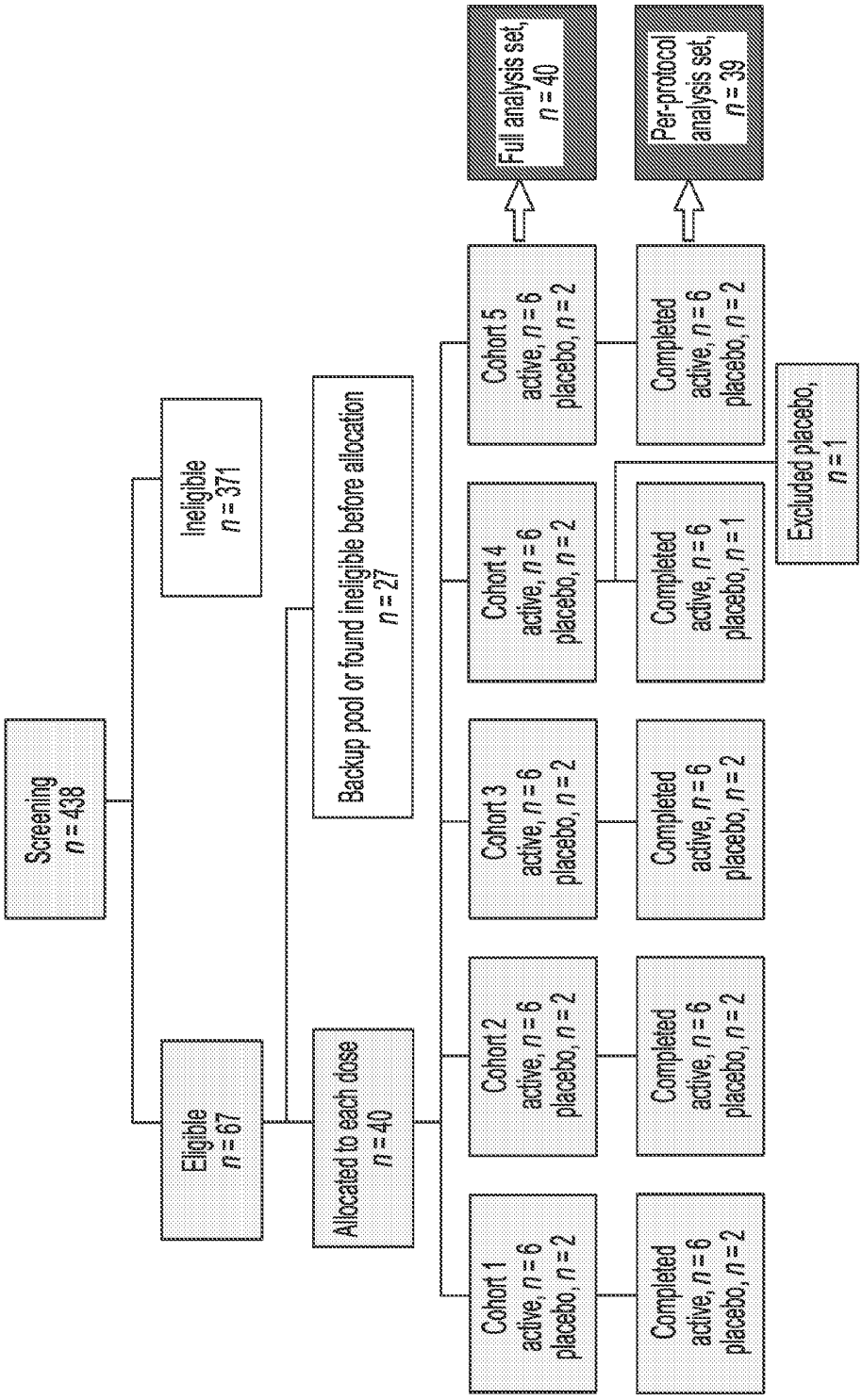

Screening
n = 438
Ineligible
n = 371
Eligible
n = 67
Backup pool or found ineligible before allocation
n = 27
Allocated to each dose
n = 40
Cohort 1
active, n = 6
placebo, n = 2
Cohort 2
active, n = 6
placebo, n = 2
Cohort 3
active, n = 6
placebo, n = 2
Cohort 4
active, n = 6
placebo, n = 2
Cohort 5
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 2
Completed
active, n = 6
placebo, n = 1
Excluded placebo,
n = 1
Full analysis set,
n = 40
Per-protocol
analysis set,
n = 39

FIG. 1

TMS-007 (mg/kg)	$AUC_{0\text{-}24\ h}$ (μg min mL^{-1})	AUC_{inf} (μg min mL^{-1})	C_{max} (μg mL^{-1})	t_{max} (min)	$t_{1/2}$ (min)	V_d ($mL.kg^{-1}$)
Rats (male)						
2	252 (12.1)	200 (27.3)	4.0 (6.6)	30.0 (30-30)	19.8 (7.1)	266 (136.5)
10	1537 (7.8)	1381 (22.4)	20.1 (13.0)	22.5 (5-30)	23.8 (5.1)	426 (76.1)
50	12150 (10.6)	12150 (10.6)	169.6 (23.2)	30.0 (15-30)	22.7 (18.0)	255 (20.2)
Rats (female)						
2	219 (16.1)	155 (18.5)	3.7 (17.9)	5.0 (5-30)	20.0 (8.1)	197 (19.7)
10	1431 (24.9)	1431 (24.9)	18.3 (12.6)	17.5 (5-30)	25.7 (19.7)	583 (21.9)
50	8486 (32.1)	8492 (32.1)	114.8 (10.4)	30.0 (30-30)	23.3 (27.5)	437 (36.6)
Monkeys (male)						
2.5	597 (11.9)	570 (10.5)	13.6 (9.9)	15.0 (15-30)	12.6 (13.8)	57.4 (6.6)
8.3	2399 (11.6)	2399 (11.6)	58.5 (8.6)	30.0 (30-30)	12.2 (3.5)	112.1 (15.6)
25	34789 (21.2)	34828 (21.2)	306.5 (8.6)	30.0 (30-30)	74.0 (22.1)	62.8 (10.7)
Monkeys (female)						
2.5	386 (9.3)	378 (9.6)	9.0 (9.1)	30.0 (30-30)	11.9 (1.3)	73.4 (13.4)
8.3	1827 (6.7)	1827 (6.7)	43.8 (8.9)	30.0 (30-30)	12.3 (1.7)	128.6 (20.2)
25	22157 (41.6)	22157 (41.6)	261.9 (14.1)	30.0 (30-30)	39.0 (73.6)	73.5 (16.6)
Humans (male)						
0.045	15 (11.9)	14 (13.0)	0.3 (8.2)	31.0 (31-31)	12.7 (21.1)	59.6 (13.3)
0.25	82 (14.8)	81 (14.4)	1.9 (8.7)	31.0 (31-31)	14.3 (11.5)	57.6 (6.3)
0.91	294 (25.7)	291 (25.6)	6.6 (22.5)	31.0 (31-31)	14.3 (8.4)	72.2 (13.6)
2.87	949 (16.3)	941 (16.5)	20.2 (14.3)	31.0 (31-31)	15.2 (8.6)	76.2 (11.8)
5.86	2308 (13.8)	2303 (14.2)	49.7 (10.7)	31.0 (31-31)	15.4 (6.2)	78.6 (6.0)

FIG. 2

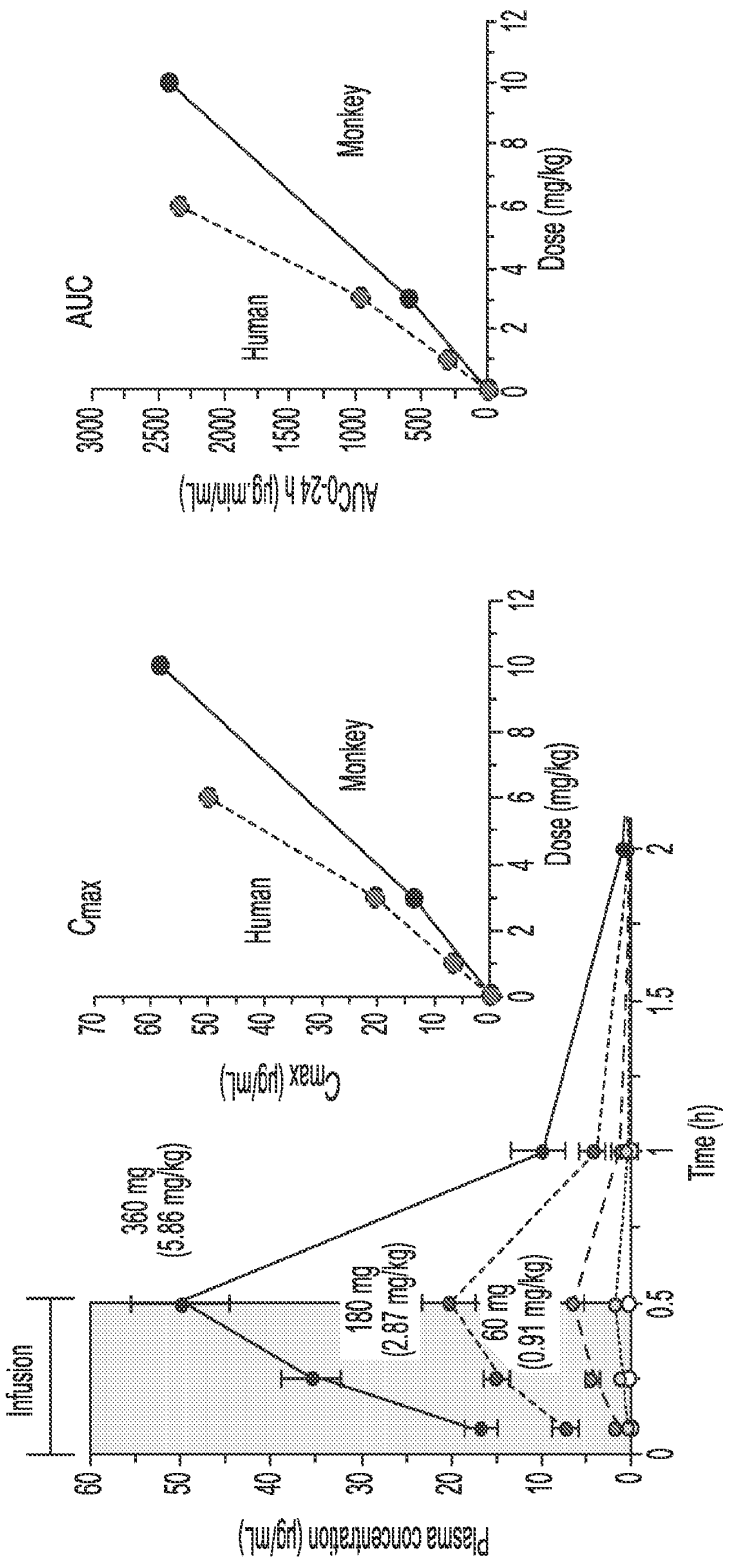

Plasma concentration (μg/mL)
Infusion
360 mg
(5.86 mg/kg)
180 mg
(2.87 mg/kg)
60 mg
(0.91 mg/kg)
Time (h)
Cmax (μg/mL)
Cmax
Human
Monkey
Dose (mg/kg)
AUC0-24 h (μg·min/mL)
AUC
Human
Monkey
Dose (mg/kg)

FIG. 3

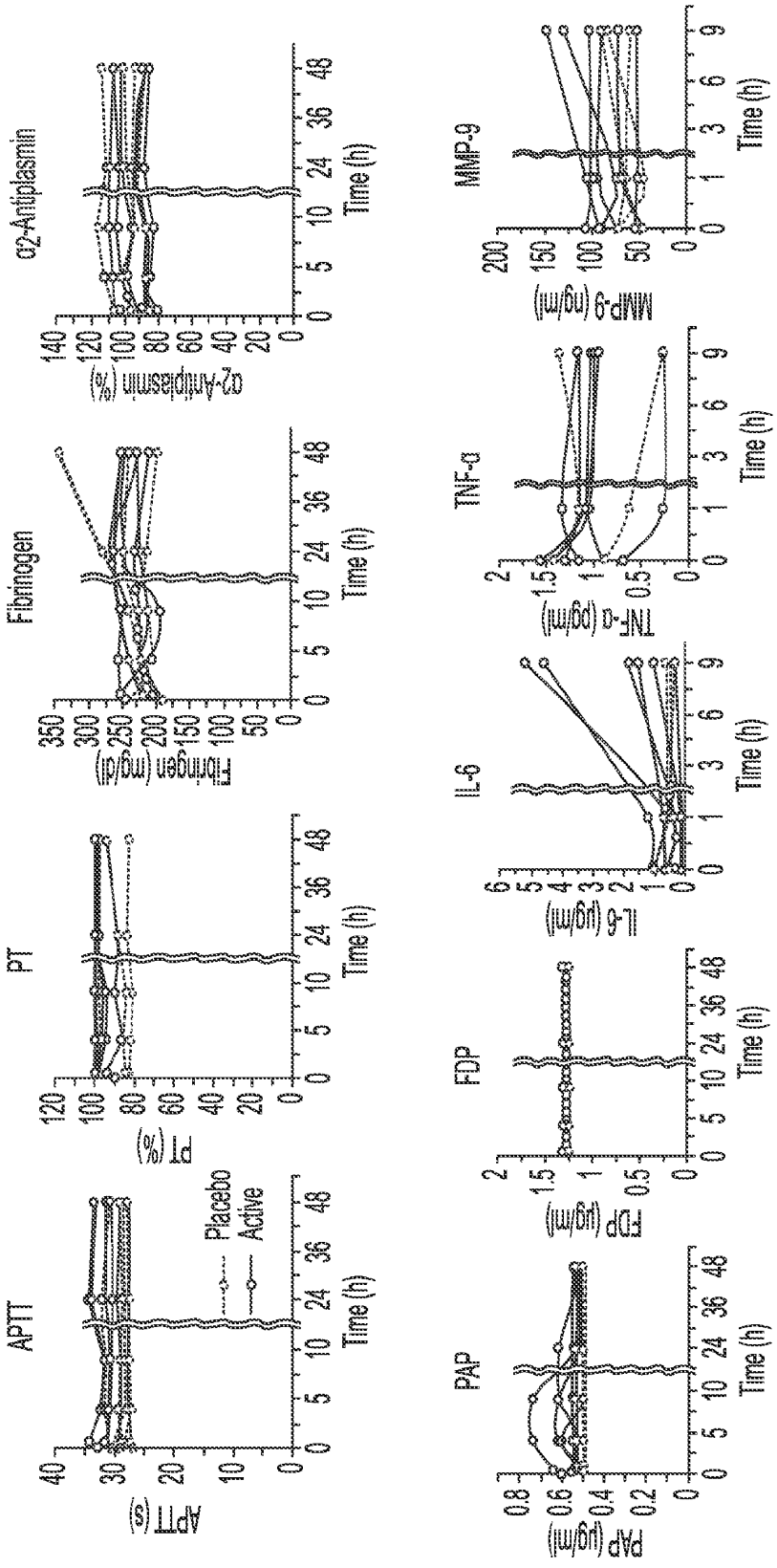

APTT
APTT (s)
Placebo
Active
PT
PT (%)
Fibrinogen
Fibrinogen (mg/dl)
α2-Antiplasmin
α2-Antiplasmin (%)
PAP
PAP (μg/ml)
FDP
FDP (μg/ml)
IL-6
IL-6 (μg/ml)
TNF-α
TNF-α (pg/ml)
MMP-9
MMP-9 (ng/ml)
Time (h)

FIG. 4

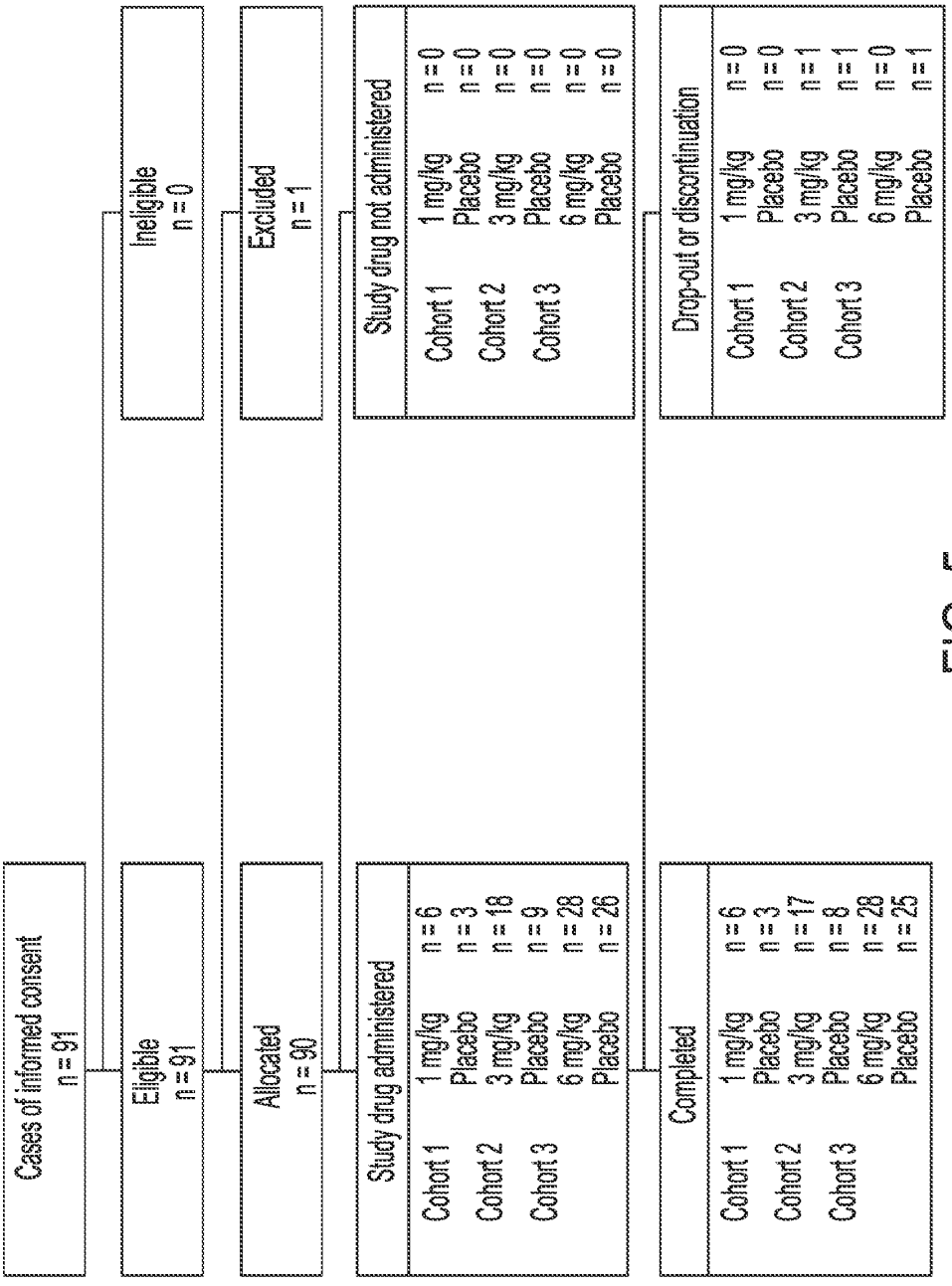

Cases of informed consent
n = 91
Ineligible
n = 0
Eligible
n = 91
Excluded
n = 1
Allocated
n = 90
Study drug not administered
Cohort 1 1 mg/kg n = 0
Placebo n = 0
Cohort 2 3 mg/kg n = 0
Placebo n = 0
Cohort 3 6 mg/kg n = 0
Placebo n = 0
Drop-out or discontinuation
Cohort 1 1 mg/kg n = 0
Placebo n = 0
Cohort 2 3 mg/kg n = 1
Placebo n = 1
Cohort 3 6 mg/kg n = 0
Placebo n = 1
Study drug administered
Cohort 1 1 mg/kg n = 6
Placebo n = 3
Cohort 2 3 mg/kg n = 18
Placebo n = 9
Cohort 3 6 mg/kg n = 28
Placebo n = 26
Completed
Cohort 1 1 mg/kg n = 6
Placebo n = 3
Cohort 2 3 mg/kg n = 17
Placebo n = 8
Cohort 3 6 mg/kg n = 28
Placebo n = 25

FIG. 5

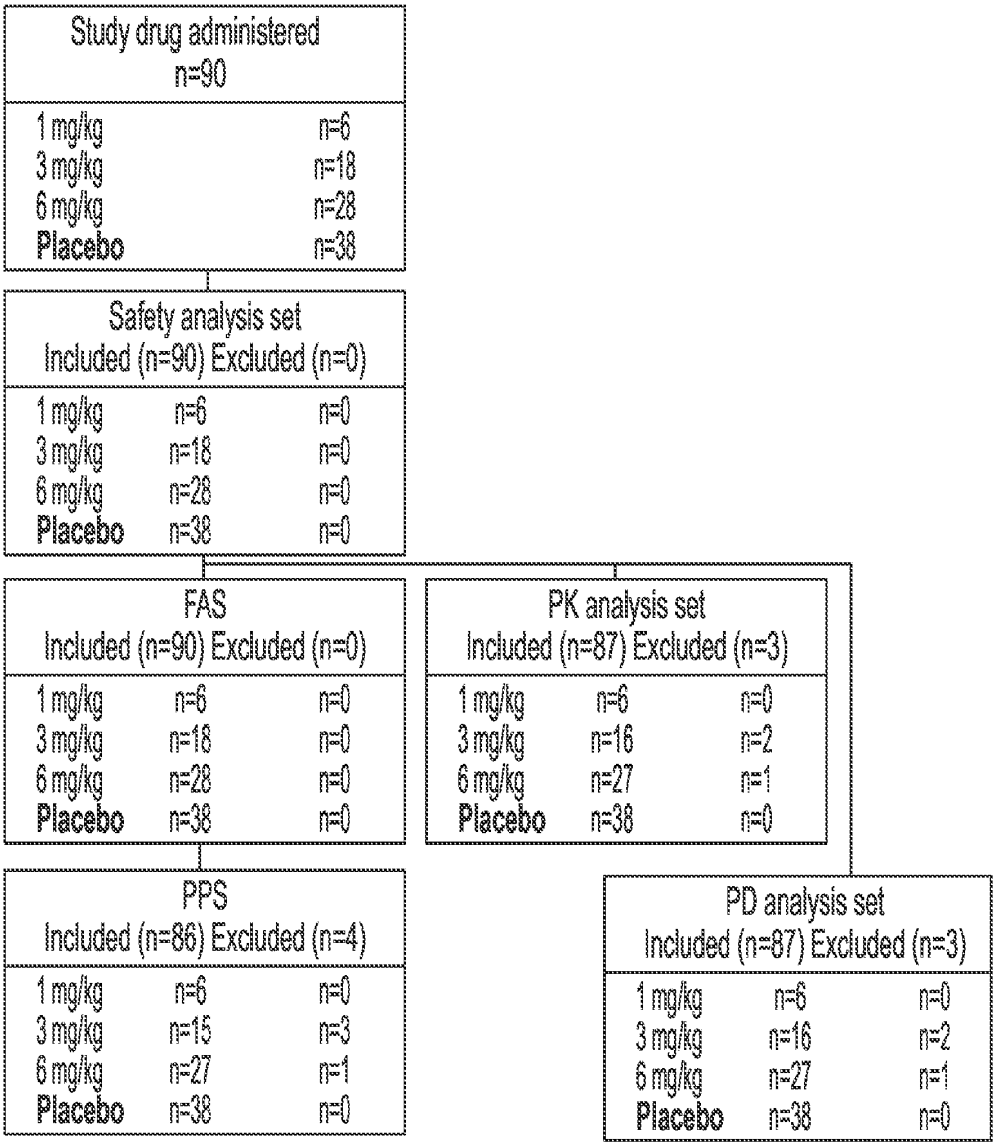

Study drug administered
n=90
1 mg/kg n=6
3 mg/kg n=18
6 mg/kg n=28
Placebo n=38
Safety analysis set
Included (n=90) Excluded (n=0)
1 mg/kg n=6 n=0
3 mg/kg n=18 n=0
6 mg/kg n=28 n=0
Placebo n=38 n=0
FAS
Included (n=90) Excluded (n=0)
1 mg/kg n=6 n=0
3 mg/kg n=18 n=0
6 mg/kg n=28 n=0
Placebo n=38 n=0
PK analysis set
Included (n=87) Excluded (n=3)
1 mg/kg n=6 n=0
3 mg/kg n=16 n=2
6 mg/kg n=27 n=1
Placebo n=38 n=0
PPS
Included (n=86) Excluded (n=4)
1 mg/kg n=6 n=0
3 mg/kg n=15 n=3
6 mg/kg n=27 n=1
Placebo n=38 n=0
PD analysis set
Included (n=87) Excluded (n=3)
1 mg/kg n=6 n=0
3 mg/kg n=16 n=2
6 mg/kg n=27 n=1
Placebo n=38 n=0

FIG. 6

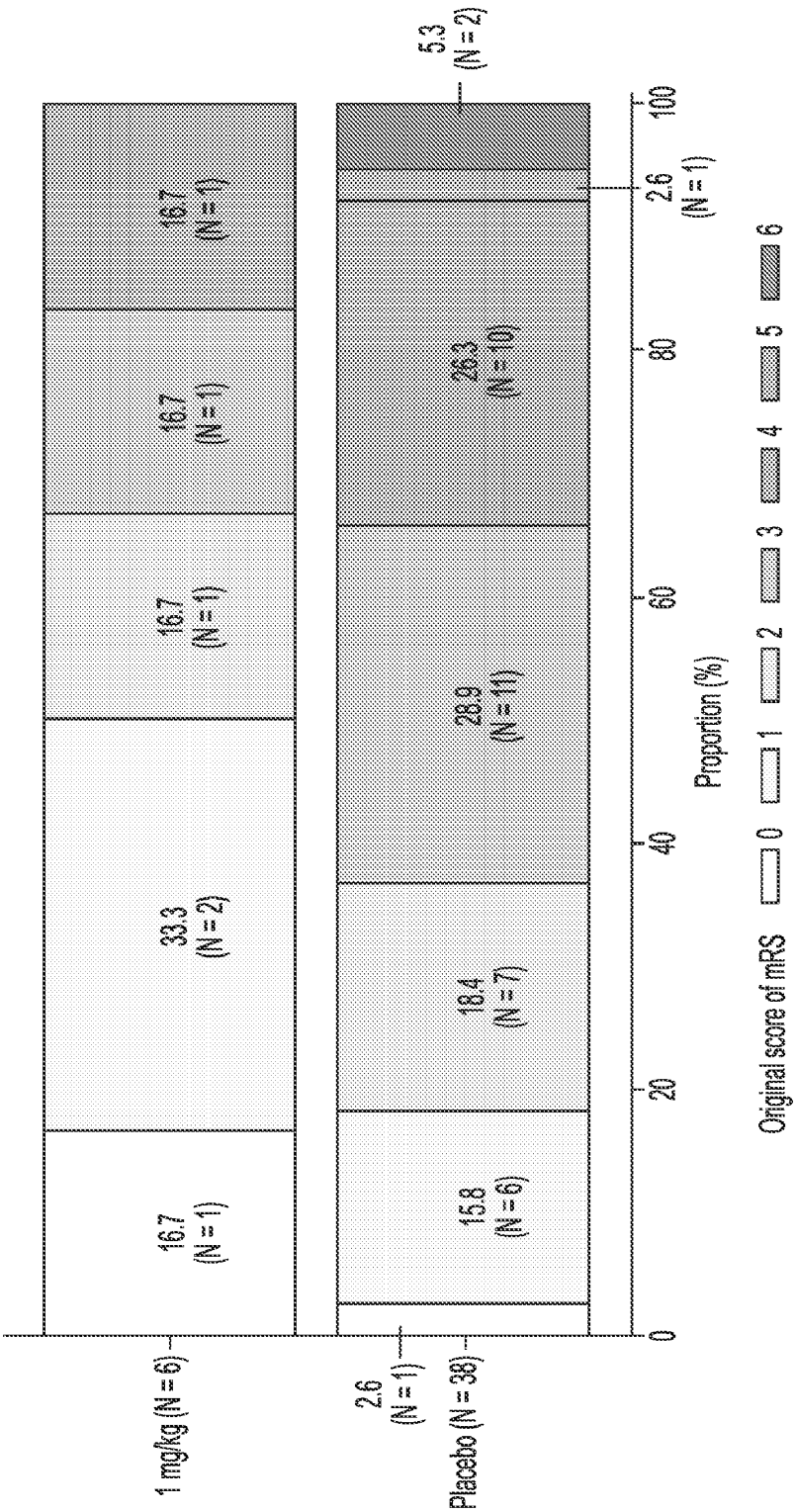

1 mg/kg (N = 6)
16.7 (N = 1)
33.3 (N = 2)
16.7 (N = 1)
16.7 (N = 1)
16.7 (N = 1)
2.6 (N = 1)
Placebo (N = 38)
15.8 (N = 6)
18.4 (N = 7)
28.9 (N = 11)
26.3 (N = 10)
5.3 (N = 2)
2.6 (N = 1)
0
20
40
60
80
100
Proportion (%)
Original score of mRS
0
1
2
3
4
5
6

FIG. 7

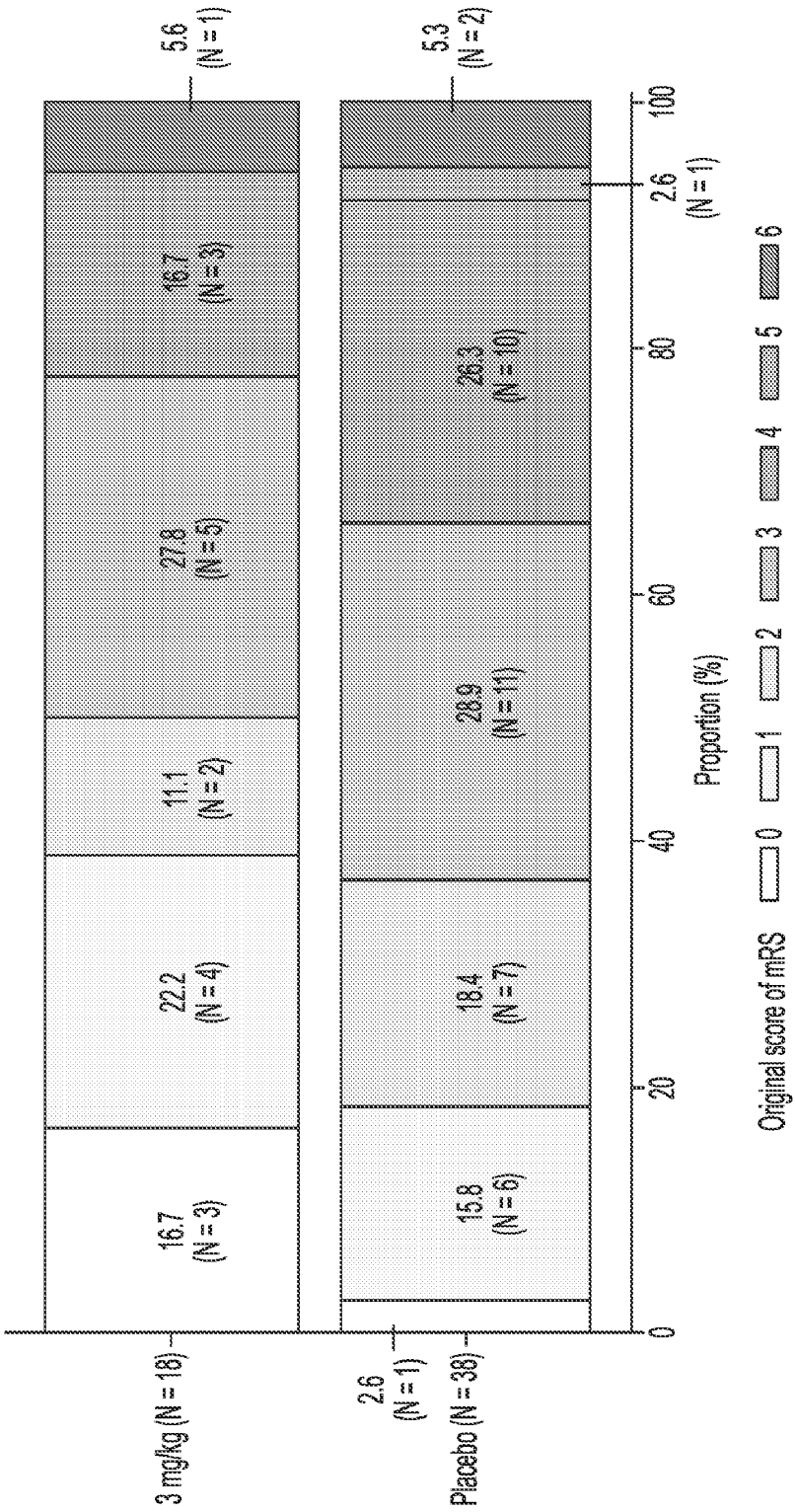

3 mg/kg (N = 18)
16.7 (N = 3)
22.2 (N = 4)
11.1 (N = 2)
27.8 (N = 5)
16.7 (N = 3)
5.6 (N = 1)
Placebo (N = 38)
15.8 (N = 6)
18.4 (N = 7)
28.9 (N = 11)
26.3 (N = 10)
5.3 (N = 2)
2.6 (N = 1)
2.6 (N = 1)
0
20
40
60
80
100
Proportion (%)
Original score of mRS
0
1
2
3
4
5
6

FIG. 8

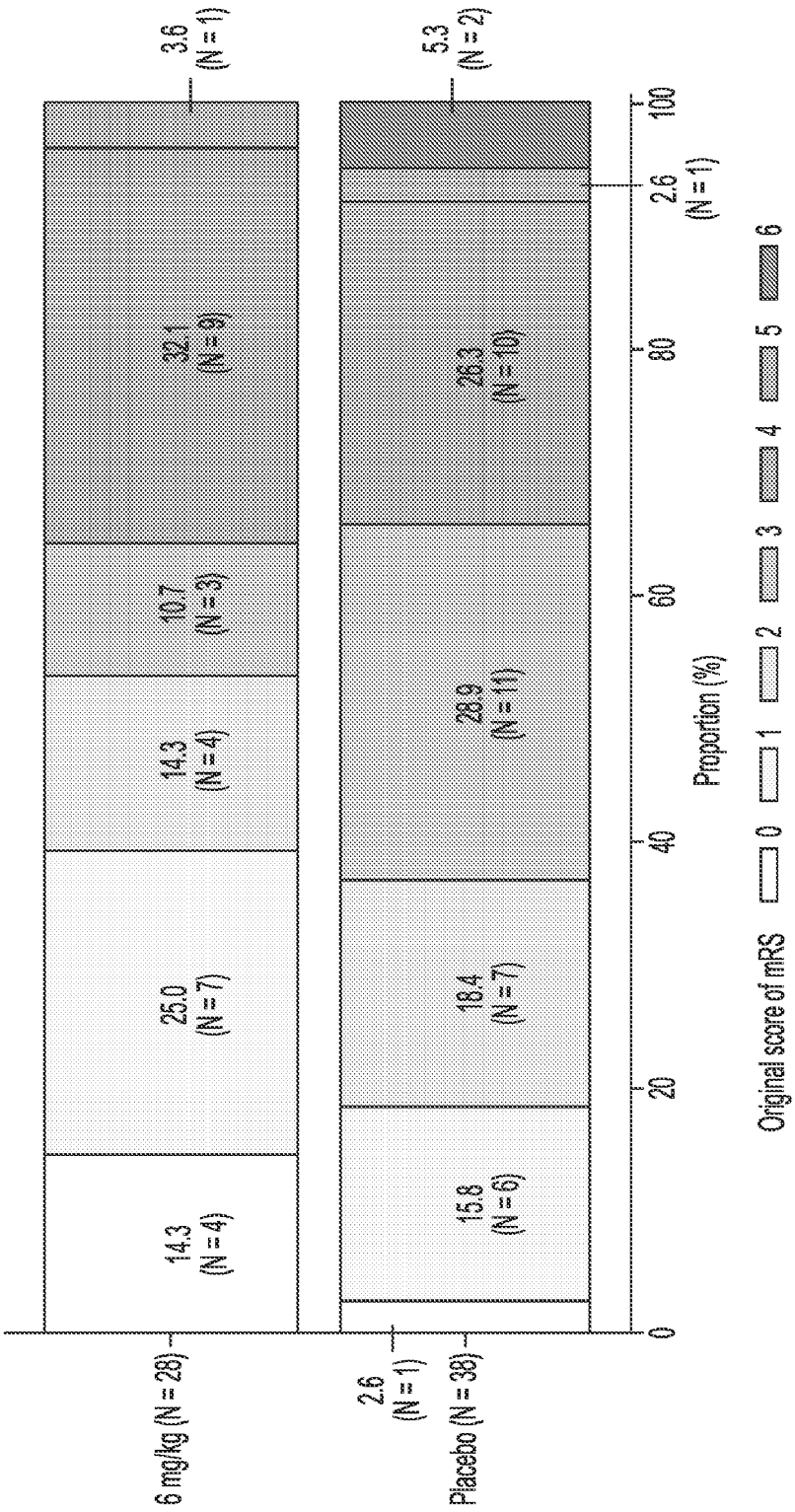

6 mg/kg (N = 28)
Placebo (N = 38)
14.3 (N = 4)
25.0 (N = 7)
14.3 (N = 4)
10.7 (N = 3)
32.1 (N = 9)
3.6 (N = 1)
15.8 (N = 6)
18.4 (N = 7)
28.9 (N = 11)
26.3 (N = 10)
5.3 (N = 2)
2.6 (N = 1)
2.6 (N = 1)
0
20
40
60
80
100
Proportion (%)
Original score of mRS
0
1
2
3
4
5
6

FIG. 9

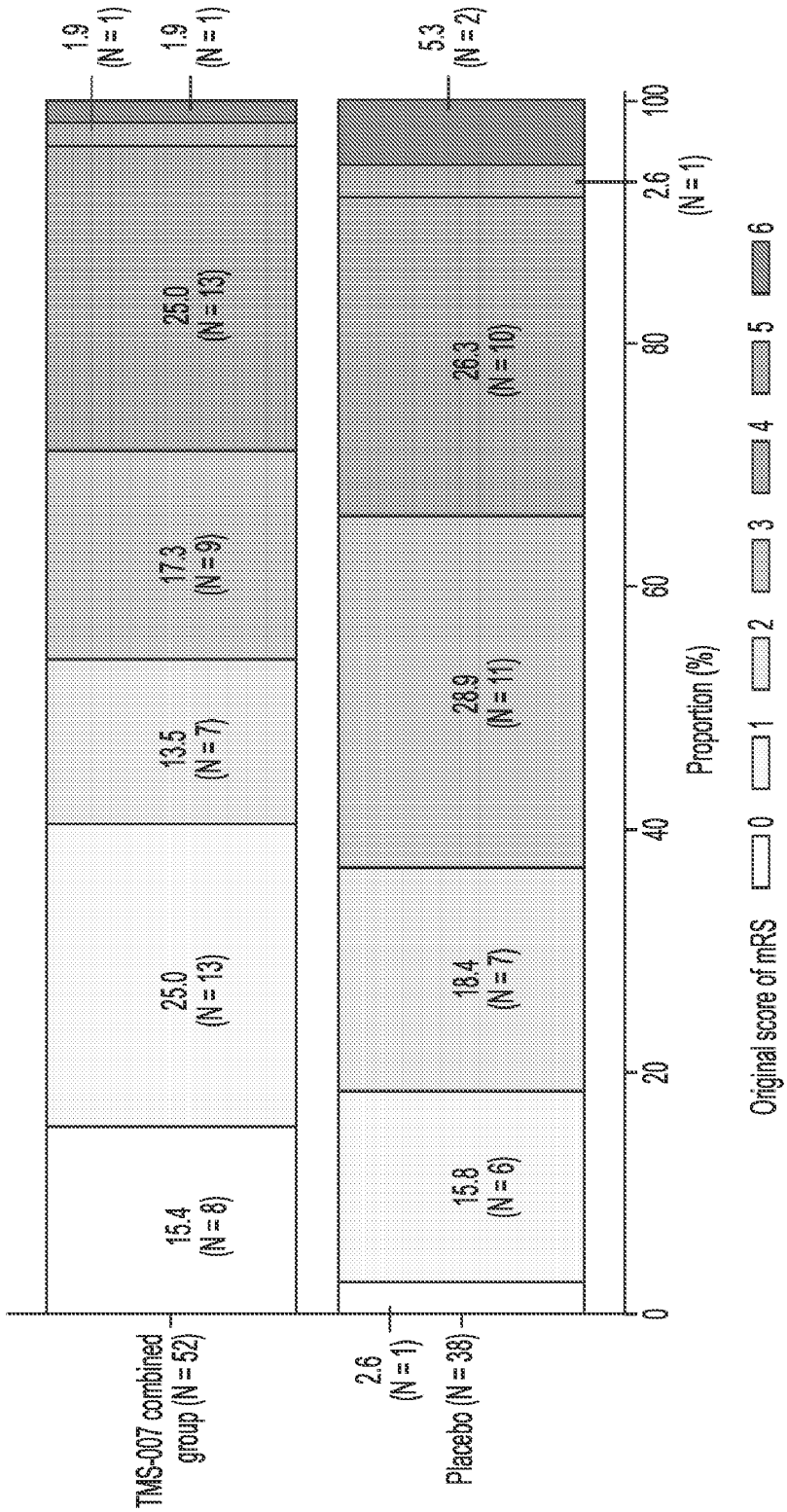

TMS-007 combined group (N = 52)
Placebo (N = 38)
15.4 (N = 8)
25.0 (N = 13)
13.5 (N = 7)
17.3 (N = 9)
25.0 (N = 13)
1.9 (N = 1)
1.9 (N = 1)
15.8 (N = 6)
18.4 (N = 7)
28.9 (N = 11)
26.3 (N = 10)
5.3 (N = 2)
2.6 (N = 1)
2.6 (N = 1)
0
20
40
60
80
100
Proportion (%)
Original score of mRS
0
1
2
3
4
5
6

FIG. 10

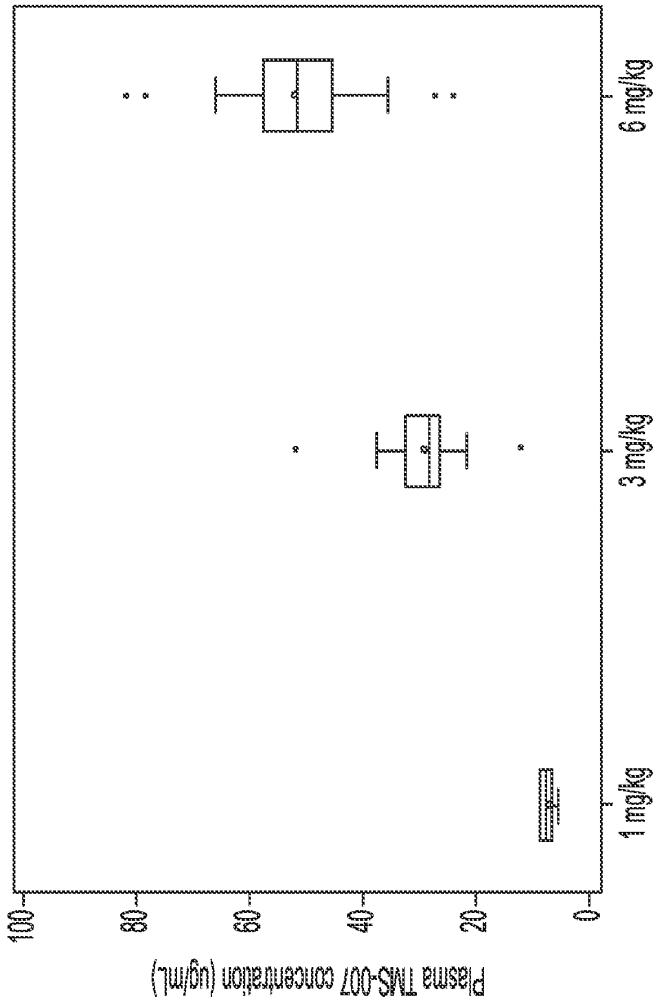

Plasma TMS-007 concentration (ug/mL)
100
80
60
40
20
0
1 mg/kg
3 mg/kg
6 mg/kg
Dose group

FIG. 11