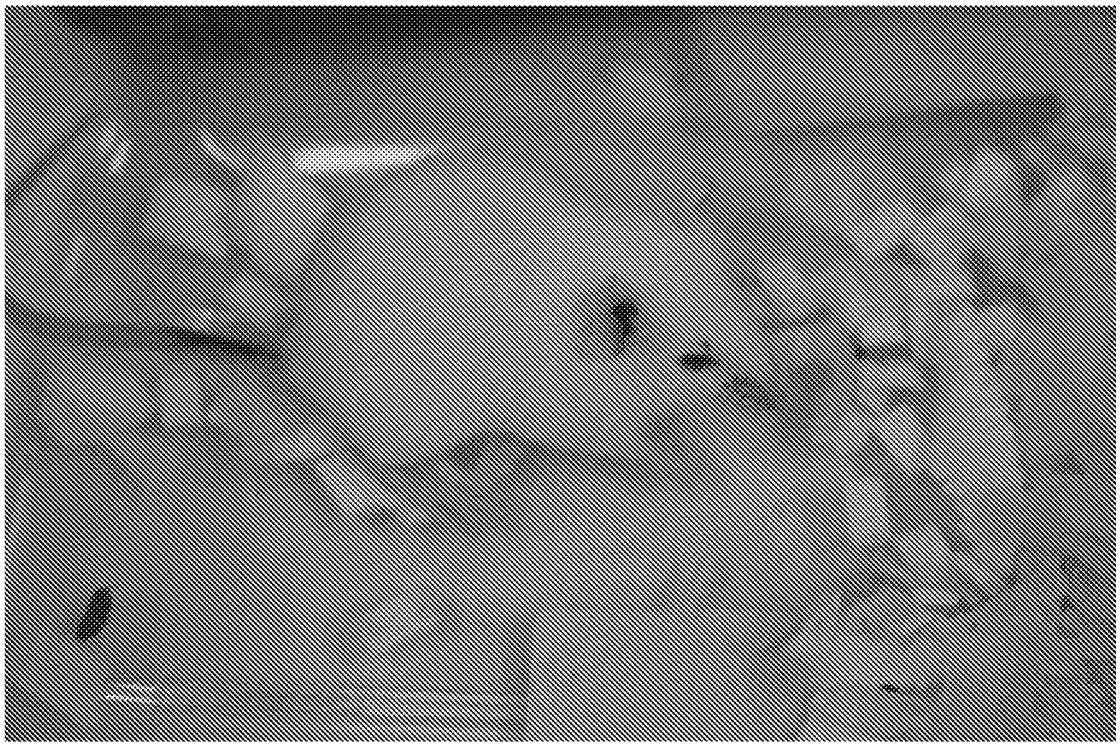


FIG. 1A



FIG. 1B

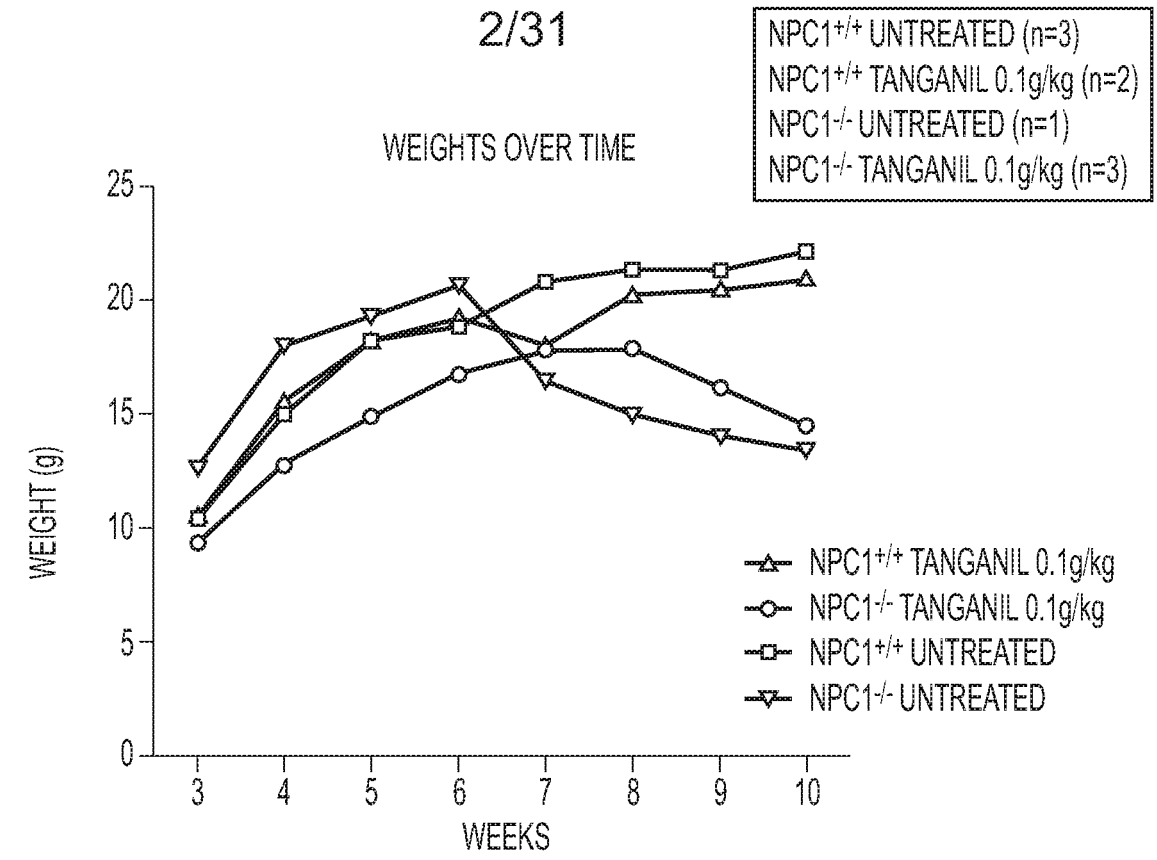
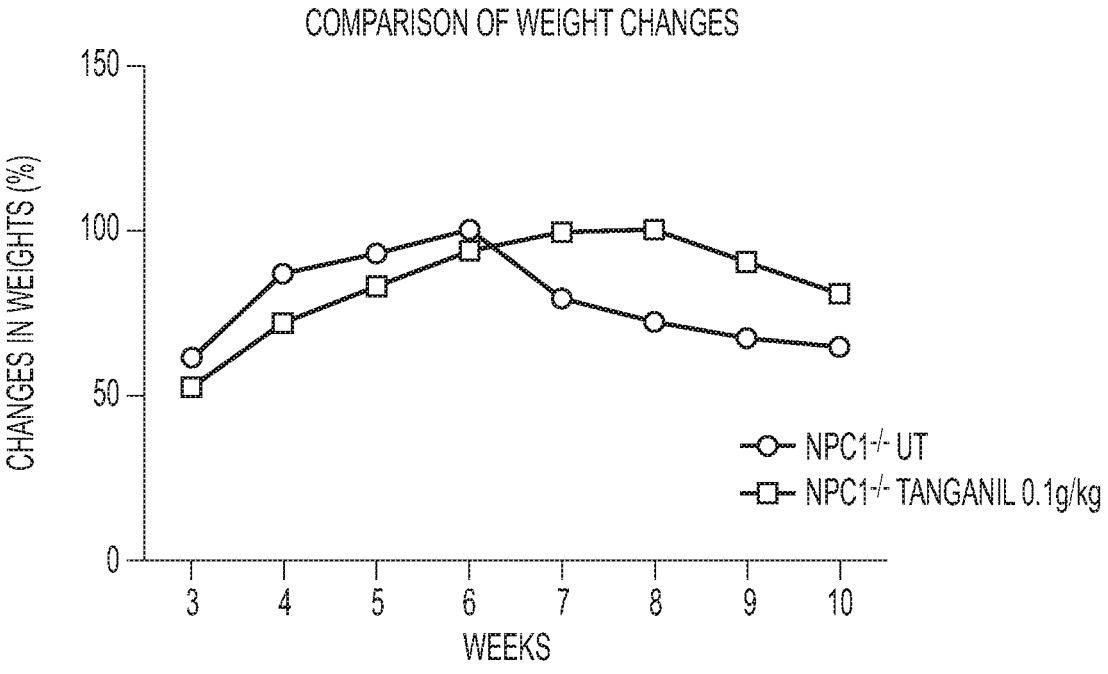


FIG. 2A



NPC1+/+ UNTREATED (n=3)
NPC1+/+ TANGANIL 0.1g/kg (n=2)
NPC1-/- UNTREATED (n=1)
NPC1-/- TANGANIL 0.1g/kg (n=3)

FIG. 2B

NPC1$^{+/+}$ UNTREATED (n=3)
NPC1$^{+/+}$ TANGANIL 0.1g/kg (n=2)
NPC1$^{-/-}$ UNTREATED (n=1)
NPC1$^{-/-}$ TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.

NPC1$^{+/+}$ UNTREATED
NPC1$^{+/+}$ TANGANIL 0.1g/kg
NPC1$^{-/-}$ UNTREATED
NPC1$^{-/-}$ TANGANIL 0.1g/kg

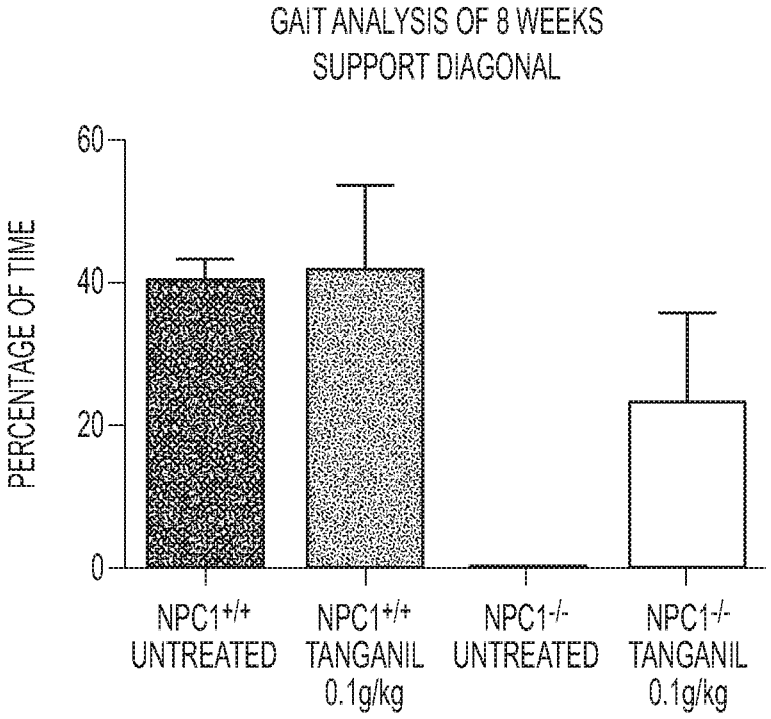


FIG. 3A

NPC1$^{+/+}$ UNTREATED (n=3)
NPC1$^{+/+}$ TANGANIL 0.1g/kg (n=2)
NPC1$^{-/-}$ UNTREATED (n=1)
NPC1$^{-/-}$ TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.

NPC1$^{+/+}$ UNTREATED
NPC1$^{+/+}$ TANGANIL 0.1g/kg
NPC1$^{-/-}$ UNTREATED
NPC1$^{-/-}$ TANGANIL 0.1g/kg

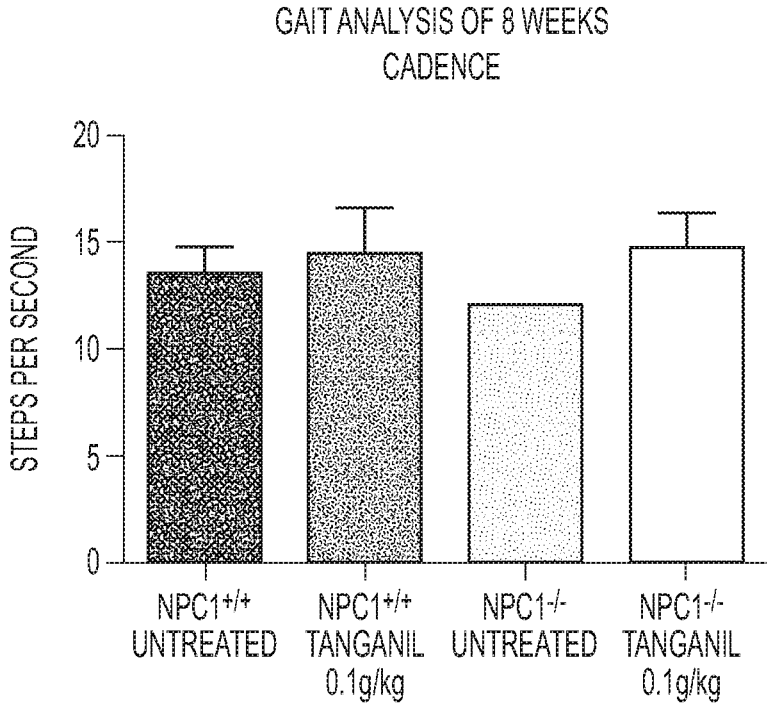


FIG. 3B

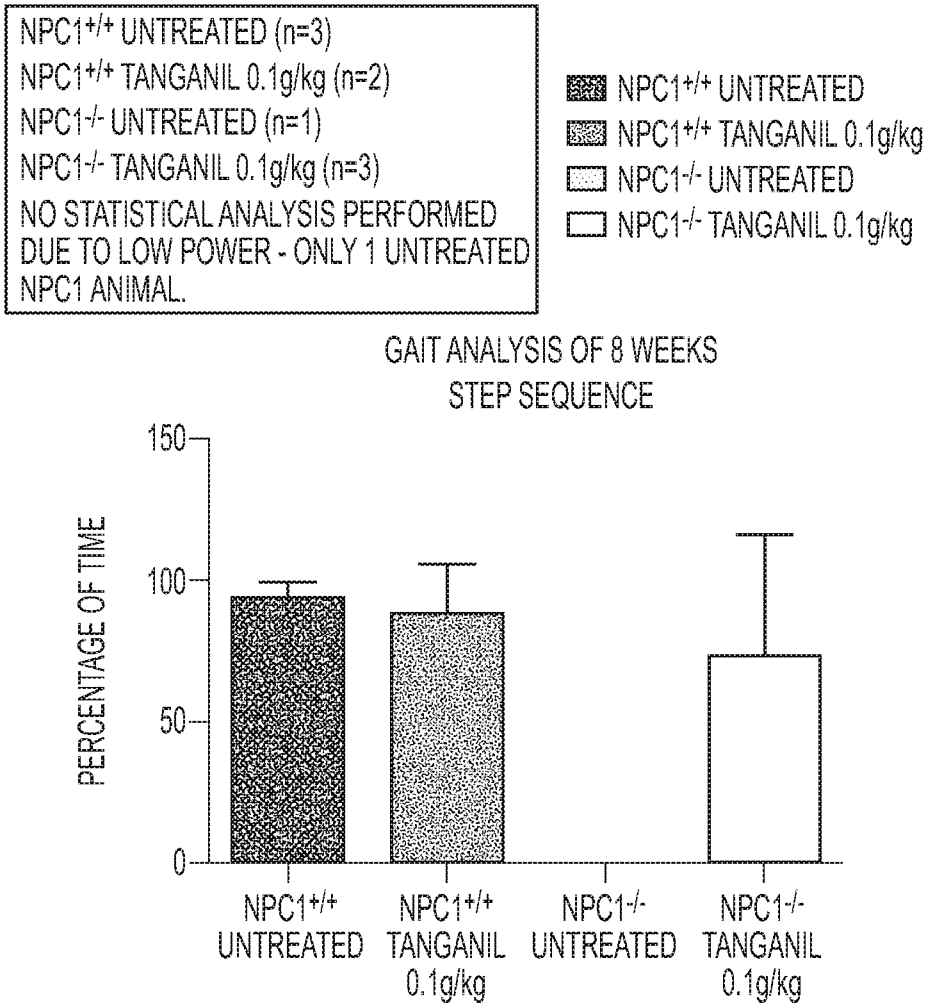

NPC1+/+ UNTREATED (n=3)
NPC1+/+ TANGANIL 0.1g/kg (n=2)
NPC1-/- UNTREATED (n=1)
NPC1-/- TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.
NPC1+/+ UNTREATED
NPC1+/+ TANGANIL 0.1g/kg
NPC1-/- UNTREATED
NPC1-/- TANGANIL 0.1g/kg
GAIT ANALYSIS OF 8 WEEKS
STEP SEQUENCE
PERCENTAGE OF TIME
150
100
50
0
NPC1+/+ UNTREATED
NPC1+/+ TANGANIL 0.1g/kg
NPC1-/- UNTREATED
NPC1-/- TANGANIL 0.1g/kg

FIG. 3C

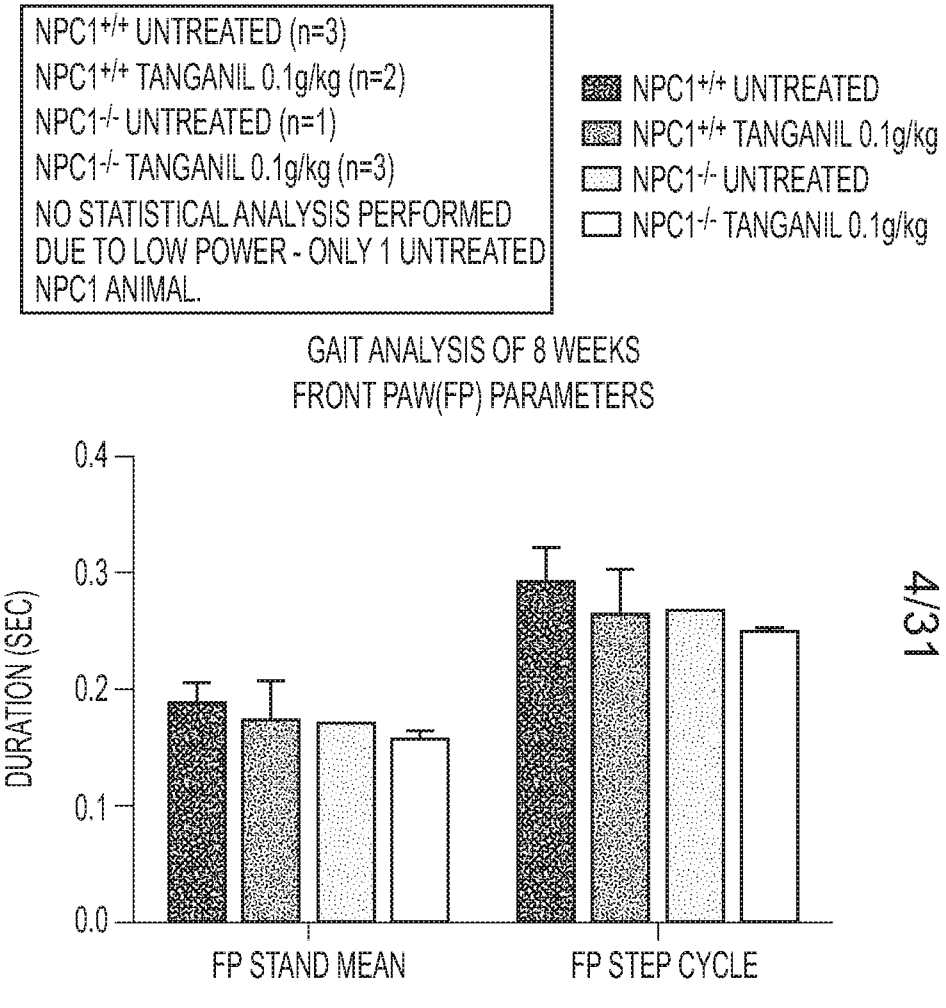

NPC1+/+ UNTREATED (n=3)
NPC1+/+ TANGANIL 0.1g/kg (n=2)
NPC1-/- UNTREATED (n=1)
NPC1-/- TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.
NPC1+/+ UNTREATED
NPC1+/+ TANGANIL 0.1g/kg
NPC1-/- UNTREATED
NPC1-/- TANGANIL 0.1g/kg
GAIT ANALYSIS OF 8 WEEKS
FRONT PAW(FP) PARAMETERS
DURATION (SEC)
0.4
0.3
0.2
0.1
0.0
FP STAND MEAN
FP STEP CYCLE

FIG. 3D

NPC1$^{+/+}$ UNTREATED (n=3)
NPC1$^{+/+}$ TANGANIL 0.1g/kg (n=2)
NPC1$^{-/-}$ UNTREATED (n=1)
NPC1$^{-/-}$ TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.

NPC1$^{+/+}$ UNTREATED
NPC1$^{+/+}$ TANGANIL 0.1g/kg
NPC1$^{-/-}$ UNTREATED
NPC1$^{-/-}$ TANGANIL 0.1g/kg

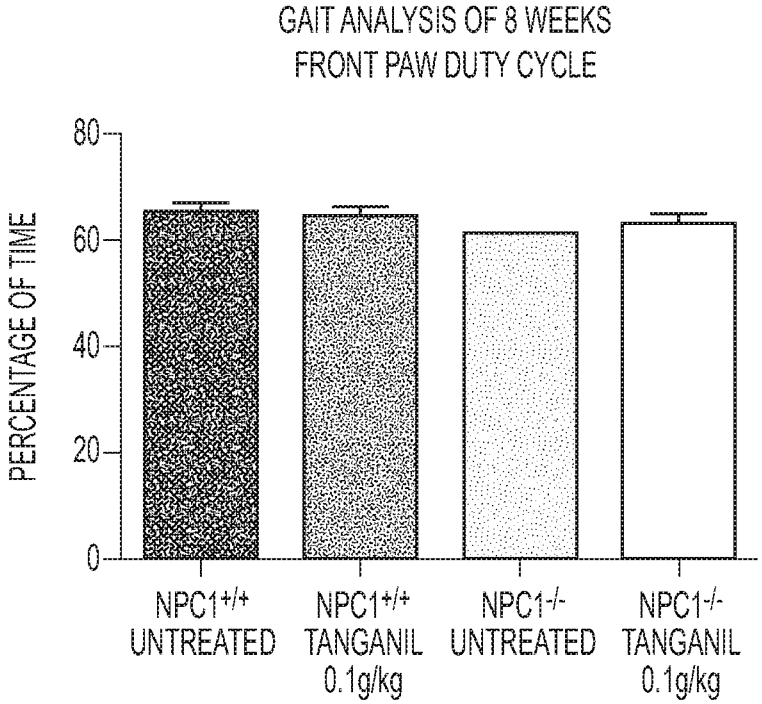


FIG. 3E

NPC1$^{+/+}$ UNTREATED (n=3)
NPC1$^{+/+}$ TANGANIL 0.1g/kg (n=2)
NPC1$^{-/-}$ UNTREATED (n=1)
NPC1$^{-/-}$ TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.

NPC1$^{+/+}$ UNTREATED
NPC1$^{+/+}$ TANGANIL 0.1g/kg
NPC1$^{-/-}$ UNTREATED
NPC1$^{-/-}$ TANGANIL 0.1g/kg

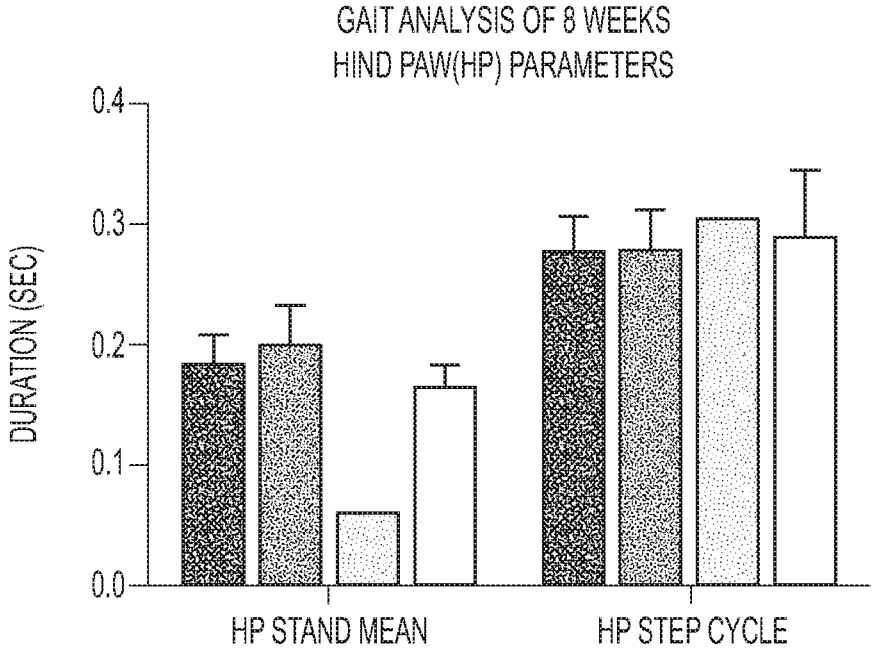


FIG. 3F

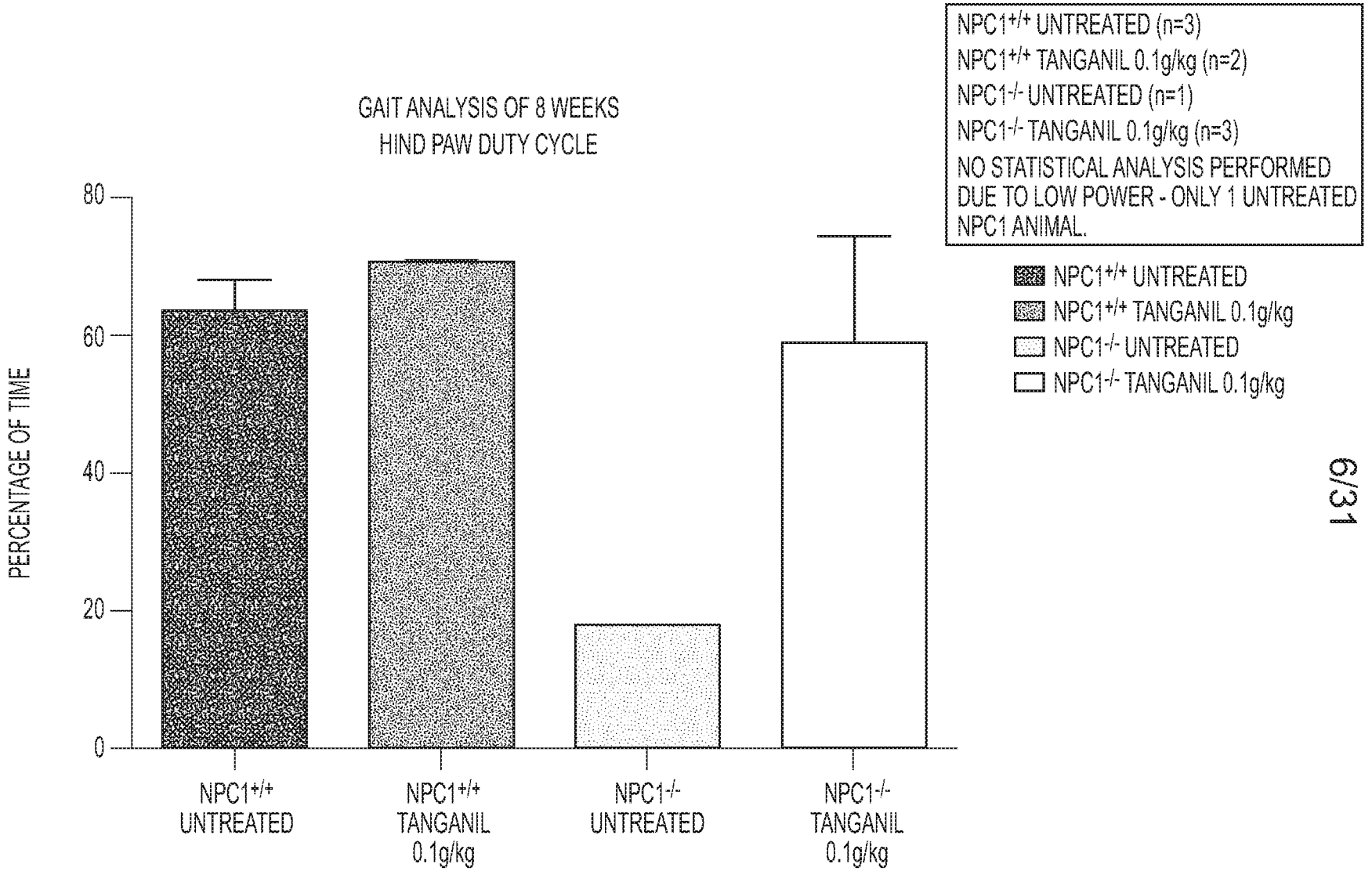

GAIT ANALYSIS OF 8 WEEKS
HIND PAW DUTY CYCLE
PERCENTAGE OF TIME
80
60
40
20
0
NPC1+/+ UNTREATED
NPC1+/+ TANGANIL 0.1g/kg
NPC1-/- UNTREATED
NPC1-/- TANGANIL 0.1g/kg
NPC1+/+ UNTREATED (n=3)
NPC1+/+ TANGANIL 0.1g/kg (n=2)
NPC1-/- UNTREATED (n=1)
NPC1-/- TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.
NPC1+/+ UNTREATED
NPC1+/+ TANGANIL 0.1g/kg
NPC1-/- UNTREATED
NPC1-/- TANGANIL 0.1g/kg

FIG. 3G

NPC1$^{+/+}$ UNTREATED (n=3)
NPC1$^{+/+}$ TANGANIL 0.1g/kg (n=2)
NPC1$^{-/-}$ UNTREATED (n=1)
NPC1$^{-/-}$ TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.

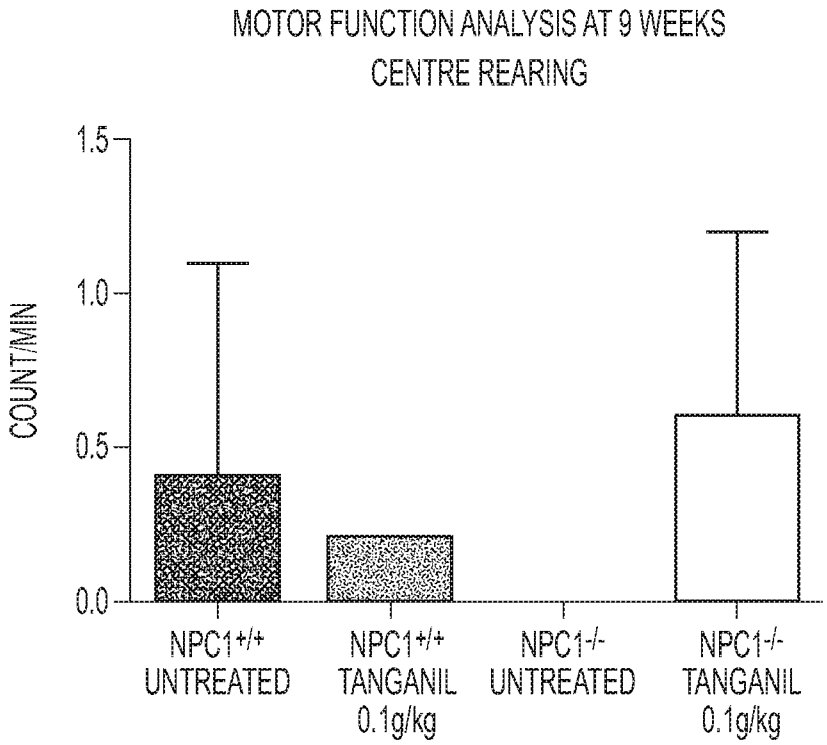


FIG. 4A

NPC1$^{+/+}$ UNTREATED (n=3)
NPC1$^{+/+}$ TANGANIL 0.1g/kg (n=2)
NPC1$^{-/-}$ UNTREATED (n=1)
NPC1$^{-/-}$ TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.

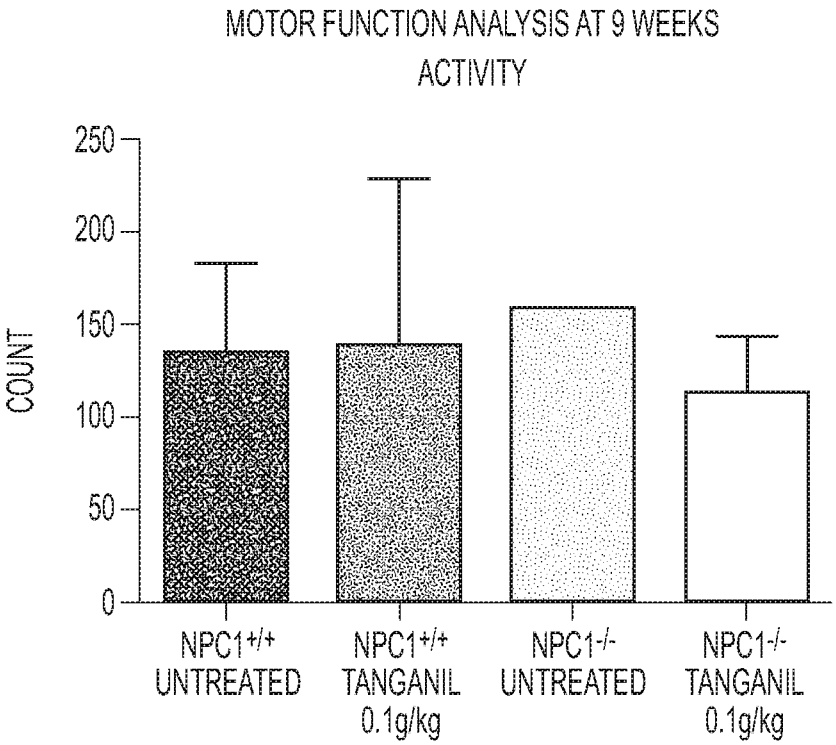


FIG. 4B

NPC1$^{+/+}$ UNTREATED (n=3)
NPC1$^{+/+}$ TANGANIL 0.1g/kg (n=2)
NPC1$^{-/-}$ UNTREATED (n=1)
NPC1$^{-/-}$ TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.

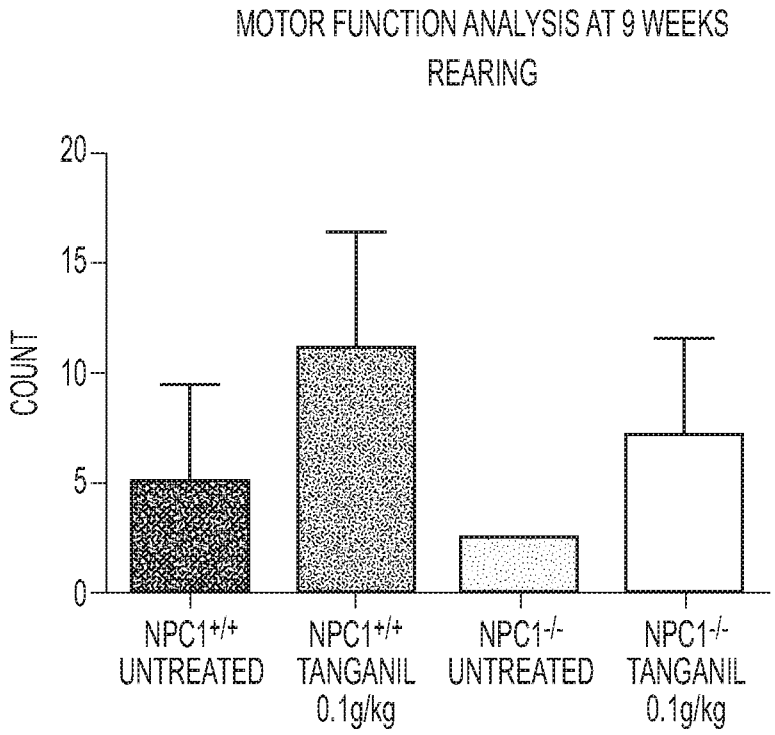


FIG. 4C

NPC1$^{+/+}$ UNTREATED (n=3)
NPC1$^{+/+}$ TANGANIL 0.1g/kg (n=2)
NPC1$^{-/-}$ UNTREATED (n=1)
NPC1$^{-/-}$ TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.

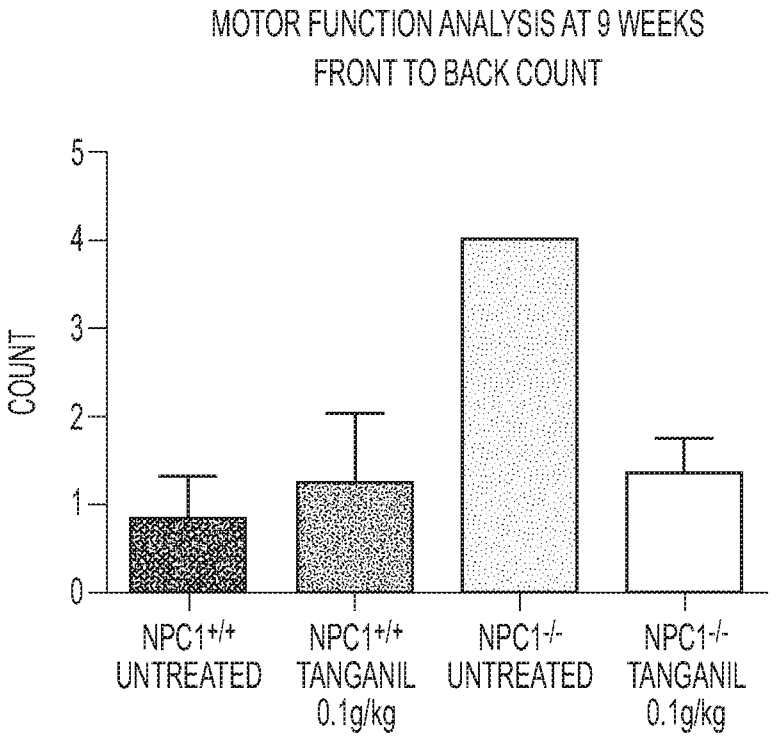


FIG. 4D

NPC1$^{+/+}$ UNTREATED (n=3)
NPC1$^{+/+}$ TANGANIL 0.1g/kg (n=2)
NPC1$^{-/-}$ UNTREATED (n=1)
NPC1$^{-/-}$ TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.

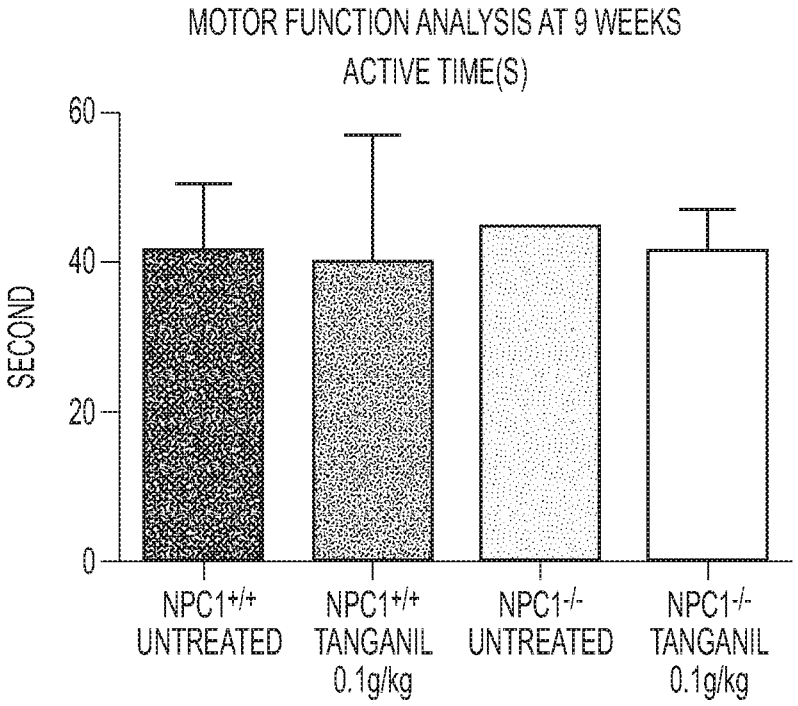


FIG. 4E

NPC1$^{+/+}$ UNTREATED (n=3)
NPC1$^{+/+}$ TANGANIL 0.1g/kg (n=2)
NPC1$^{-/-}$ UNTREATED (n=1)
NPC1$^{-/-}$ TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.

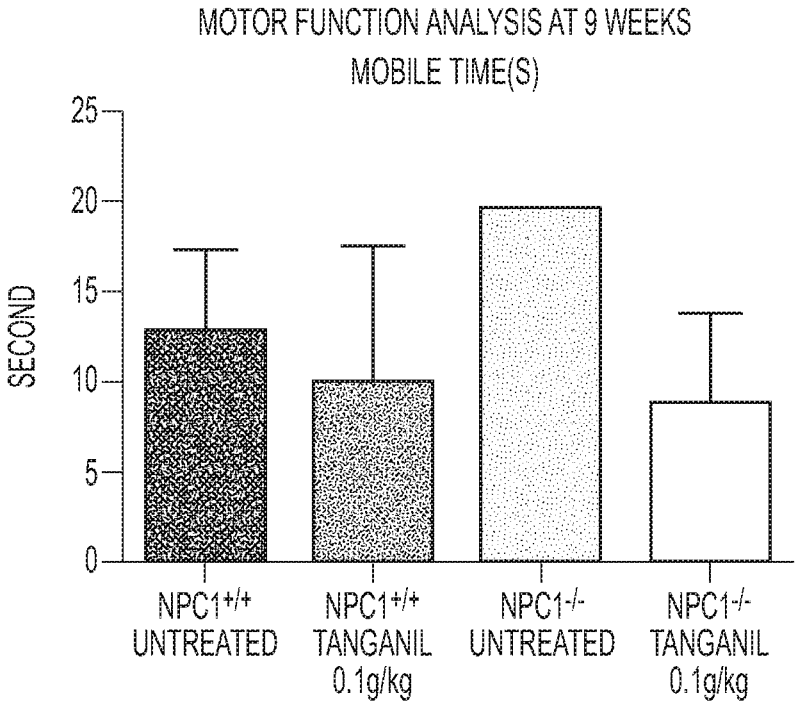


FIG. 4F

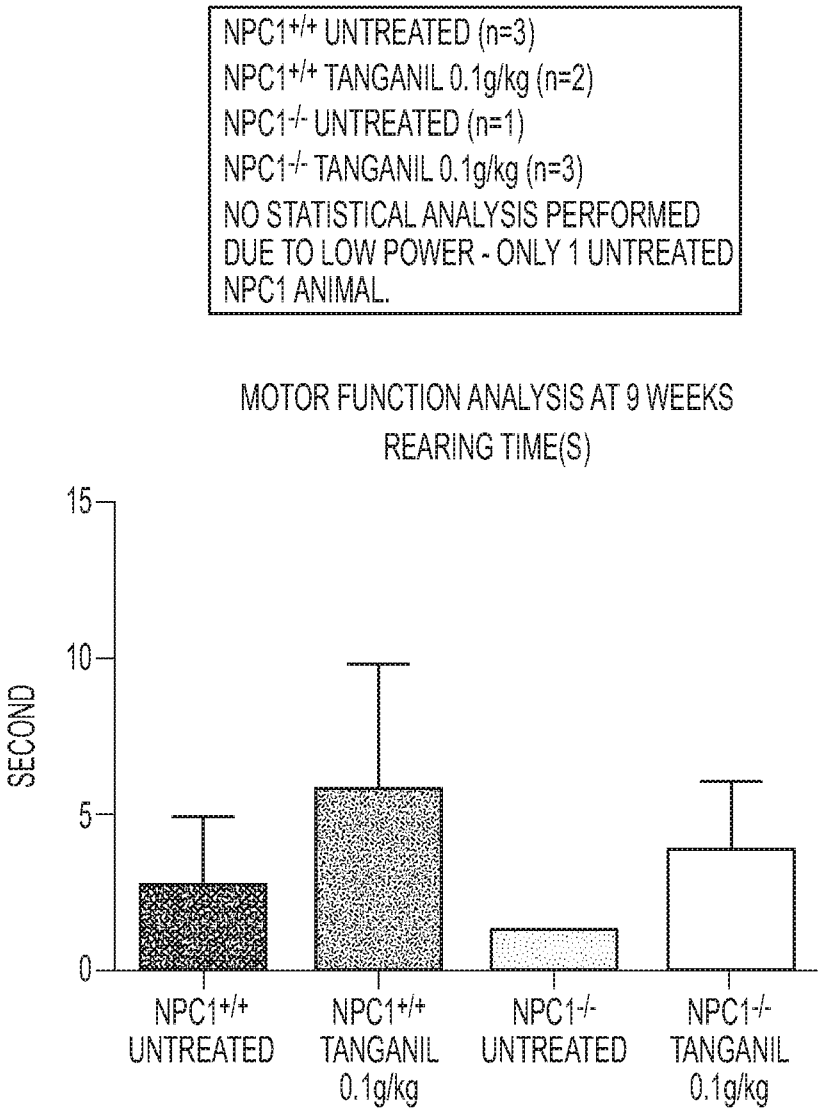

NPC1+/+ UNTREATED (n=3)
NPC1+/+ TANGANIL 0.1g/kg (n=2)
NPC1-/- UNTREATED (n=1)
NPC1-/- TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.
MOTOR FUNCTION ANALYSIS AT 9 WEEKS
REARING TIME(S)
SECOND
15
10
5
0
NPC1+/+ UNTREATED
NPC1+/+ TANGANIL 0.1g/kg
NPC1-/- UNTREATED
NPC1-/- TANGANIL 0.1g/kg

FIG. 4G

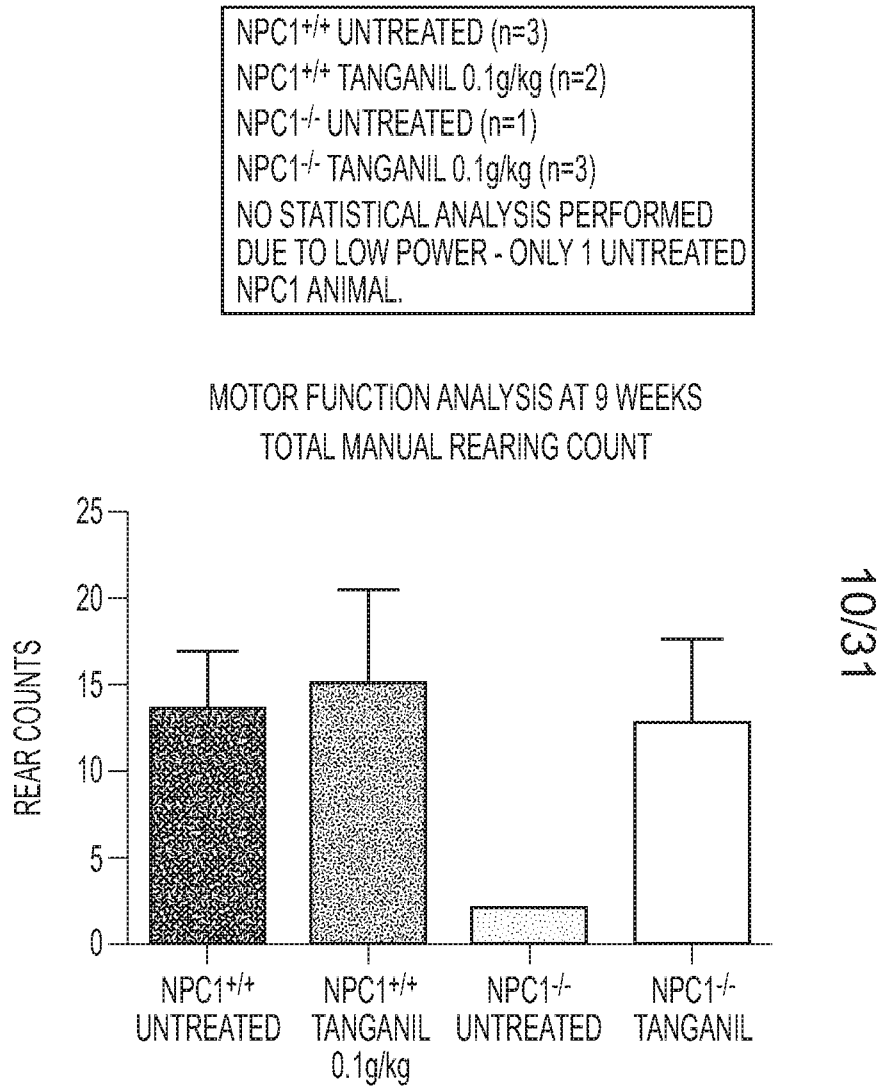

NPC1+/+ UNTREATED (n=3)
NPC1+/+ TANGANIL 0.1g/kg (n=2)
NPC1-/- UNTREATED (n=1)
NPC1-/- TANGANIL 0.1g/kg (n=3)
NO STATISTICAL ANALYSIS PERFORMED DUE TO LOW POWER - ONLY 1 UNTREATED NPC1 ANIMAL.
MOTOR FUNCTION ANALYSIS AT 9 WEEKS
TOTAL MANUAL REARING COUNT
REAR COUNTS
25
20
15
10
5
0
NPC1+/+ UNTREATED
NPC1+/+ TANGANIL 0.1g/kg
NPC1-/- UNTREATED
NPC1-/- TANGANIL

FIG. 4H

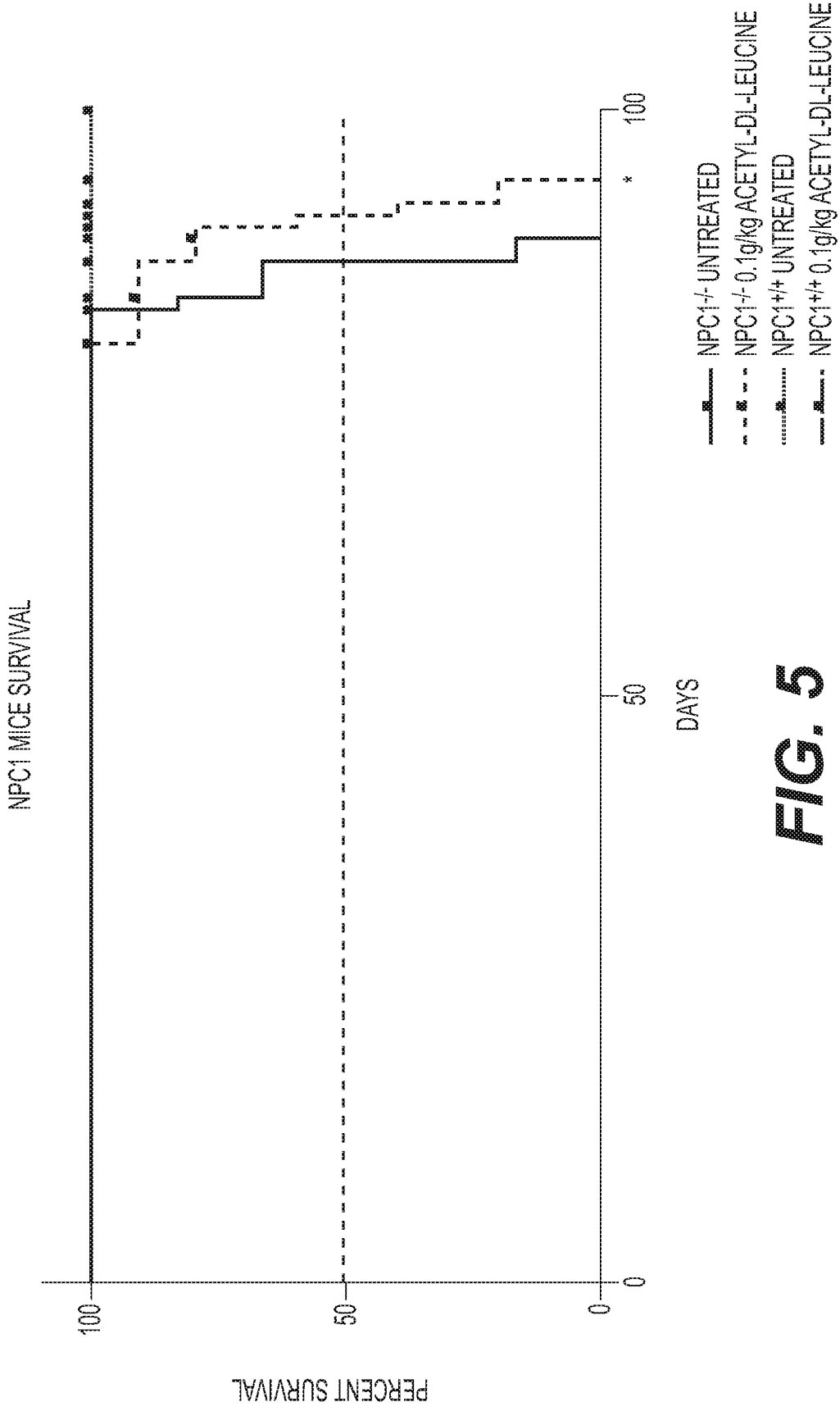

NPC1 MICE SURVIVAL
PERCENT SURVIVAL
100
50
0
0
50
100
DAYS
*
NPC1-/- UNTREATED
NPC1-/- 0.1g/kg ACETYL-DL-LEUCINE
NPC1+/+ UNTREATED
NPC1+/+ 0.1g/kg ACETYL-DL-LEUCINE

FIG. 5

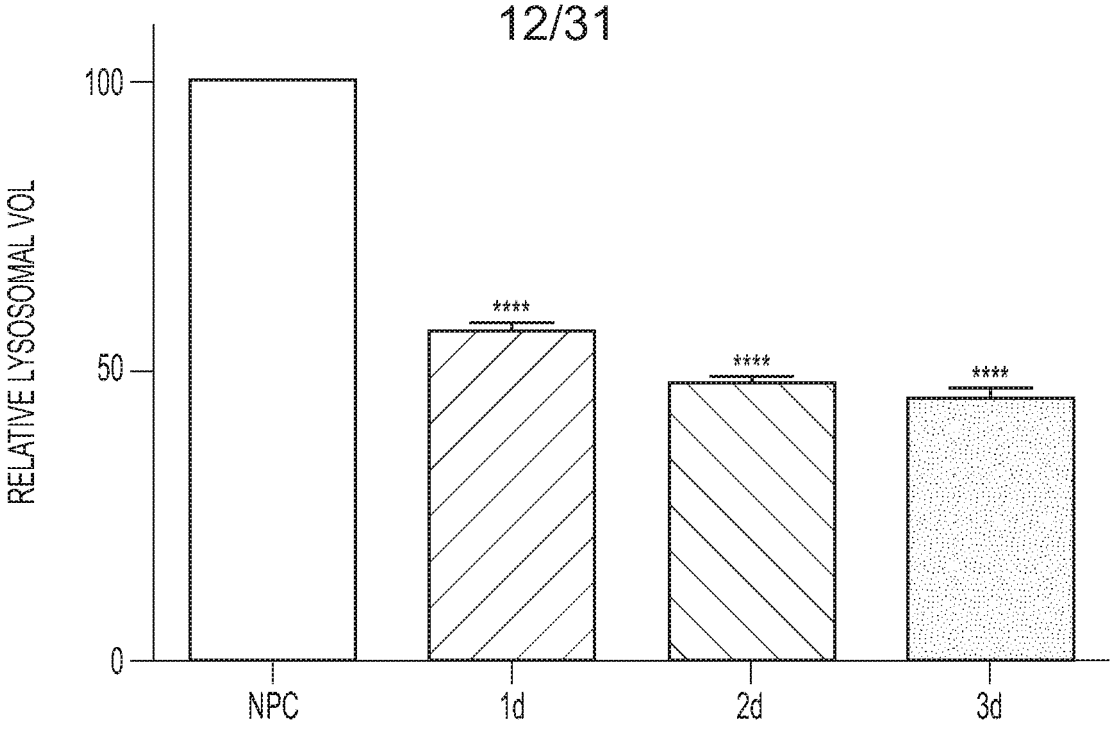

RELATIVE LYSOSOMAL VOL
100
50
0
****
****
****
NPC
1d
2d
3d

FIG. 6A

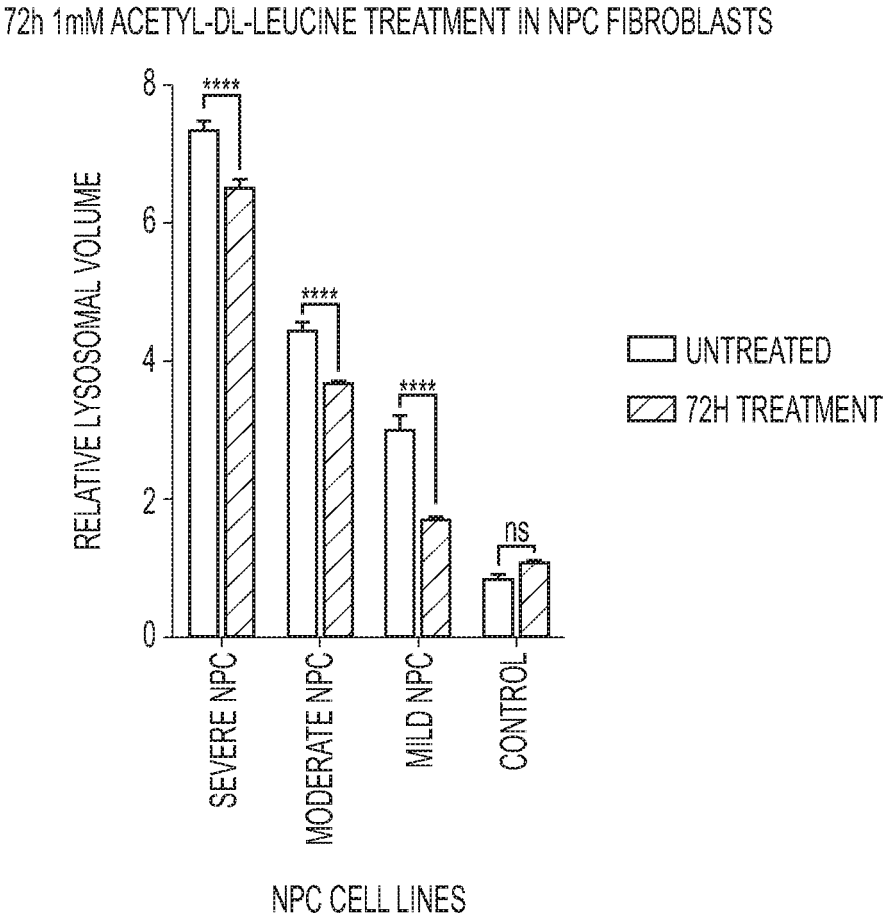

72h 1mM ACETYL-DL-LEUCINE TREATMENT IN NPC FIBROBLASTS
RELATIVE LYSOSOMAL VOLUME
8
6
4
2
0
****
****
****
ns
UNTREATED
72H TREATMENT
SEVERE NPC
MODERATE NPC
MILD NPC
CONTROL
NPC CELL LINES

FIG. 6B

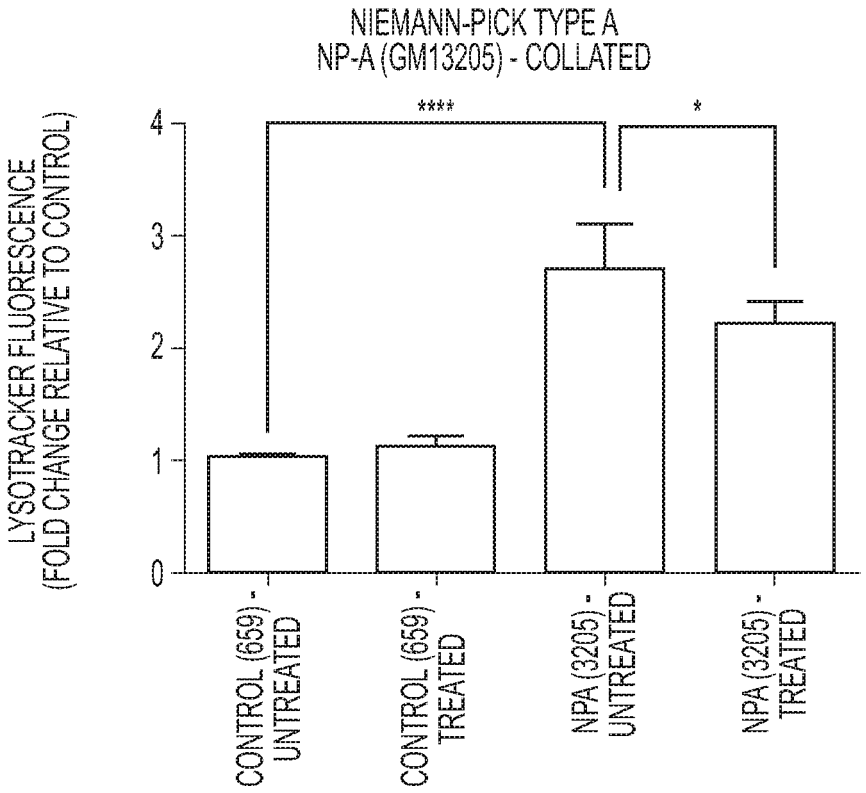

NIEMANN-PICK TYPE A
NP-A (GM13205) - COLLATED
LYSOTRACKER FLUORESCENCE
(FOLD CHANGE RELATIVE TO CONTROL)
****
*
4
3
2
1
0
CONTROL (659) - UNTREATED
CONTROL (659) - TREATED
NPA (3205) - UNTREATED
NPA (3205) - TREATED

FIG. 6C

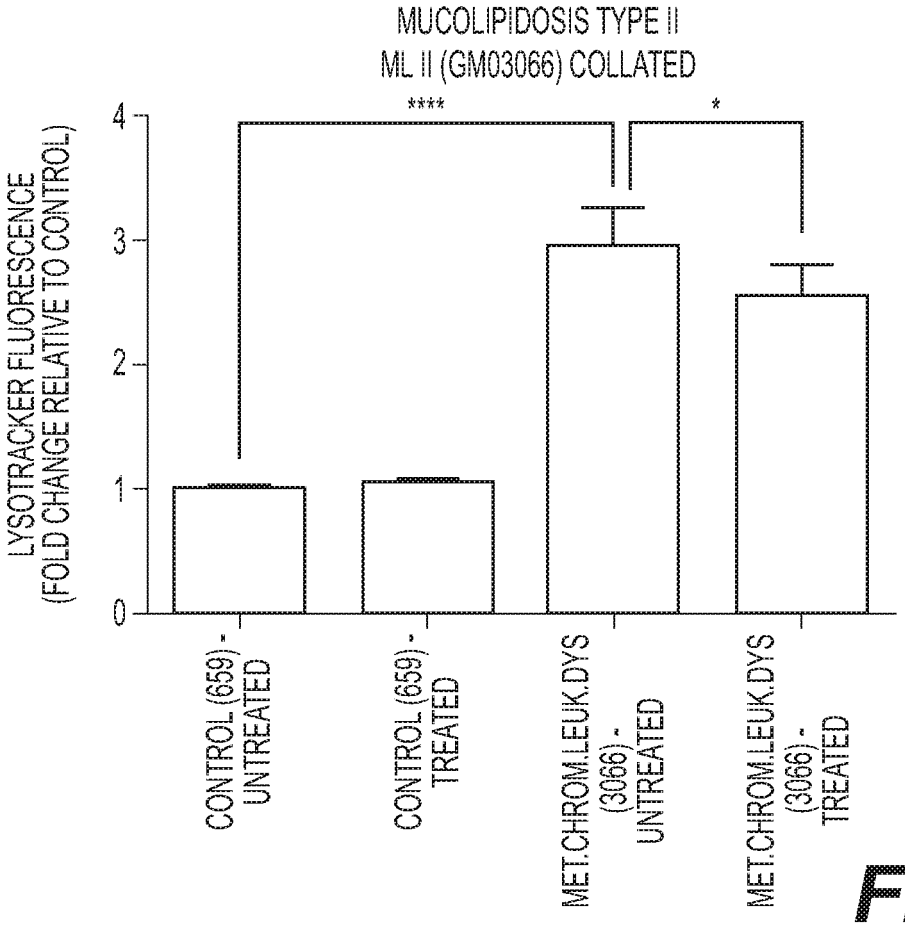

MUCOLIPIDOSIS TYPE II
ML II (GM03066) COLLATED
LYSOTRACKER FLUORESCENCE
(FOLD CHANGE RELATIVE TO CONTROL)
****
*
4
3
2
1
0
CONTROL (659) - UNTREATED
CONTROL (659) - TREATED
MET.CHROM.LEUK.DYS (3066) - UNTREATED
MET.CHROM.LEUK.DYS (3066) - TREATED

FIG. 6D

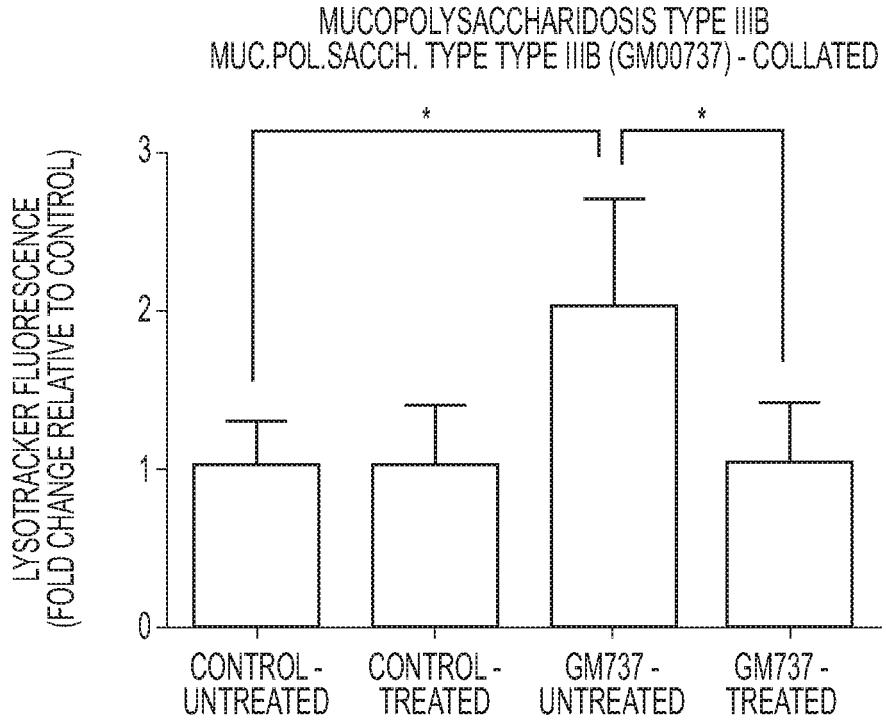

MUCOPOLYSACCHARIDOSIS TYPE IIIB
MUC.POL.SACCH. TYPE TYPE IIIB (GM00737) - COLLATED
LYSOTRACKER FLUORESCENCE
(FOLD CHANGE RELATIVE TO CONTROL)
*
*
3
2
1
0
CONTROL - UNTREATED
CONTROL - TREATED
GM737 - UNTREATED
GM737 - TREATED

FIG. 6E

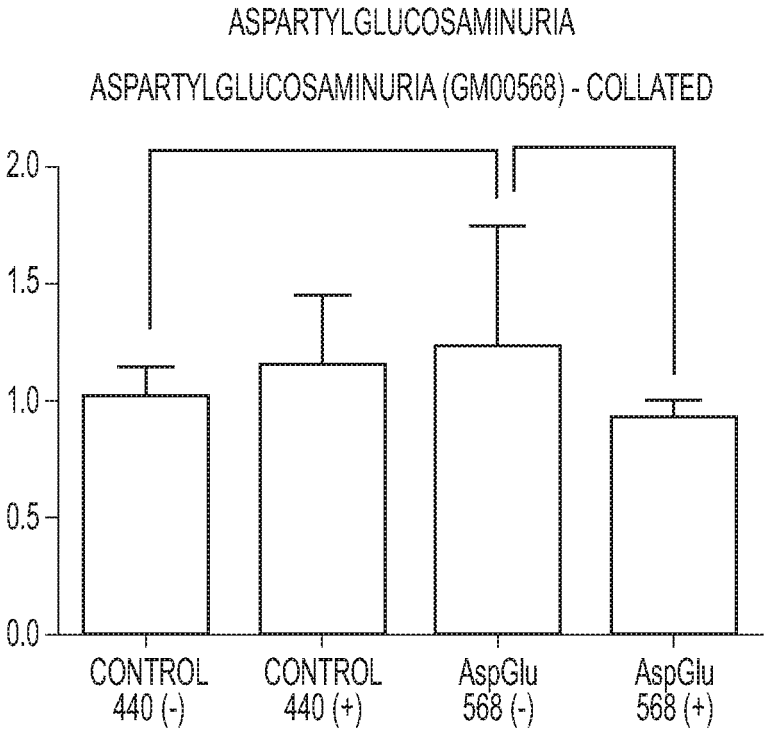

ASPARTYLGLUCOSAMINURIA
ASPARTYLGLUCOSAMINURIA (GM00568) - COLLATED
2.0
1.5
1.0
0.5
0.0
CONTROL 440 (-)
CONTROL 440 (+)
AspGlu 568 (-)
AspGlu 568 (+)

FIG. 6F

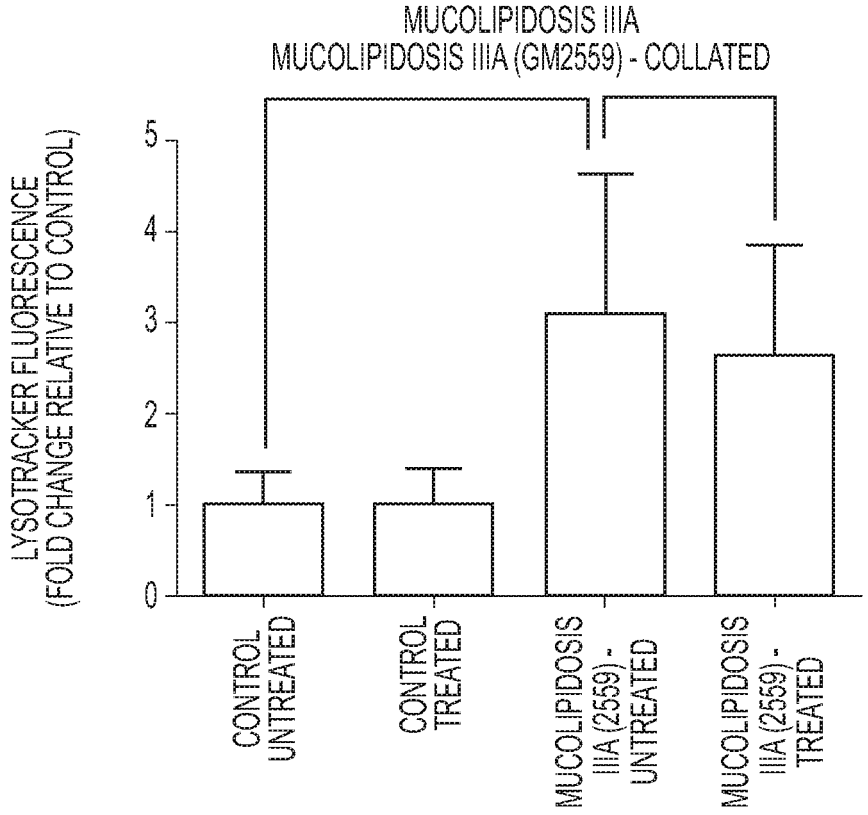

MUCOLIPIDOSIS IIIA
MUCOLIPIDOSIS IIIA (GM2559) - COLLATED
LYSOTRACKER FLUORESCENCE
(FOLD CHANGE RELATIVE TO CONTROL)
5
4
3
2
1
0
CONTROL UNTREATED
CONTROL TREATED
MUCOLIPIDOSIS IIIA (2559) - UNTREATED
MUCOLIPIDOSIS IIIA (2559) - TREATED

FIG. 6G

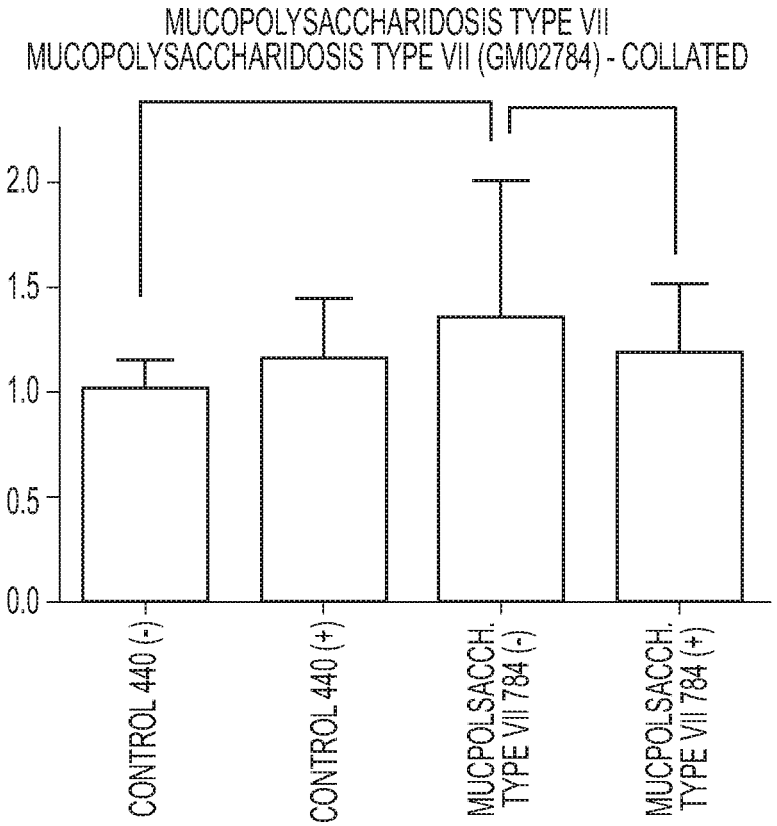

MUCOPOLYSACCHARIDOSIS TYPE VII
MUCOPOLYSACCHARIDOSIS TYPE VII (GM02784) - COLLATED
2.0
1.5
1.0
0.5
0.0
CONTROL 440 (-)
CONTROL 440 (+)
MUCPOLSACCH. TYPE VII 784 (-)
MUCPOLSACCH. TYPE VII 784 (+)

FIG. 6H

	HEXB$^{-/-}$ UNTREATED	HEXB$^{-/-}$ ACETYL-DL-LEUCINE 0.1g/kg
MEDIAN SURVIVAL	112	120

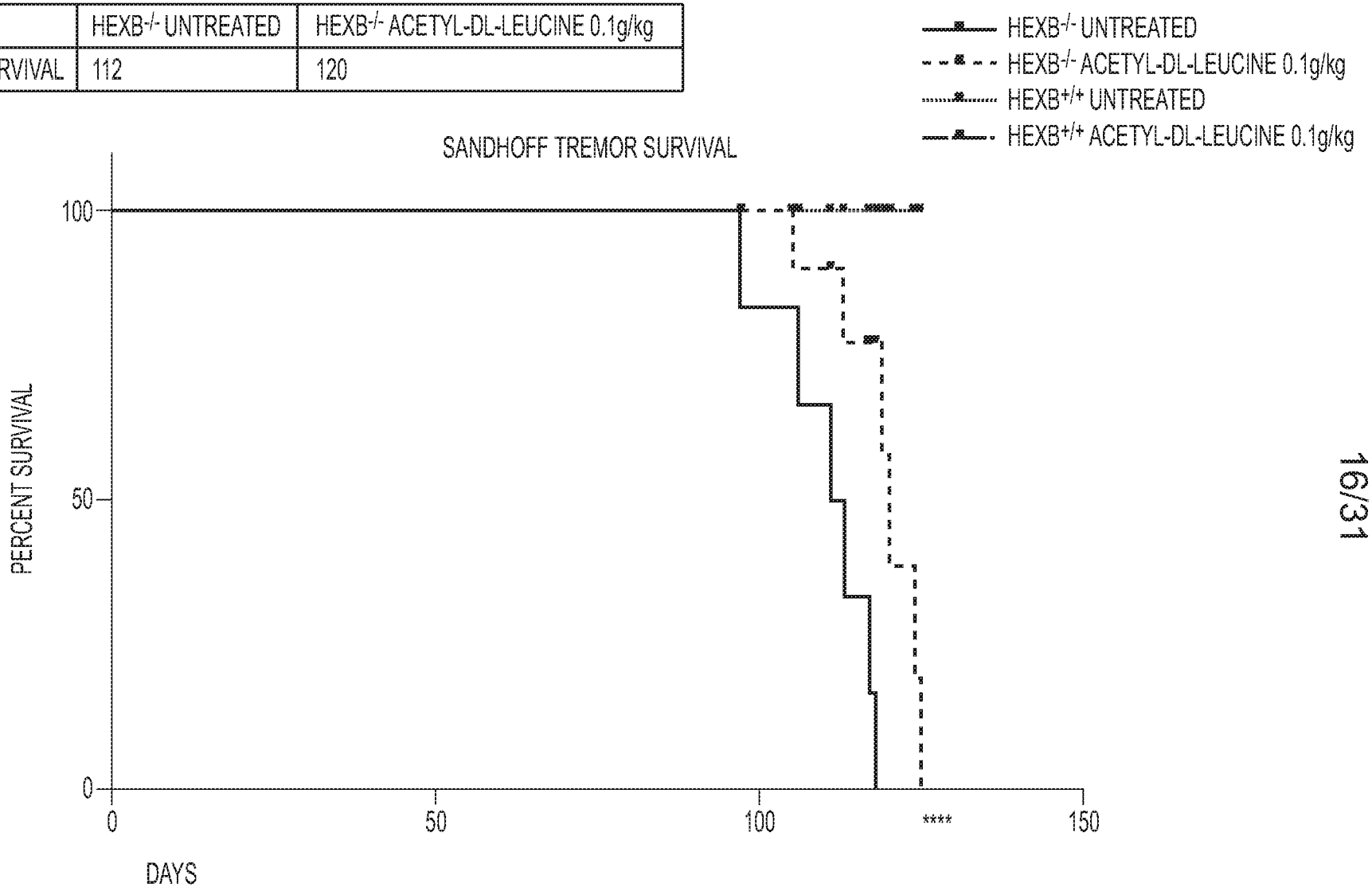


FIG. 7A

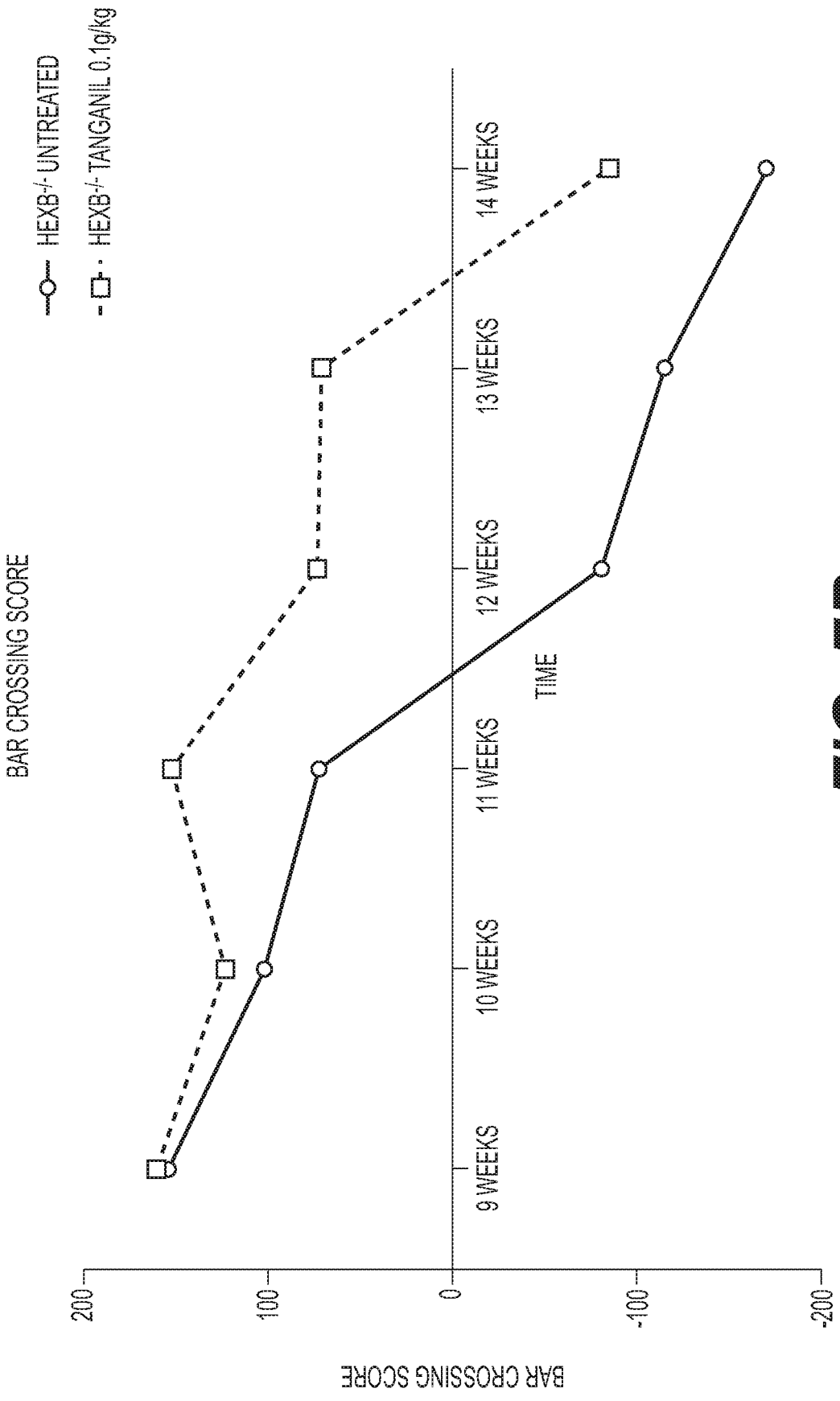

BAR CROSSING SCORE
HEXB-/- UNTREATED
HEXB-/- TANGANIL 0.1g/kg
200
100
0
-100
-200
9 WEEKS
10 WEEKS
11 WEEKS
12 WEEKS
13 WEEKS
14 WEEKS
TIME
BAR CROSSING SCORE

FIG. 7B

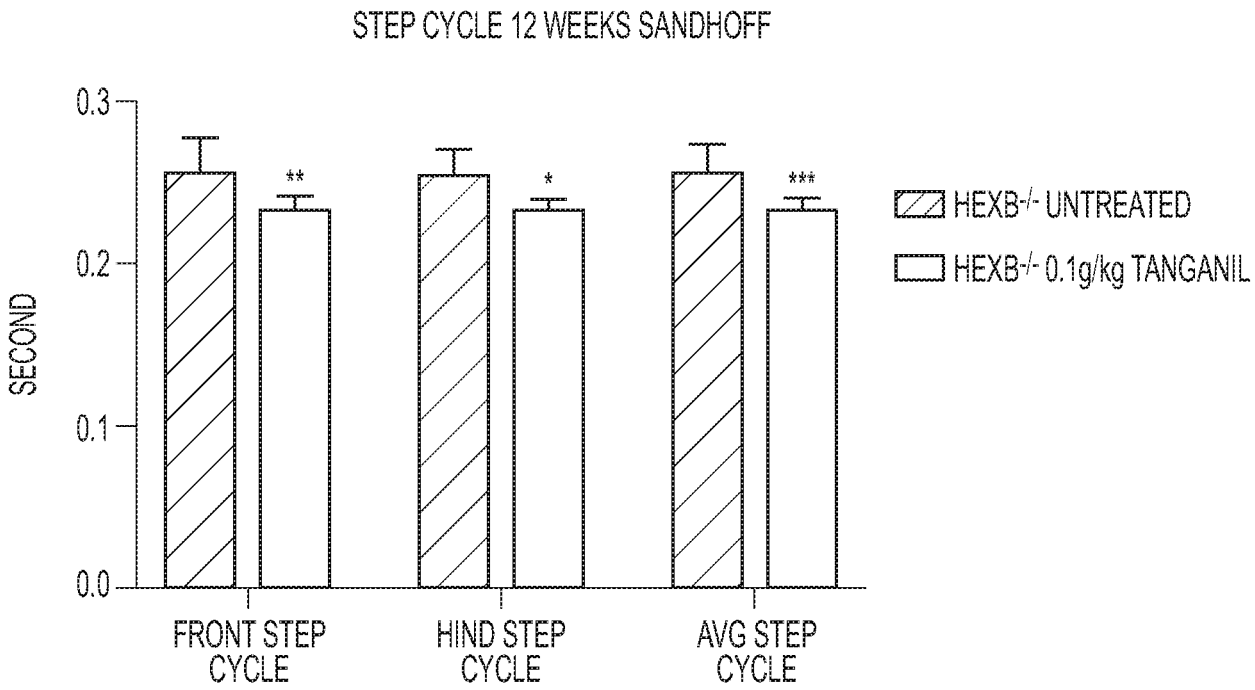

STEP CYCLE 12 WEEKS SANDHOFF
SECOND
0.3
0.2
0.1
0.0
**
*
***
HEXB-/- UNTREATED
HEXB-/- 0.1g/kg TANGANIL
FRONT STEP CYCLE
HIND STEP CYCLE
AVG STEP CYCLE

FIG. 7C

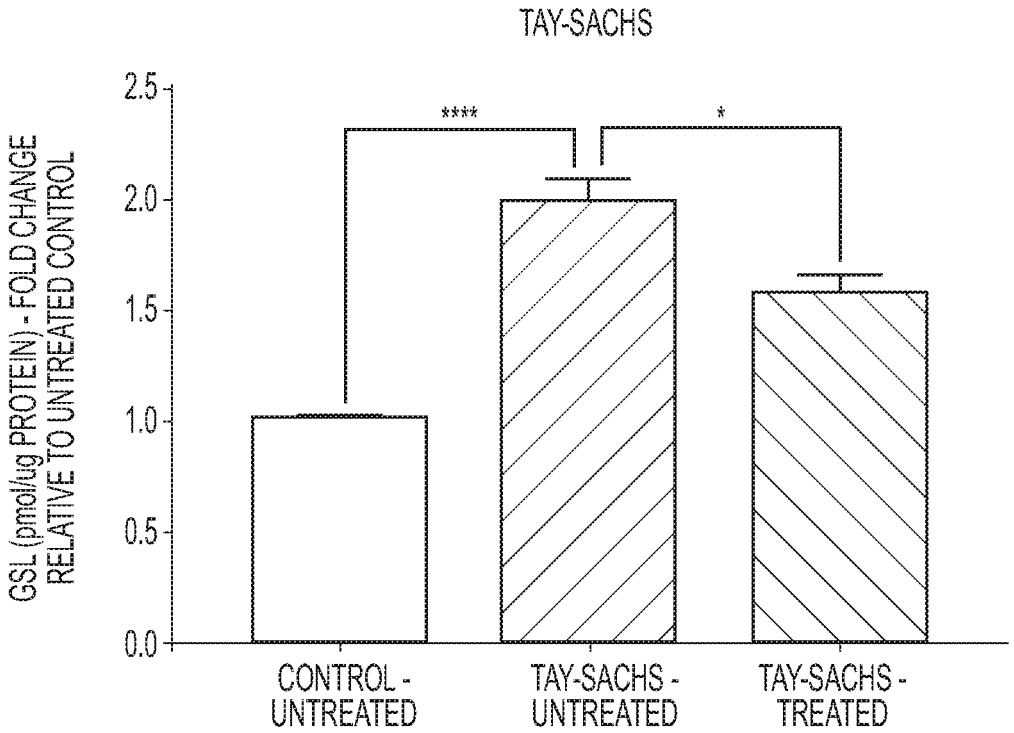

TAY-SACHS
GSL (pmol/ug PROTEIN) - FOLD CHANGE RELATIVE TO UNTREATED CONTROL
2.5
2.0
1.5
1.0
0.5
0.0
****
*
CONTROL - UNTREATED
TAY-SACHS - UNTREATED
TAY-SACHS - TREATED

FIG. 8A

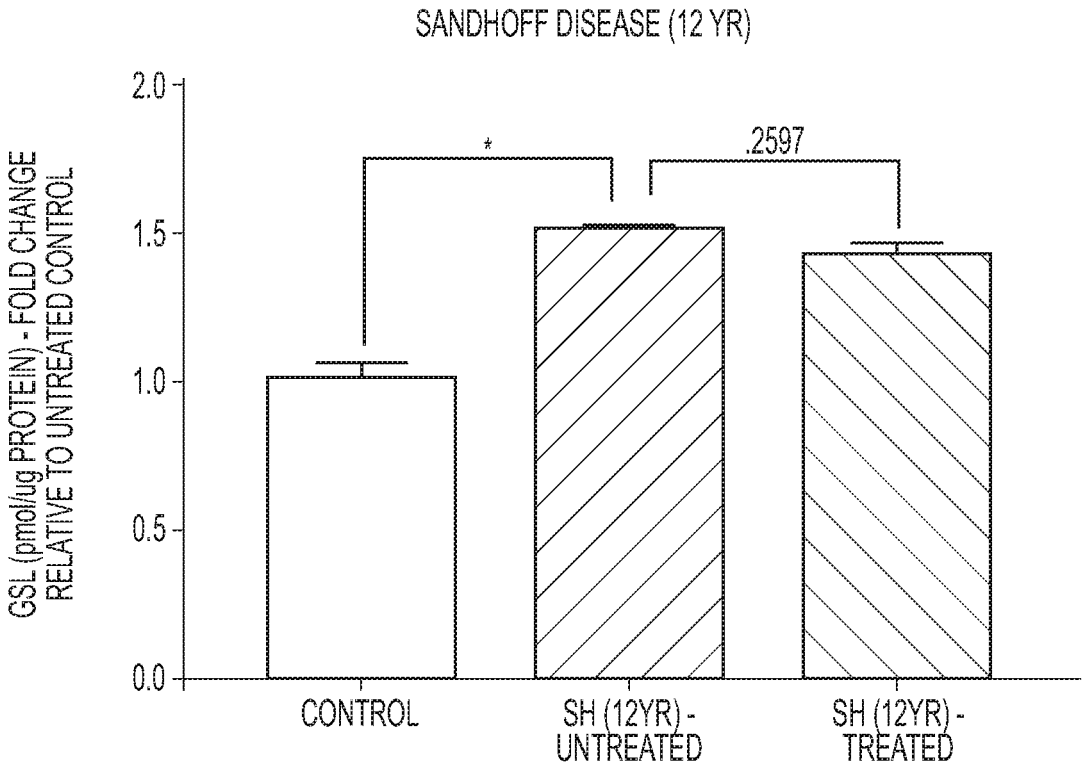

SANDHOFF DISEASE (12 YR)
GSL (pmol/ug PROTEIN) - FOLD CHANGE RELATIVE TO UNTREATED CONTROL
2.0
1.5
1.0
0.5
0.0
*
.2597
CONTROL
SH (12YR) - UNTREATED
SH (12YR) - TREATED

FIG. 8B

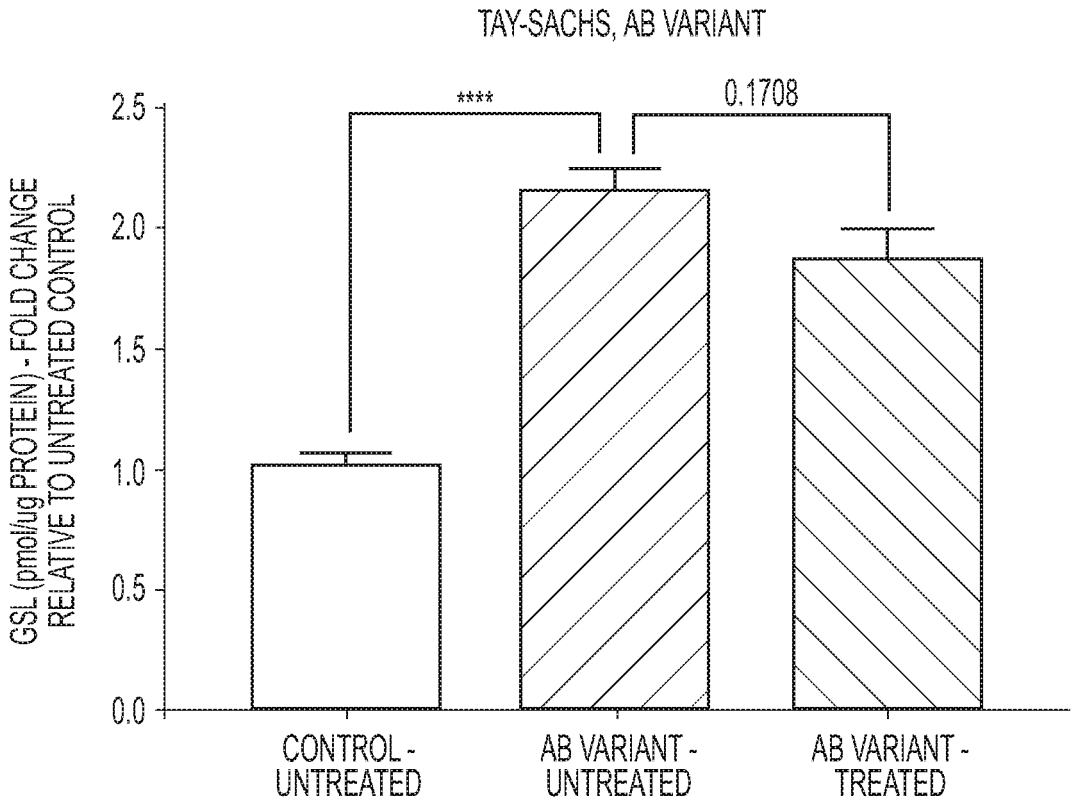
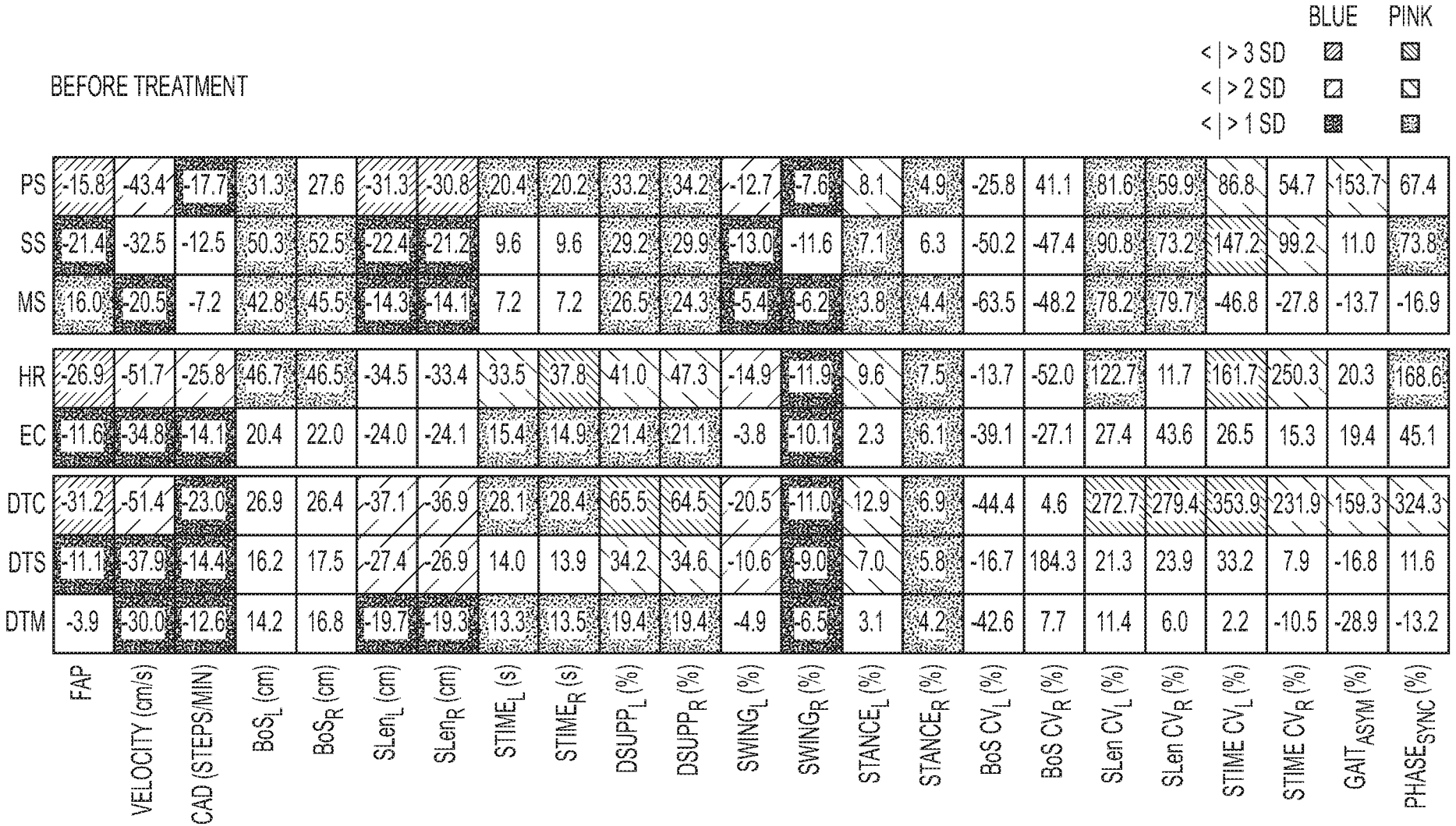

TAY-SACHS, AB VARIANT
GSL (pmol/ug PROTEIN) - FOLD CHANGE RELATIVE TO UNTREATED CONTROL
2.5
2.0
1.5
1.0
0.5
0.0
****
0.1708
CONTROL - UNTREATED
AB VARIANT - UNTREATED
AB VARIANT - TREATED

FIG. 8C


BLUE
PINK
< | > 3 SD
< | > 2 SD
< | > 1 SD
BEFORE TREATMENT
PS -15.8 -43.4 -17.7 31.3 27.6 -31.3 -30.8 20.4 20.2 33.2 34.2 -12.7 -7.6 8.1 4.9 -25.8 41.1 81.6 59.9 86.8 54.7 153.7 67.4
SS -21.4 -32.5 -12.5 50.3 52.5 -22.4 -21.2 9.6 9.6 29.2 29.9 -13.0 -11.6 7.1 6.3 -50.2 -47.4 90.8 73.2 147.2 99.2 11.0 73.8
MS 16.0 -20.5 -7.2 42.8 45.5 -14.3 -14.1 7.2 7.2 26.5 24.3 -5.4 -6.2 3.8 4.4 -63.5 -48.2 78.2 79.7 -46.8 -27.8 -13.7 -16.9
HR -26.9 -51.7 -25.8 46.7 46.5 -34.5 -33.4 33.5 37.8 41.0 47.3 -14.9 -11.9 9.6 7.5 -13.7 -52.0 122.7 11.7 161.7 250.3 20.3 168.6
EC -11.6 -34.8 -14.1 20.4 22.0 -24.0 -24.1 15.4 14.9 21.4 21.1 -3.8 -10.1 2.3 6.1 -39.1 -27.1 27.4 43.6 26.5 15.3 19.4 45.1
DTC -31.2 -51.4 -23.0 26.9 26.4 -37.1 -36.9 28.1 28.4 65.5 64.5 -20.5 -11.0 12.9 6.9 -44.4 4.6 272.7 279.4 353.9 231.9 159.3 324.3
DTS -11.1 -37.9 -14.4 16.2 17.5 -27.4 -26.9 14.0 13.9 34.2 34.6 -10.6 -9.0 7.0 5.8 -16.7 184.3 21.3 23.9 33.2 7.9 -16.8 11.6
DTM -3.9 -30.0 -12.6 14.2 16.8 -19.7 -19.3 13.3 13.5 19.4 19.4 -4.9 -6.5 3.1 4.2 -42.6 7.7 11.4 6.0 2.2 -10.5 -28.9 -13.2
FAP
VELOCITY (cm/s)
CAD (STEPS/MIN)
BoS_L (cm)
BoS_R (cm)
$SLen_L$ (cm)
$SLen_R$ (cm)
$STIME_L$ (s)
$STIME_R$ (s)
$DSUPP_L$ (%)
$DSUPP_R$ (%)
$SWING_L$ (%)
$SWING_R$ (%)
$STANCE_L$ (%)
$STANCE_R$ (%)
BoS CV_L (%)
BoS CV_R (%)
SLen CV_L (%)
SLen CV_R (%)
STIME CV_L (%)
STIME CV_R (%)
$GAIT_{ASYM}$ (%)
$PHASE_{SYNC}$ (%)

20/31

FIG. 9

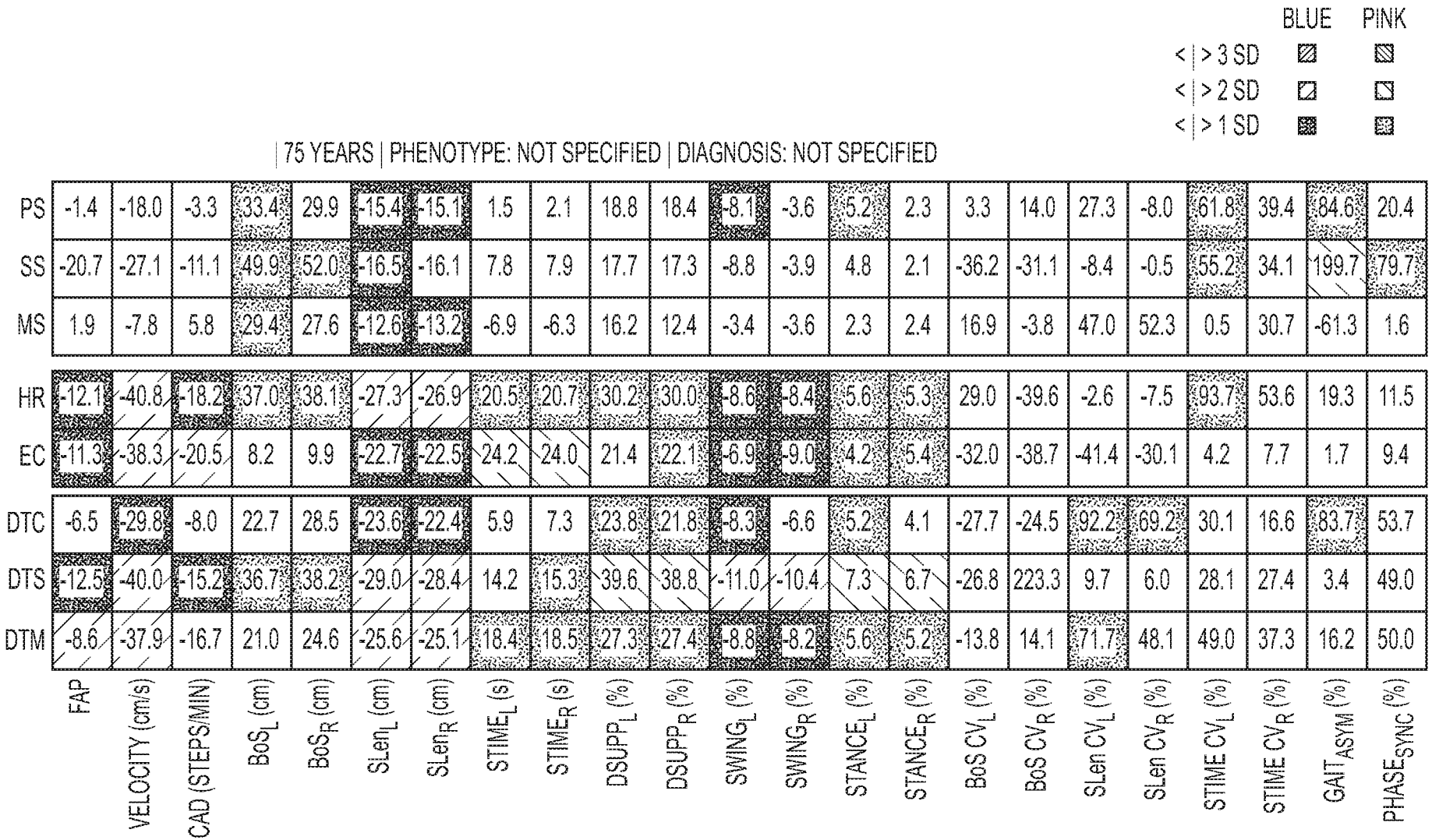

BLUE PINK
< | > 3 SD
< | > 2 SD
< | > 1 SD
| 75 YEARS | PHENOTYPE: NOT SPECIFIED | DIAGNOSIS: NOT SPECIFIED
PS -1.4 -18.0 -3.3 33.4 29.9 -15.4 -15.1 1.5 2.1 18.8 18.4 -8.1 -3.6 5.2 2.3 3.3 14.0 27.3 -8.0 61.8 39.4 84.6 20.4
SS -20.7 -27.1 -11.1 49.9 52.0 -16.5 -16.1 7.8 7.9 17.7 17.3 -8.8 -3.9 4.8 2.1 -36.2 -31.1 -8.4 -0.5 55.2 34.1 199.7 79.7
MS 1.9 -7.8 5.8 29.4 27.6 -12.6 -13.2 -6.9 -6.3 16.2 12.4 -3.4 -3.6 2.3 2.4 16.9 -3.8 47.0 52.3 0.5 30.7 -61.3 1.6
HR -12.1 -40.8 -18.2 37.0 38.1 -27.3 -26.9 20.5 20.7 30.2 30.0 -8.6 -8.4 5.6 5.3 29.0 -39.6 -2.6 -7.5 93.7 53.6 19.3 11.5
EC -11.3 -38.3 -20.5 8.2 9.9 -22.7 -22.5 24.2 24.0 21.4 22.1 -6.9 -9.0 4.2 5.4 -32.0 -38.7 -41.4 -30.1 4.2 7.7 1.7 9.4
DTC -6.5 -29.8 -8.0 22.7 28.5 -23.6 -22.4 5.9 7.3 23.8 21.8 -8.3 -6.6 5.2 4.1 -27.7 -24.5 92.2 69.2 30.1 16.6 83.7 53.7
DTS -12.5 -40.0 -15.2 36.7 38.2 -29.0 -28.4 14.2 15.3 39.6 38.8 -11.0 -10.4 7.3 6.7 -26.8 223.3 9.7 6.0 28.1 27.4 3.4 49.0
DTM -8.6 -37.9 -16.7 21.0 24.6 -25.6 -25.1 18.4 18.5 27.3 27.4 -8.8 -8.2 5.6 5.2 -13.8 14.1 71.7 48.1 49.0 37.3 16.2 50.0
FAP
VELOCITY (cm/s)
CAD (STEPS/MIN)
BoS$_L$ (cm)
BoS$_R$ (cm)
SLen$_L$ (cm)
SLen$_R$ (cm)
STIME$_L$ (s)
STIME$_R$ (s)
DSUPP$_L$ (%)
DSUPP$_R$ (%)
SWING$_L$ (%)
SWING$_R$ (%)
STANCE$_L$ (%)
STANCE$_R$ (%)
BoS CV$_L$ (%)
BoS CV$_R$ (%)
SLen CV$_L$ (%)
SLen CV$_R$ (%)
STIME CV$_L$ (%)
STIME CV$_R$ (%)
GAIT$_{ASYM}$ (%)
PHASE$_{SYNC}$ (%)

FIG. 9
(CONT.)

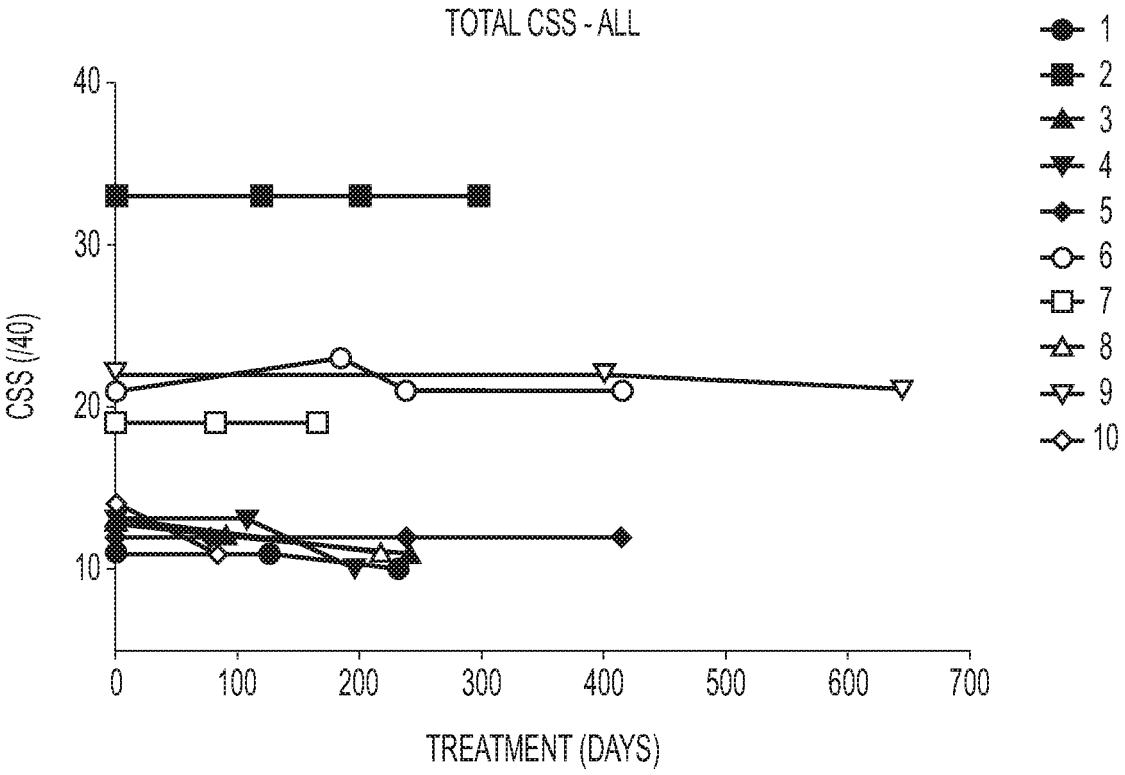


FIG. 10A

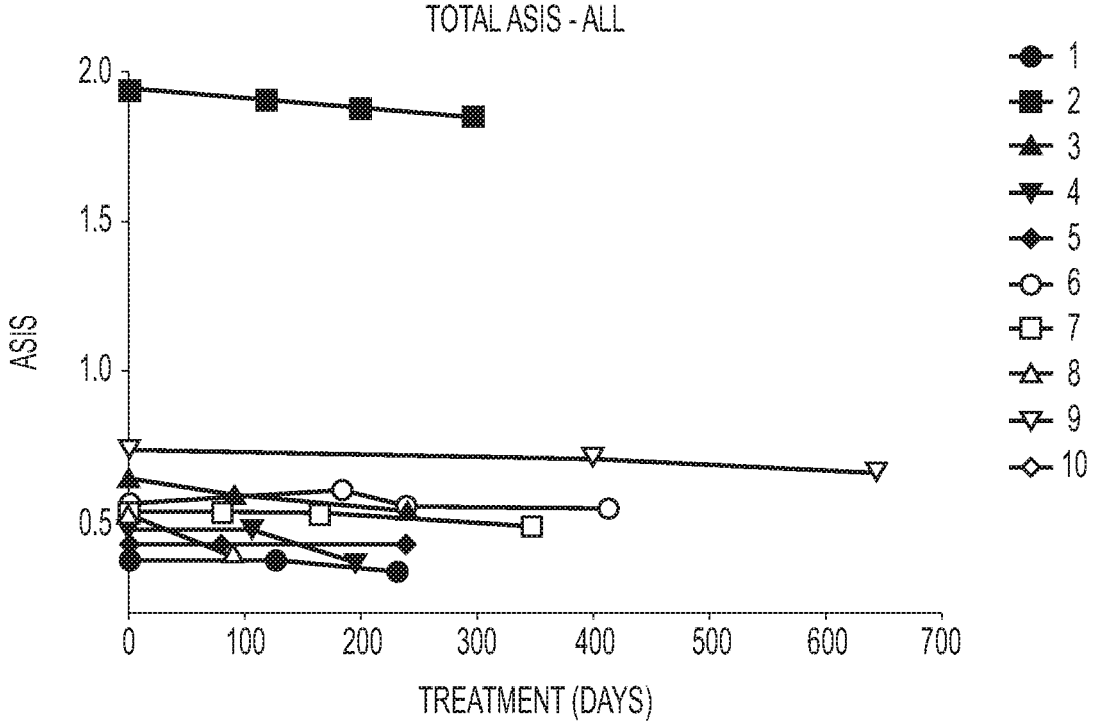


FIG. 10B

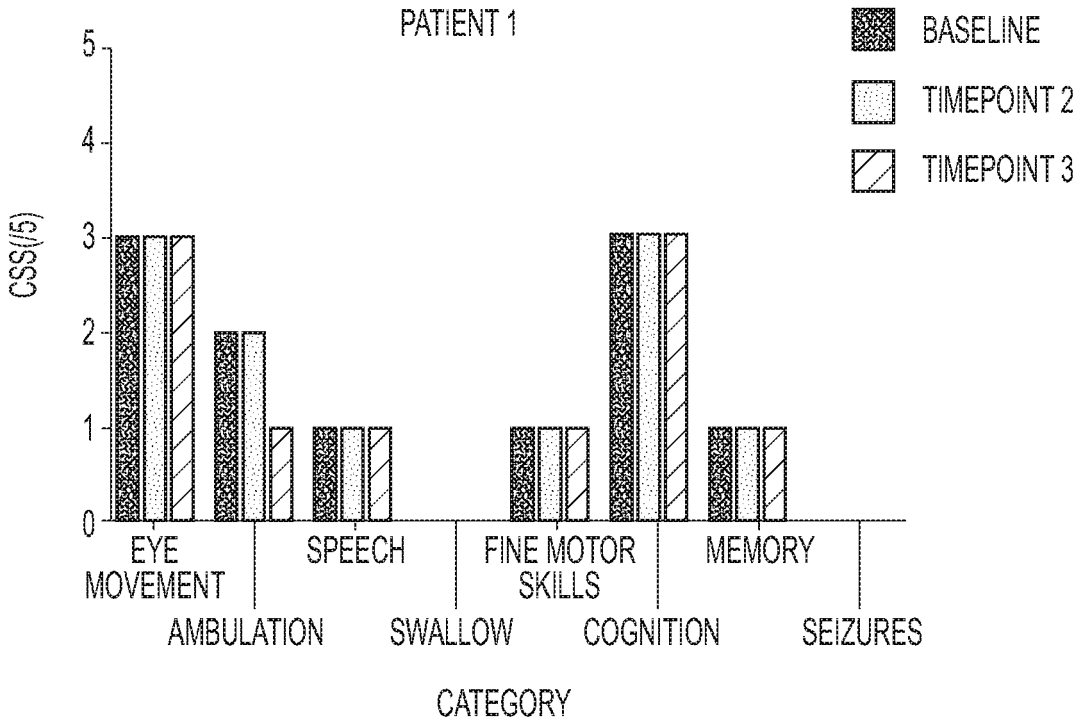


FIG. 11A

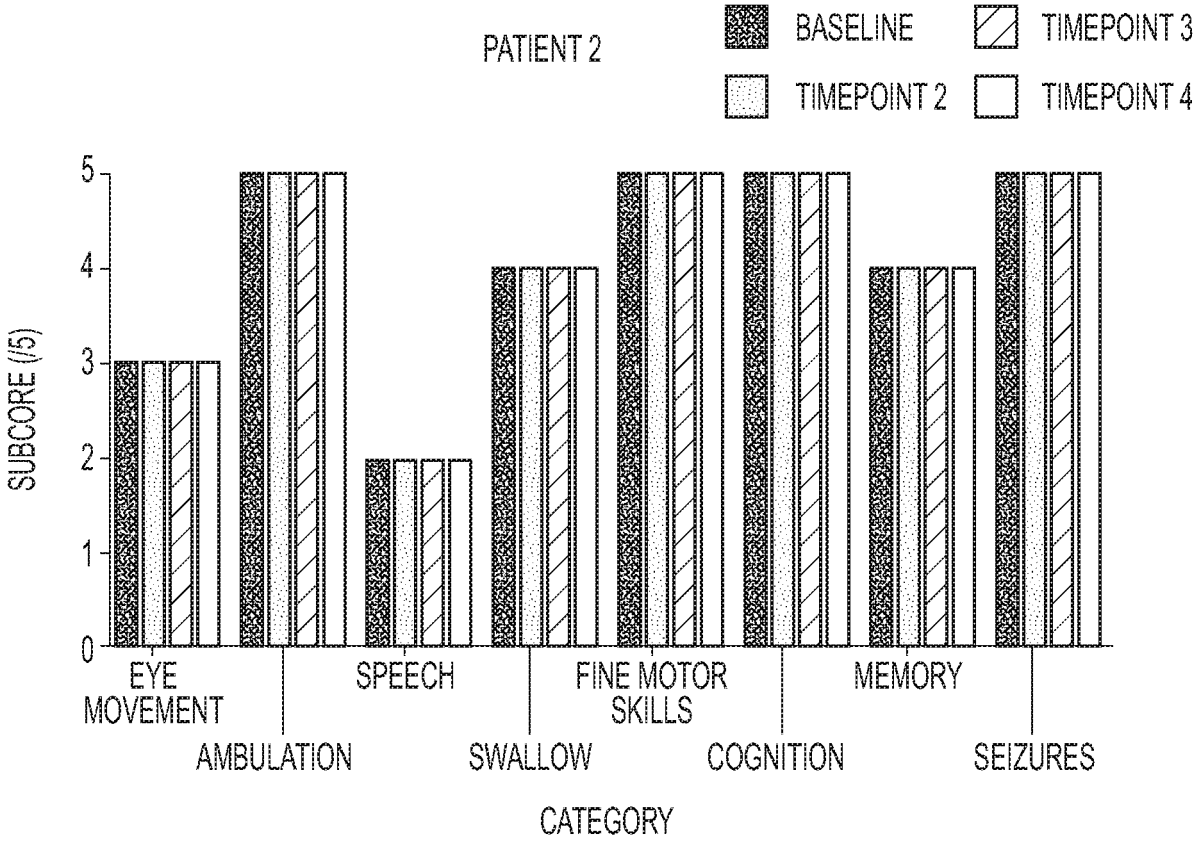


FIG. 11B

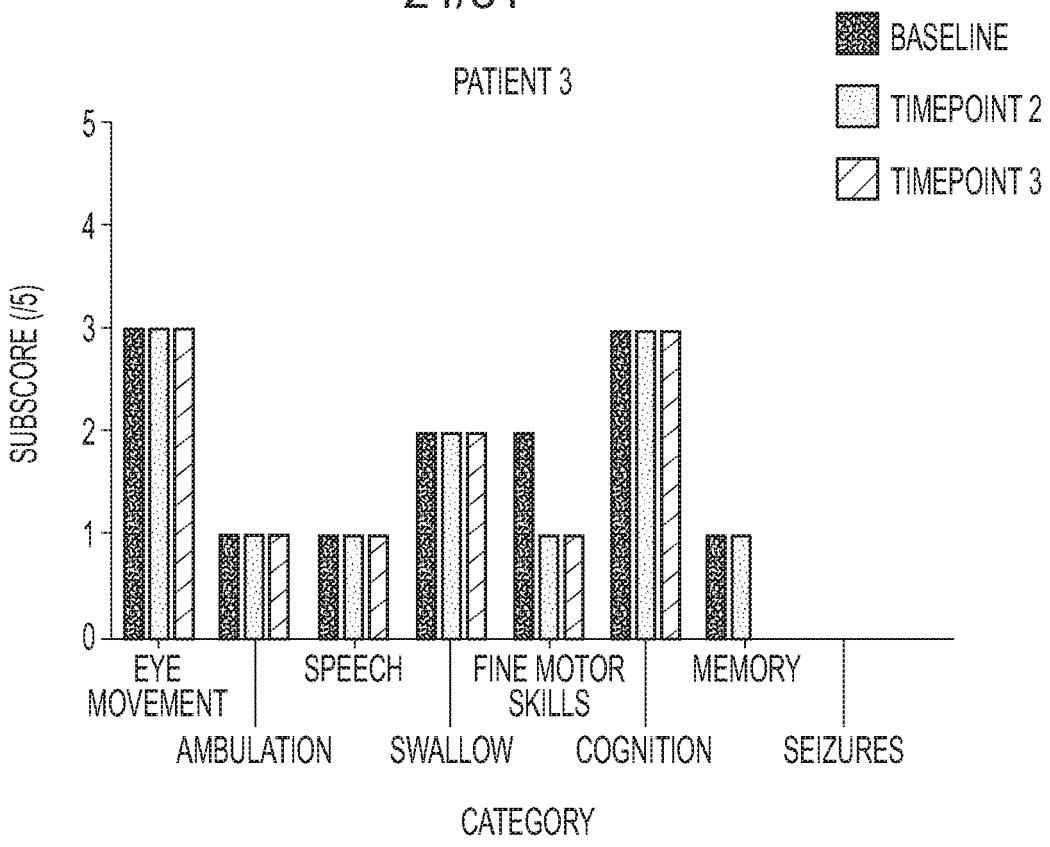


FIG. 11C

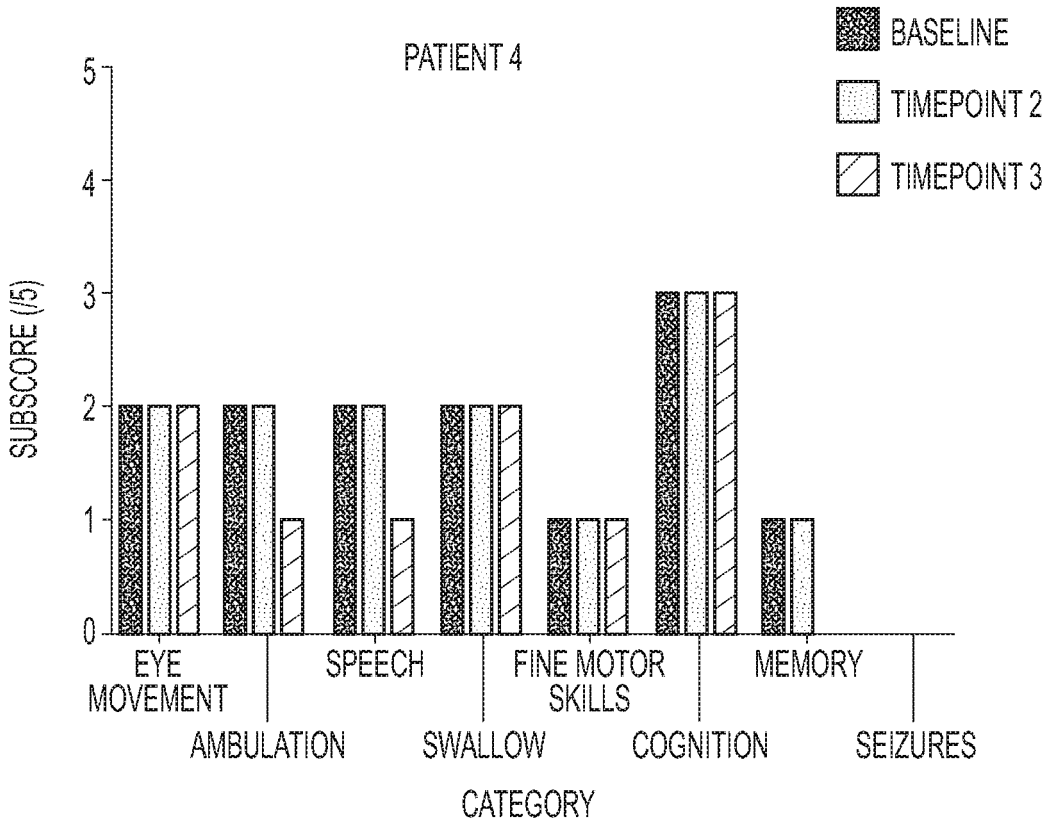


FIG. 11D

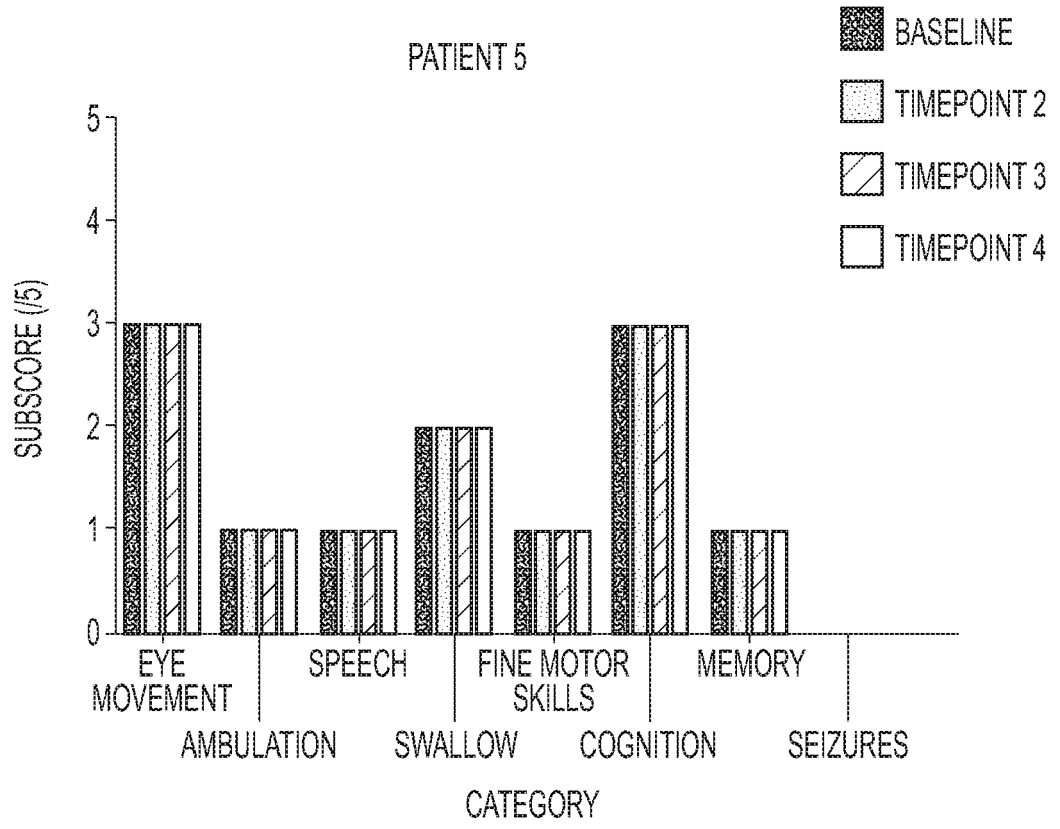


FIG. 11E

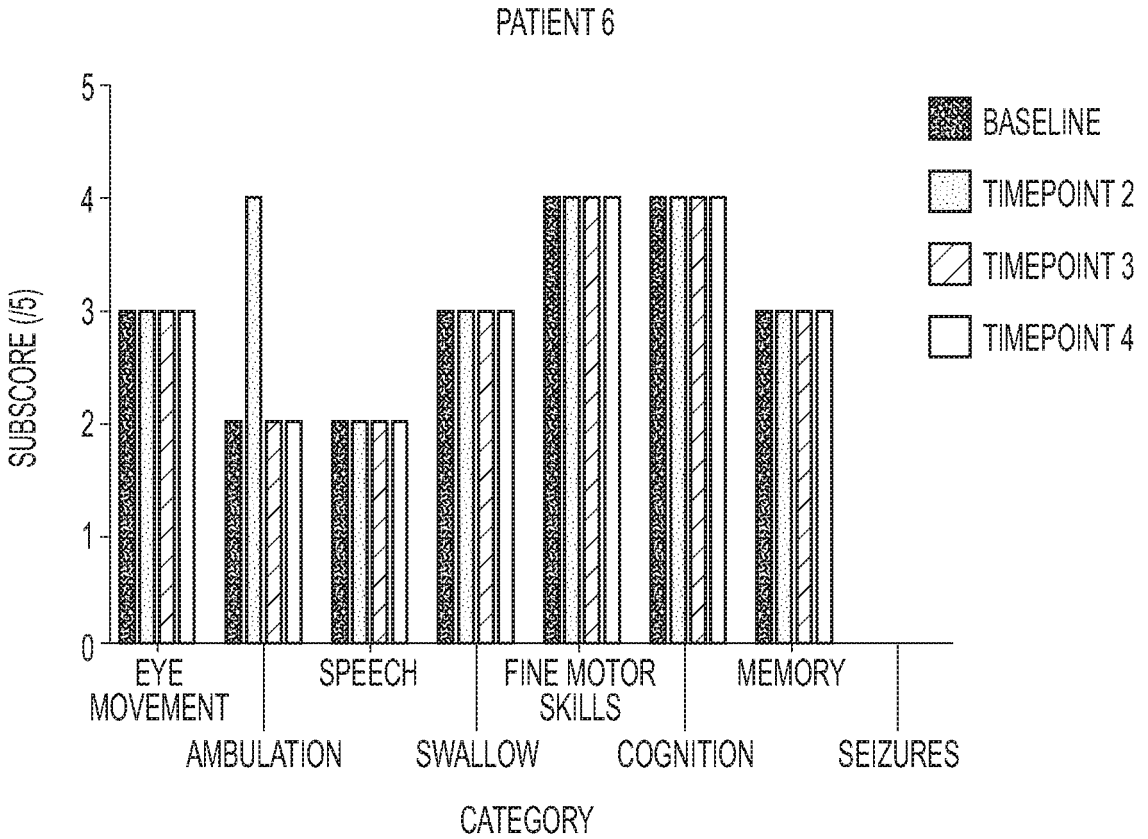


FIG. 11F

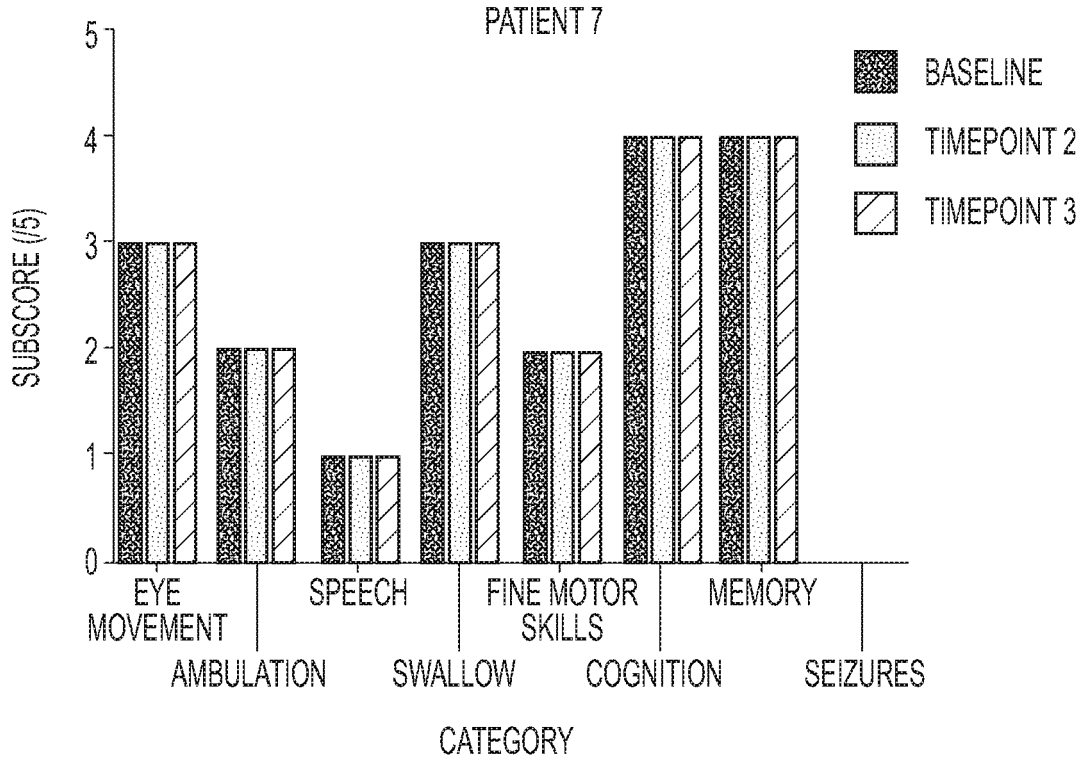


FIG. 11G

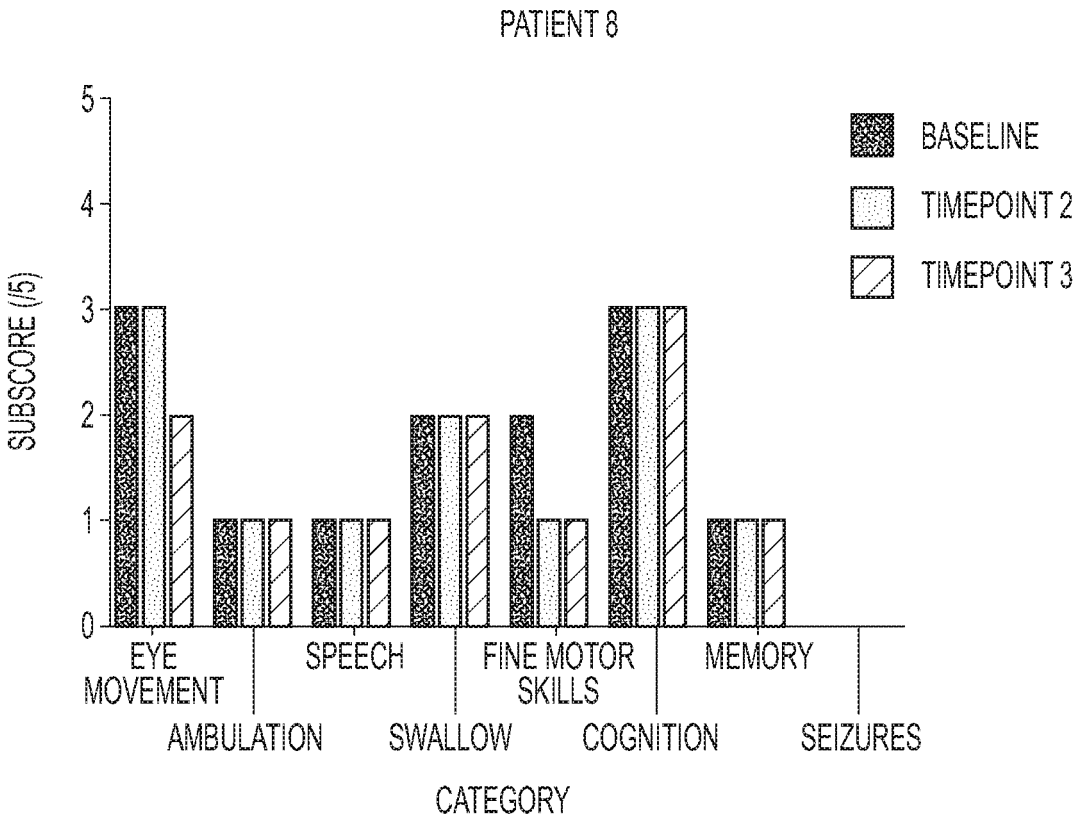


FIG. 11H

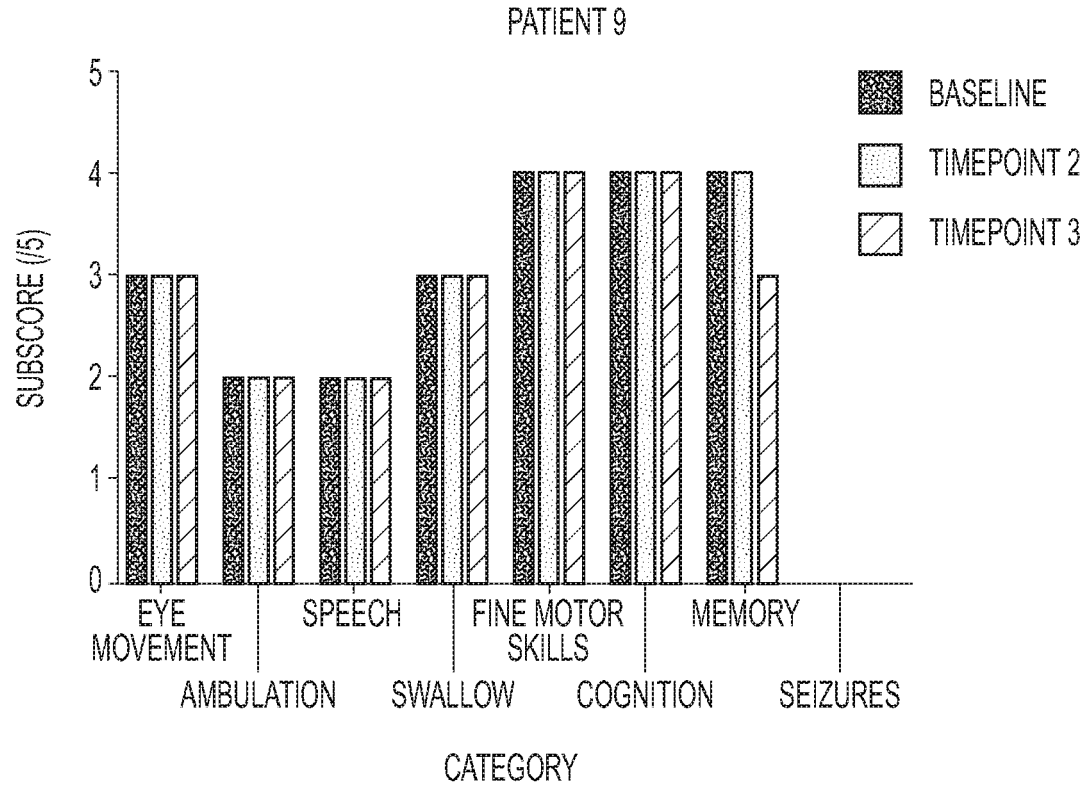


FIG. 11I

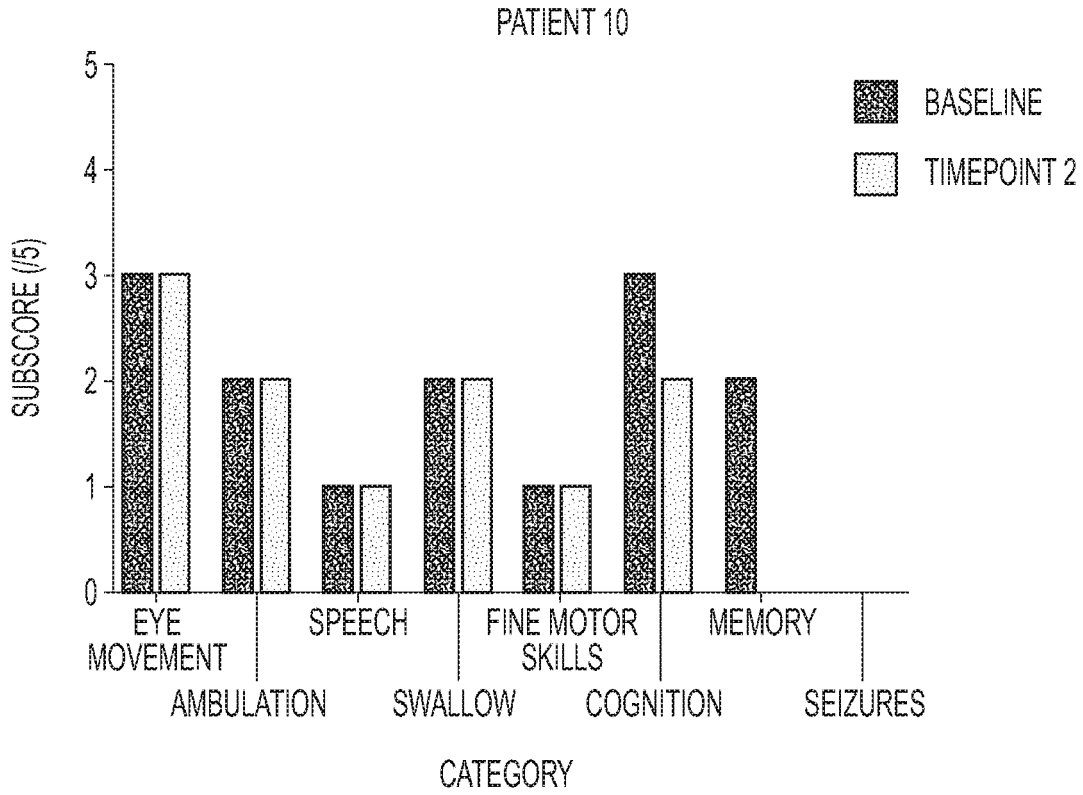


FIG. 11J

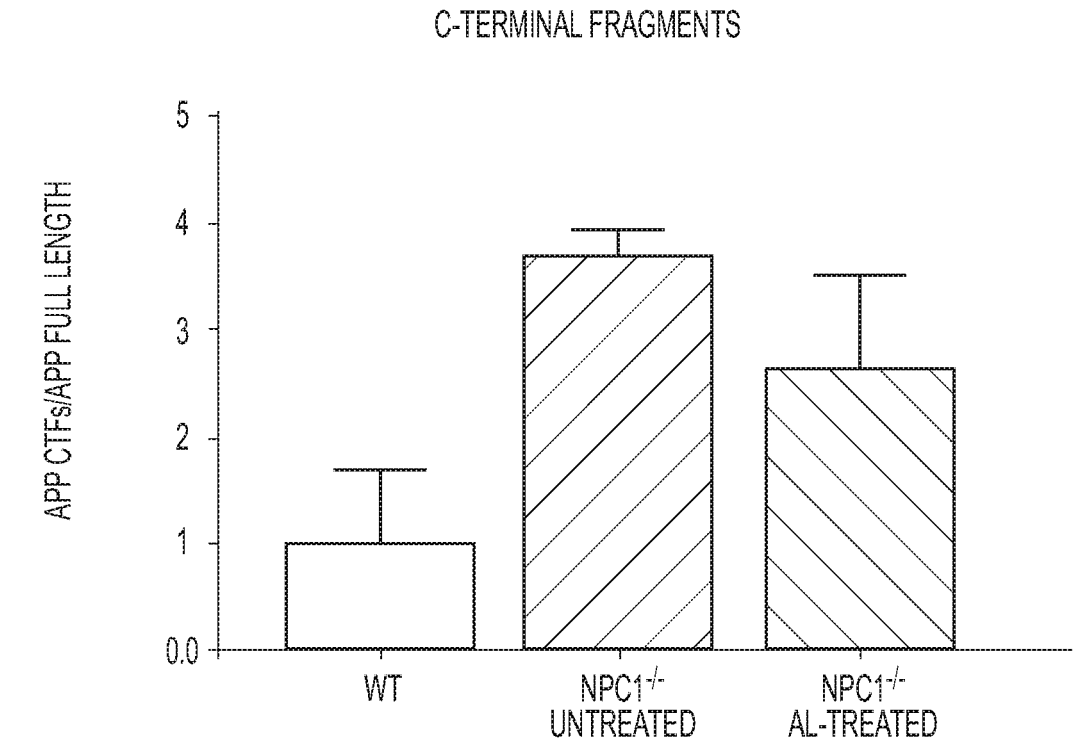


FIG. 12A

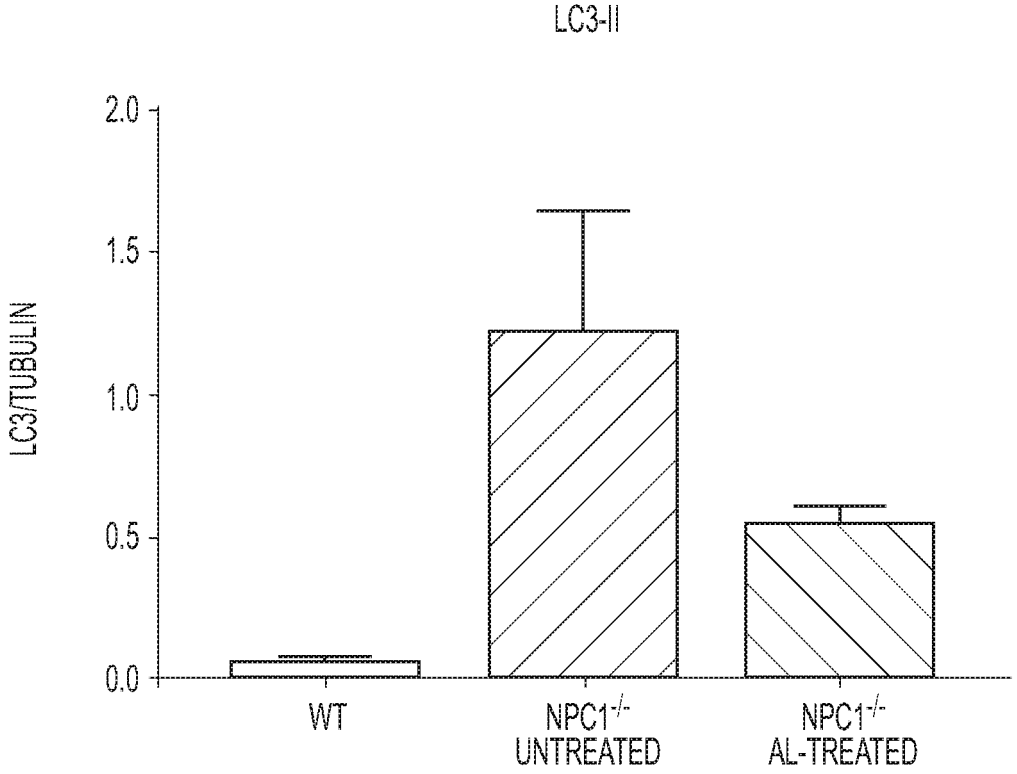


FIG. 12B

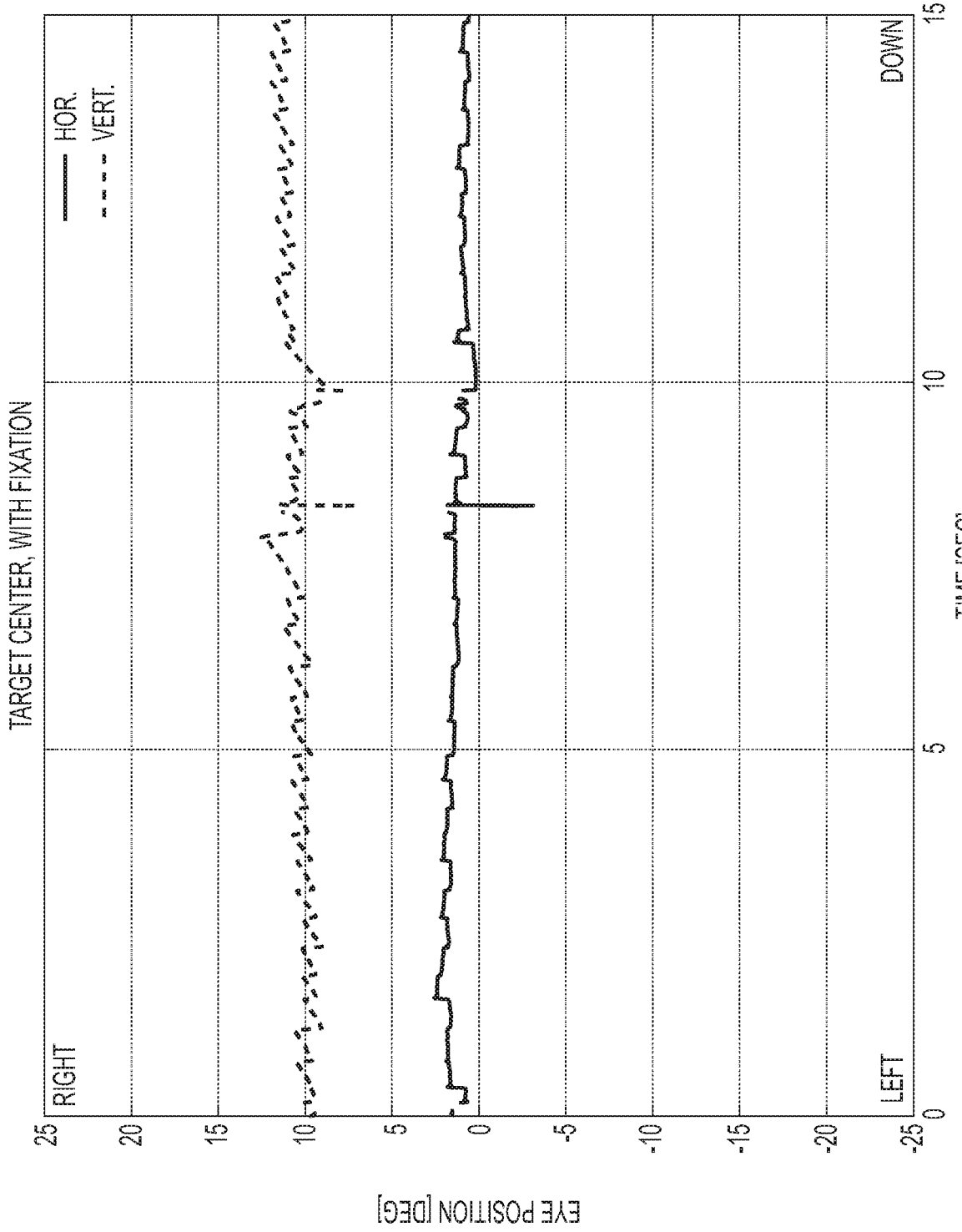

TARGET CENTER, WITH FIXATION
HOR.
VERT.
RIGHT
LEFT
DOWN
EYE POSITION [DEG]
TIME [SEC]
25
20
15
10
5
0
-5
-10
-15
-20
-25
0
5
10
15

FIG. 13A

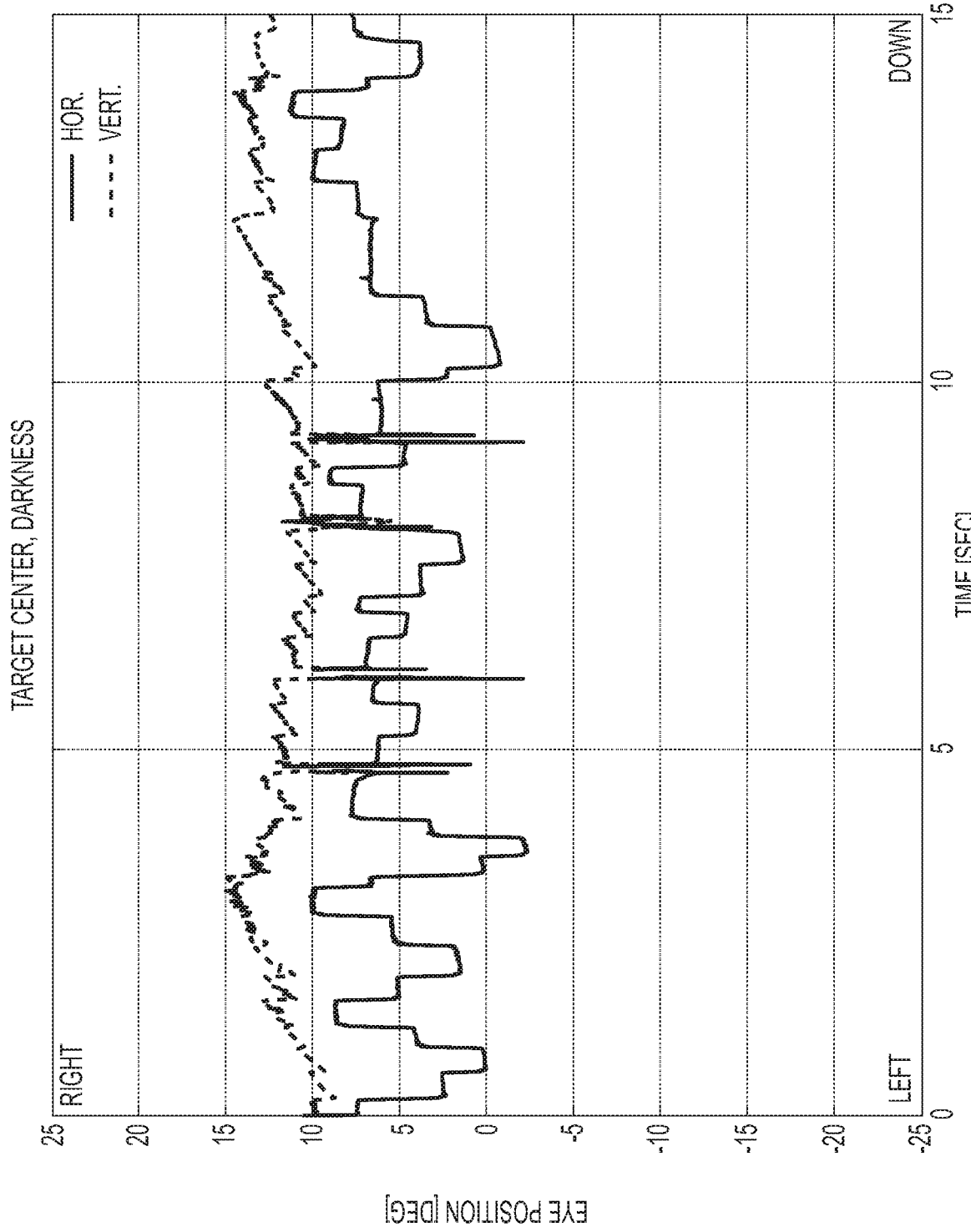

TARGET CENTER, DARKNESS
HOR.
VERT.
RIGHT
LEFT
DOWN
TIME [SEC]
EYE POSITION [DEG]
25
20
15
10
5
0
-5
-10
-15
-20
-25
0
5
10
15

FIG. 13B

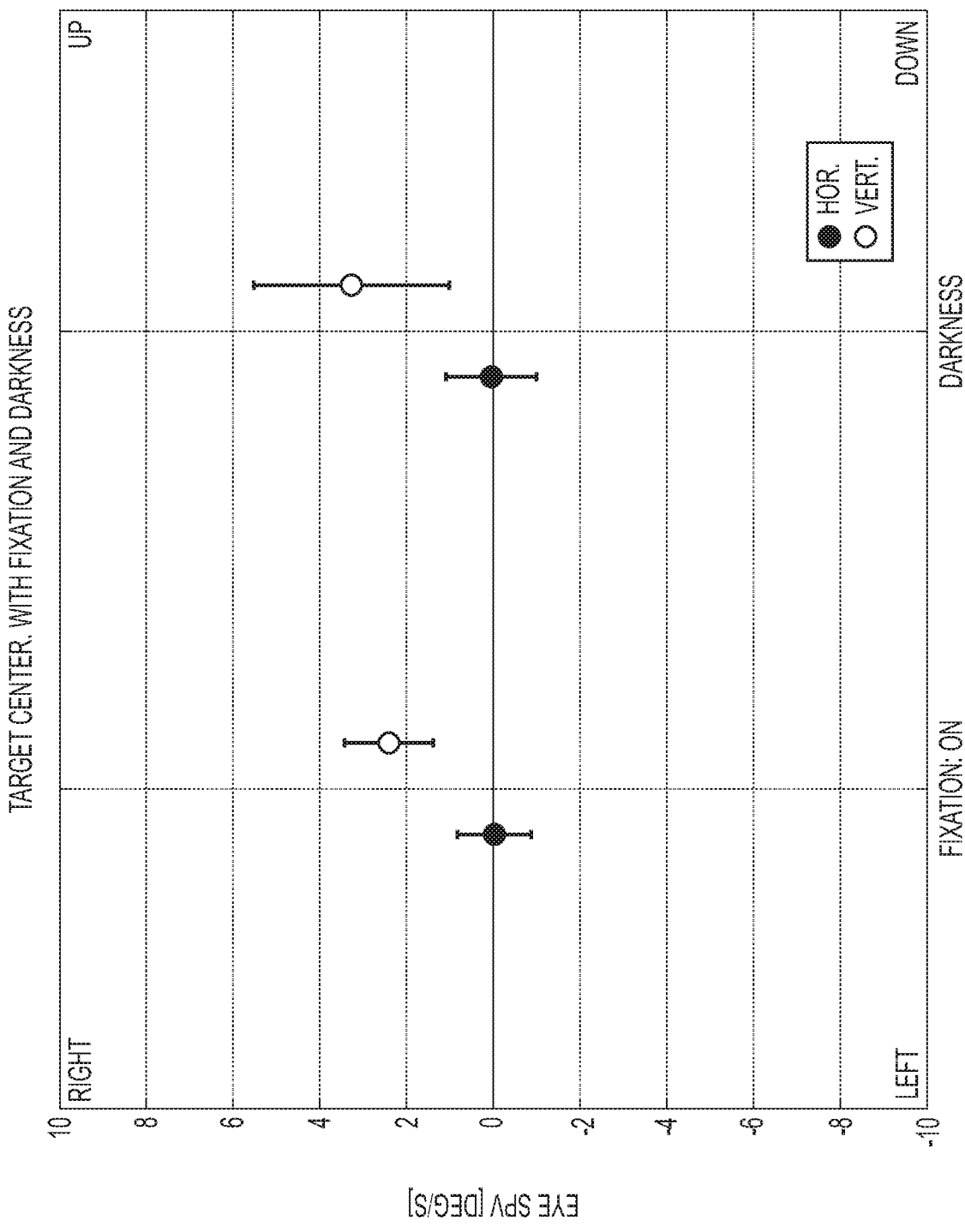

TARGET CENTER. WITH FIXATION AND DARKNESS
UP
RIGHT
LEFT
DOWN
FIXATION: ON
DARKNESS
HOR.
VERT.
EYE SPV [DEG/S]
10
8
6
4
2
0
-2
-4
-6
-8
-10

FIG. 13C