	1 (16.7%)	0
SKIN ABRASION	0	0	0	1 (33.3%)	0	1 (16.7%)
HEADACHE	1 (33.3%)	1 (33.3%)	0	0	1 (16.7%)	1 (16.7%)
VERTIGO POSITIONAL	0	1 (33.3%)	0	0	0	1 (16.7%)
FOREIGN BODY SENSATION IN EYES	0	1 (33.3%)	0	0	0	1 (16.7%)
CATHETER SITE SWELLING	0	1 (33.3%)	0	0	0	1 (16.7%)
ACUTE SINUSITIS	0	1 (33.3%)	0	0	0	1 (16.7%)
THYROXINE DECREASED	1 (33.3%)	0	0	0	1 (16.7%)	0
RHINORRHEA	1 (33.3%)	0	0	0	1 (16.7%)	0
PRURITUS	0	1 (33.3%)	0	0	0	1 (16.7%)
RASH	0	1 (33.3%)	0	0	0	1 (16.7%)

FOR EACH PREFERRED TERM SUBJECTS REPORTING MORE THAN ONE ADVERSE EVENT ARE COUNTED ONLY ONCE USING THE CLOSEST RELATIONSHIP TO STUDY DRUG. ADVERSE EVENTS ARE CODED TO SYSTEM ORGAN CLASS AND PREFERRED TERM USING MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES, VERSION 23.0. RELATED INCLUDES ALL EVENTS REPORTED AS POSSIBLY OR PROBABLY RELATED TO STUDY DRUG AFTER INVESTIGATOR ASSESSMENT.

FIG. 17

PARAMETER	ALL PATIENTS RECEIVING 0.1 MG/KG DOSE (N = 3)	ALL PATIENTS RECEIVING 0.3 MG/KG DOSE (N = 3)	ALL PATIENTS (N = 6)
AGE, YEARS MEDIAN (MIN, MAX)	54 (50, 63)	53 (46, 64)	53.5 (46, 64)
SEX, N (%)			
MALE	1 (33.3%)	3 (100%)	4 (66.7%)
FEMALE	2 (66.7%)	0	2 (33.3%)
WEIGHT, KG MEDIAN (MIN, MAX)	82 (70, 89)	84 (83, 90)	84 (70, 90)
MUTATION STATUS, N (%)			
P. H110D	0	1 (33%)	1 (17%)
P. S97Y	1 (33%)	1 (33%)	2 (33%)
P. T80A	2 (67%)	1 (33%)	3 (50%)
PRIOR THERAPY, N (%)			
NONE	1 (33%)	2 (67%)	3 (50%)
DIFLUNISAL	2 (67%)	1 (33%)	3 (50%)
CLINICAL SCORES, N (%)			
POLYNEUROPATHY DISABILITY SCORE 1	3 (100%)	3 (100%)	6 (100%)
NYHA FUNCTIONAL CLASSIFICATION I	3 (100%)	3 (100%)	6 (100%)
NT-PROBNP (NG/L), MEDIAN (MIN, MAX)	127 (89, 596)	119 (50, 359)	123 (50, 596)
YEARS SINCE DIAGNOSIS (MIN, MAX)	2 (2, 9)	3 (1, 11)	2.5 (1, 11)

FIG. 18

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DOSE (mg/kg)	PATIENT	WEIGHT (kg)	ACTUAL DOSE (mg)	TTR GENOTYPE	NT-PROBNP BASELINE (ng/L)	TIMEPOINT	%TTR REDUCTION
0.1	COHORT1SUBJECT1 (C1S1)	82.1	8.2	S77Y	89.0	DAY 7	-19.00
						DAY 14	-45.63
						DAY 28	-56.47
						DAY 56	-52.67
						MONTH 4	-47.22
						MONTH 6	-46.36
						MONTH 9	-53.35
						DAY 7	-16.34
						DAY 14	-29.97
0.1	C1S2	70.4	7.0	T60A	596.0	DAY 14	-46.75
						DAY 28	-18.89
						MONTH 4	-18.15
						MONTH 6	13.90
						MONTH 9	-20.24
						MONTH 12	-14.12
						DAY 7	-45.28
						DAY 14	-52.30
						DAY 28	-54.69
0.1	C1S3	89.1	8.9	T60A,T80A	127.0	DAY 7	-43.86
						DAY 14	-32.55
						DAY 28	-47.81
						MONTH 4	-43.78
						MONTH 6	-73.40
						MONTH 9	-80.34
						DAY 7	-75.84
						DAY 14	-77.84
						DAY 28	-80.76
0.3	C2S1	83.3	25.0	S77Y	118.0	DAY 7	-85.69
						DAY 14	
						DAY 28	
						DAY 56	
						MONTH 4	
						MONTH 6	
						MONTH 9	
						DAY 7	
						DAY 14	

FIG. 19A

DOSE (mg/kg)	PATIENT	WEIGHT (kg)	ACTUAL DOSE(mg)	TTR GENOTYPE	NT-PROBNPX BASELINE (ng/L)	TIMEPOINT	%TTR REDUCTION
0.3	C2S2	84.0	25.2	T60A	359.0	DAY 7	-30.43
						DAY 14	-78.74
						DAY 28	-83.79
						DAY 56	-76.72
						MONTH 4	-75.48
						MONTH 6	-77.83
0.3	C2S3	89.9	27.0	H90D	<50.0	MONTH 9	-80.03
						DAY 7	-71.98
						DAY 14	-93.34
						DAY 28	-95.73
						DAY 56	-90.55
						MONTH 4	-91.47
0.7	C4S1	62.4	43.7	E42D	58.0	MONTH 6	-94.04
						MONTH 9	-92.68
						DAY 7	-21.34
						DAY 14	-61.60
						DAY 28	-66.19
						DAY 56	-73.03
0.7	C4S2	97.6	68.3	E74G	<50.0	DAY 7	-63.17
						DAY 14	-89.34
						DAY 28	-94.45
						DAY 56	-94.79

FIG. 19B

DOSE (mg/kg)	PATIENT	WEIGHT (kg)	ACTUAL DOSE(mg)	TTR GENOTYPE	NT-PROBNPX BASELINE (ng/L)	TIMEPOINT	%TTR REDUCTION
0.7	C4S3	86.7	60.7	T60A	195.0	DAY 7	-78.34
						DAY 14	-94.45
						DAY 28	-97.37
						DAY 56	-95.20
						MONTH 4	-93.86
						MONTH 6	-95.07
1.0	C3S1	75.9	75.9	E42D	56.0	DAY 7	-42.92
						DAY 14	-79.83
						DAY 28	-88.25
						UNSCHEDULED VISIT	-89.51
						MONTH 4	-88.60
						MONTH 6	-88.16
1.0	C3S2	69.2	69.2	S50R	544.0	DAY 7	-79.84
						DAY 14	-87.53
						DAY 28	-87.47
						DAY 56	-80.06
						MONTH 4	-89.83
						MONTH 6	-83.36
1.0	C3S3	88.6	88.6	T60A	84.0	DAY 7	-87.13
						DAY 14	-96.74
						DAY 28	-97.64
						DAY 56	-98.83
						MONTH 4	-98.64

FIG. 19C

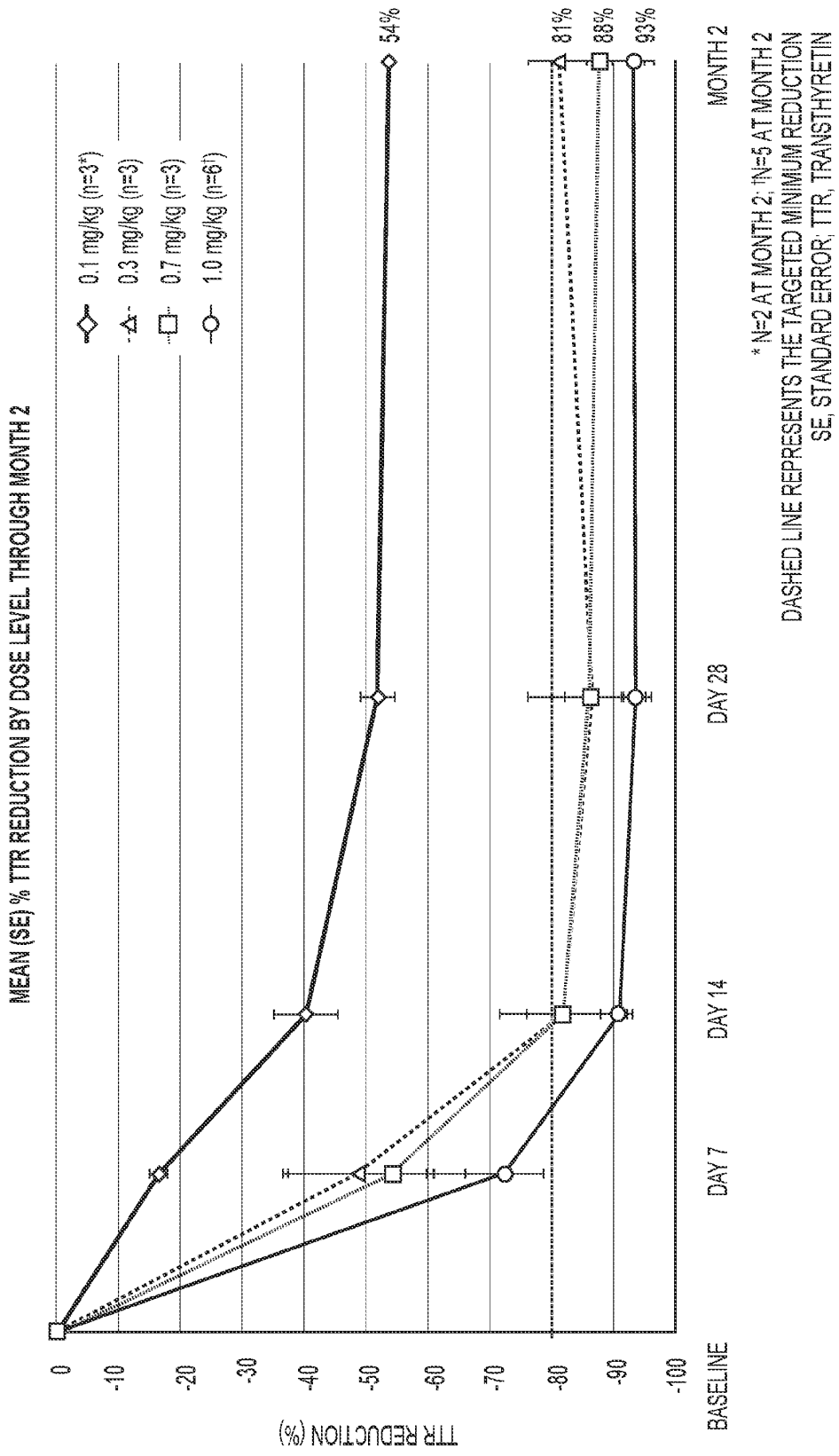


FIG. 20



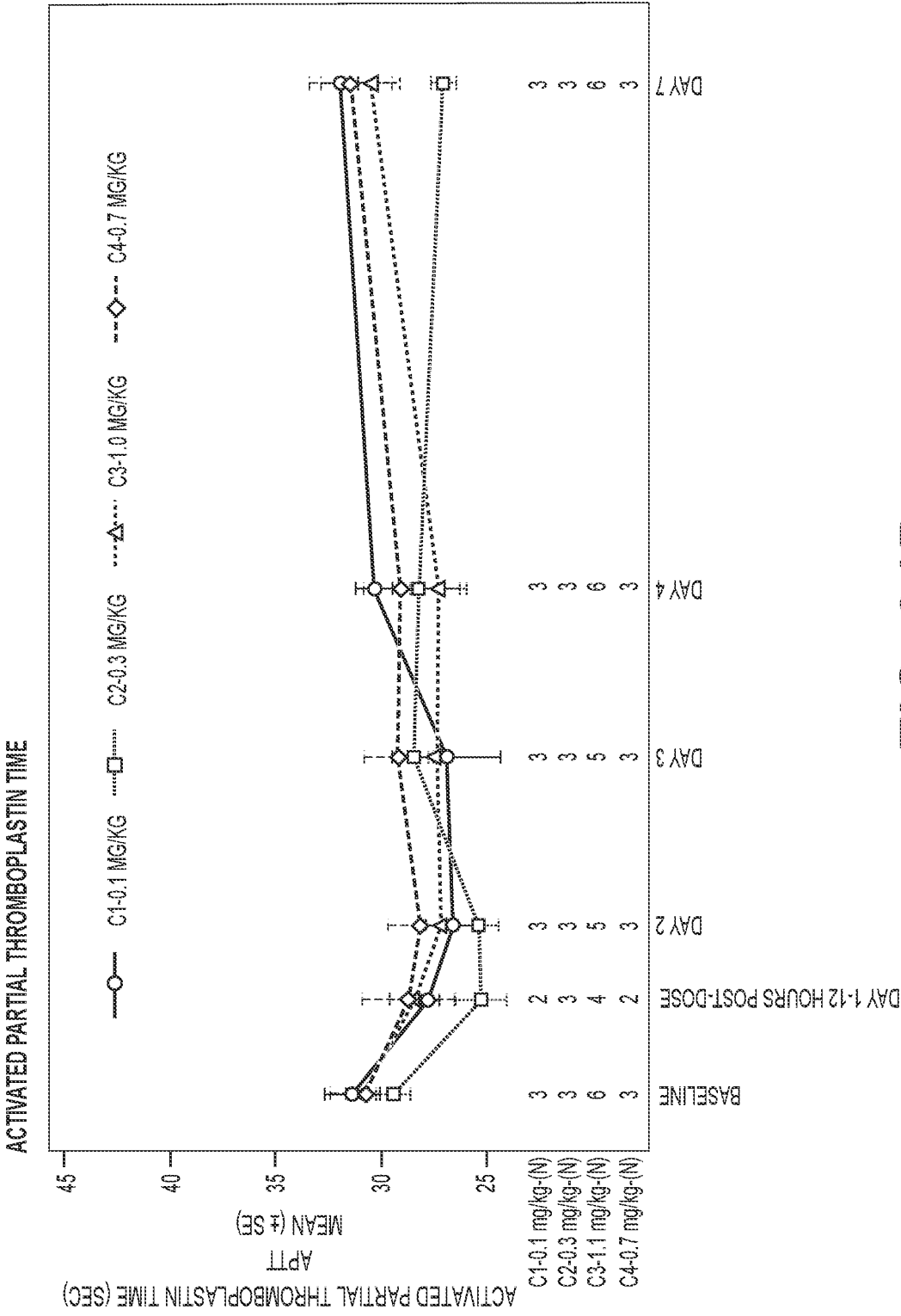


FIG. 21B

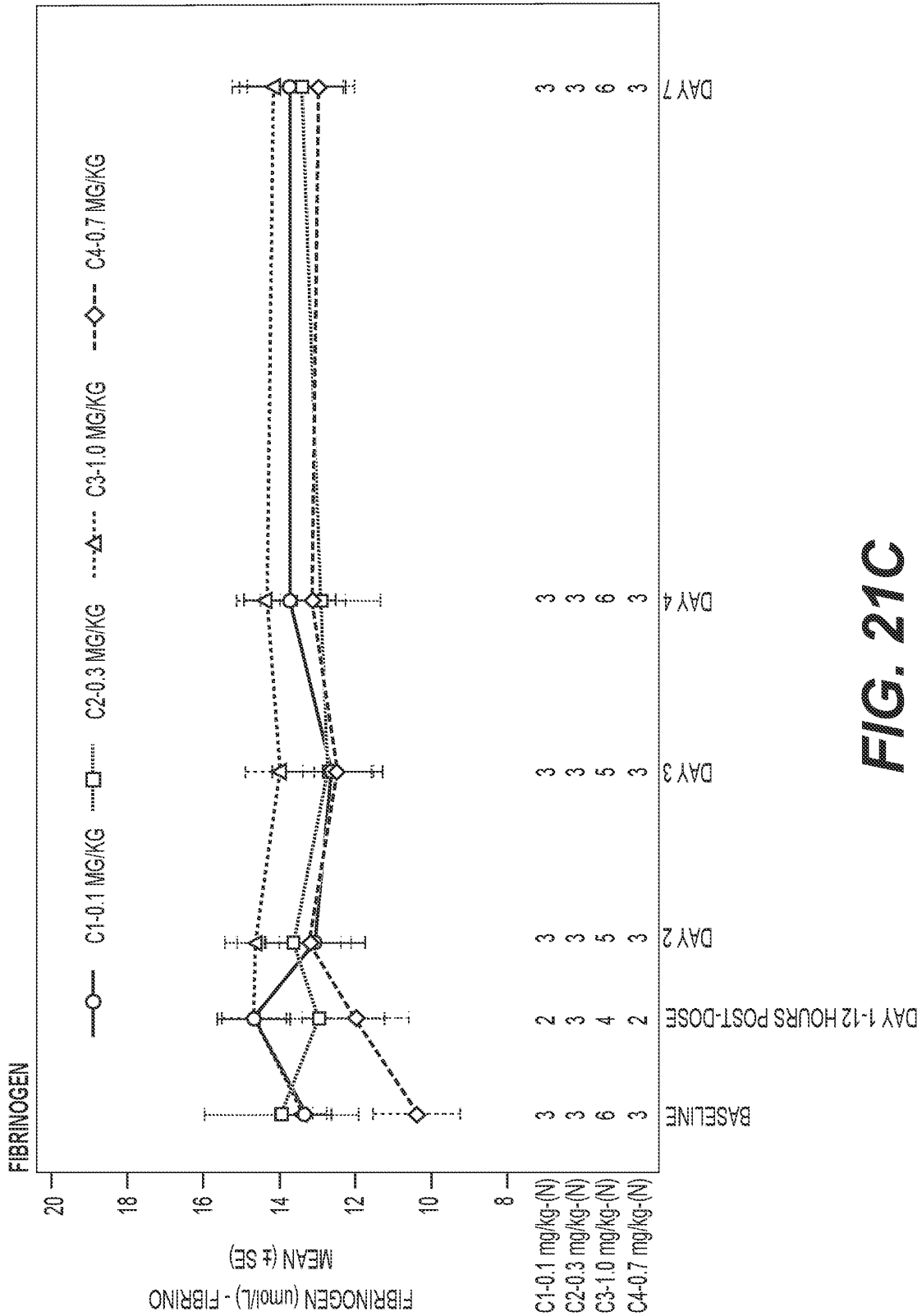


FIG. 21C

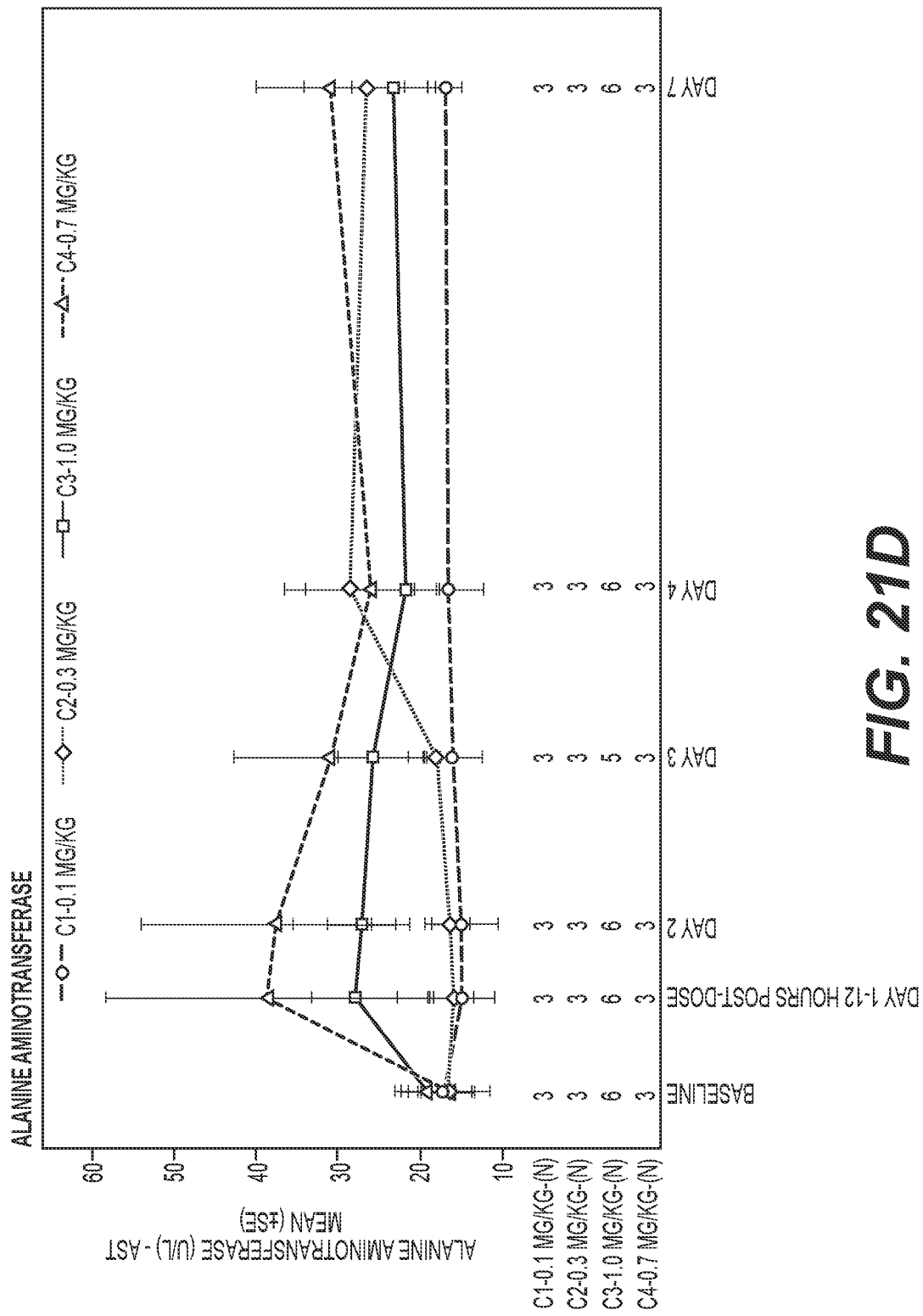


FIG. 21D

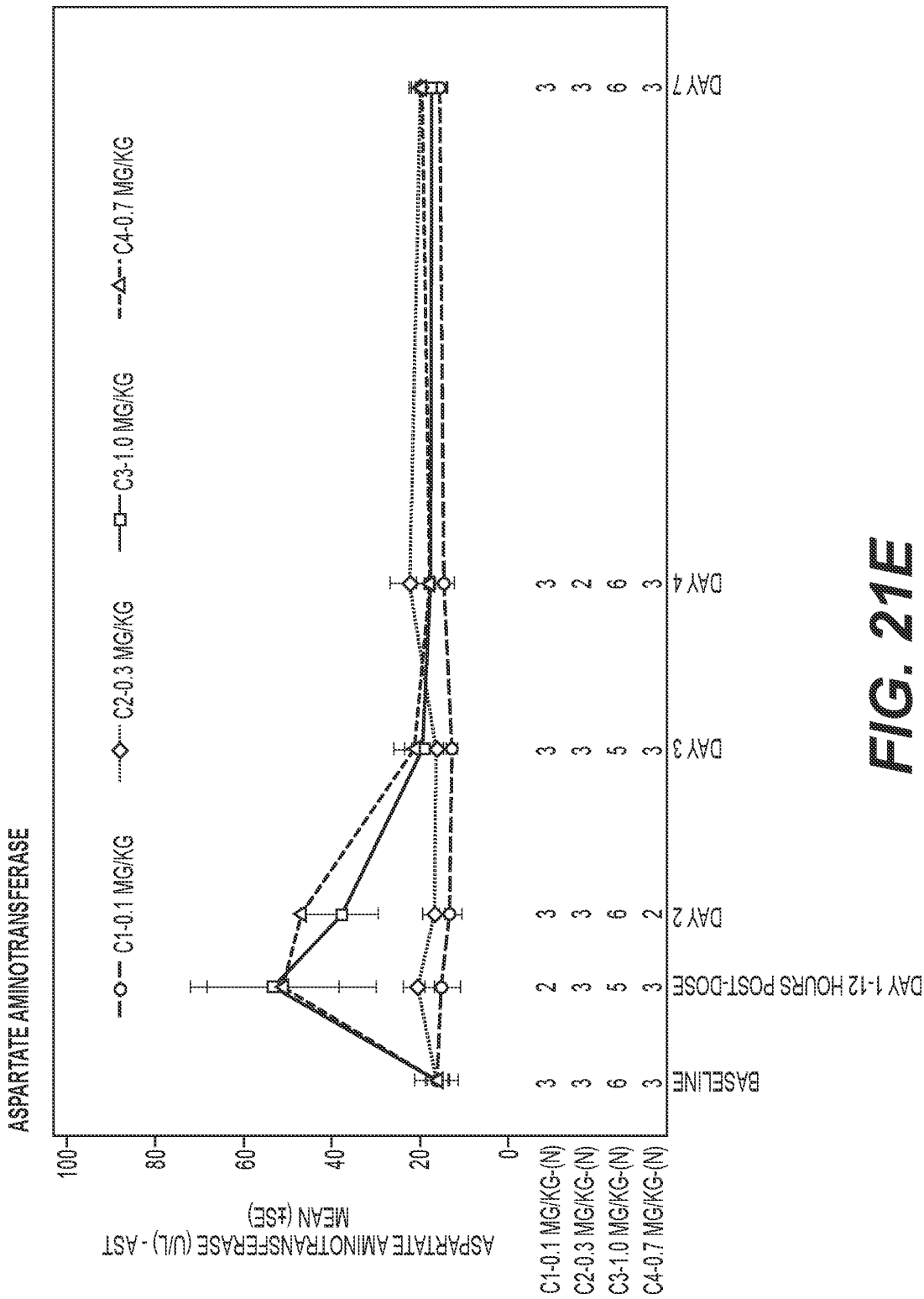


FIG. 21E

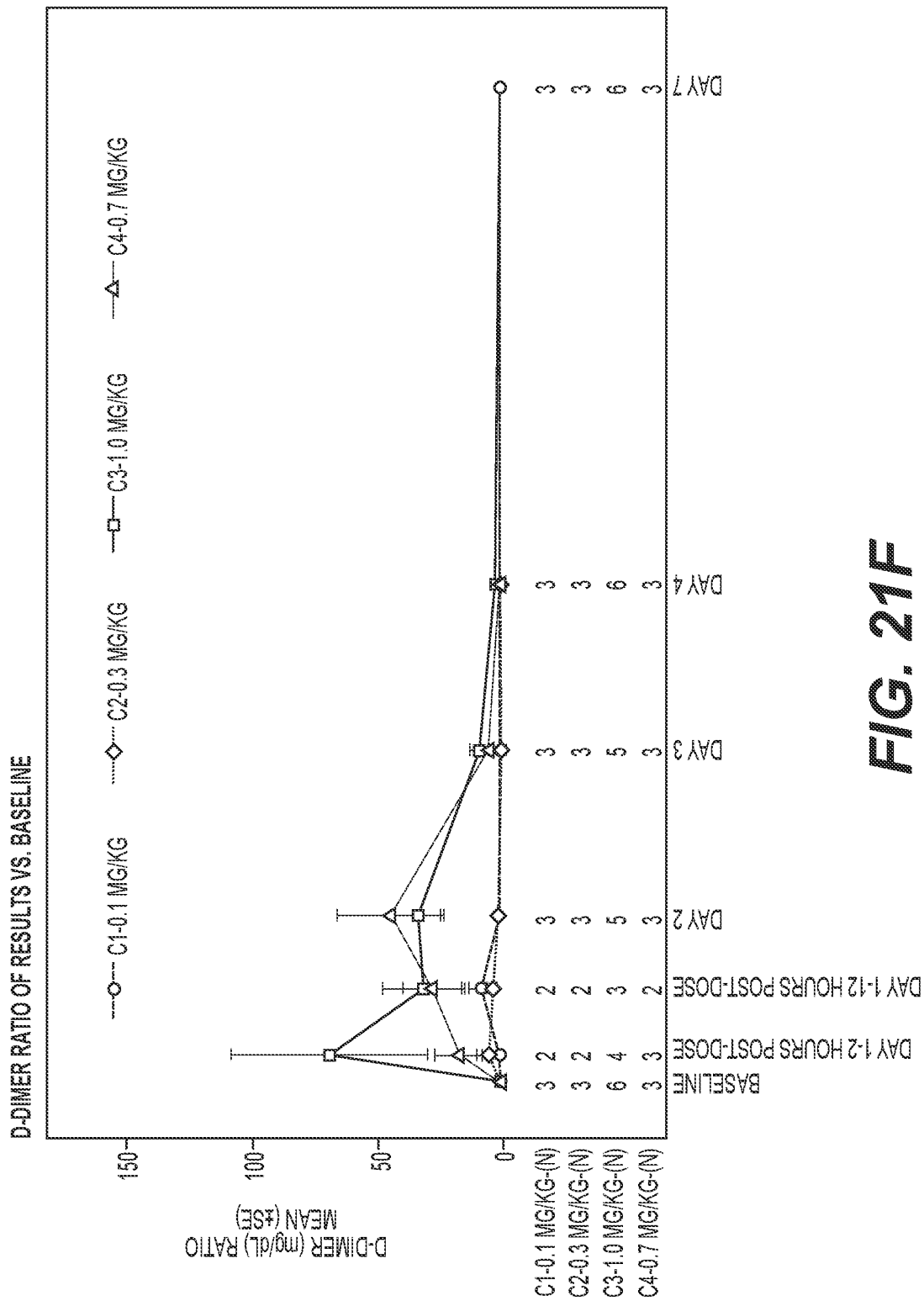


FIG. 21F

PARAMETER	0.1 mg/kg N=3			0.3 mg/kg N=3			0.7 mg/kg N=3			0.1 mg/kg N=6			ALL N=15		
	GR.1	GR.2	GR.3	GR.1	GR.2	GR.3	GR.1	GR.2	GR.3	GR.1	GR.2	GR.3	GR.1	GR.2	GR.3
PATIENTS WITH AT LEAST ONE TEAE	3	—	—	3	—	—	2	—	1*	3	2	1†	11	2	2
HEADACHE	2	—	—	—	—	—	2	—	—	3	—	—	7	—	—
INFUSION-RELATED REACTION	1	—	—	—	—	—	2	—	—	4	—	—	7	—	—
BACK PAIN	1	—	—	—	—	—	2	1	—	1	—	—	4	1	—
RASH	1	—	—	—	—	—	—	—	—	3	—	—	4	—	—
NAUSEA	1	—	—	—	—	—	1	—	—	1	—	—	3	—	—

ADVERSE EVENTS REPORTED IN MORE THAN 2 PATIENTS
PATIENTS COUNTED ONCE PER ROW, PER DOSE LEVEL, AS HIGHEST GRADE REPORTED
* UNRELATED GRADE 3 (SAE) OF COVID-19 PNEUMONIA
† RELATED GRADE 3 (SAE) OF VOMITING IN A PATIENT WITH CONCOMITANT MEDICAL HISTORY OF GASTROPARESIS

FIG. 22

PARAMETER	0.1 mg/kg N=3	0.3 mg/kg N=3	0.7 mg/kg N=3	1.0 mg/kg N=6	ALL PATIENTS N=15
AGE, YEARS MEDIAN (MIN, MAX)	54 (50, 63)	53 (46, 64)	51 (19, 58)	61 (49, 70)	55 (19, 70)
SEX, N (%)					
MALE	1 (33%)	3 (100%)	2 (67%)	3 (50%)	9 (60%)
FEMALE	2 (67%)	—	1 (33%)	3 (50%)	8 (40%)
SELF-REPORTED RACE, N (%)					
WHITE OR CAUCASIAN	1 (33%)	3 (100%)	2 (67%)	4 (67%)	10 (67%)
WESTERN EUROPEAN	2 (67%)	—	—	1 (17%)	3 (20%)
ASIAN	—	—	—	1 (17%)	1 (7%)
NATIVE HAWAIIAN / OTHER PACIFIC ISLANDER	—	—	1 (33%)	—	1 (7%)
WEIGHT, kg, MADIAN (MIN, MAX)	82 (70, 89)	84 (83, 90)	87 (62, 98)	75 (59, 111)	83 (59, 111)

FIG. 23A

PARAMETER	0.1 mg/kg n=3	0.3 mg/kg n=3	0.7 mg/kg n=3	1.0 mg/kg n=6	ALL PATIENTS n=15
TTR GENOTYPE, N (%)					
P.H110D	0	1 (33%)	0	0	1 (7%)
P.S97Y	1 (33%)	1 (33%)	0	0	2 (13%)
P.E94G	0	0	1 (33%)	0	1 (7%)
P.T80A	2 (67%)	1 (33%)	1 (33%)	2 (33%)	6 (40%)
P.S70R	0	0	0	1 (17%)	1 (7%)
D.E62D	0	0	1 (33%)	2 (33%)	3 (20%)
D.V50M	0	0	0	1 (17%)	1 (7%)
CLINICAL SCORES, N (%)					
PN DISABILITY SCORE					
1	3 (100%)	3 (100%)	3 (100%)	4 (67%)	13 (87%)
2	0	0	0	2 (33%)	2 (13%)
NYHA CLASSIFICATION					
I	3 (100%)	3 (100%)	3 (100%)	4 (67%)	13 (87%)
II	0	0	0	1 (17%)	1 (7%)
NO DIAGNOSIS OF HF	0	0	0	1 (17%)	1 (7%)
NT-PROBNP(ng/L)*, MEDIAN (MIN. MAX)	127 (89, 596)	118 (<50, 359)	58 (<50, 195)	112 (<50, 544)	118 (<50, 596)

* NT-PROBNP ULN = 125 ng/L
HF, HEART FAILURE; NT-PROBNP, N-TERMINAL PRO B-TYPE NATRIURETIC PEPTIDE;
NYHA, NEW YORK HEART ASSOCIATION; PN, PERIPHERAL NEUROPATHY;
TTR, TRANSTHYRETIN; ULN, UPPER LIMIT OF NORMAL

FIG. 23B

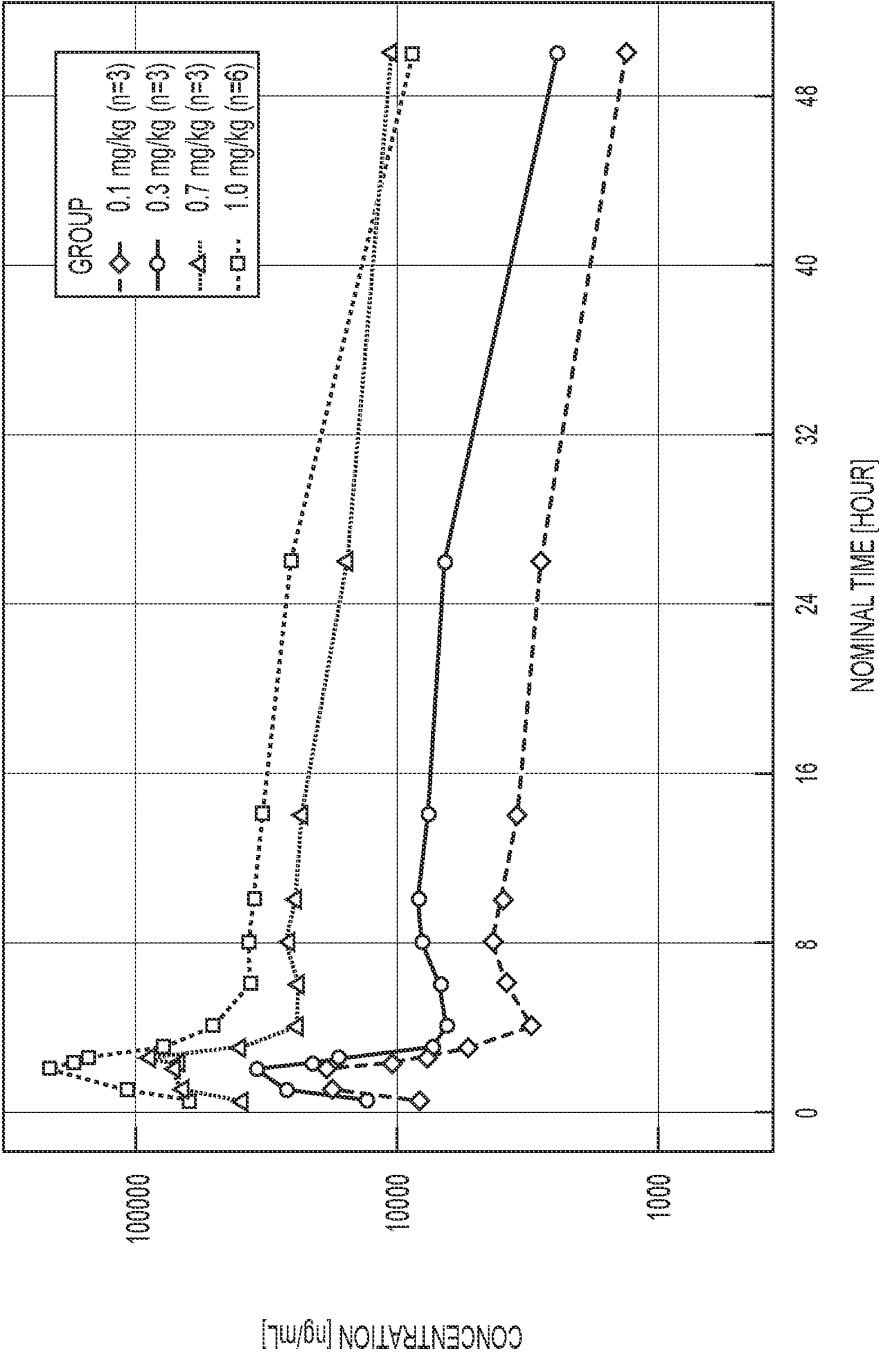


FIG. 24

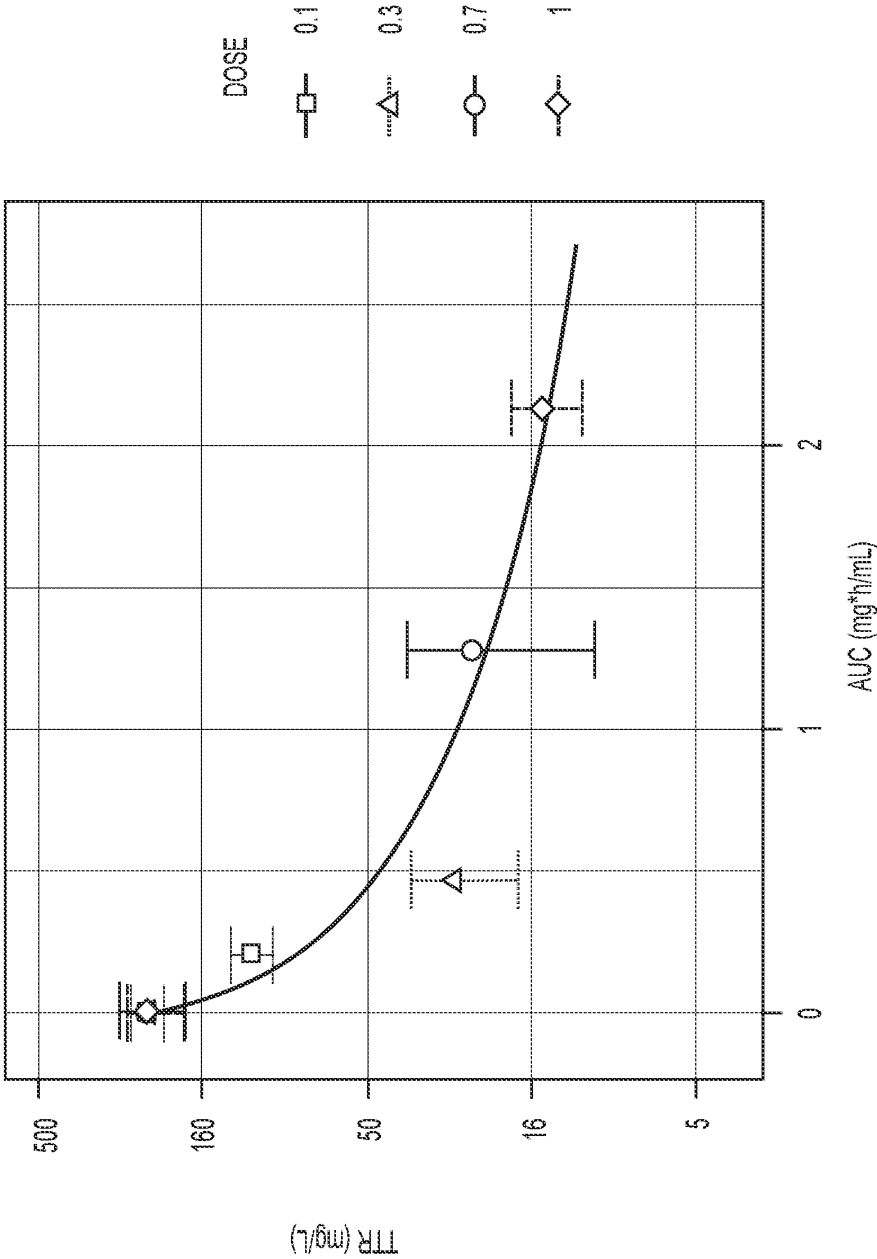
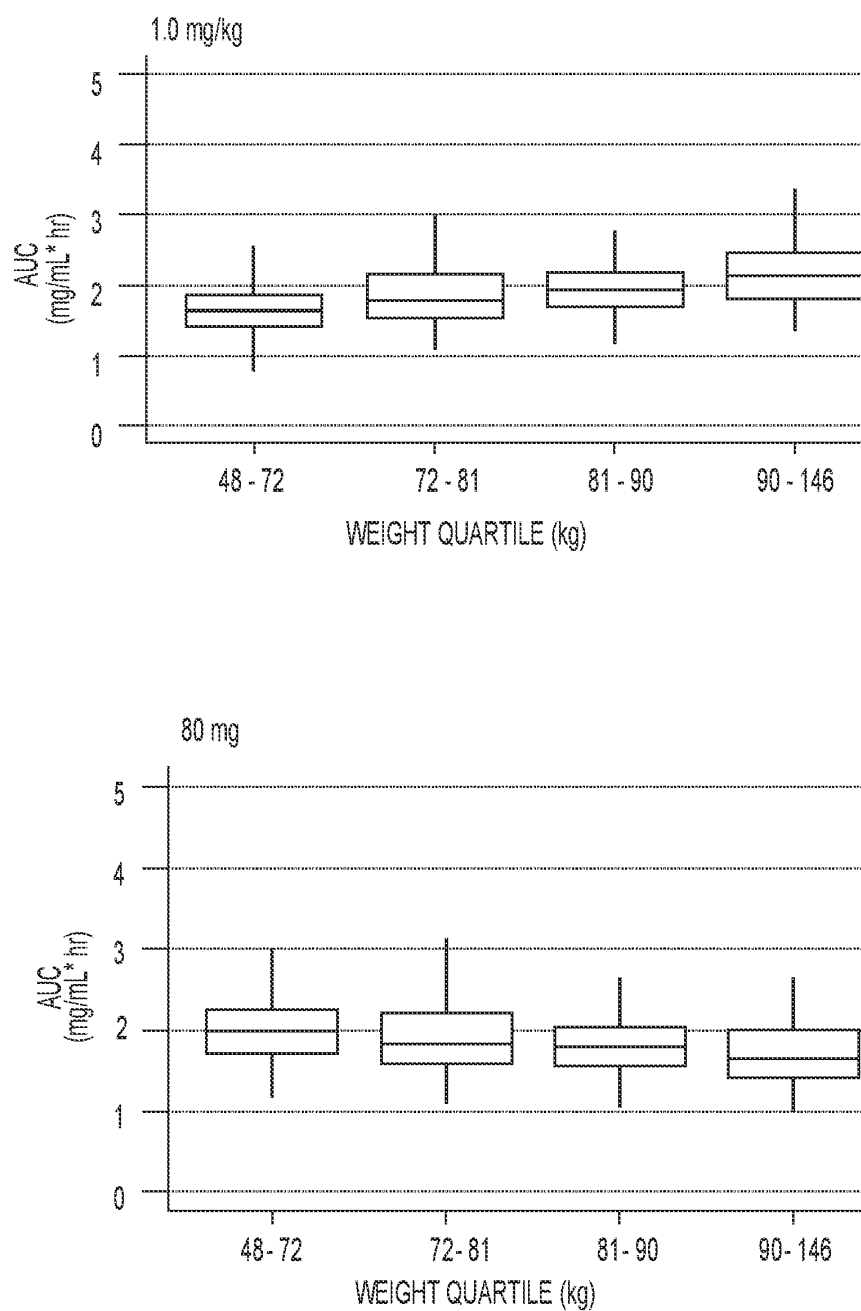


FIG. 25

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**FIG. 26**

SUBSTITUTE SHEET (RULE 26)

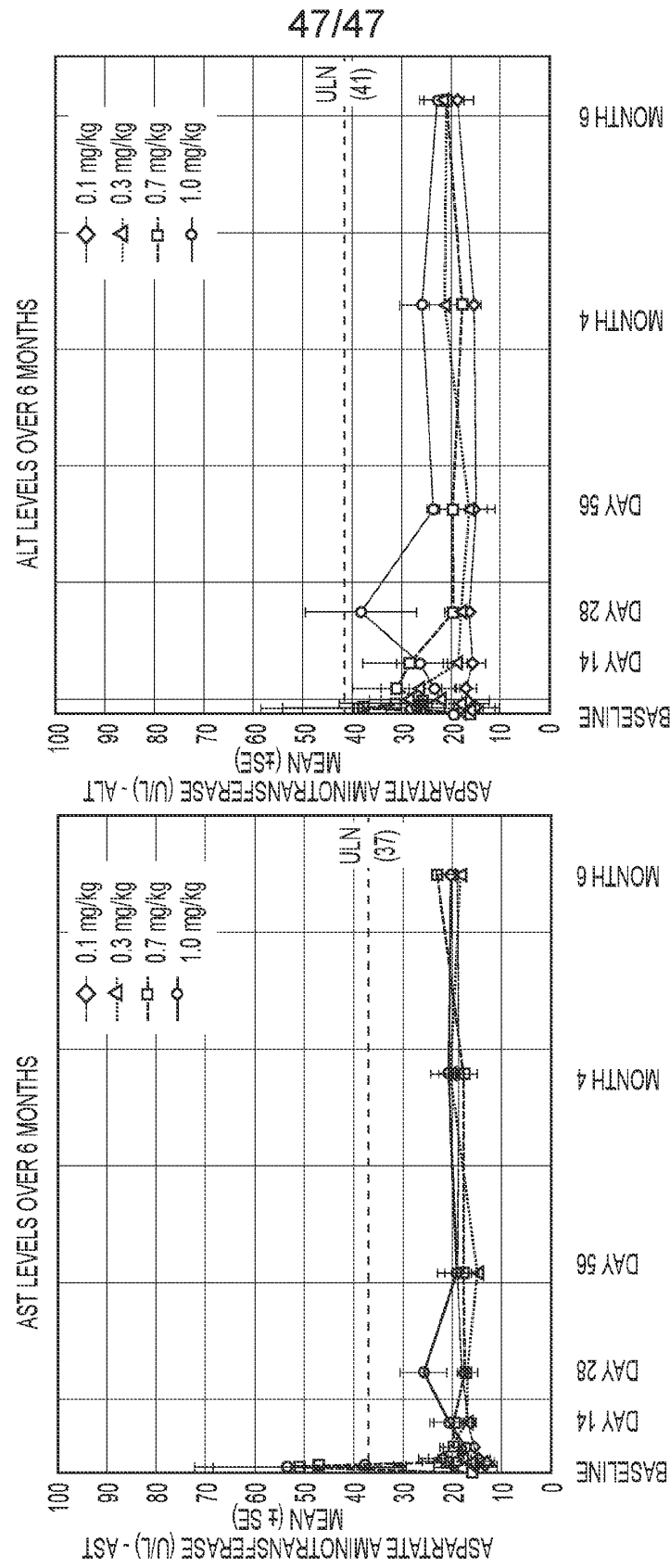


FIG. 27