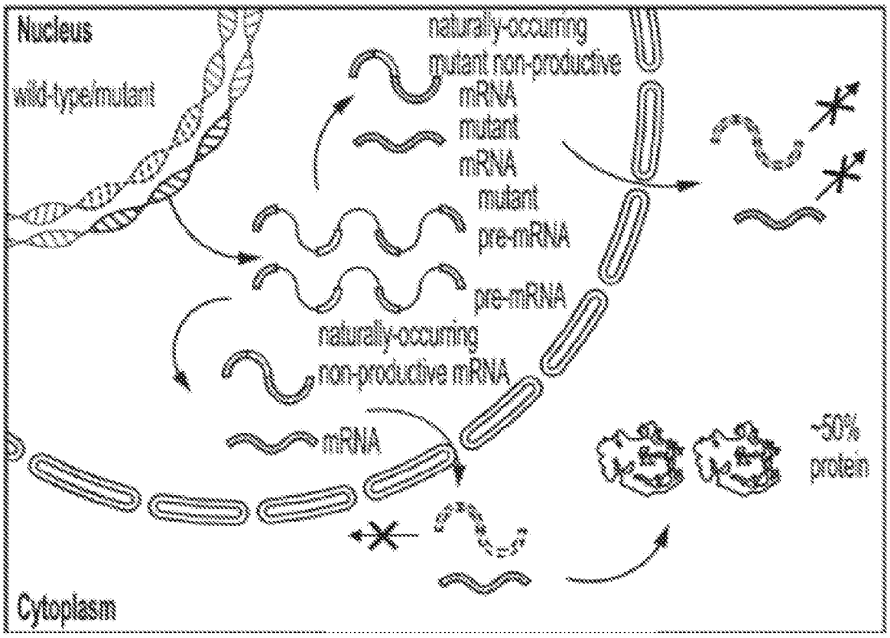
Nucleus
wild-type/mutant
naturally-occurring
mutant non-productive
mRNA
mutant
mRNA
mutant
pre-mRNA
pre-mRNA
naturally-occurring
non-productive mRNA
mRNA
~50%
protein
Cytoplasm

FIG. 1A

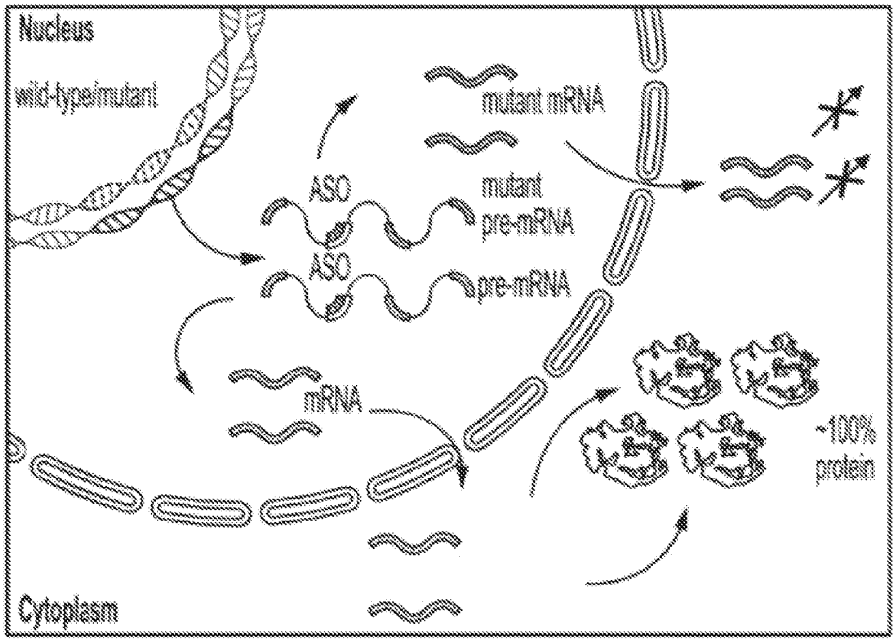
Nucleus
wild-type/mutant
mutant mRNA
ASO
mutant
pre-mRNA
ASO
pre-mRNA
mRNA
~100%
protein
Cytoplasm

FIG. 1B

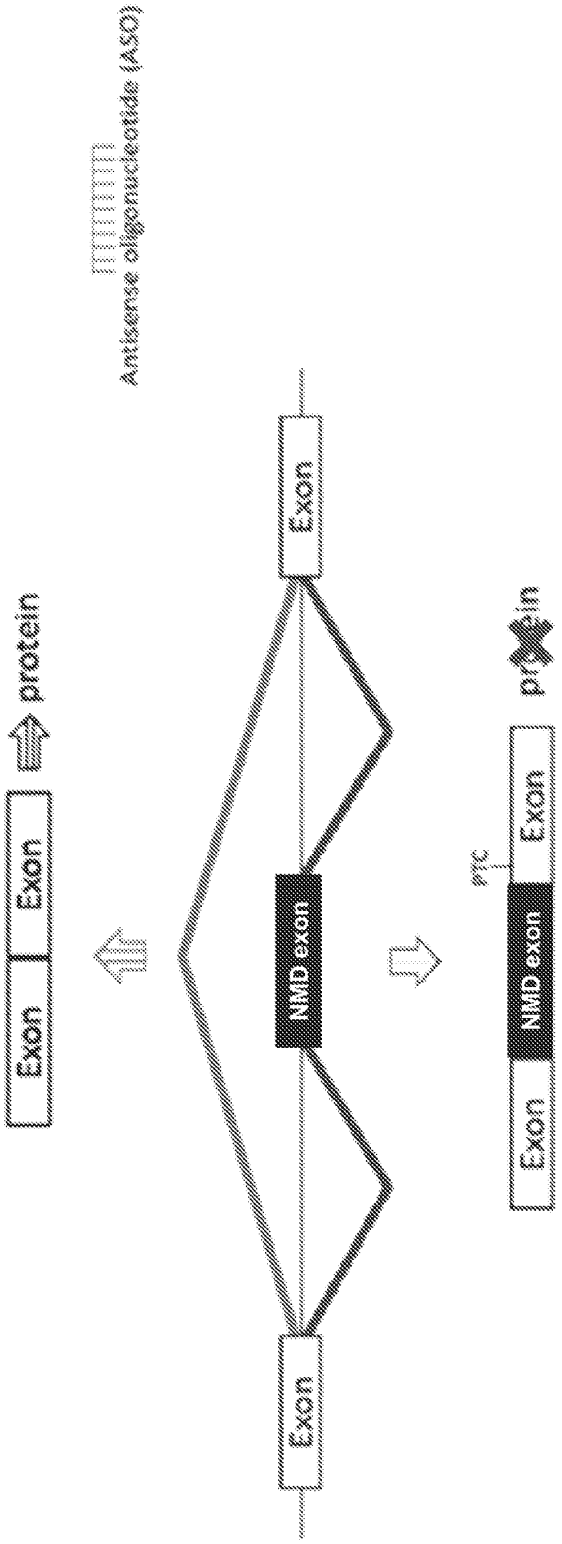
Antisense oligonucleotide (ASO)
Exon
Exon
protein
Exon
NMD exon
Exon
PTC
Exon
NMD exon
Exon
protein

FIG. 1C

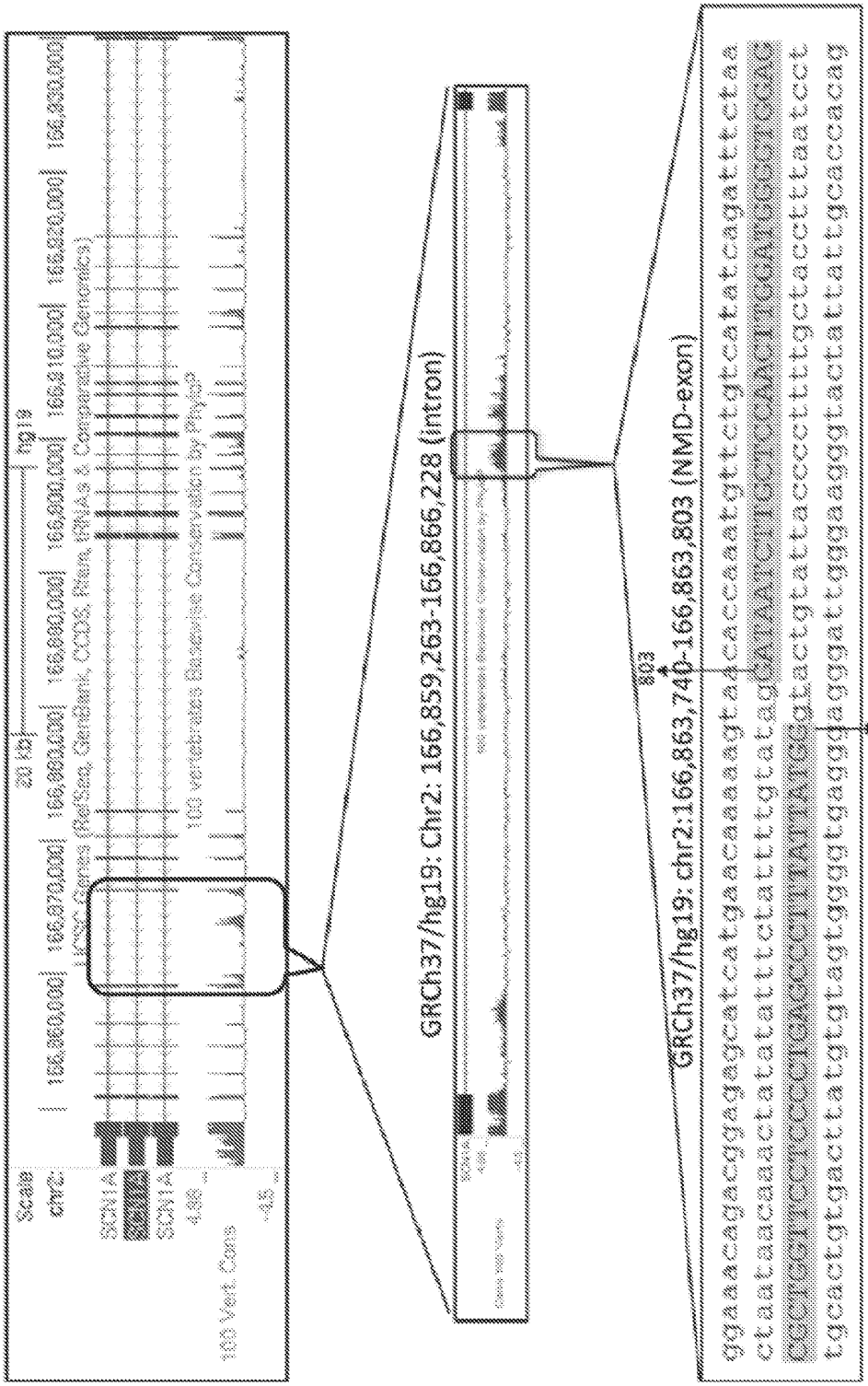
Scale
chr2:
SCN1A
SCN1A
100 Vert. Cons
20 kb
hg19
GRCh37/hg19: Chr2: 166,859,263-166,866,228 (intron)
GRCh37/hg19: chr2:166,863,740-166,863,803 (NMD-exon)
803
740

FIG. 1D

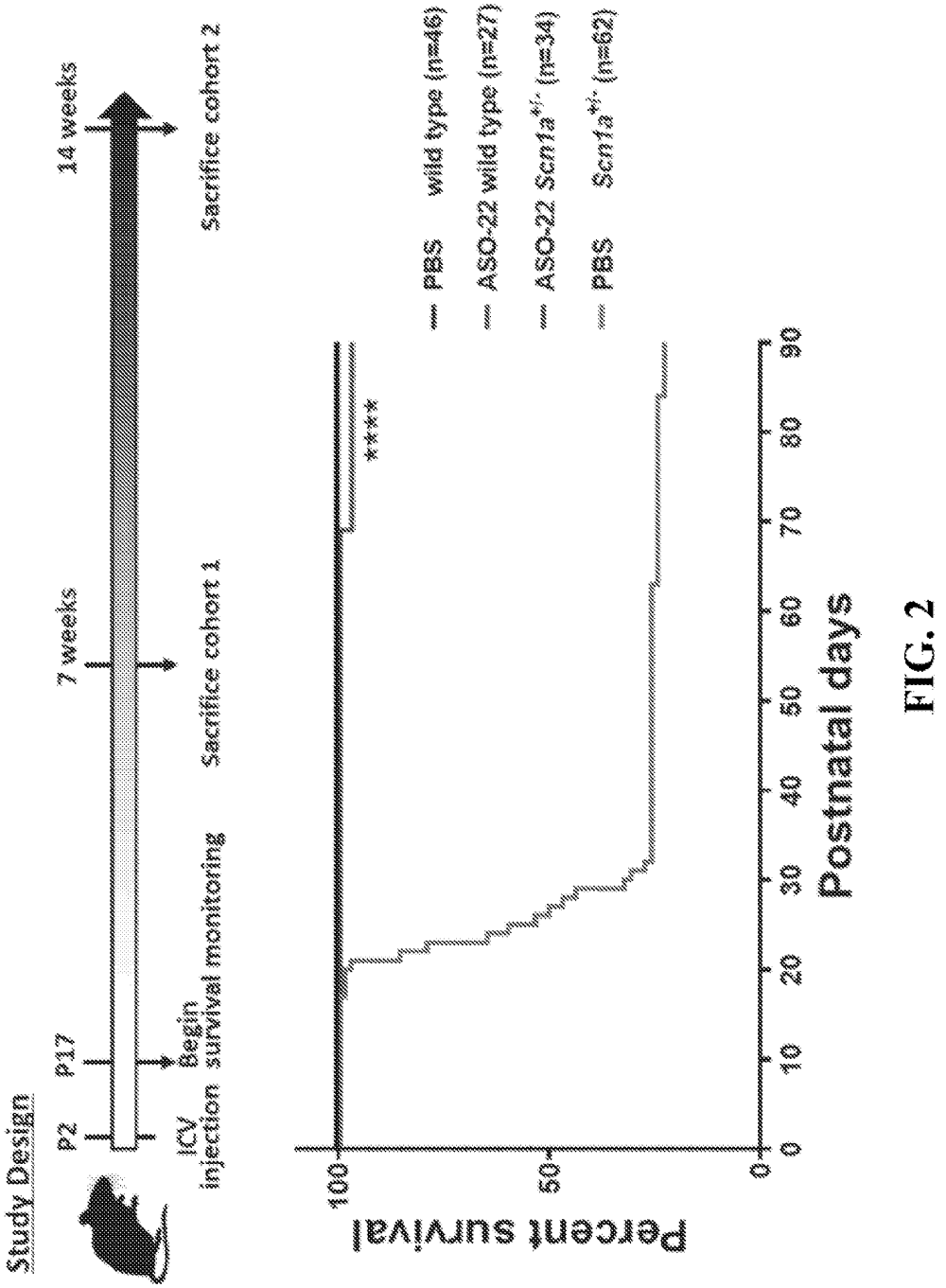
Study Design
P2
P17
ICV injection
Begin survival monitoring
7 weeks
Sacrifice cohort 1
14 weeks
Sacrifice cohort 2
PBS wild type (n=46)
ASO-22 wild type (n=27)
ASO-22 Scn1a+/- (n=34)
PBS Scn1a+/- (n=62)
****
Percent survival
100
50
0
0
10
20
30
40
50
60
70
80
90
Postnatal days

FIG. 2

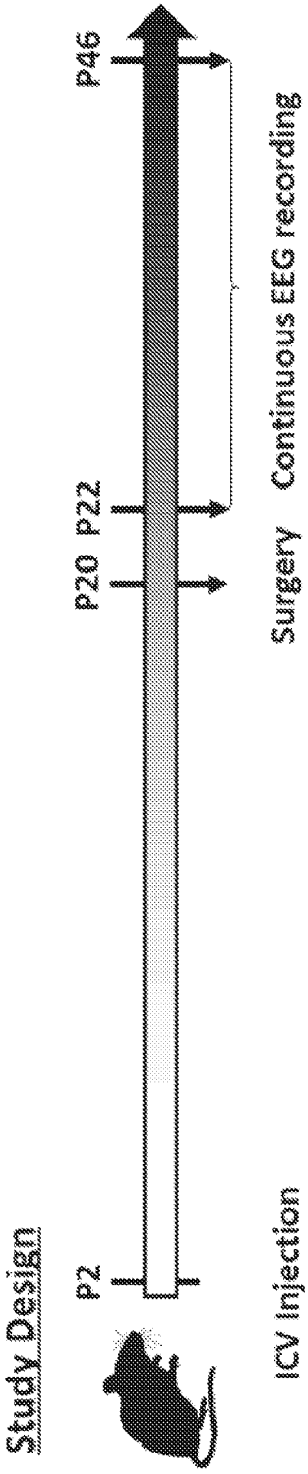
Study Design
P2
P20 P22
P46
ICV Injection
Surgery
Continuous EEG recording

FIG. 3

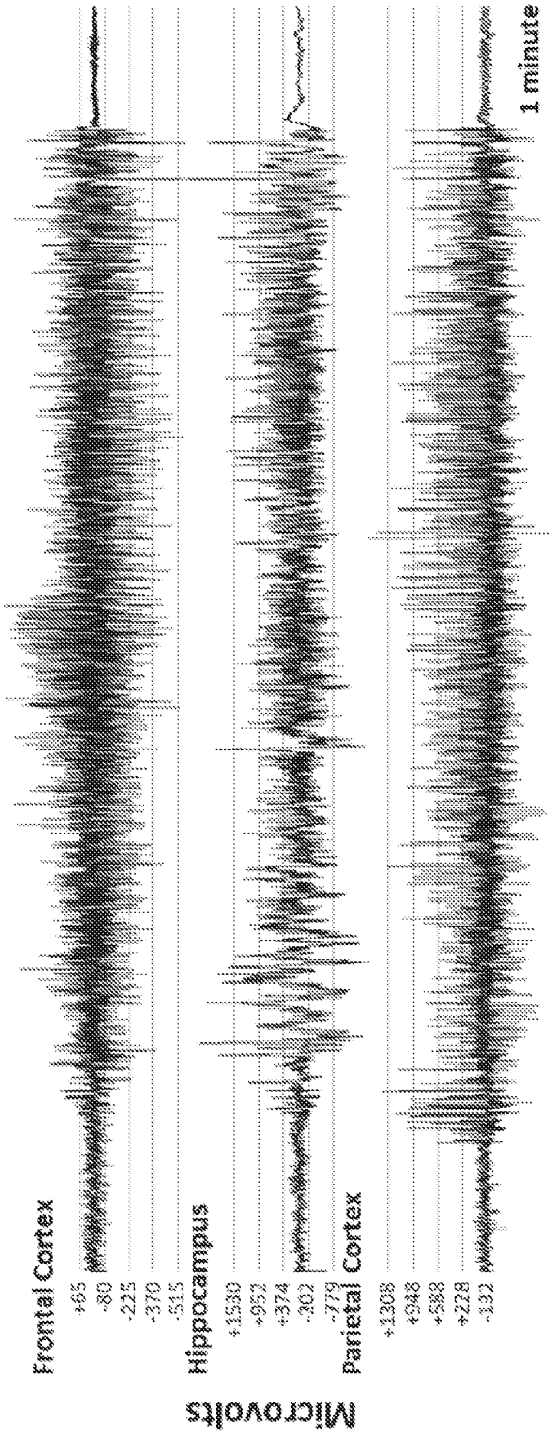
Frontal Cortex
+65
-80
-225
-370
-515
Hippocampus
+1530
+952
+374
-202
-779
Parietal Cortex
+1308
+948
+588
+228
-332
Microvolts
1 minute

FIG. 4A

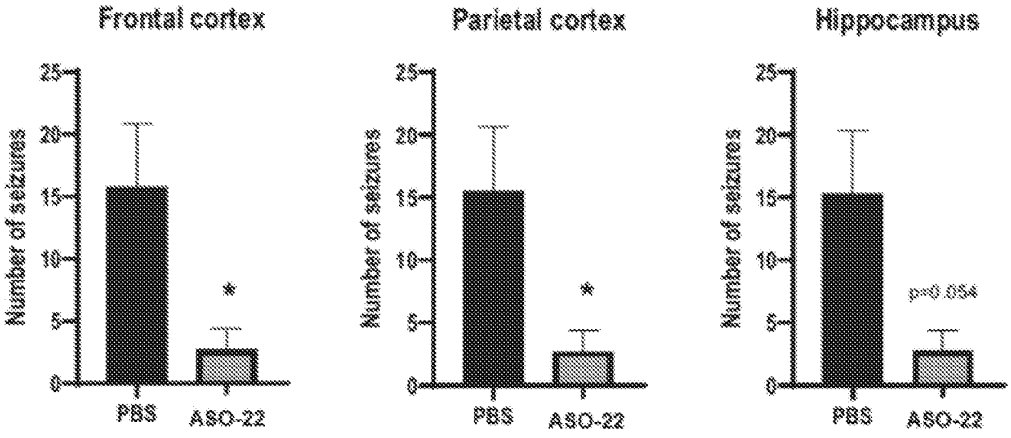

FIG. 4B

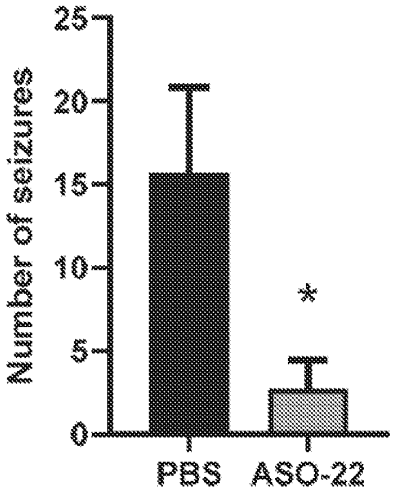

FIG. 4C

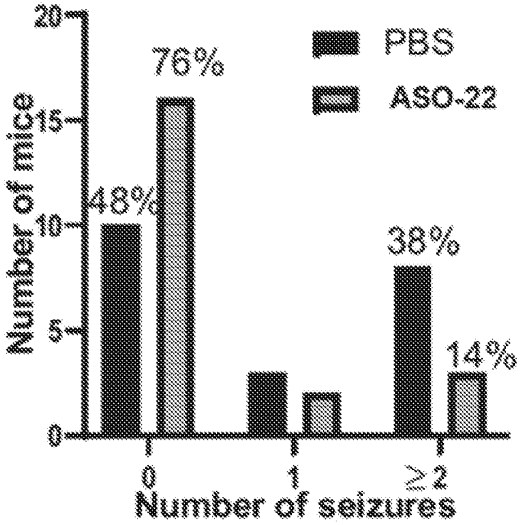

FIG. 4D

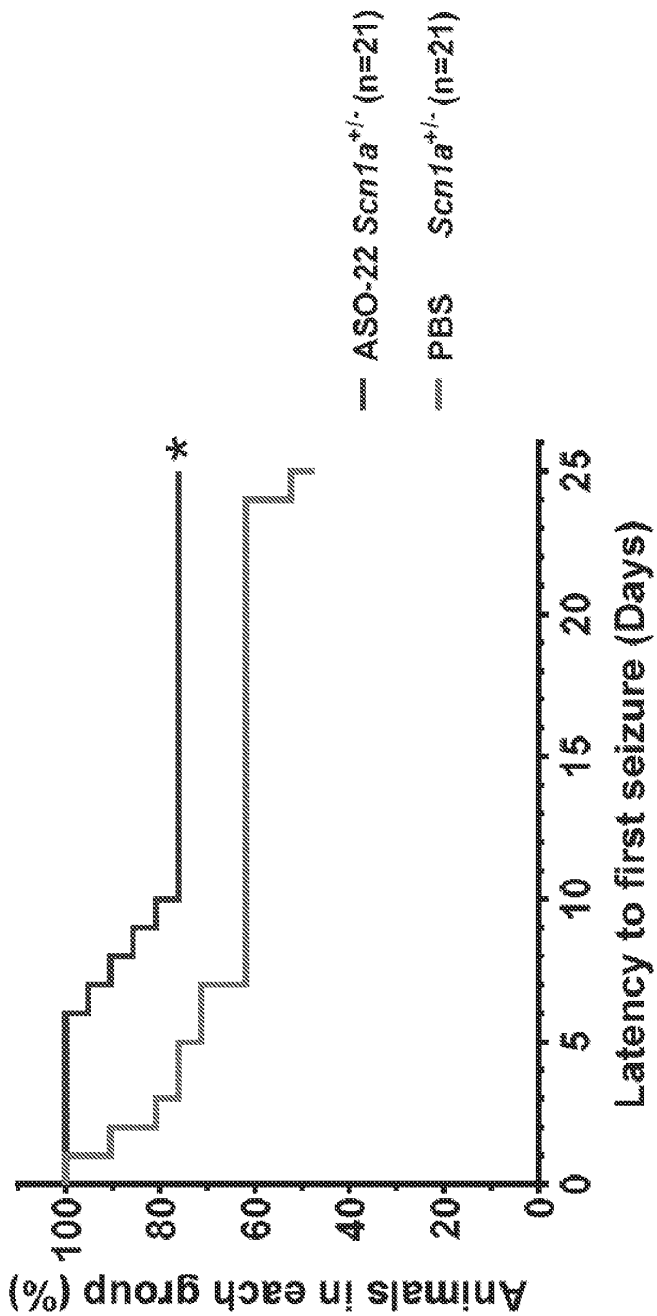
ASO-22 Scn1a+/- (n=21)
PBS Scn1a+/- (n=21)
*
Animals in each group (%)
100
80
60
40
20
0
0
5
10
15
20
25
Latency to first seizure (Days)

FIG. 4E

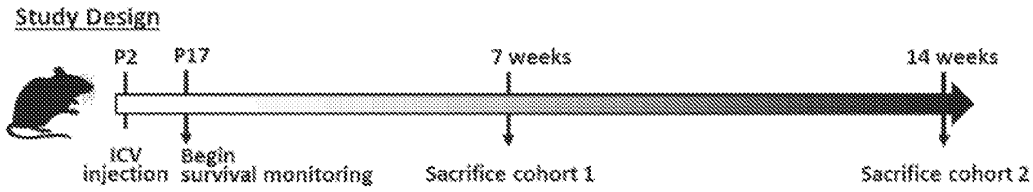
Study Design
P2
P17
7 weeks
14 weeks
ICV injection
Begin survival monitoring
Sacrifice cohort 1
Sacrifice cohort 2

FIG. 5A

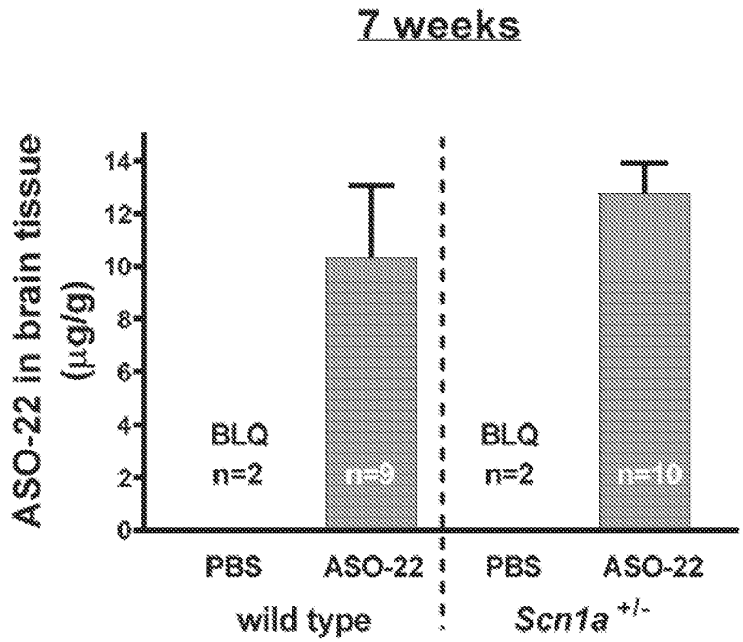
7 weeks
ASO-22 in brain tissue (µg/g)
0
2
4
6
8
10
12
14
BLQ n=2
n=9
BLQ n=2
n=10
PBS
ASO-22
PBS
ASO-22
wild type
Scn1a +/-

FIG. 5B

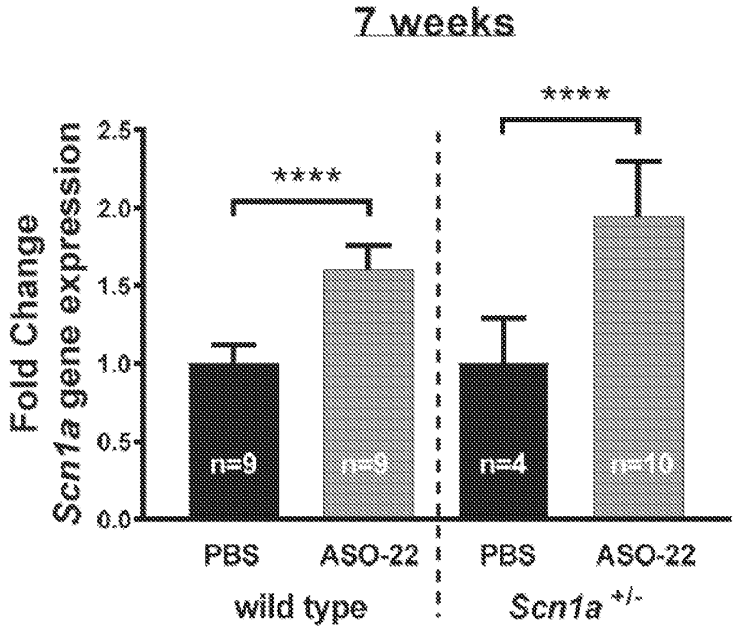
7 weeks
****
****
Fold Change
Scn1a gene expression
2.5
2.0
1.5
1.0
0.5
0.0
n=9
n=9
n=4
n=10
PBS
ASO-22
PBS
ASO-22
wild type
Scn1a +/-

FIG. 5C

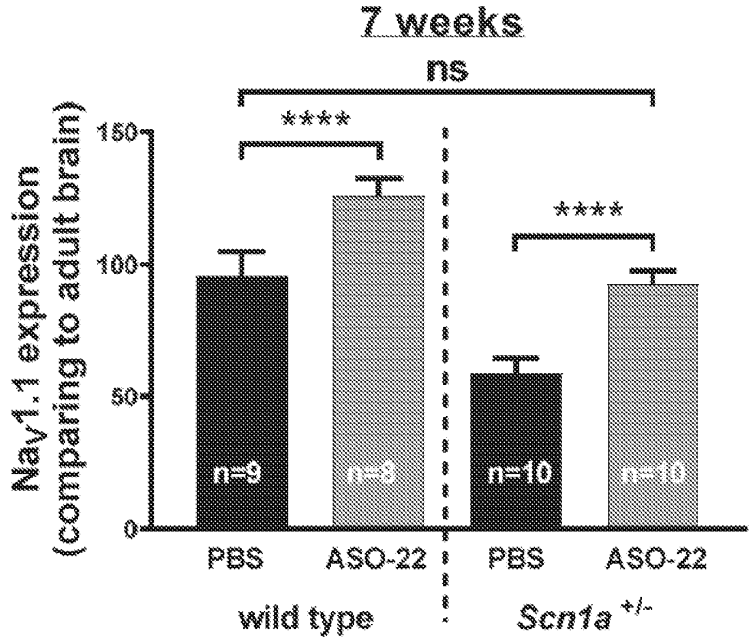
7 weeks
ns
****
****
Nav1.1 expression
(comparing to adult brain)
150
100
50
0
n=9
n=9
n=10
n=10
PBS
ASO-22
PBS
ASO-22
wild type
Scn1a +/-

FIG. 5D

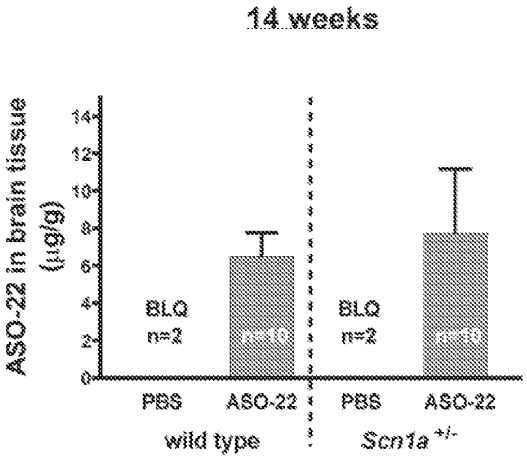

FIG. 5E

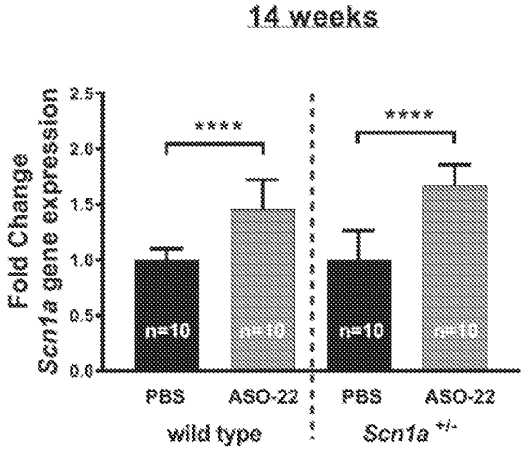

FIG. 5F

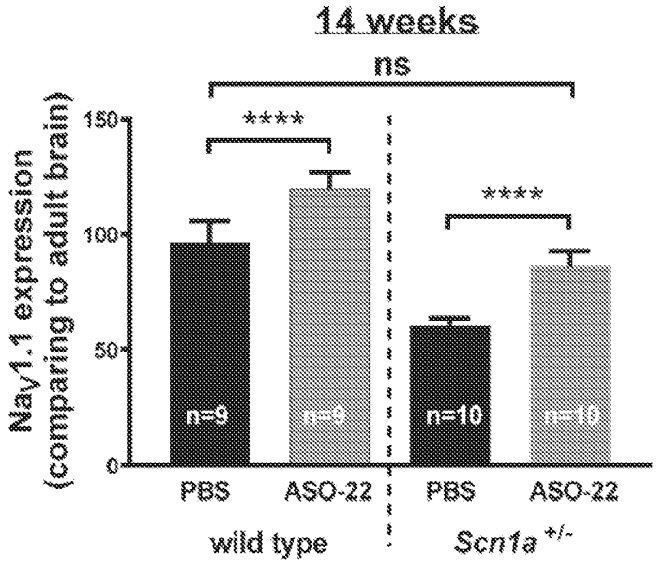

FIG. 5G

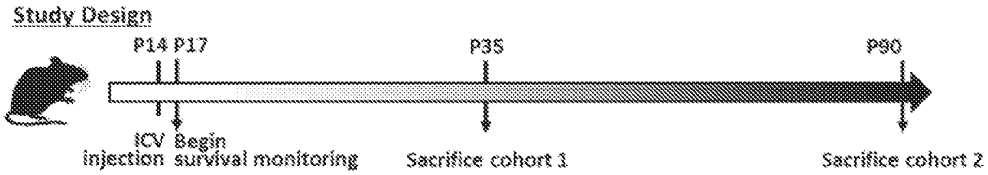
Study Design
P14 P17
P35
P90
ICV Begin injection survival monitoring
Sacrifice cohort 1
Sacrifice cohort 2

FIG. 6A

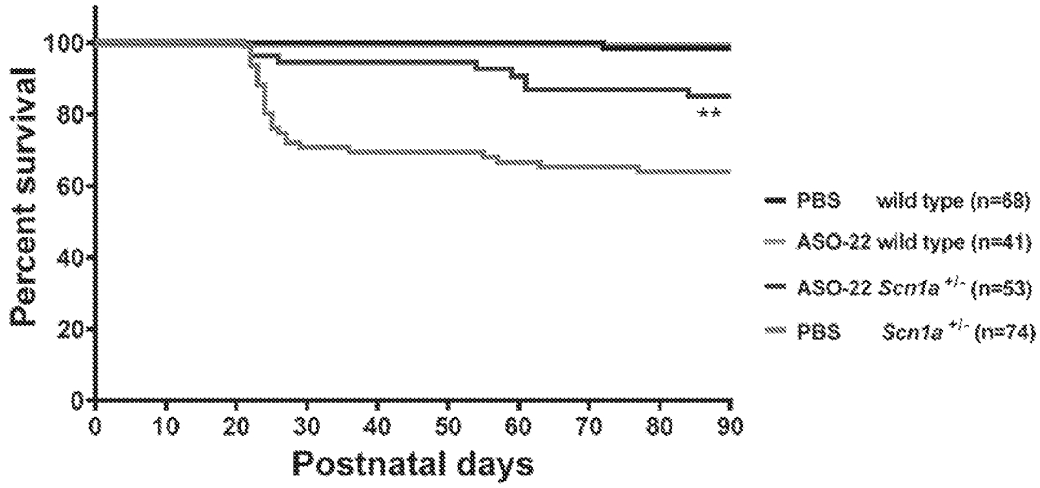
Percent survival
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
Postnatal days
**
PBS wild type (n=68)
ASO-22 wild type (n=41)
ASO-22 Scn1a +/- (n=53)
PBS Scn1a +/- (n=74)

FIG. 6B

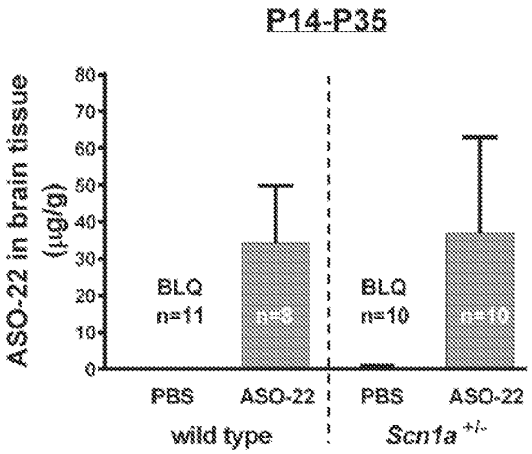

FIG. 7A

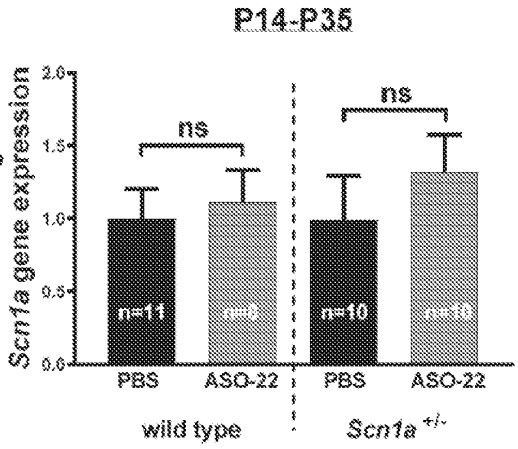

FIG. 7B

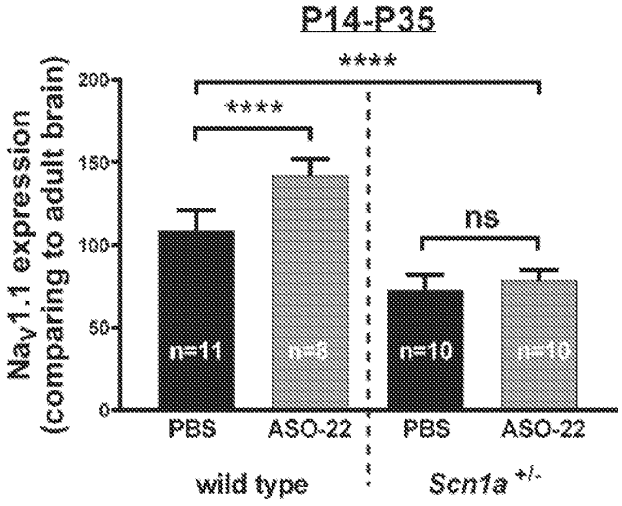

FIG. 7C

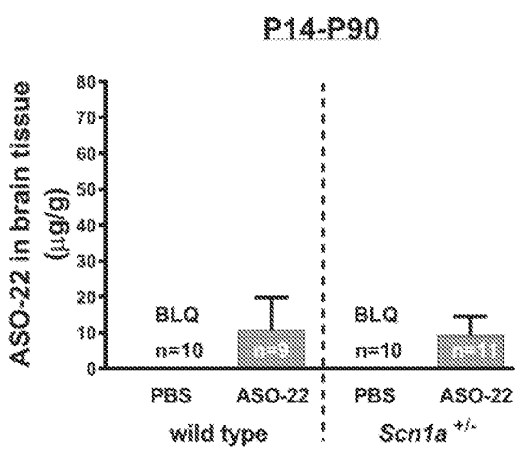

FIG. 7D

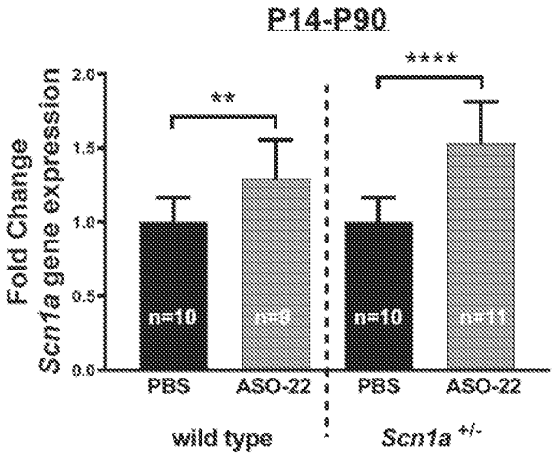

FIG. 7E

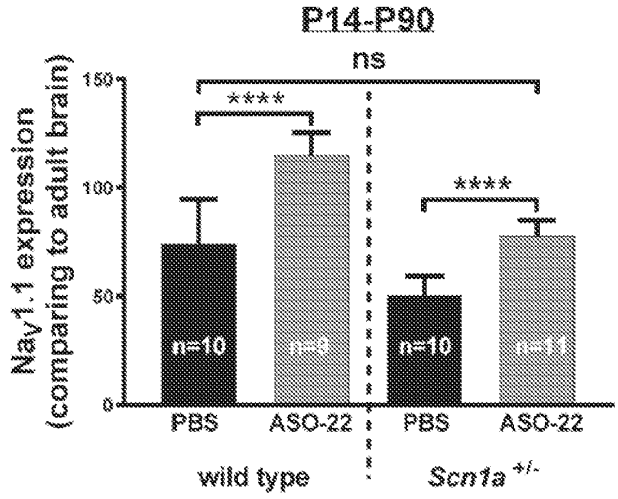

FIG. 7F

Treatment	Dose	Day 3 Necropsy	Day 29 Necropsy
Vehicle (aCSF)	na	2 Male	2 Male
ASO-22	Low	3 Male	3 Male
ASO-22	High	3 Male	3 Male

FIG. 8

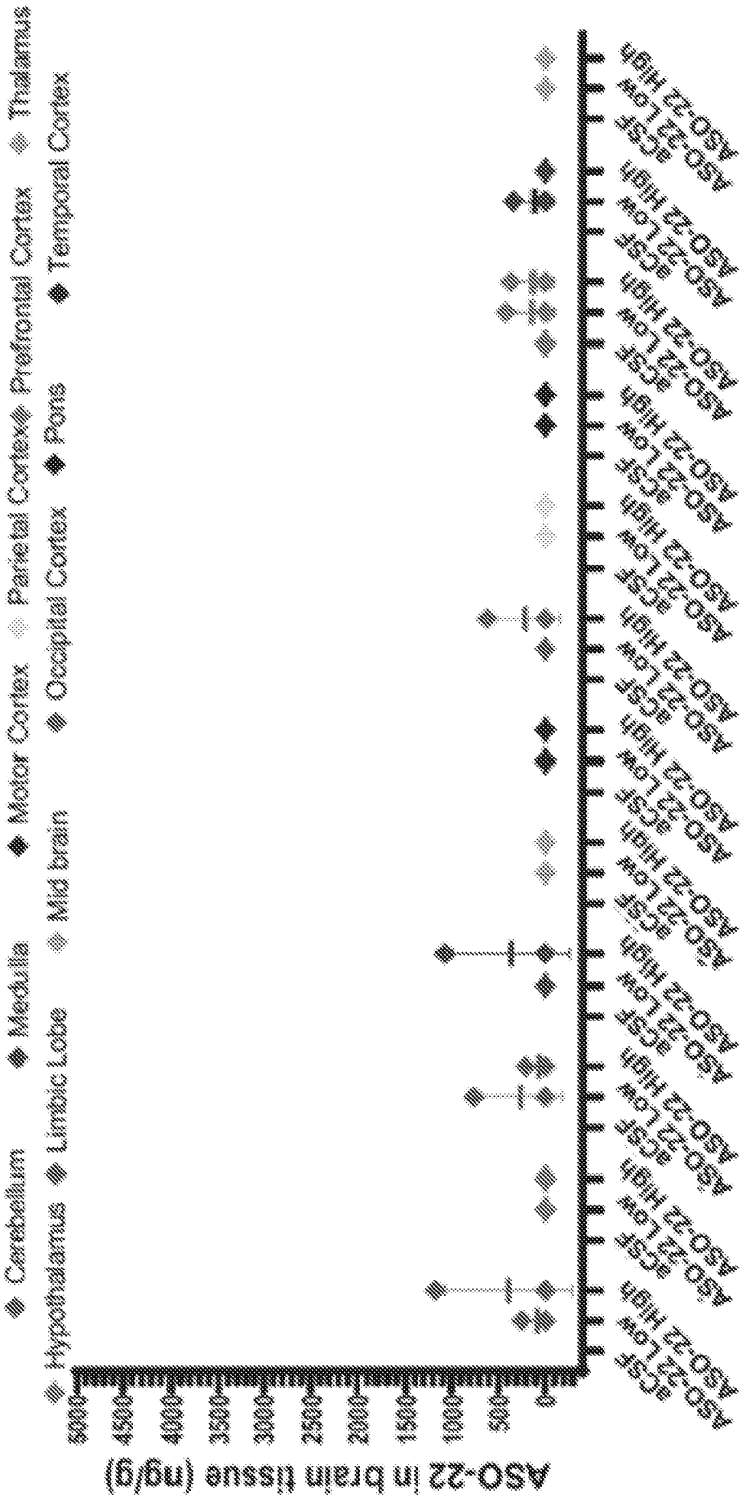
Cerebellum
Medulla
Motor Cortex
Parietal Cortex
Prefrontal Cortex
Thalamus
Hypothalamus
Limbic Lobe
Mid brain
Occipital Cortex
Pons
Temporal Cortex
ASO-22 in brain tissue (ng/g)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
aCSF
ASO-22 Low
ASO-22 High

FIG. 9A

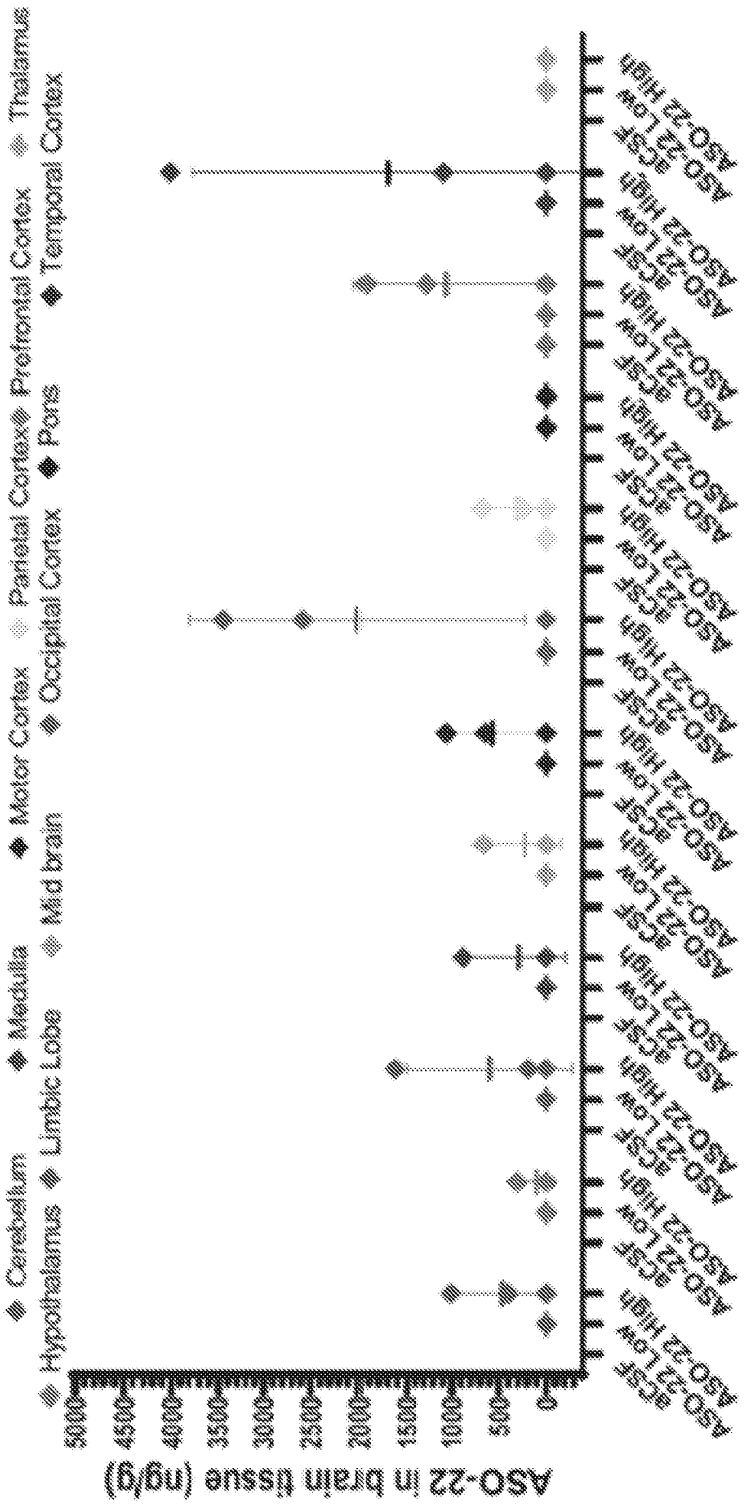
Cerebellum
Medulla
Motor Cortex
Parietal Cortex
Prefrontal Cortex
Thalamus
Hypothalamus
Limbic Lobe
Mid brain
Occipital Cortex
Pons
Temporal Cortex
ASO-22 in brain tissue (ng/g)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
aCSF
ASO-22 Low
ASO-22 High

FIG. 9B

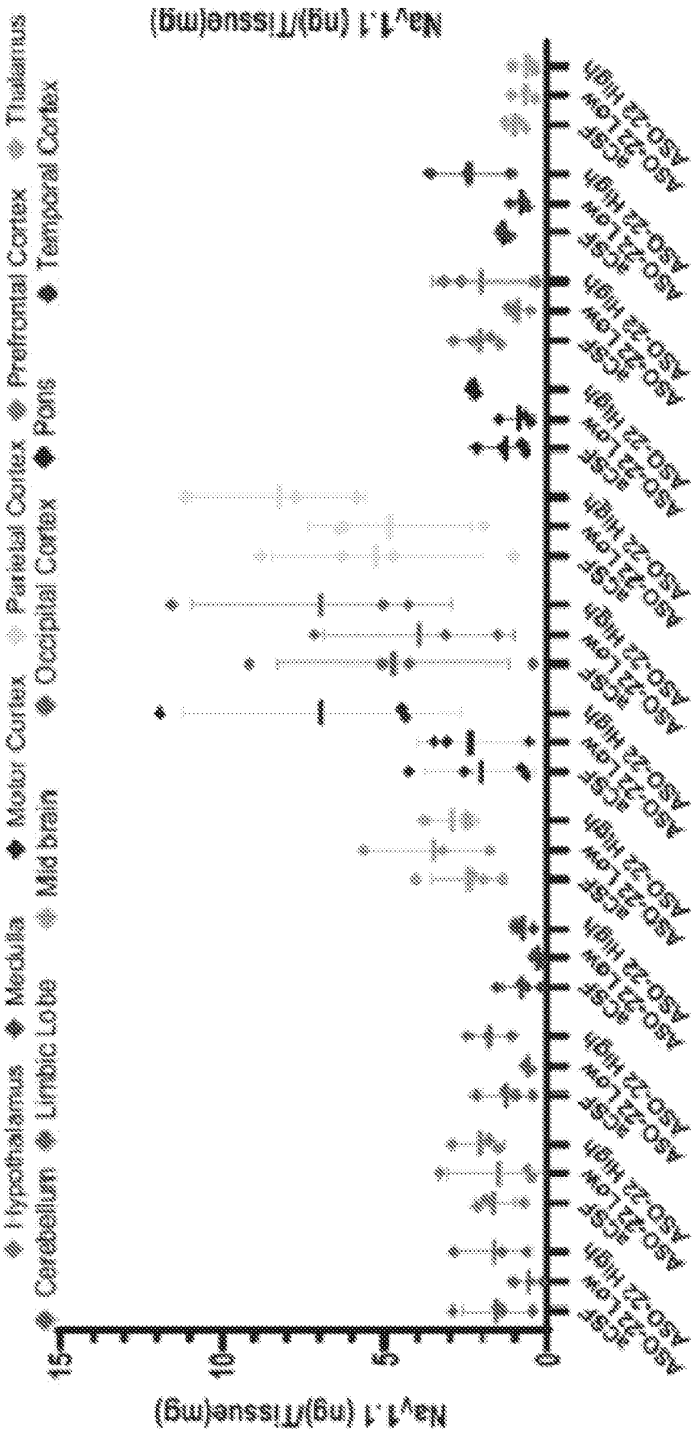
Hypothalamus
Medulla
Motor Cortex
Parietal Cortex
Prefrontal Cortex
Thalamus
Cerebellum
Limbic Lobe
Mid brain
Occipital Cortex
Pons
Temporal Cortex
Nav1.1 (ng)/Tissue(mg)
15
10
5
0
ASO-22 HIGH
ASO-22 LOW
ASO-23 HIGH
ASO-23 LOW
SCRF HIGH
SCRF LOW

FIG. 10A

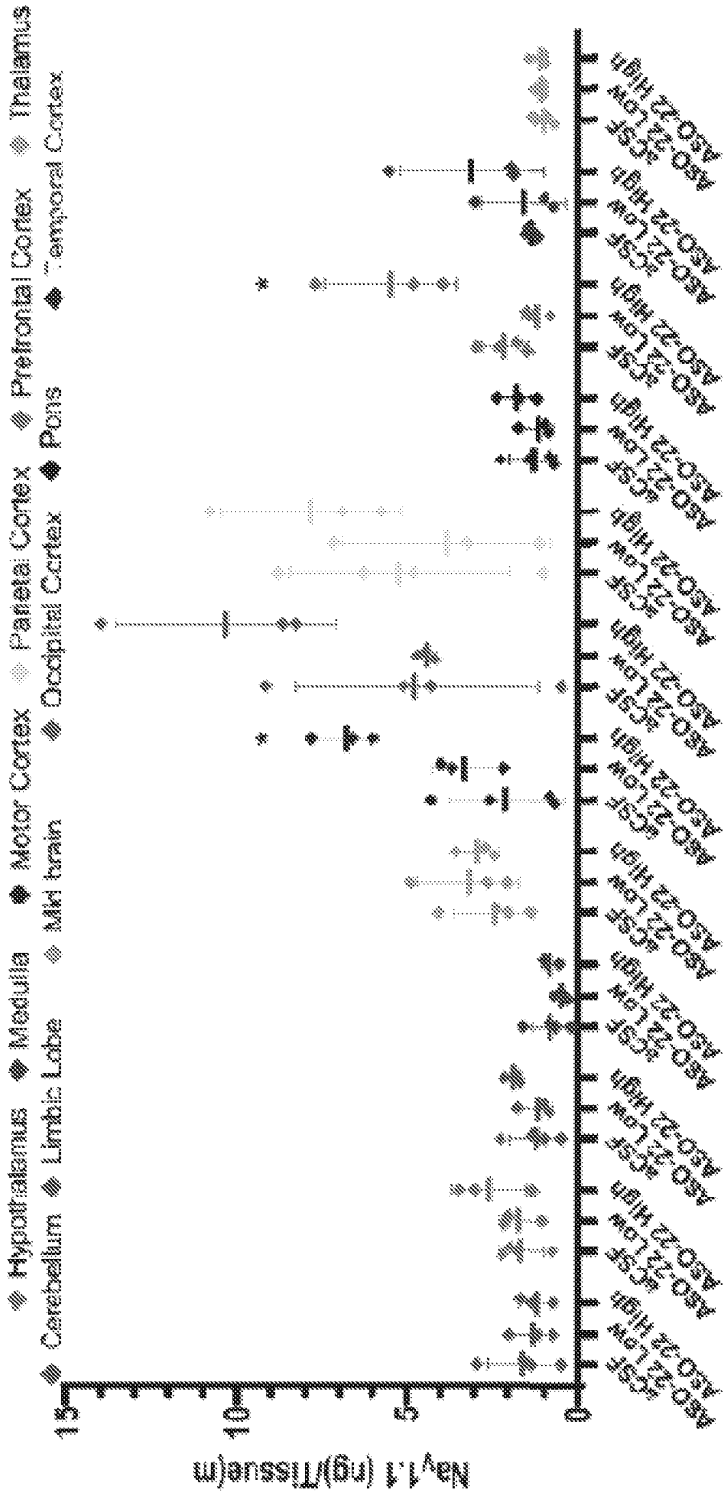
Hypothalamus
Medulla
Motor Cortex
Parietal Cortex
Prefrontal Cortex
Thalamus
Cerebellum
Limbic Lobe
Mid brain
Occipital Cortex
Pons
Temporal Cortex
Nav1.1 (ng)/Tissue(m
15
10
5
0
aCSF
ASO-22 Low
ASO-22 High

FIG. 10B

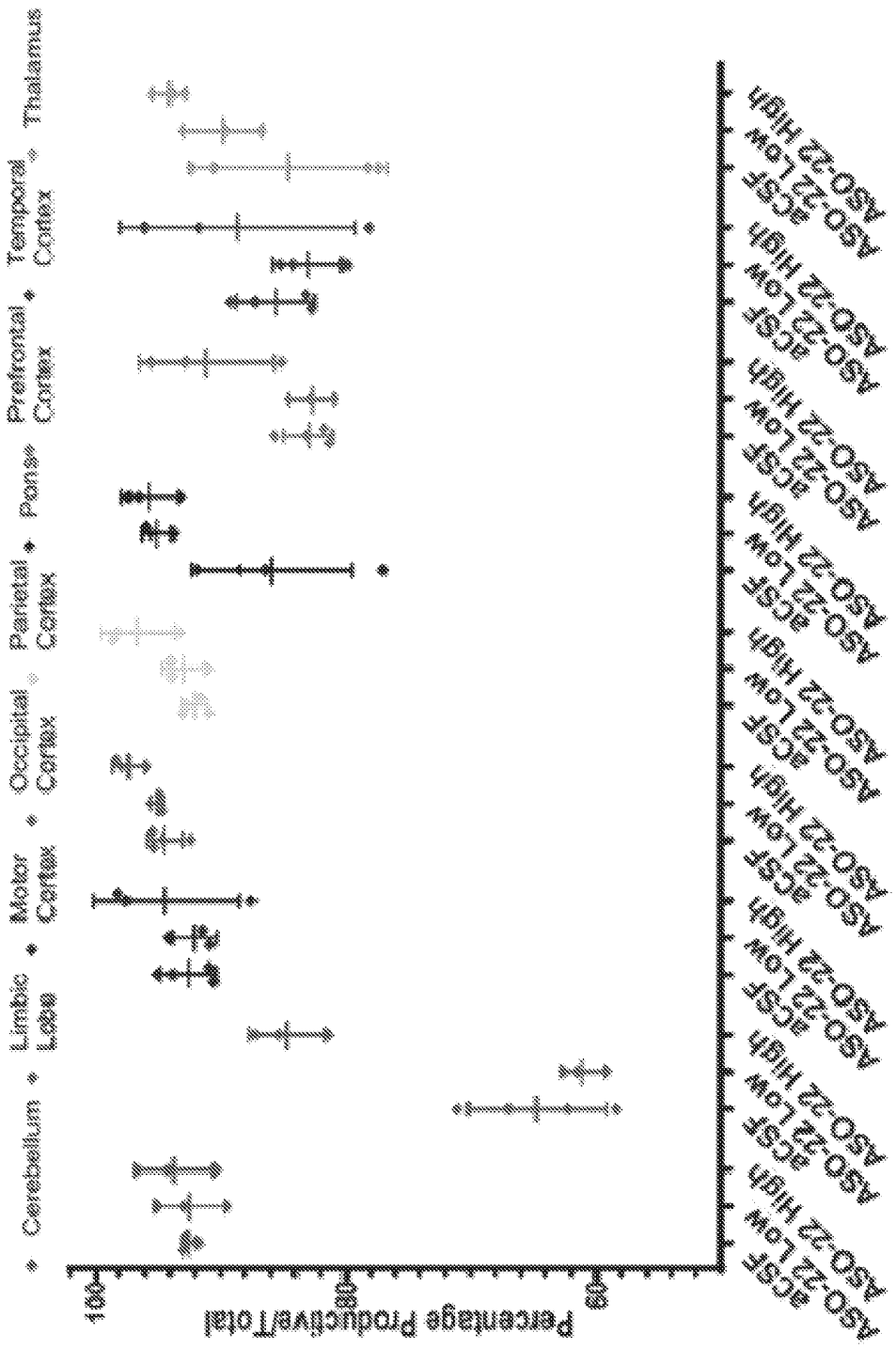
Cerebellum
Limbic Lobe
Motor Cortex
Occipital Cortex
Parietal Cortex
Pons
Prefrontal Cortex
Temporal Cortex
Thalamus
Percentage Productive/Total
100
80
60
aCSF Low
ASO-22 High
aCSF Low
ASO-22 High
aCSF Low
ASO-22 High
aCSF Low
ASO-22 High
aCSF Low
ASO-22 High
aCSF Low
ASO-22 High
aCSF Low
ASO-22 High
aCSF Low
ASO-22 High
aCSF Low
ASO-22 High

FIG. 11A

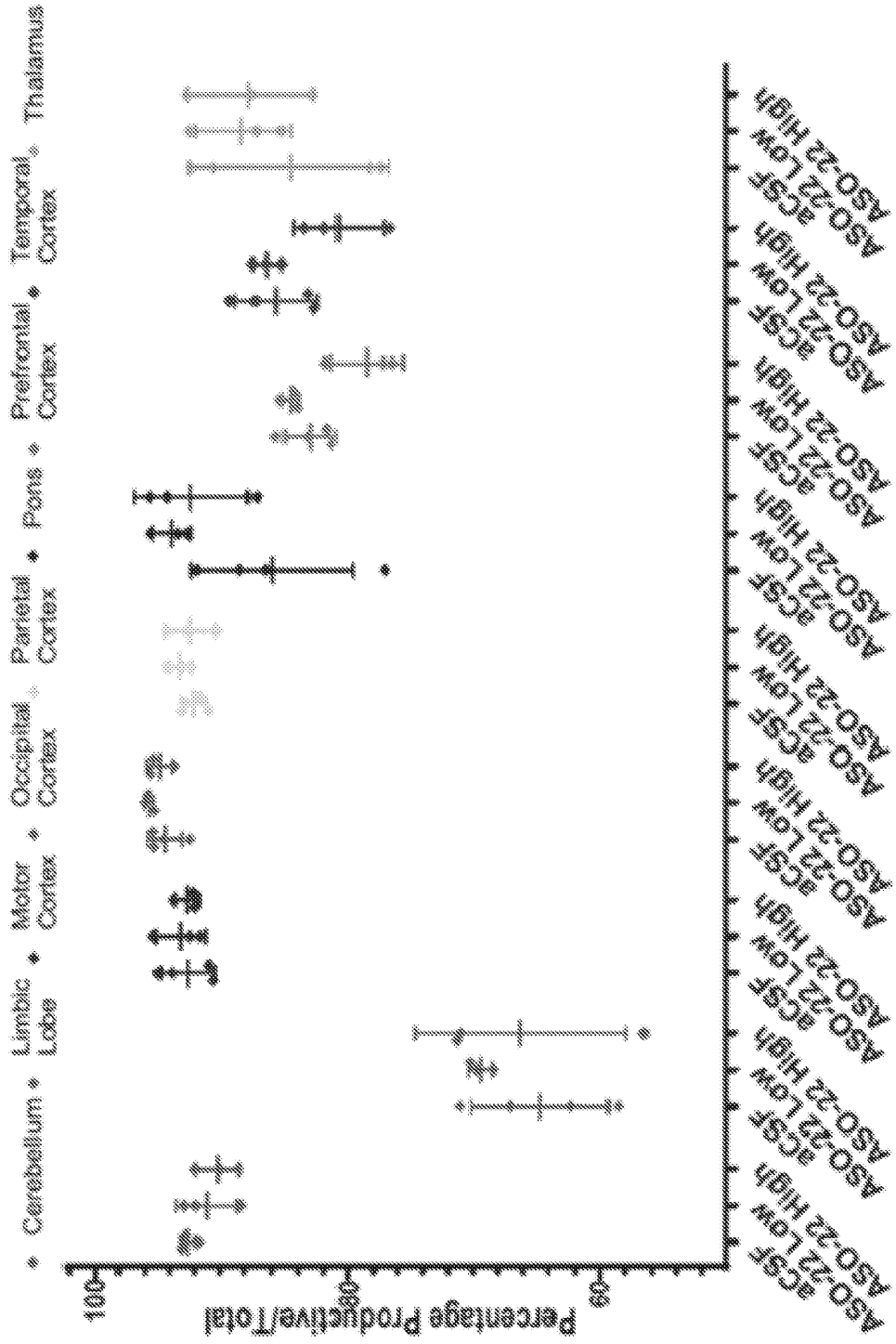
Cerebellum
Limbic Lobe
Motor Cortex
Occipital Cortex
Parietal Cortex
Pons
Prefrontal Cortex
Temporal Cortex
Thalamus
Percentage Productive/Total
100
50
0
aCSF
ASO-22 Low
ASO-22 High

FIG. 11B

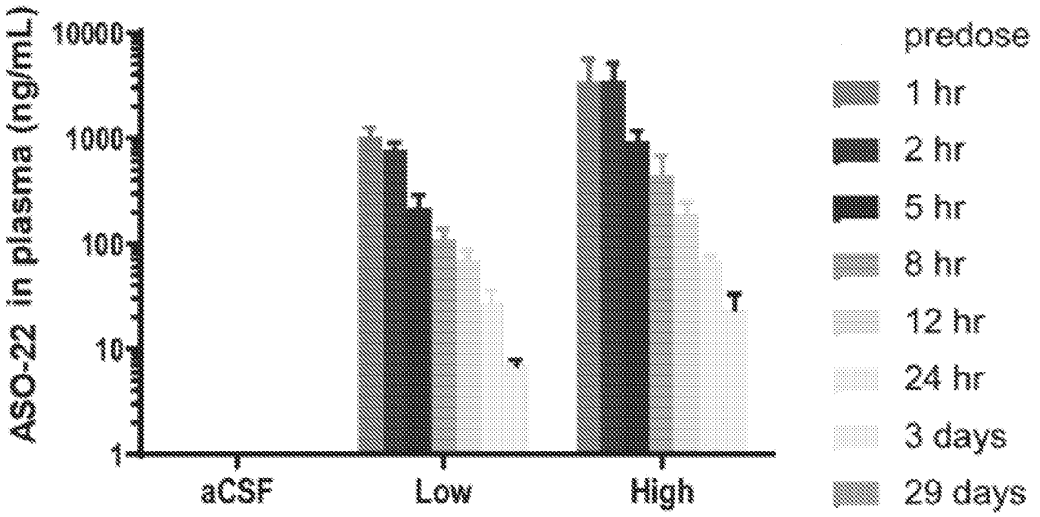

FIG. 12A

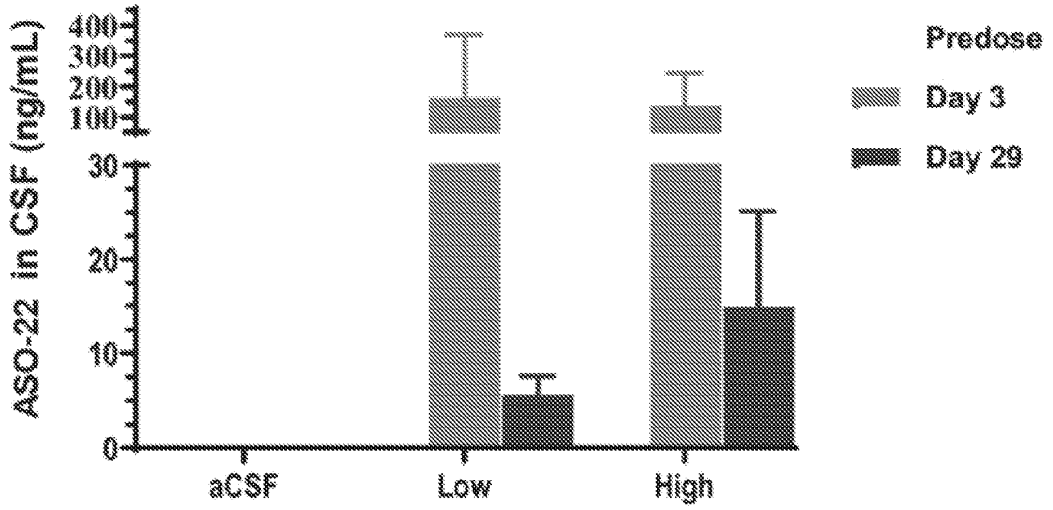

FIG. 12B

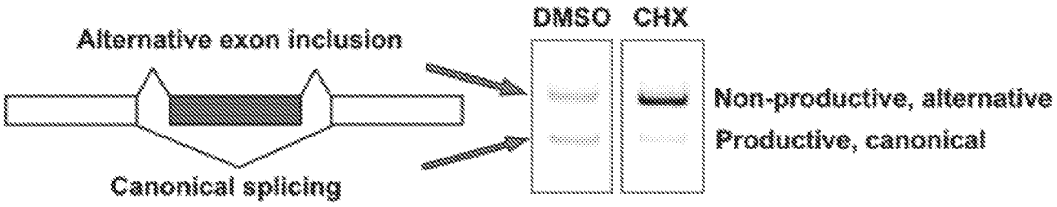

FIG. 13A

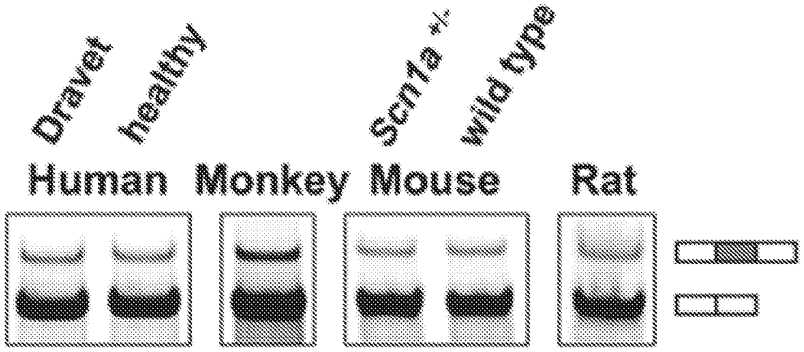

FIG. 13B

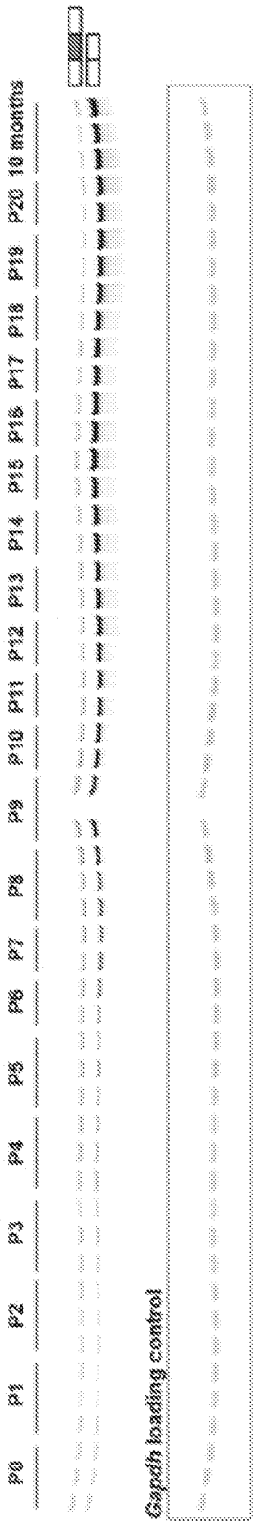
P0
P1
P2
P3
P4
P5
P6
P7
P8
P9
P10
P11
P12
P13
P14
P15
P16
P17
P18
P19
P20
10 months
Gapdh loading control

FIG. 13C

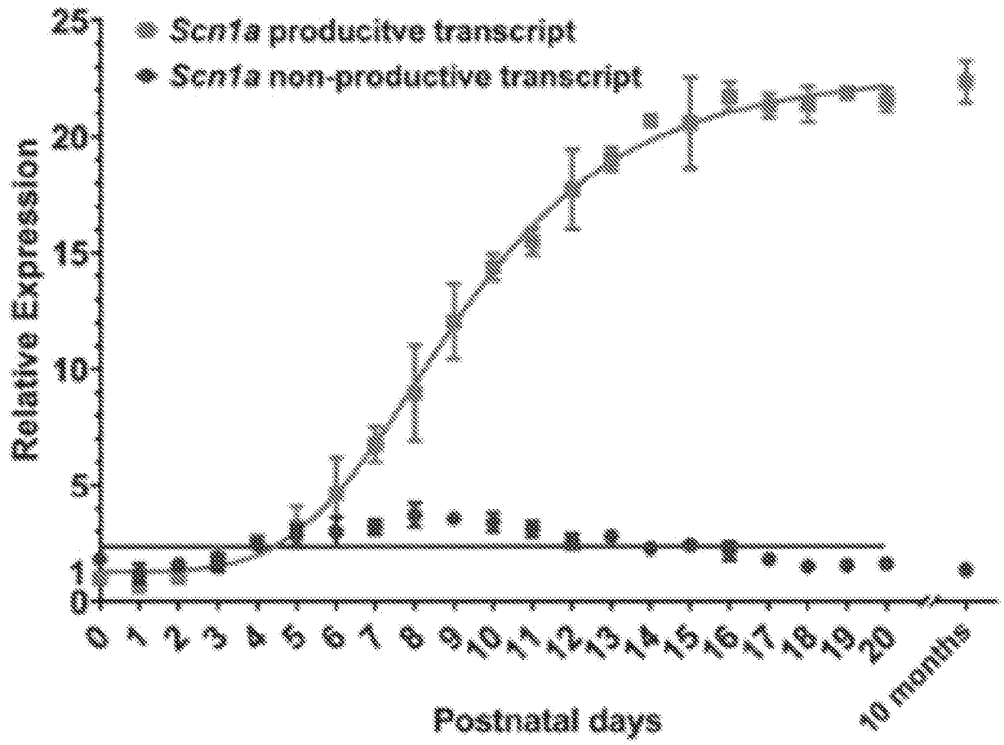
Scn1a producitve transcript
Scn1a non-productive transcript
Relative Expression
25
20
15
10
5
1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
10 months
Postnatal days

FIG. 13D

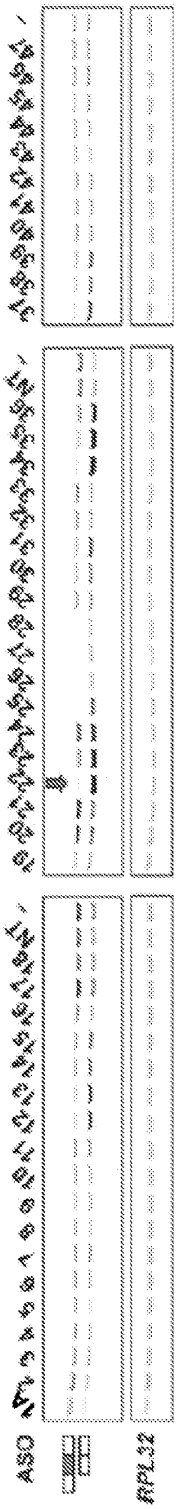

FIG. 14A

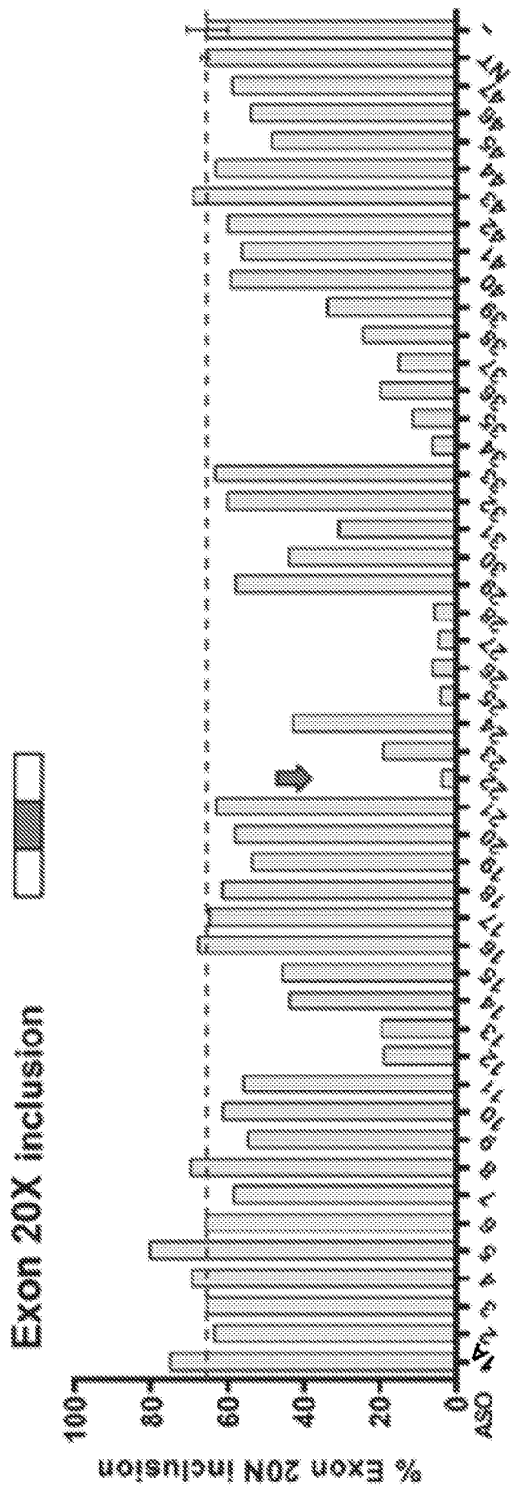

FIG. 14B

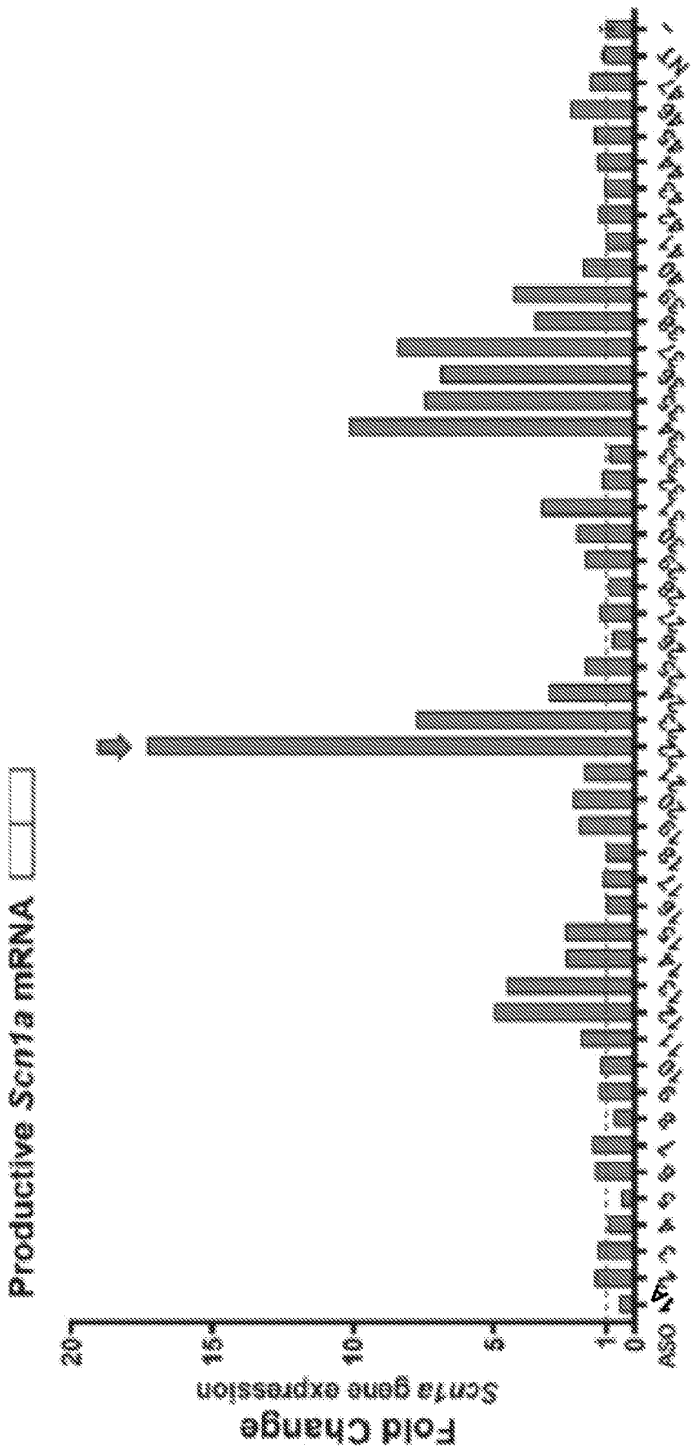
Productive Scn1a mRNA
Fold Change
Scn1a gene expression
20
15
10
5
1
0
ASO

FIG. 14C

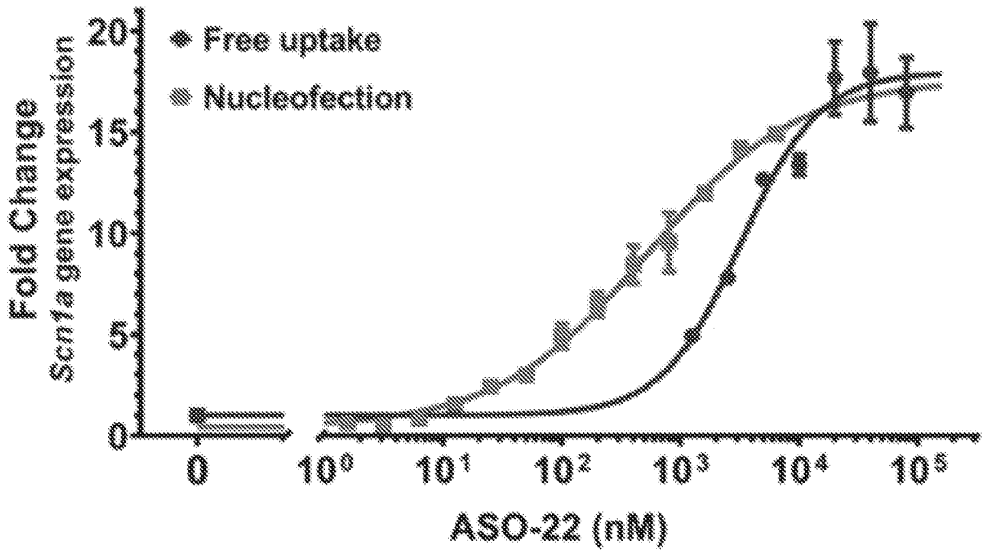
Free uptake
Nucleofection
Fold Change
Scn1a gene expression
20
15
10
5
0
0
10^0
10^1
10^2
10^3
10^4
10^5
ASO-22 (nM)

FIG. 14D

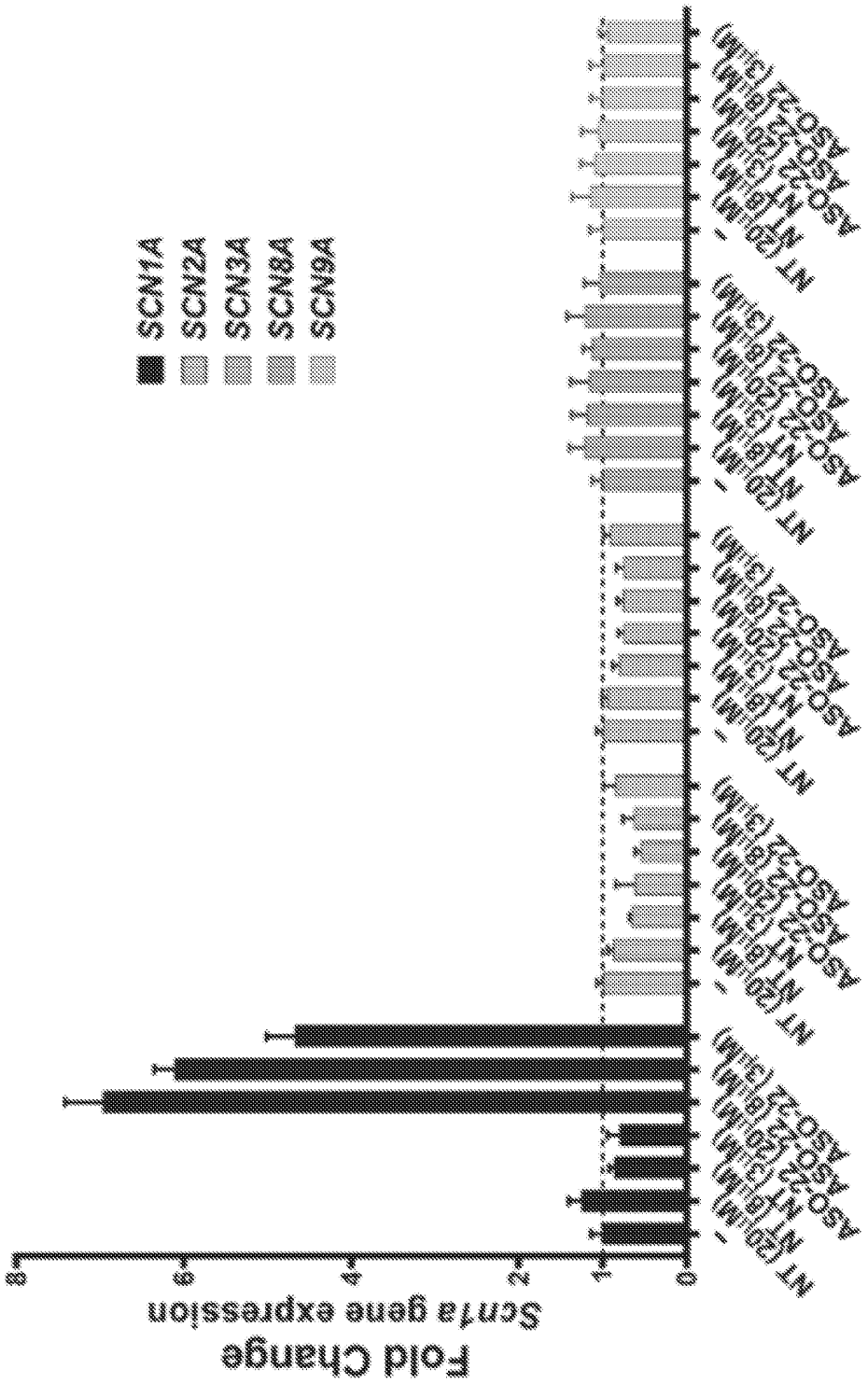
SCN1A
SCN2A
SCN3A
SCN8A
SCN9A
Fold Change
Scn1a gene expression
0
1
2
4
6
8
NT (20 μM)
NT (8 μM)
ASO-22 (20 μM)
ASO-22 (8 μM)
ASO-22 (3 μM)

FIG. 14E

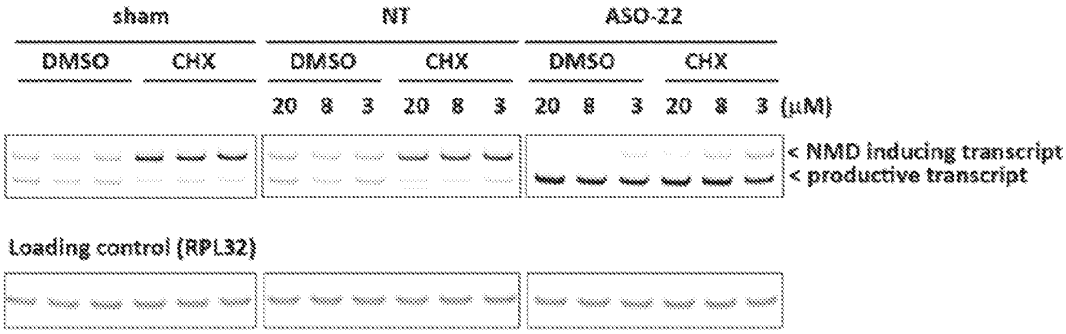

FIG. 15A

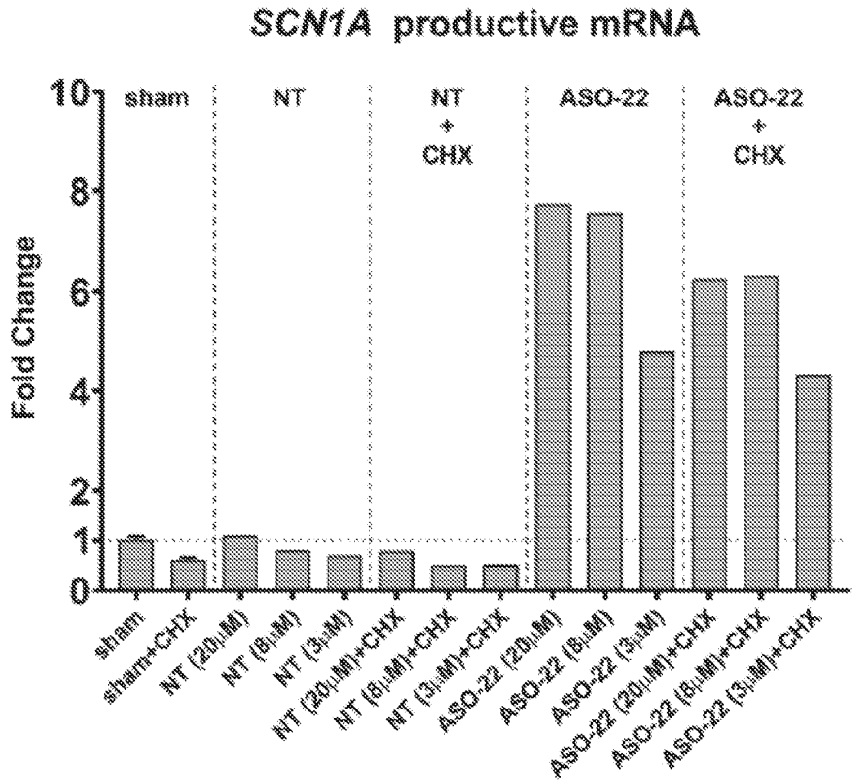

FIG. 15B

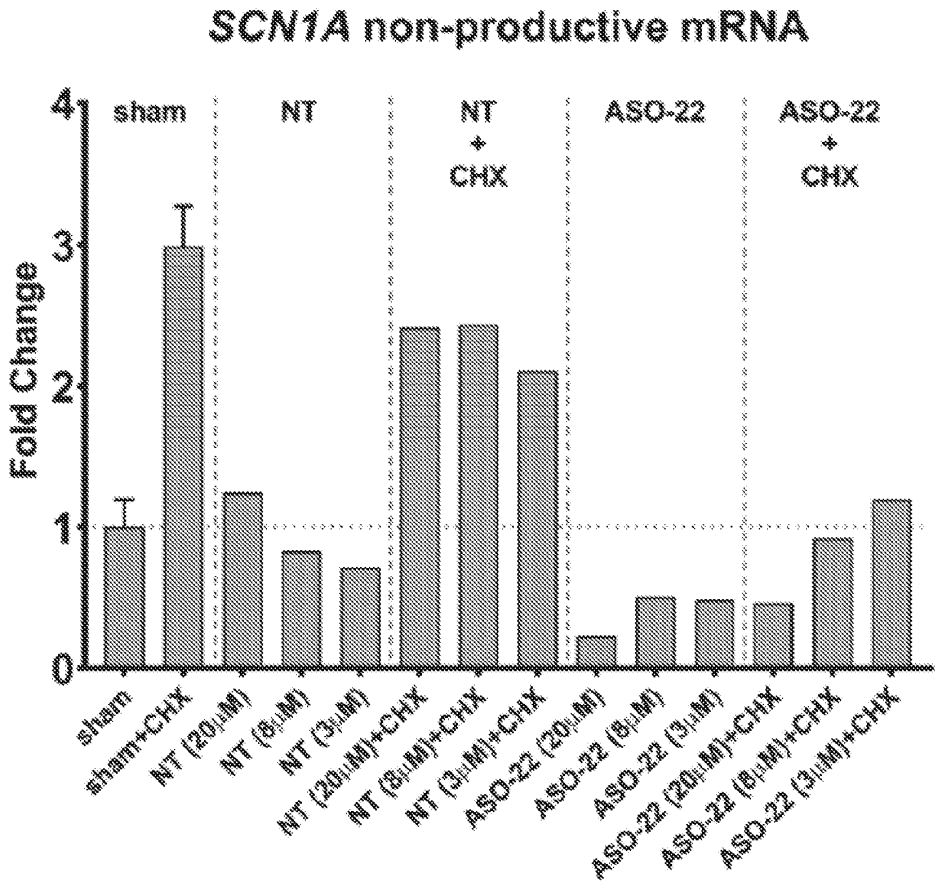
SCN1A non-productive mRNA
sham
NT
NT + CHX
ASO-22
ASO-22 + CHX
Fold Change
0
1
2
3
4
sham
sham+CHX
NT (20μM)
NT (8μM)
NT (3μM)
NT (20μM)+CHX
NT (8μM)+CHX
NT (3μM)+CHX
ASO-22 (20μM)
ASO-22 (8μM)
ASO-22 (3μM)
ASO-22 (20μM)+CHX
ASO-22 (8μM)+CHX
ASO-22 (3μM)+CHX

FIG. 15C

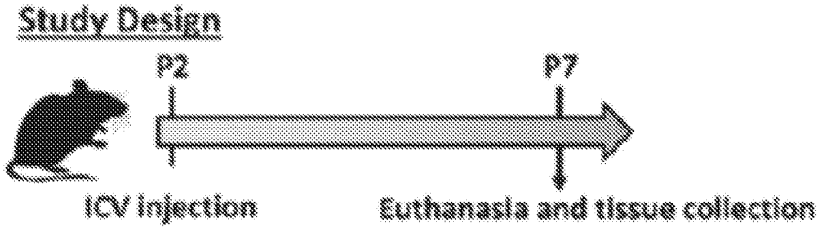

FIG. 16A

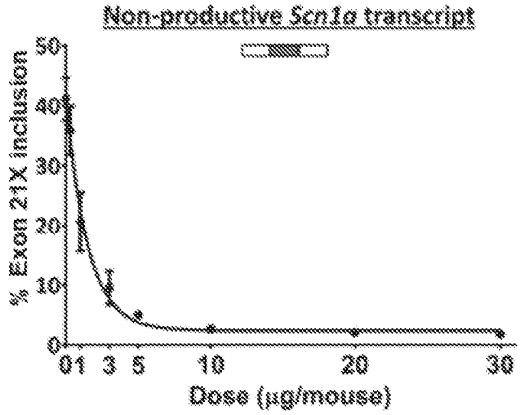

FIG. 16B

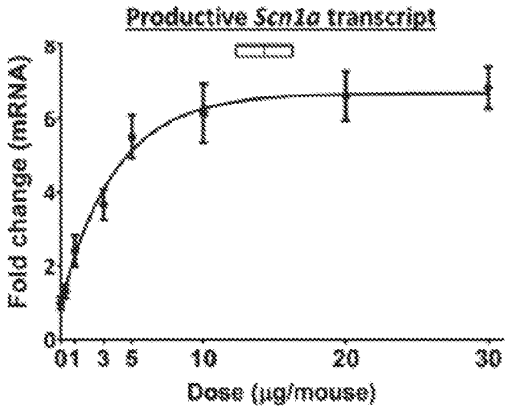

FIG. 16C

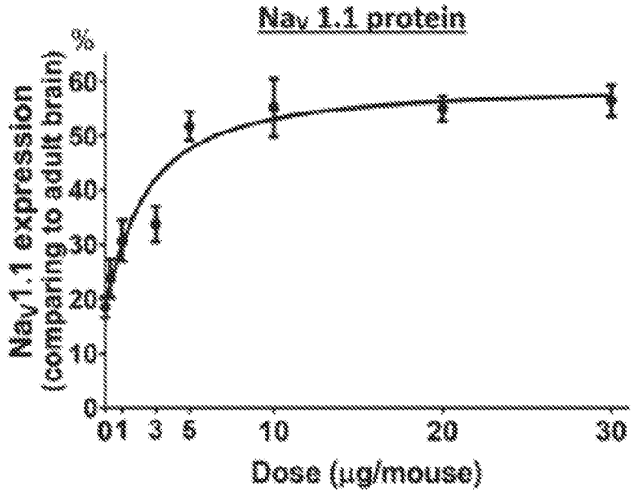

FIG. 16D

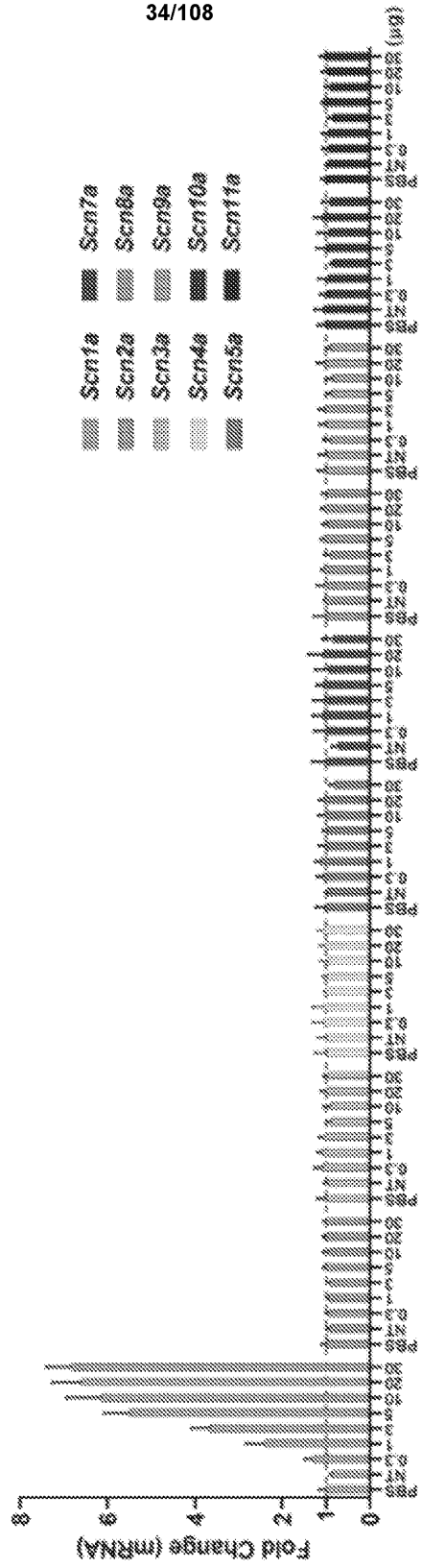
Scn1a
Scn2a
Scn3a
Scn4a
Scn5a
Scn7a
Scn8a
Scn9a
Scn10a
Scn11a
Fold Change (mRNA)
0
1
2
4
6
8

FIG. 16E

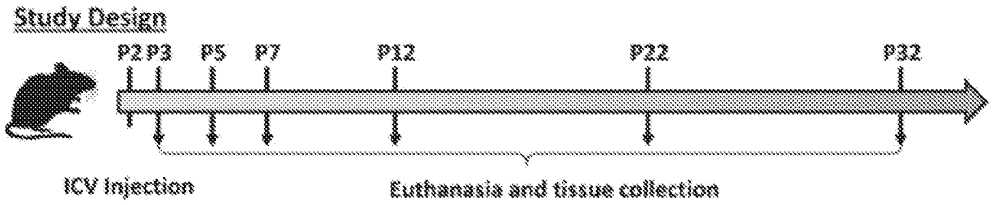

FIG. 16F

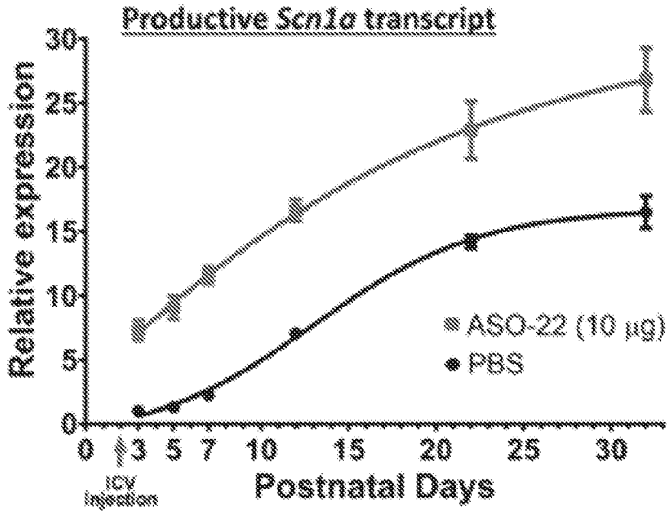

FIG. 16G

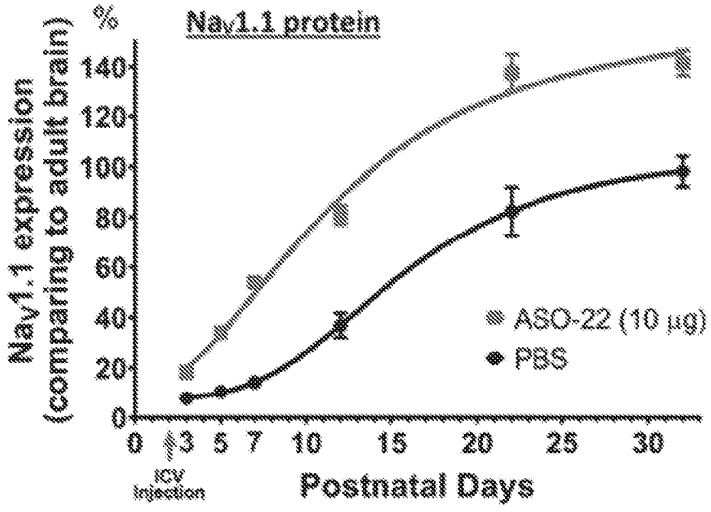

FIG. 16H

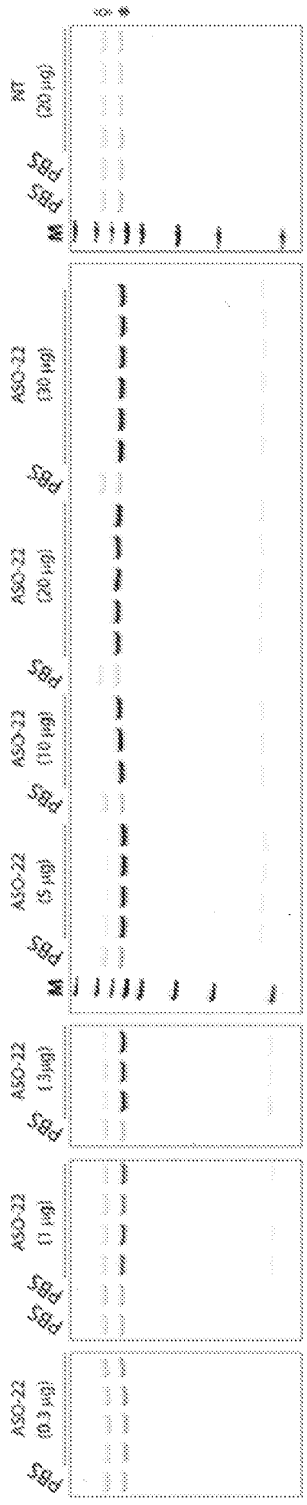
PBS
ASO-22 (0.3 mg)
PBS
ASO-22 (1 mg)
PBS
ASO-22 (3 mg)
PBS
ASO-22 (5 mg)
PBS
ASO-22 (10 mg)
PBS
ASO-22 (20 mg)
PBS
ASO-22 (30 mg)
WT
PBS
WT (20 mg)

FIG. 17

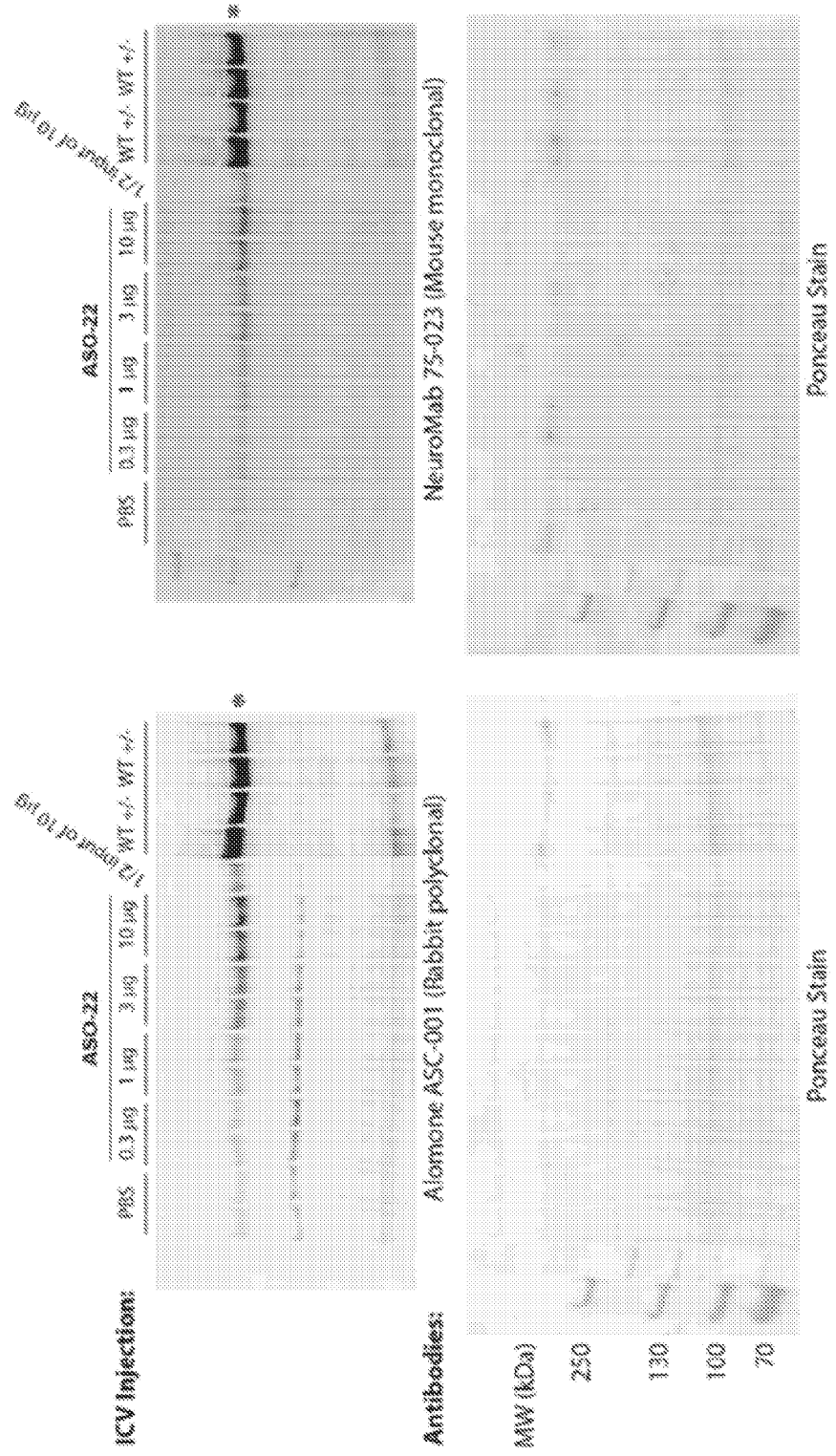
ICV Injection:
ASO-22
PBS
0.3 µg
1 µg
3 µg
10 µg
1/2 input of 10 µg
WT +/-
WT +/-
Antibodies:
Alomone ASC-001 (Rabbit polyclonal)
MW (kDa)
250
130
100
70
Ponceau Stain
NeuroMab 75-023 (Mouse monoclonal)

FIG. 18

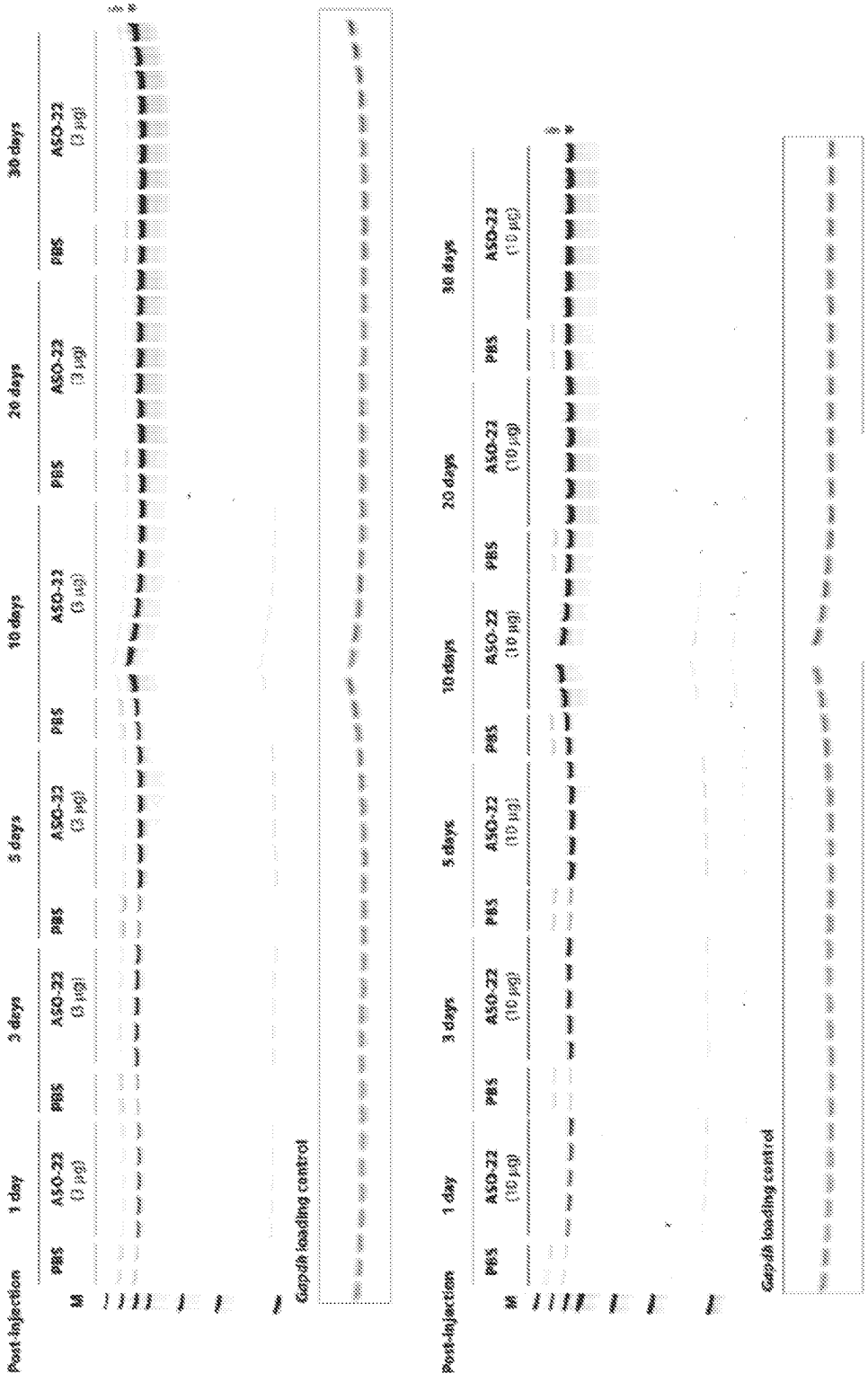
Post-injection
1 day
3 days
5 days
10 days
20 days
30 days
PBS
ASO-22 (3 μg)
ASO-22 (10 μg)
Gapdh loading control

FIG. 19

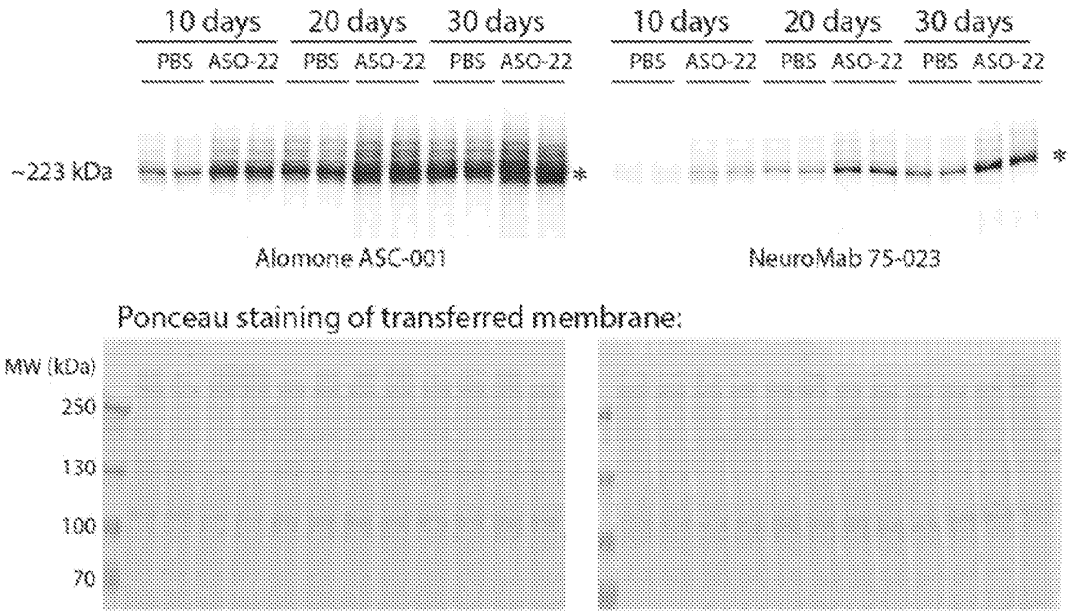
10 days
20 days
30 days
10 days
20 days
30 days
PBS
ASO-22
PBS
ASO-22
PBS
ASO-22
PBS
ASO-22
PBS
ASO-22
PBS
ASO-22
~223 kDa
*
*
Alomone ASC-001
NeuroMab 75-023
Ponceau staining of transferred membrane:
MW (kDa)
250
130
100
70

FIG. 20

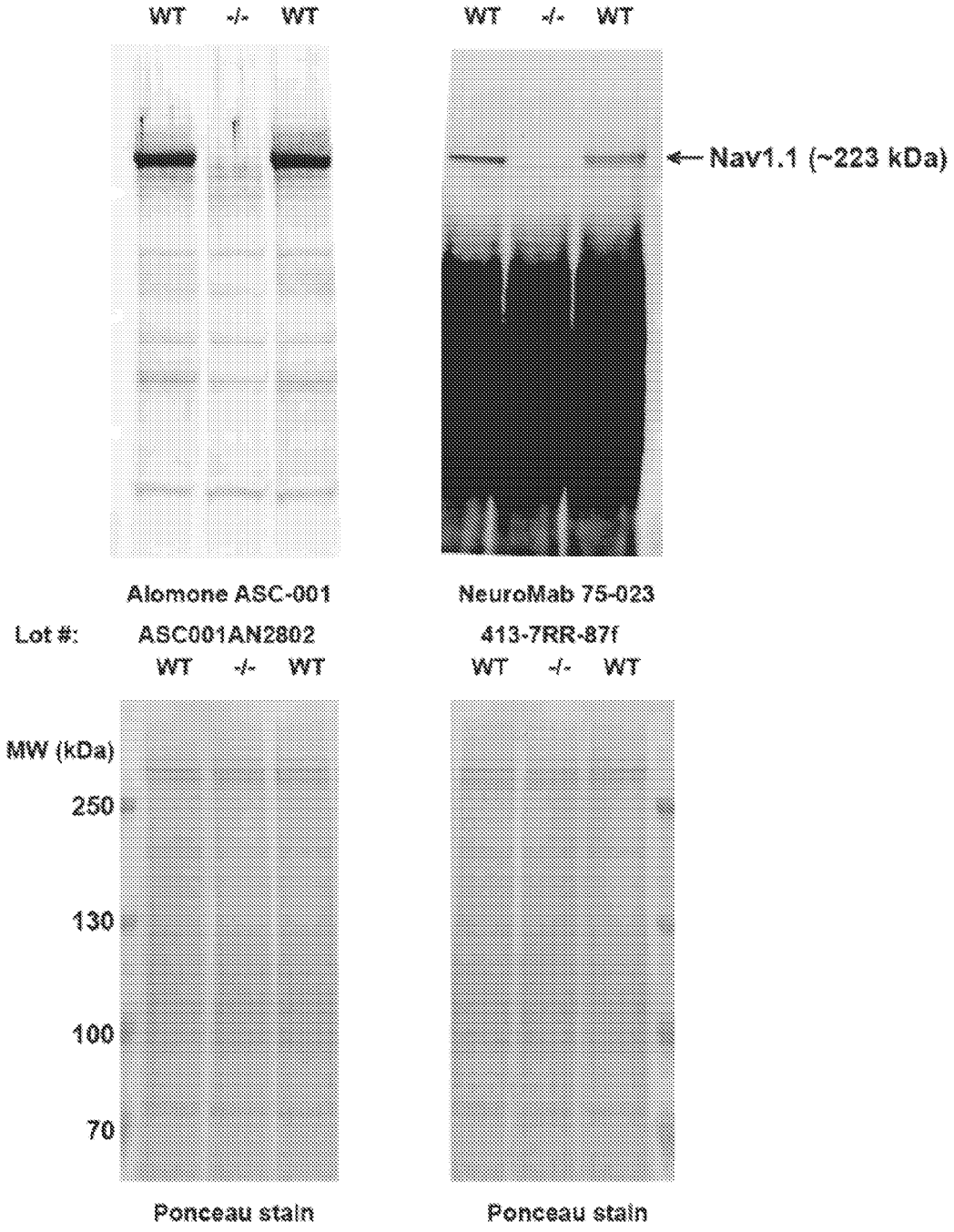
WT -/- WT
WT -/- WT
Nav1.1 (~223 kDa)
Alomone ASC-001
NeuroMab 75-023
Lot #:
ASC001AN2802
413-7RR-87f
WT -/- WT
WT -/- WT
MW (kDa)
250
130
100
70
Ponceau stain
Ponceau stain

FIG. 21

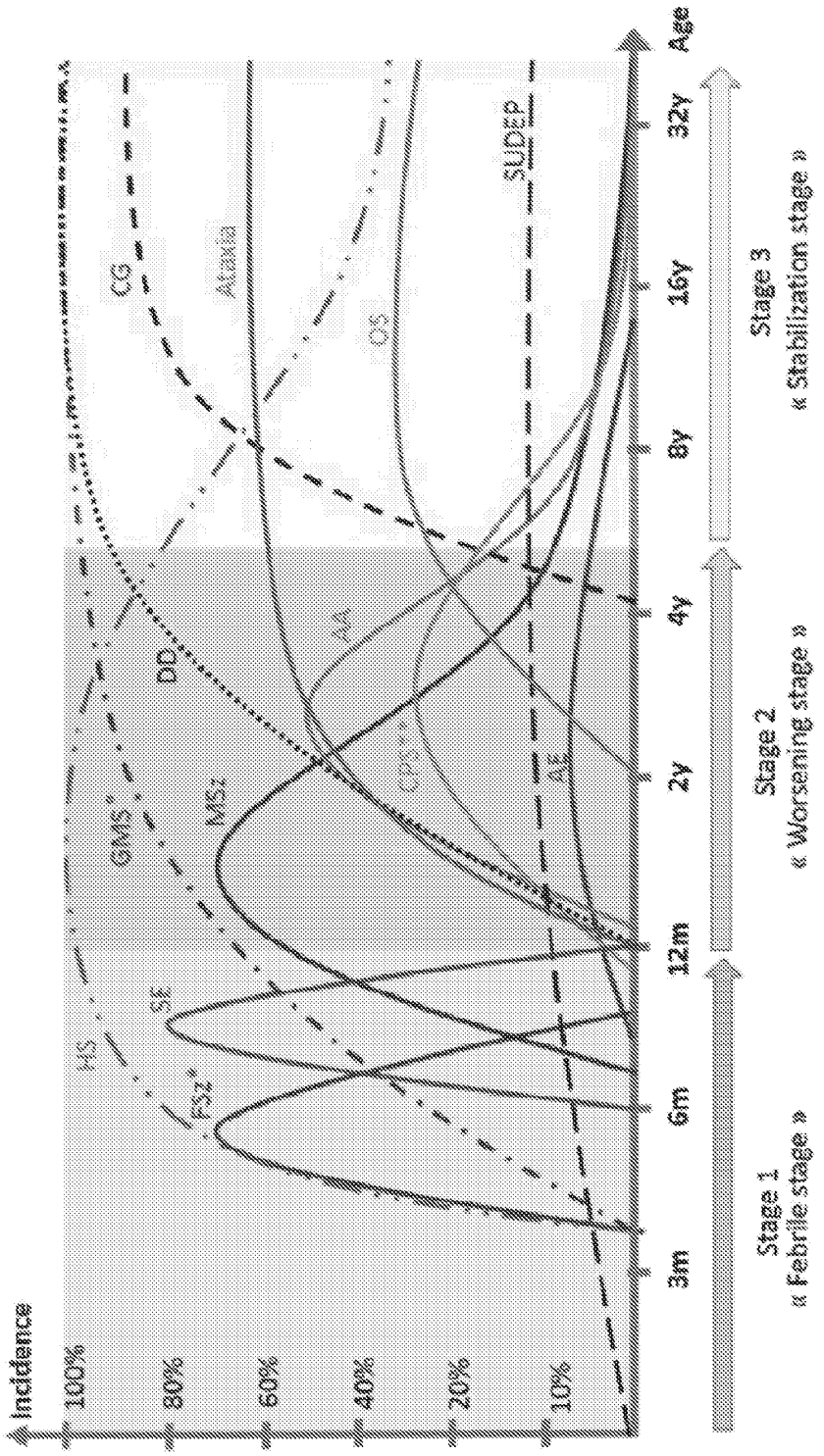
Incidence
100%
80%
60%
40%
20%
10%
Age
3m
6m
12m
2y
4y
8y
16y
32y
HS
FSz*
SE
GMS*
MSz
DD
CG
Ataxia
OS
AA
CPS**
AE
SUDEP
Stage 1
« Febrile stage »
Stage 2
« Worsening stage »
Stage 3
« Stabilization stage »

FIG. 22

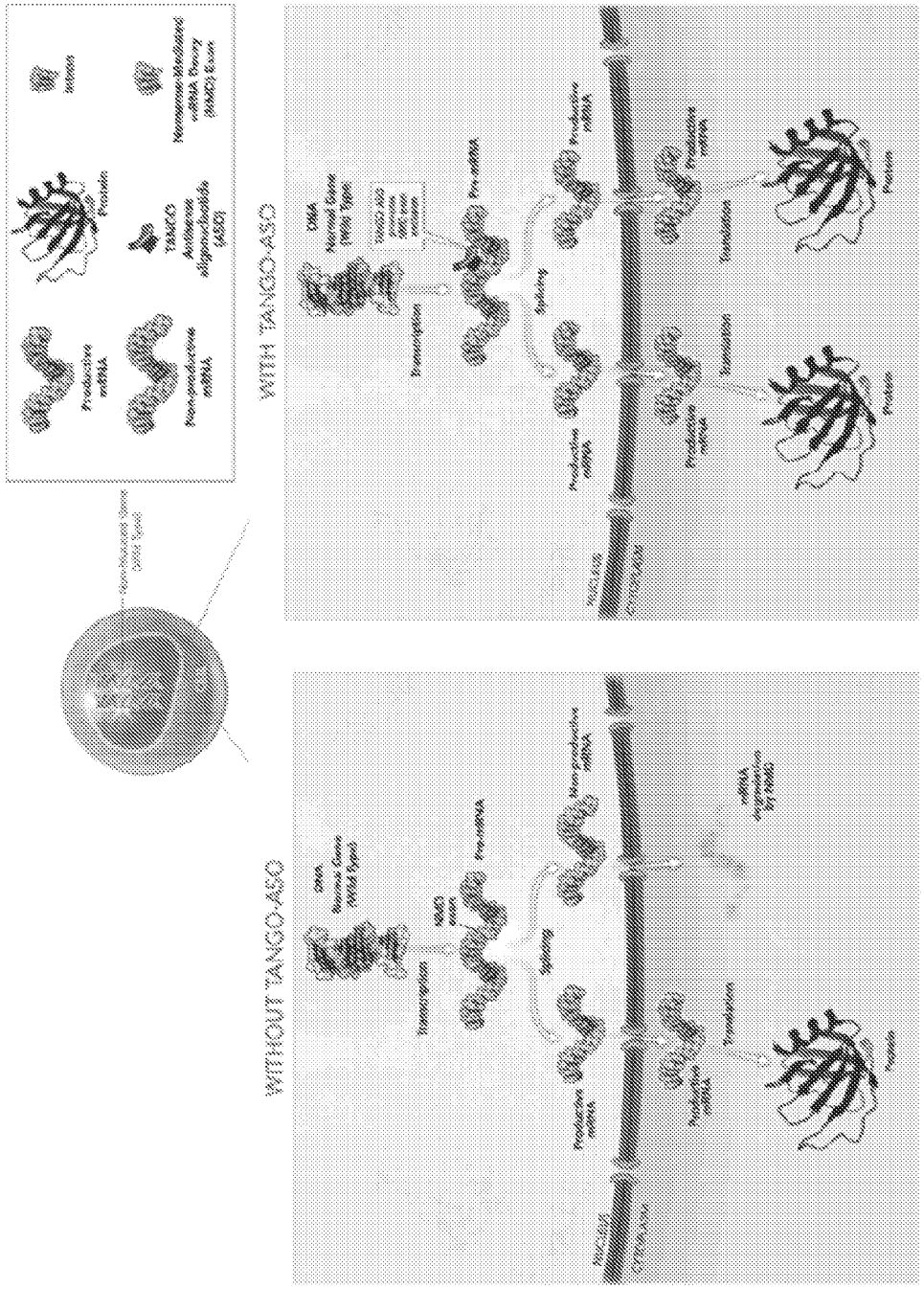

FIG. 23

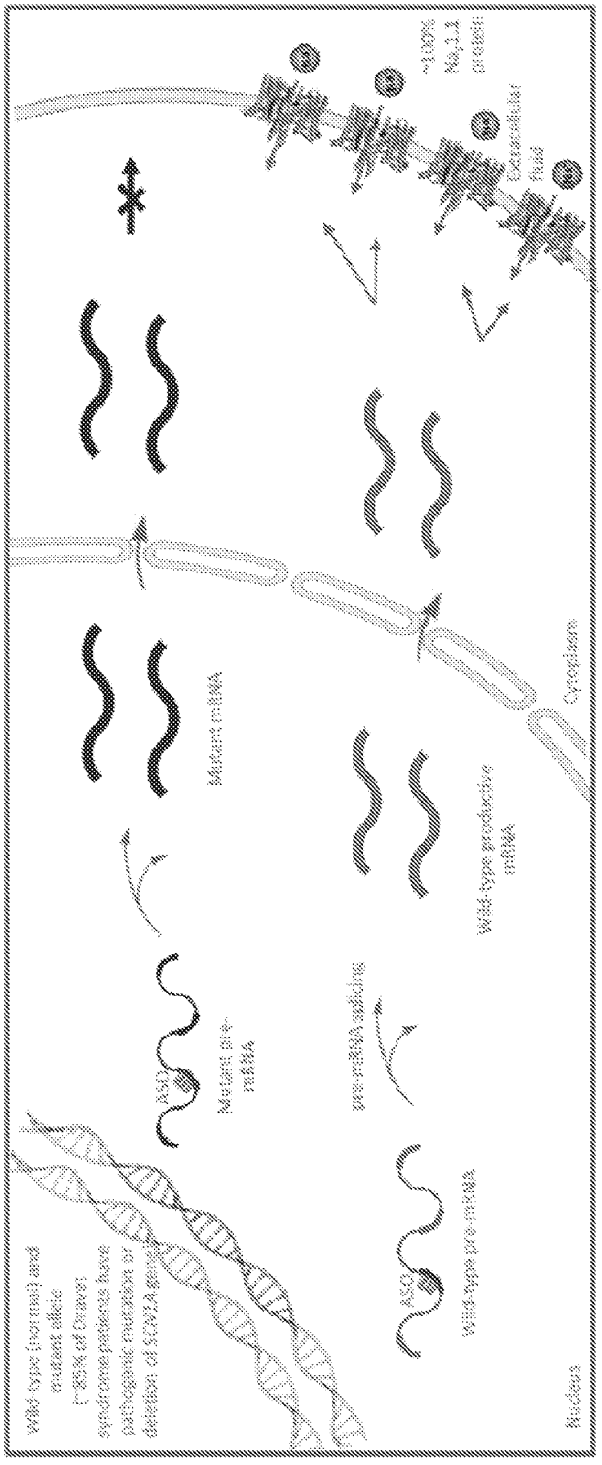
Wild-type (normal) and mutant allele
(~85% of Dravet syndrome patients have pathogenic mutation or deletion of SCN1A gene)
ASO
Mutant pre-mRNA
pre-mRNA splicing
Wild-type pre-mRNA
Mutant mRNA
Wild-type productive mRNA
Cytoplasm
Nucleus
Extracellular fluid
~100% Na1.1 protein

FIG. 24

Study Parameters	Parameter Properties
Cohorts	Single Ascending Doses (SAD) and Multiple Ascending Doses (MAD)
Study duration	7-9 months / patient
Number of patients	<70

FIG. 25

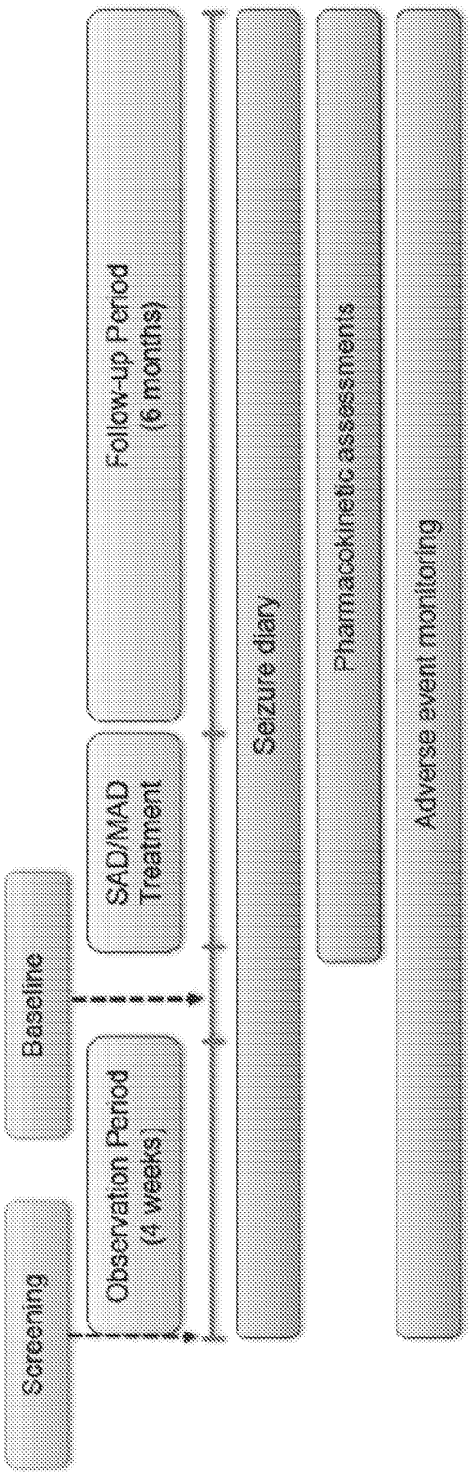
Screening
Baseline
Observation Period
(4 weeks)
SAD/MAD
Treatment
Follow-up Period
(6 months)
Seizure diary
Pharmacokinetic assessments
Adverse event monitoring

FIG. 26

Inclusion Criteria	Exclusion Criteria
Aged 2-18 years (inclusive)	Known pathogenic mutation in another gene that causes epilepsy
DS onset <12 months of age with recurrent seizures (focal motor, hemiconvulsive, or generalized tonic-clonic) – No history of causal MRI lesion (MRI not required) – No other known etiology – Normal development at seizure onset	Currently being treated with an anti-epileptic drug acting primarily as a sodium channel blocker, as maintenance treatment
Documented pathogenic, likely pathogenic variant, or variant of uncertain significance in *SCN1A*	Clinically significant unstable medical condition(s) other than epilepsy
≥2 prior treatments for epilepsy that lacked adequate seizure control or had to be discontinued due to adverse events (AEs)	Clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to screening or dosing on day 1, other than epilepsy
≥1 anti-epileptic drug (and any other treatments) at a stable dose for ≥4 weeks	Any other significant disease or disorder, in the investigator's opinion, that may put the patient at risk, influence the study results, or affect the patient's ability to participate in the study

FIG. 27

Primary Outcome Measures	
Safety assessments	• Adverse events
Pharmacokinetics	• Plasma concentrations of Compound-A
Cerebral spinal fluid (CSF)	• Compound-A levels
Secondary Outcome Measures	
Seizure frequency	• Measured by paper diary
Clinical status (caregiver)	• Caregiver Global Impression of Change (CaGIC): 7-level scale from very much improved to very much worse
Clinical status (clinician)	• Clinical Global Impression of Change (CGIC): 7-level scale from very much improved to very much worse
Quality of life	• EQ-5D-Y (patients ≥8 years will complete themselves [Self Complete version] if able): scale 0-100

FIG. 28

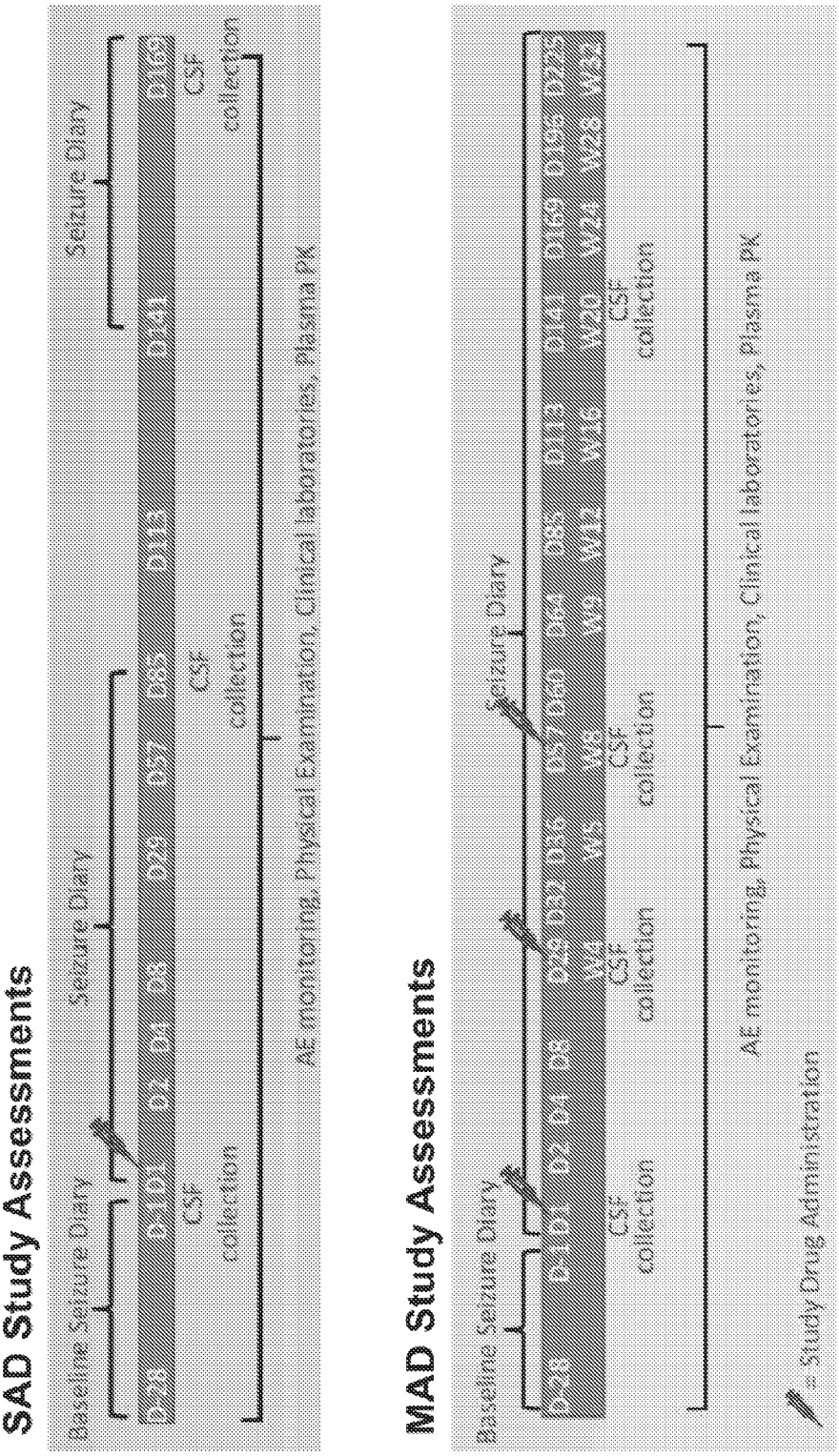
SAD Study Assessments
Baseline Seizure Diary
Seizure Diary
D-28
D1
D2
D4
D8
D15
D29
D57
D85
D113
D141
D169
CSF collection
CSF collection
AE monitoring, Physical Examination, Clinical laboratories, Plasma PK
MAD Study Assessments
Baseline Seizure Diary
Seizure Diary
D-28
D1
D2
D4
D8
D15
D29
D43
D57
D85
D113
D141
D169
D183
D225
W6
W12
W20
W24
W32
CSF collection
CSF collection
AE monitoring, Physical Examination, Clinical laboratories, Plasma PK
= Study Drug Administration

FIG. 29

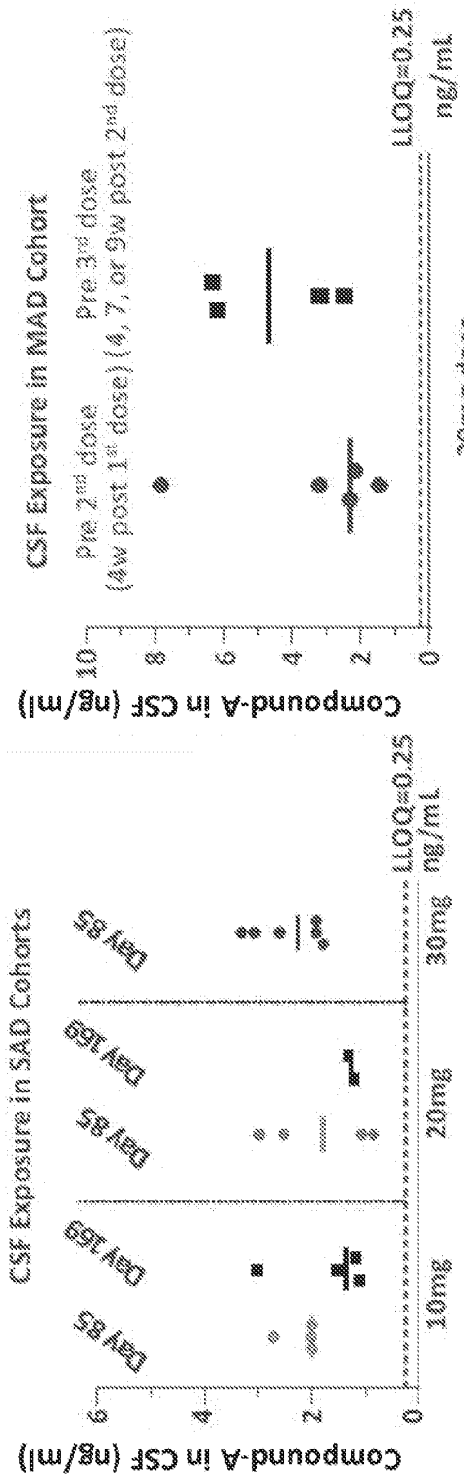
CSF Exposure in SAD Cohorts
Compound-A in CSF (ng/ml)
0
2
4
6
Day 85
Day 169
Day 85
Day 169
Day 85
10mg
20mg
30mg
LLOQ=0.25
ng/mL
CSF Exposure in MAD Cohort
Pre 2nd dose
(4w post 1st dose)
Pre 3rd dose
(4, 7, or 9w post 2nd dose)
0
2
4
6
8
10
20mg dose
LLOQ=0.25
ng/mL
LLOQ = lower level of quantification

FIG. 30

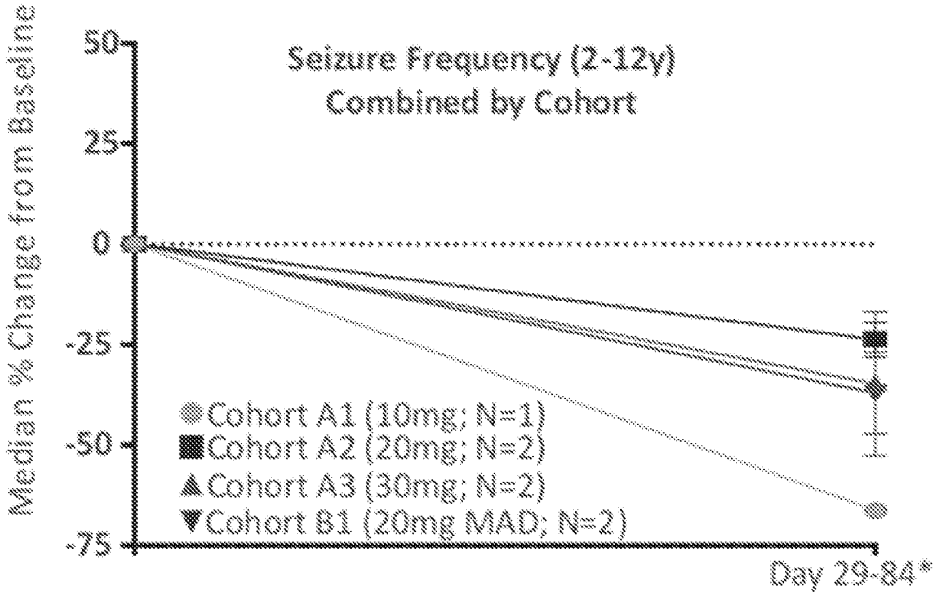

FIG. 31A

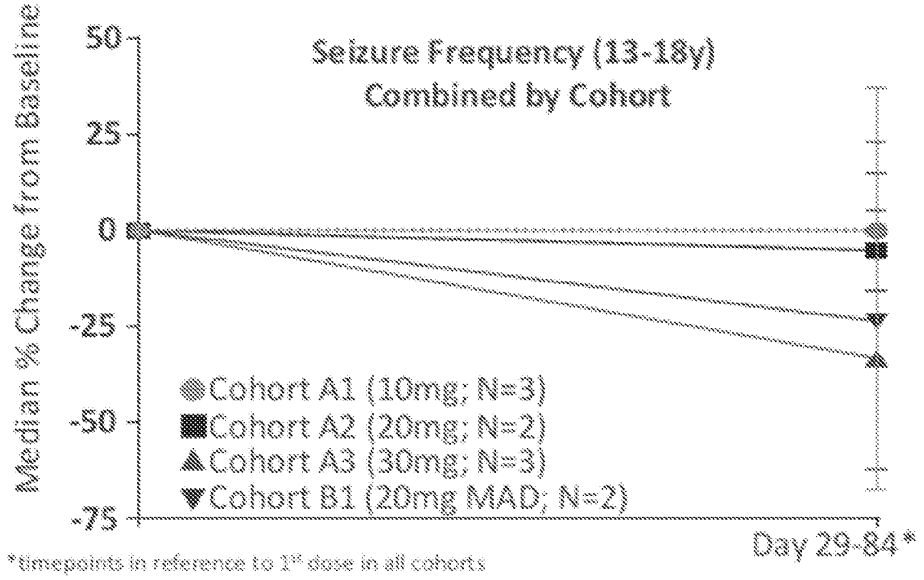

FIG. 31B

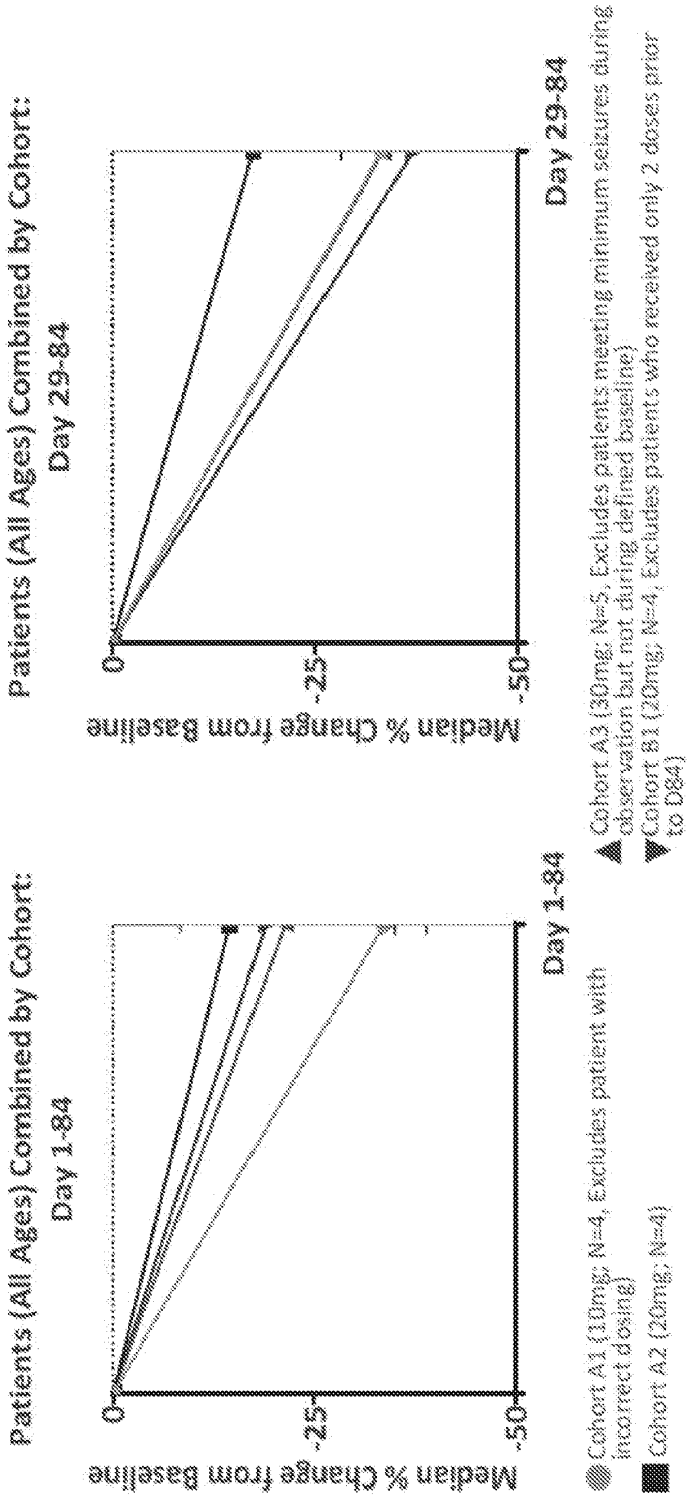

FIG. 32A

FIG. 32B

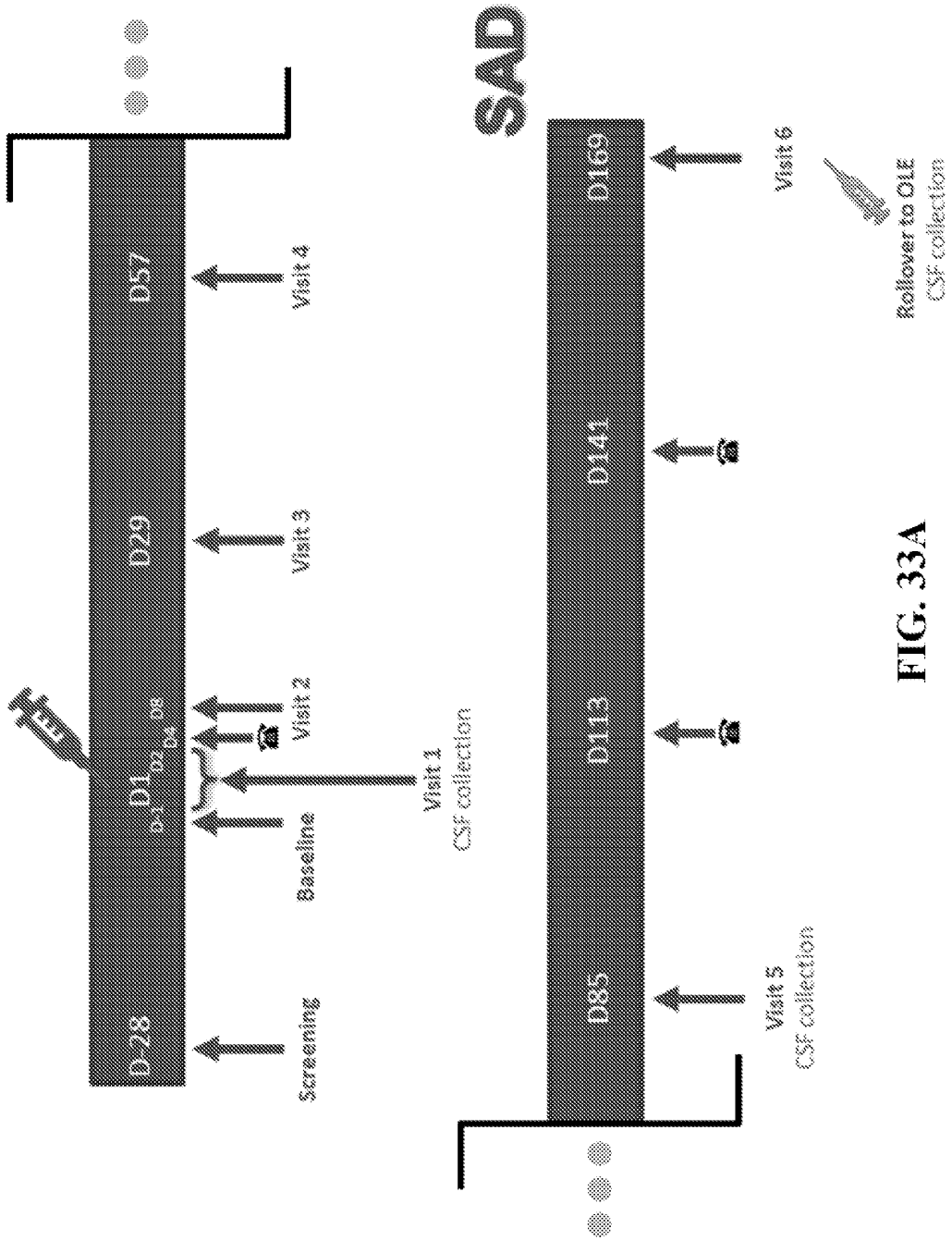
SAD
D-28
D1
D29
D57
D85
D113
D141
D169
Screening
Baseline
Visit 1
CSF collection
Visit 2
Visit 3
Visit 4
Visit 5
CSF collection
Visit 6
Rollover to OLE
CSF collection

FIG. 33A

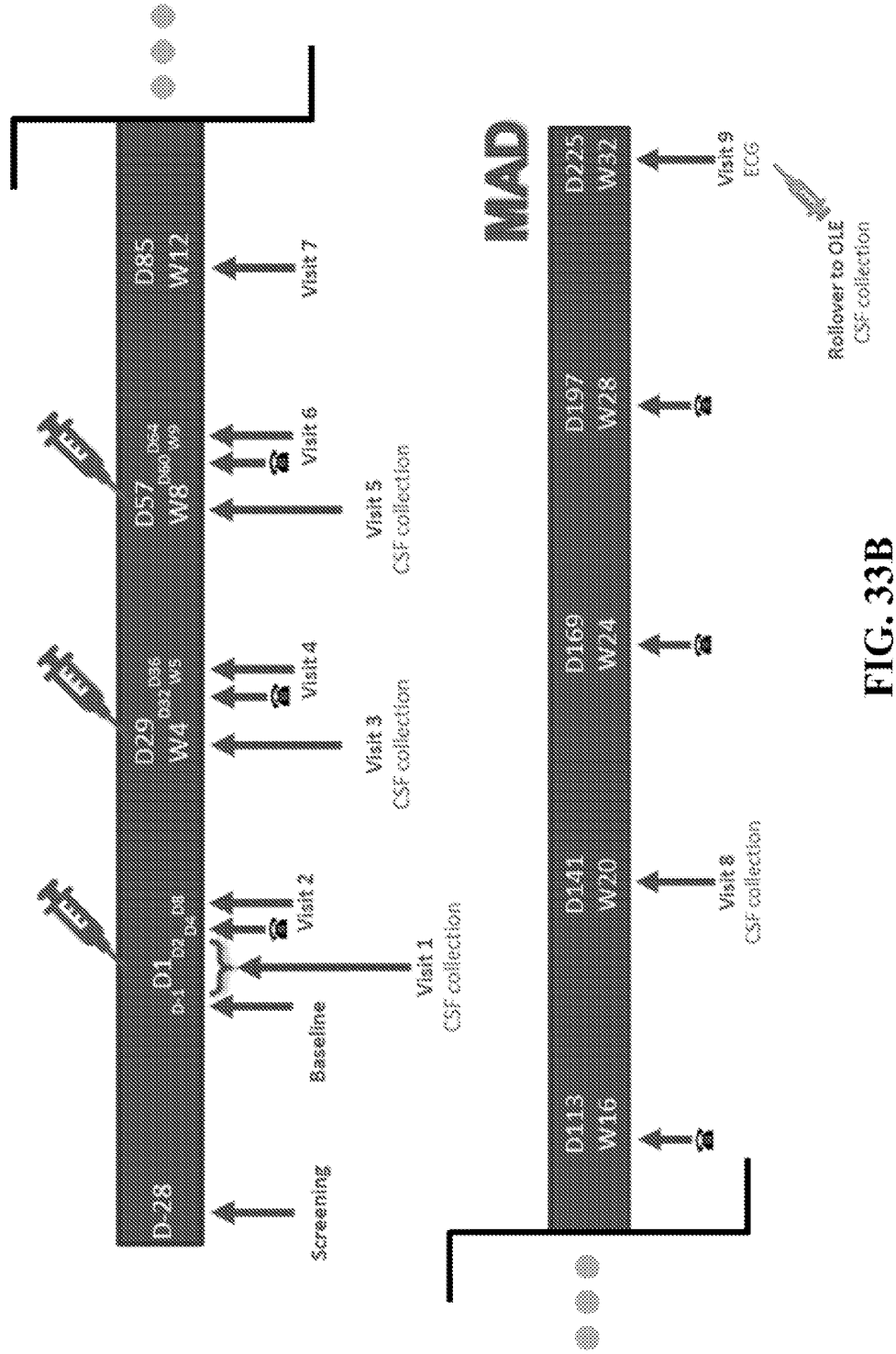
MAD
D-28
Screening
D1
Baseline
Visit 1
CSF collection
Visit 2
Visit 3
CSF collection
Visit 4
Visit 5
CSF collection
Visit 6
Visit 7
Visit 8
CSF collection
Visit 9
ECG
Rollover to OLE
CSF collection
D29
W4
D57
W8
D85
W12
D113
W16
D141
W20
D169
W24
D197
W28
D225
W32

FIG. 33B

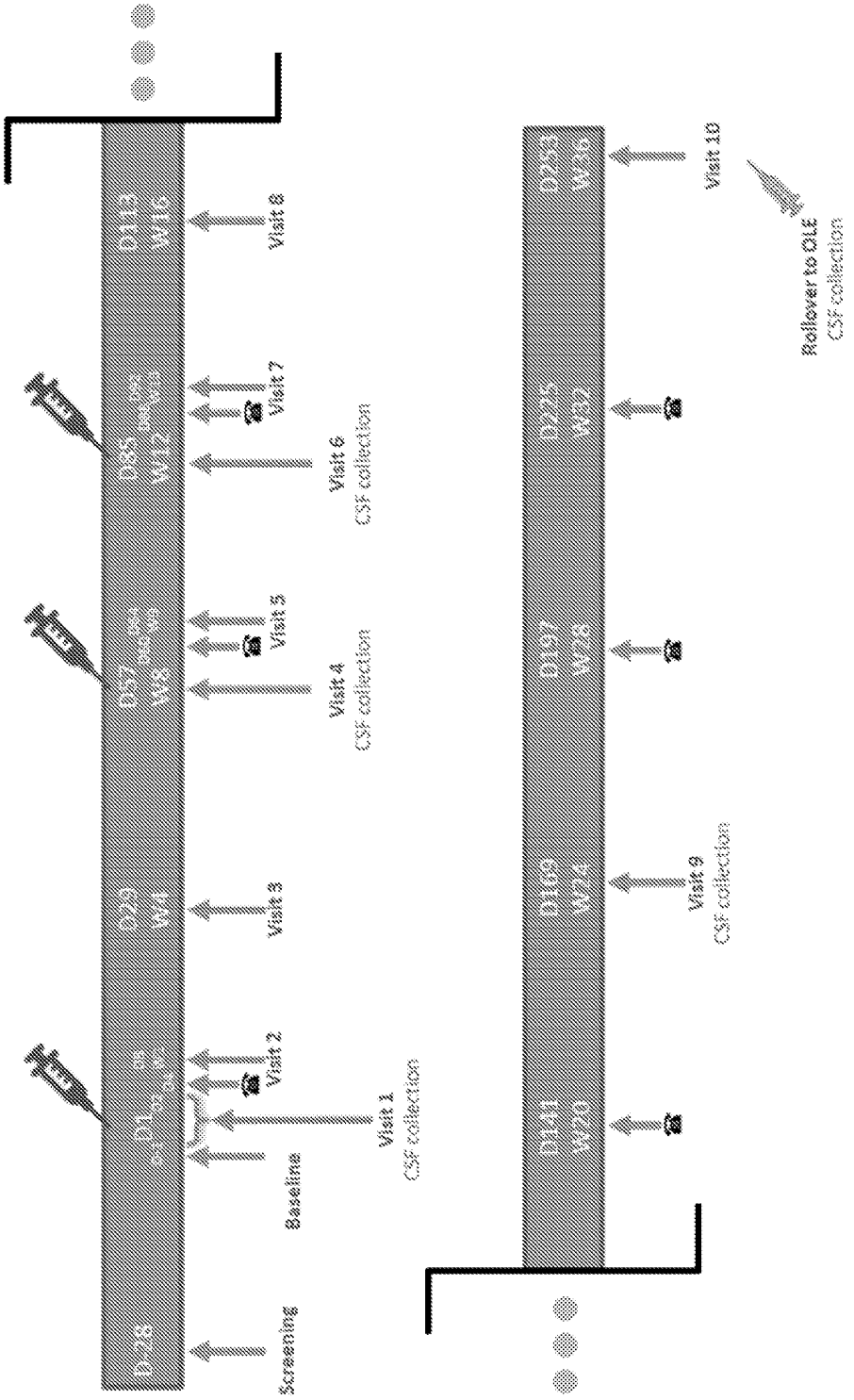
D-28
Screening
Baseline
Visit 1
CSF collection
Visit 2
D29
W5
Visit 3
D57
W9
Visit 4
CSF collection
Visit 5
D85
W13
Visit 6
CSF collection
Visit 7
D113
W17
Visit 8
D141
W21
D169
W25
Visit 9
CSF collection
D197
W29
D225
W33
D253
W37
Visit 10
Rollover to OLE
CSF collection

FIG. 33C

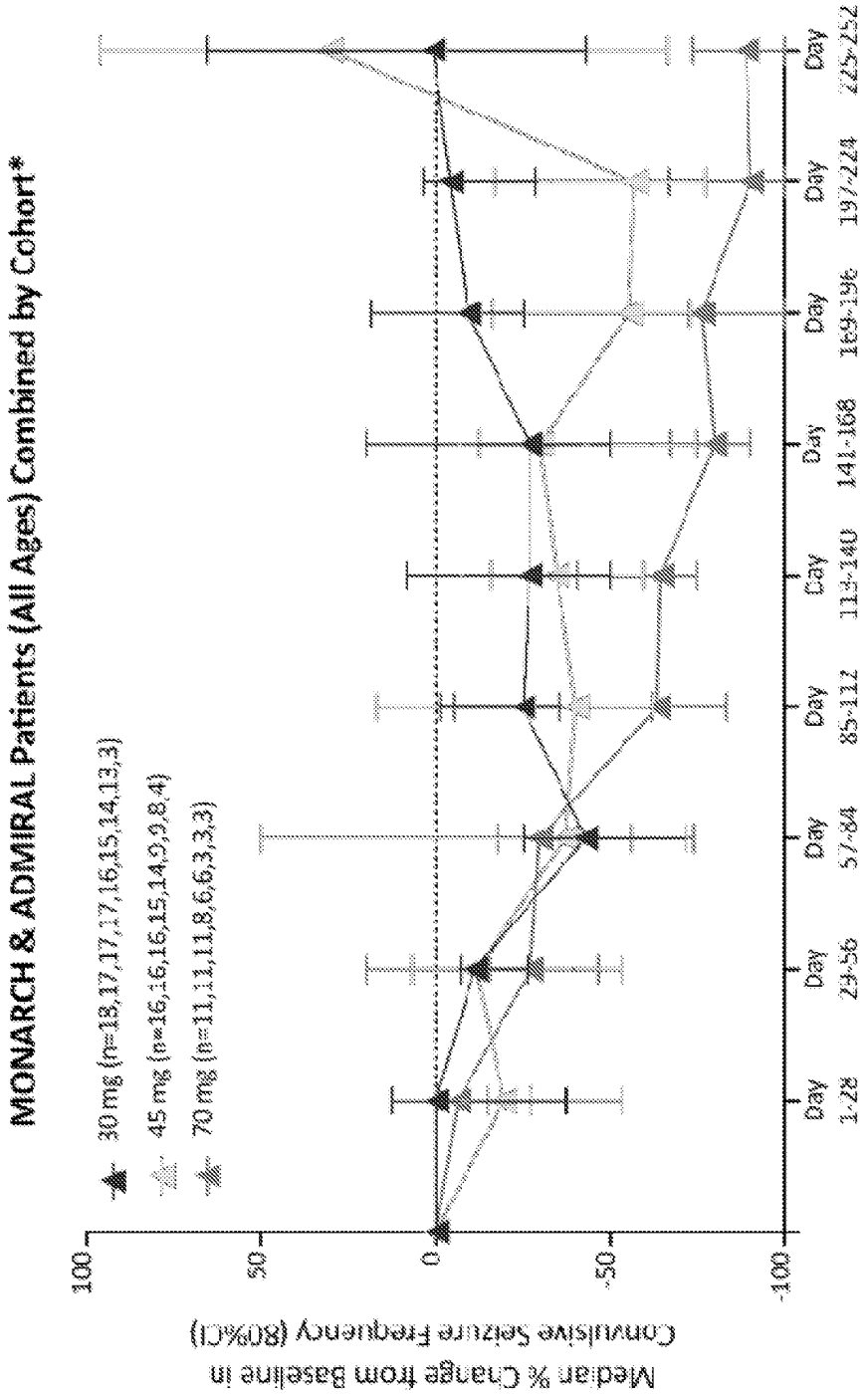
MONARCH & ADMIRAL Patients (All Ages) Combined by Cohort*
30 mg (n=18,17,17,17,16,15,14,13,3)
45 mg (n=16,16,16,15,14,9,8,4)
70 mg (n=11,11,11,8,6,3,3,3)
Median % Change from Baseline in Convulsive Seizure Frequency (80%CI)
100
50
0
-50
-100
Day 1-28
Day 29-56
Day 57-84
Day 85-112
Day 113-140
Day 141-168
Day 169-196
Day 197-224
Day 225-252

FIG. 34

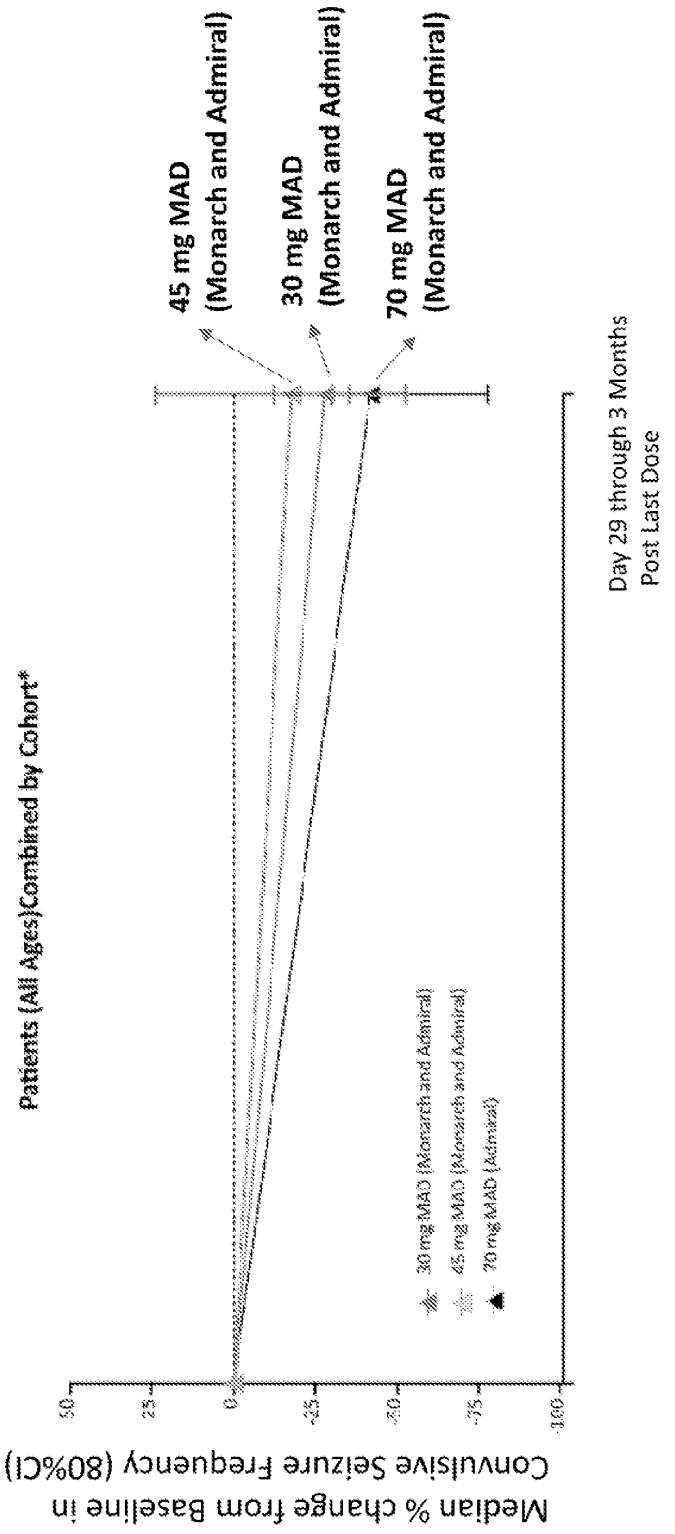
45 mg MAD
(Monarch and Admiral)
30 mg MAD
(Monarch and Admiral)
70 mg MAD
(Monarch and Admiral)
Patients (All Ages)Combined by Cohort*
Median % change from Baseline in
Convulsive Seizure Frequency (80%CI)
Day 29 through 3 Months
Post Last Dose
30 mg MAD (Monarch and Admiral)
45 mg MAD (Monarch and Admiral)
70 mg MAD (Admiral)
50
25
0
-25
-50
-75
-100

FIG. 35

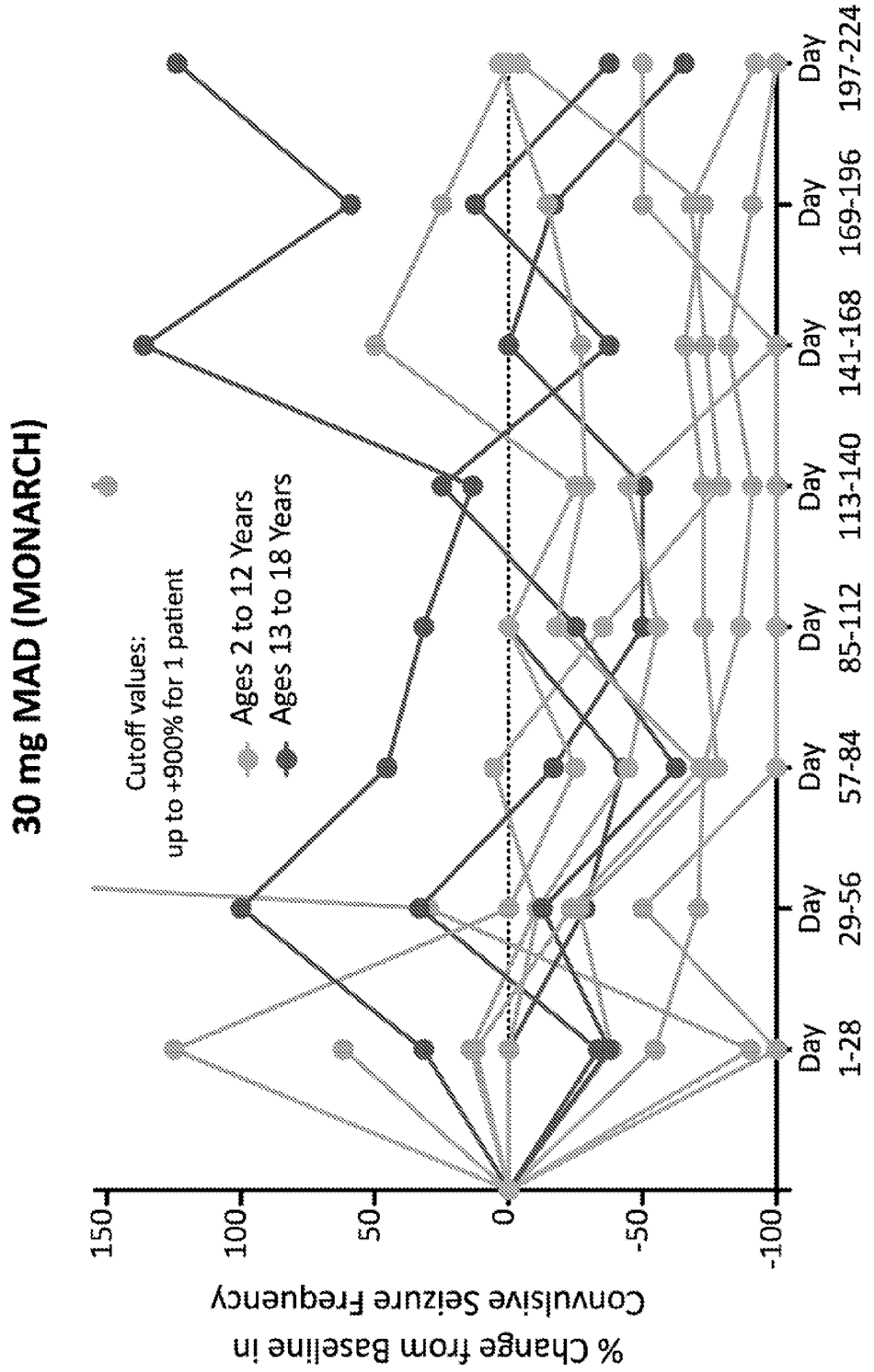
30 mg MAD (MONARCH)
Cutoff values:
up to +900% for 1 patient
Ages 2 to 12 Years
Ages 13 to 18 Years
% Change from Baseline in
Convulsive Seizure Frequency
150
100
50
0
-50
-100
Day 1-28
Day 29-56
Day 57-84
Day 85-112
Day 113-140
Day 141-168
Day 169-196
Day 197-224

FIG. 36A

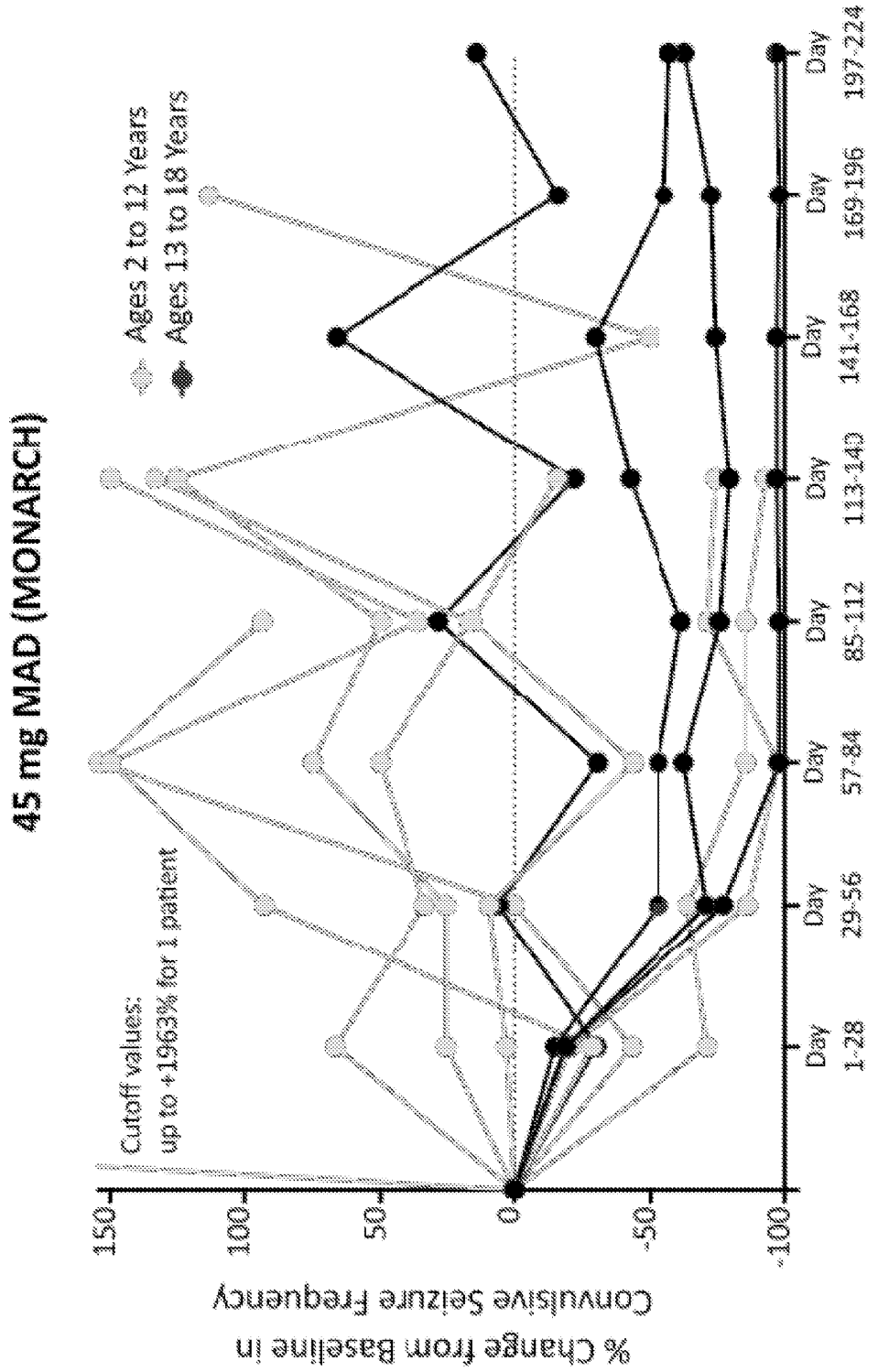
45 mg MAD (MONARCH)
Ages 2 to 12 Years
Ages 13 to 18 Years
Cutoff values:
up to +1963% for 1 patient
% Change from Baseline in
Convulsive Seizure Frequency
150
100
50
0
-50
-100
Day 1-28
Day 29-56
Day 57-84
Day 85-112
Day 113-140
Day 141-168
Day 169-196
Day 197-224

FIG. 36B

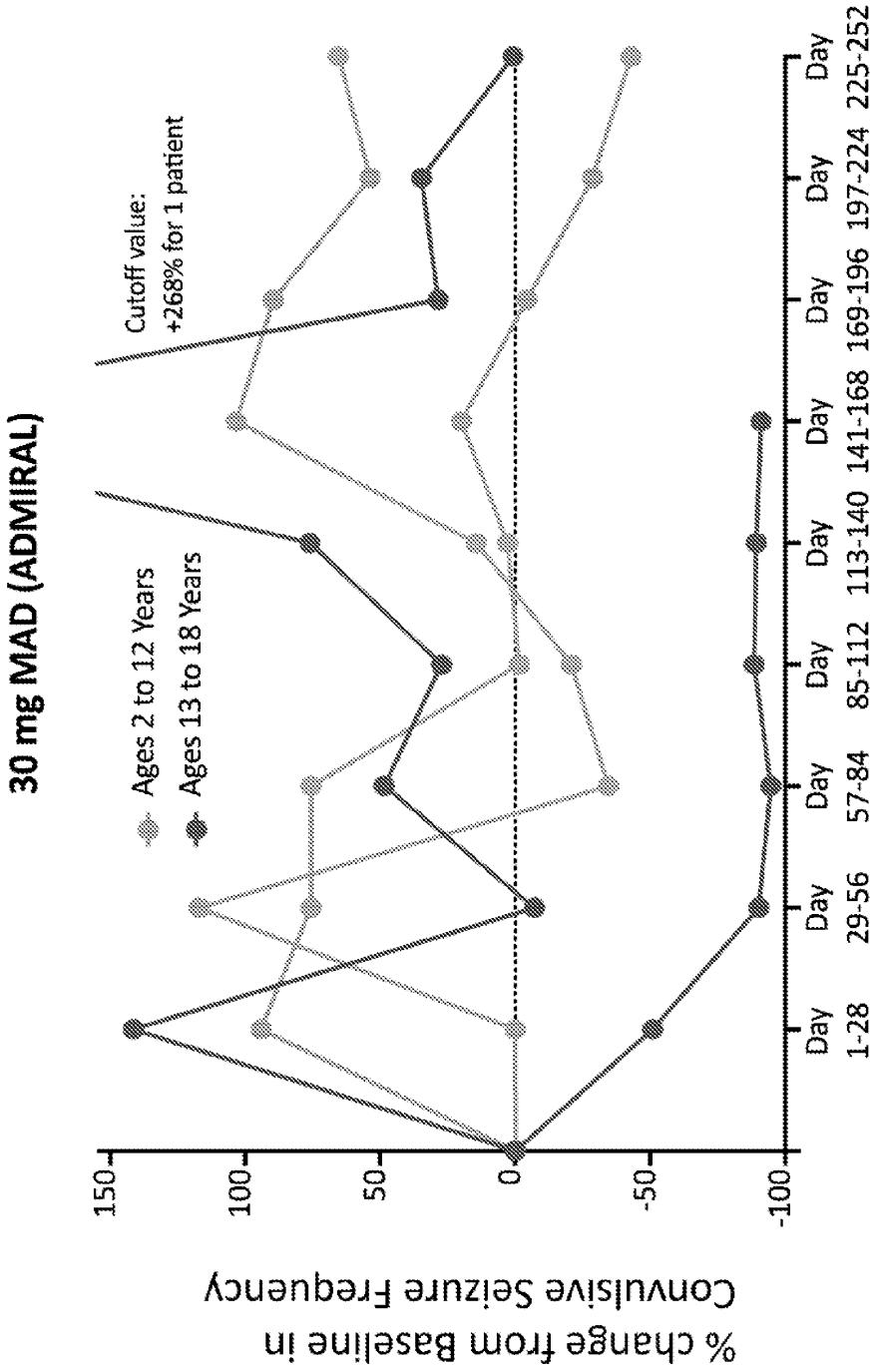
30 mg MAD (ADMIRAL)
Ages 2 to 12 Years
Ages 13 to 18 Years
Cutoff value:
+268% for 1 patient
% change from Baseline in
Convulsive Seizure Frequency
150
100
50
0
-50
-100
Day 1-28
Day 29-56
Day 57-84
Day 85-112
Day 113-140
Day 141-168
Day 169-196
Day 197-224
Day 225-252

FIG. 37A

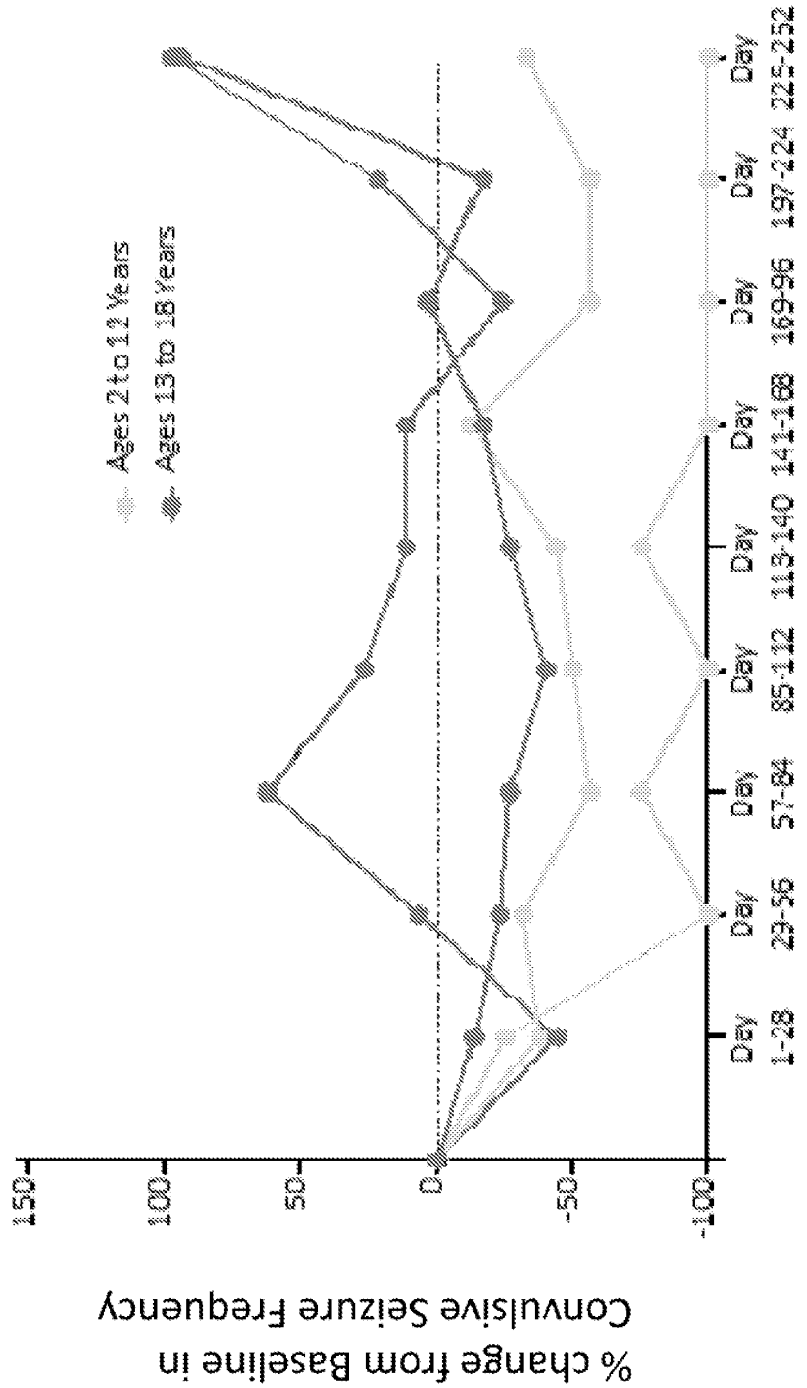
45 mg MAD (ADMIRAL)
Ages 2 to 12 Years
Ages 13 to 18 Years
% change from Baseline in
Convulsive Seizure Frequency
150
100
50
0
-50
-100
Day 1-28
Day 29-56
Day 57-84
Day 85-112
Day 113-140
Day 141-168
Day 169-96
Day 197-224
Day 225-252

FIG. 37B

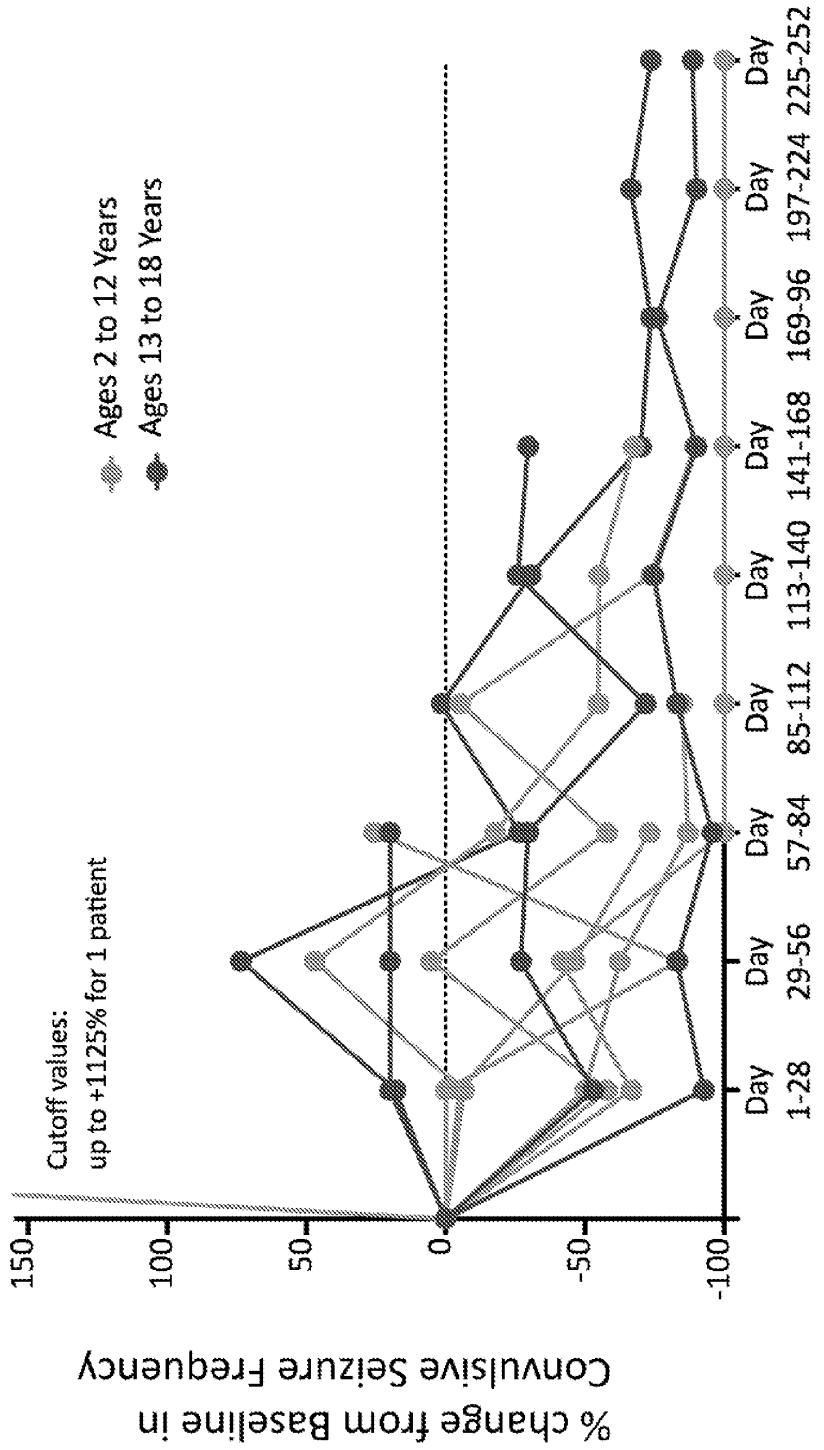
70 mg MAD (ADMIRAL)
Ages 2 to 12 Years
Ages 13 to 18 Years
Cutoff values:
up to +1125% for 1 patient
% change from Baseline in
Convulsive Seizure Frequency
150
100
50
0
-50
-100
Day 1-28
Day 29-56
Day 57-84
Day 85-112
Day 113-140
Day 141-168
Day 169-96
Day 197-224
Day 225-252

FIG. 37C

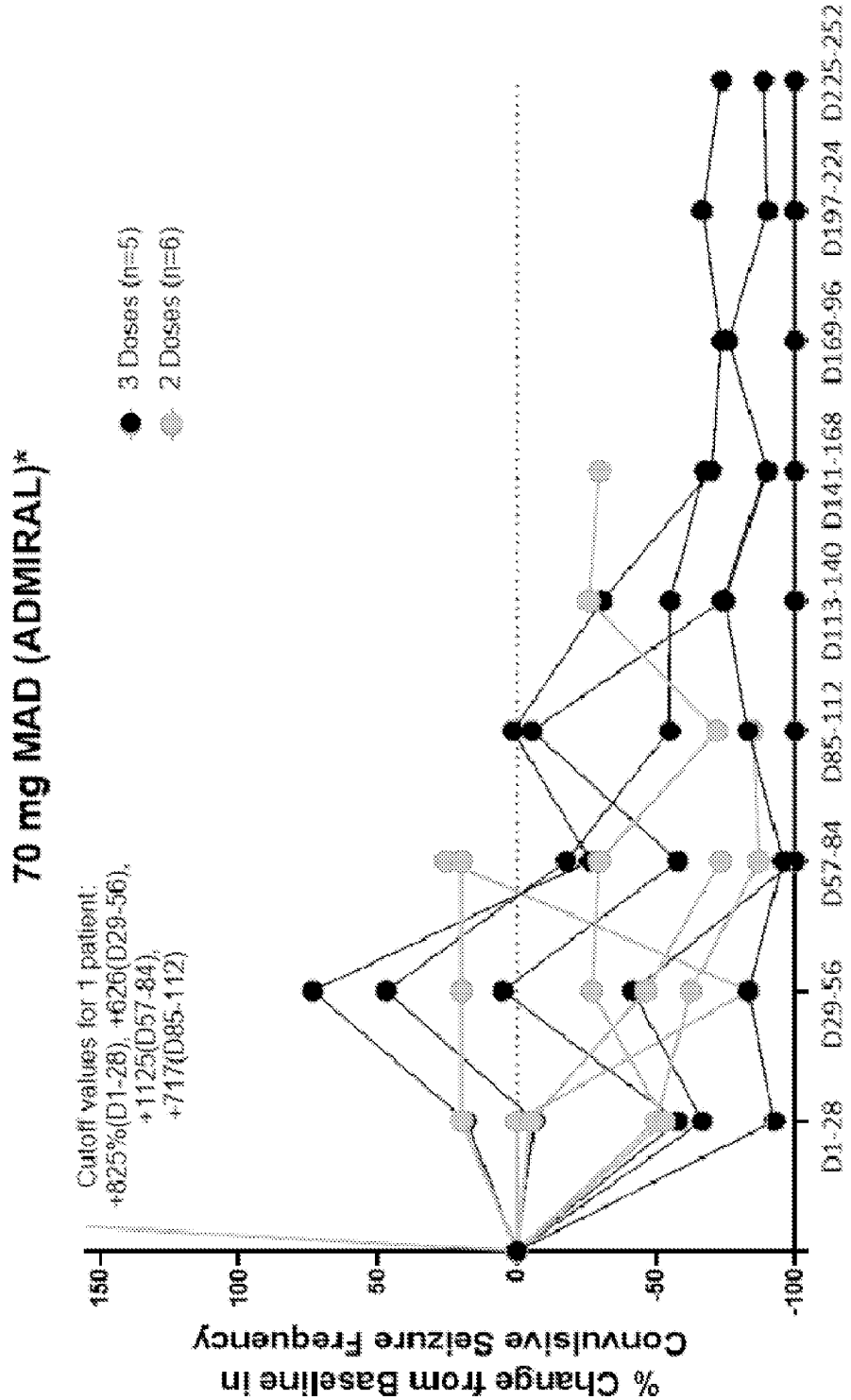
70 mg MAD (ADMIRAL)*
3 Doses (n=5)
2 Doses (n=6)
Cutoff values for 1 patient:
+825%(D1-28), +626(D29-56),
+1125(D57-84),
+717(D85-112)
% Change from Baseline in
Convulsive Seizure Frequency
150
100
50
0
-50
-100
D1-28
D29-56
D57-84
D85-112
D113-140
D141-168
D169-96
D197-224
D225-252

FIG. 38

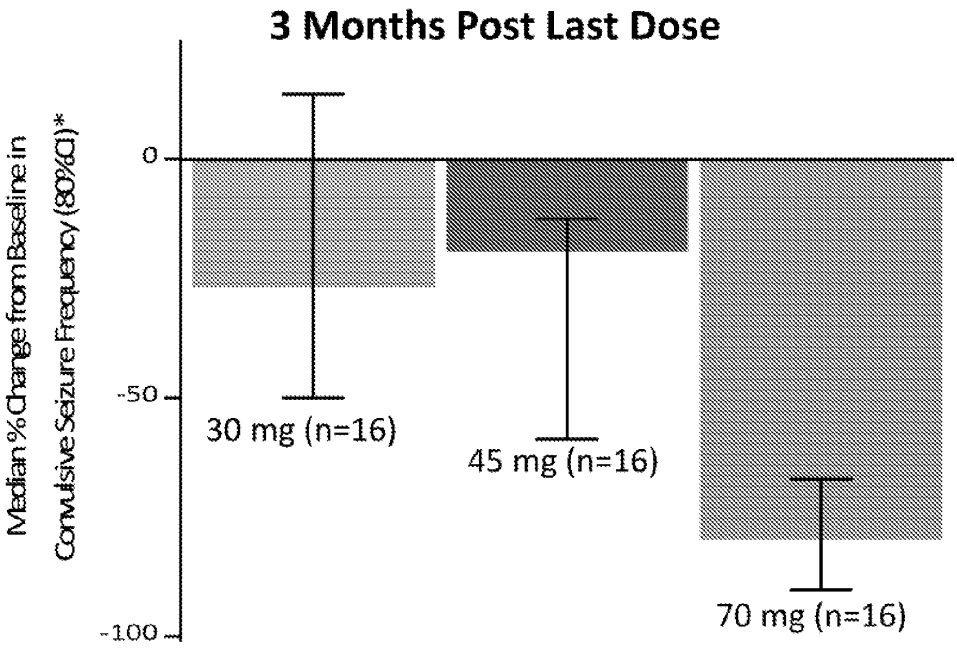

FIG. 39A

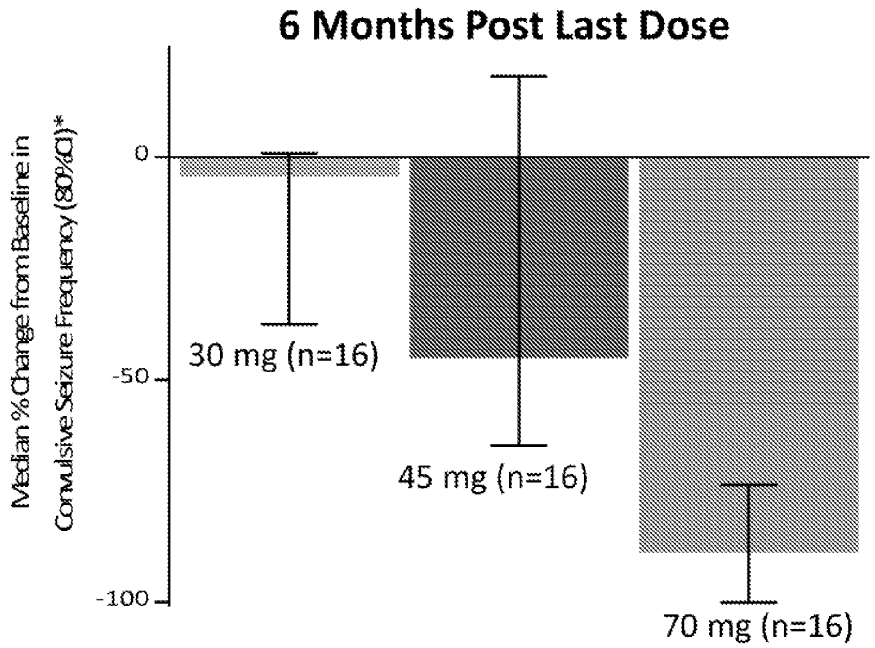

FIG. 39B

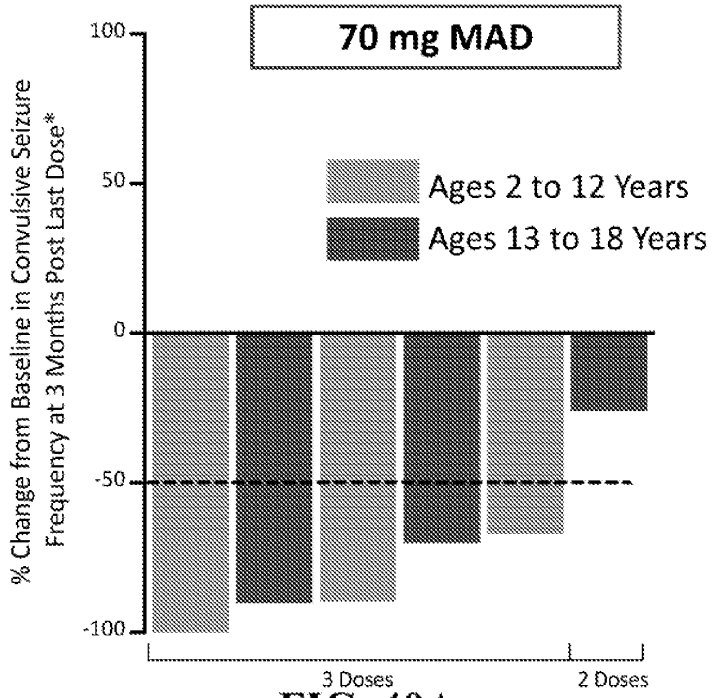

FIG. 40A

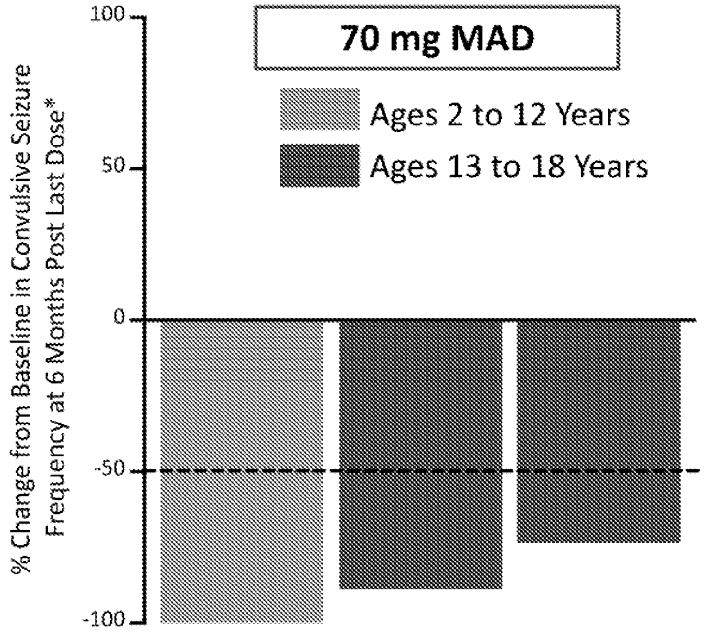

FIG. 40B

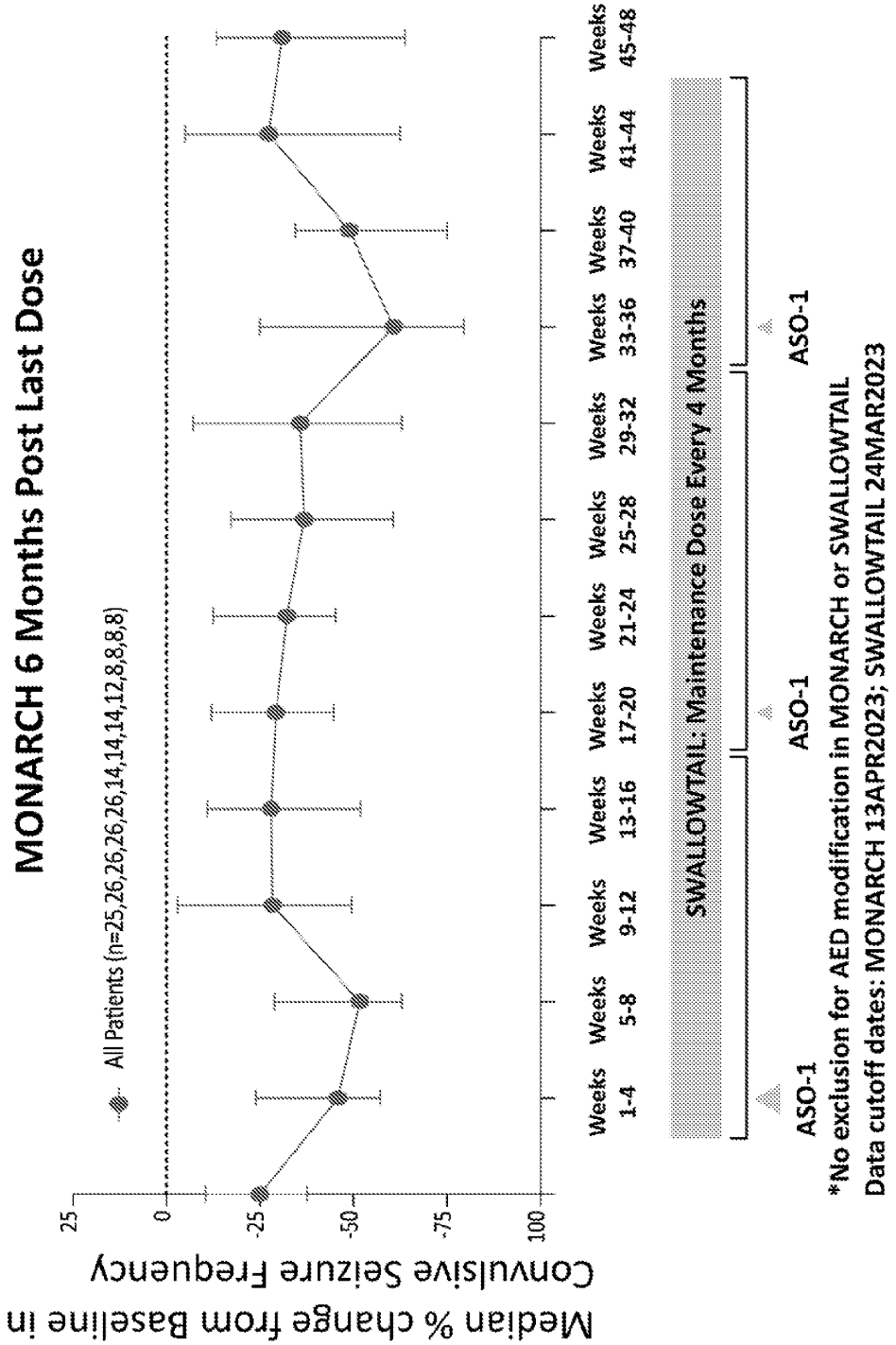
MONARCH 6 Months Post Last Dose
All Patients (n=25,26,26,26,26,14,14,14,12,8,8,8,8)
Median % change from Baseline in Convulsive Seizure Frequency
25
0
-25
-50
-75
100
Weeks 1-4
Weeks 5-8
Weeks 9-12
Weeks 13-16
Weeks 17-20
Weeks 21-24
Weeks 25-28
Weeks 29-32
Weeks 33-36
Weeks 37-40
Weeks 41-44
Weeks 45-48
SWALLOWTAIL: Maintenance Dose Every 4 Months
ASO-1
ASO-1
ASO-1
*No exclusion for AED modification in MONARCH or SWALLOWTAIL
Data cutoff dates: MONARCH 13APR2023; SWALLOWTAIL 24MAR2023

FIG. 41

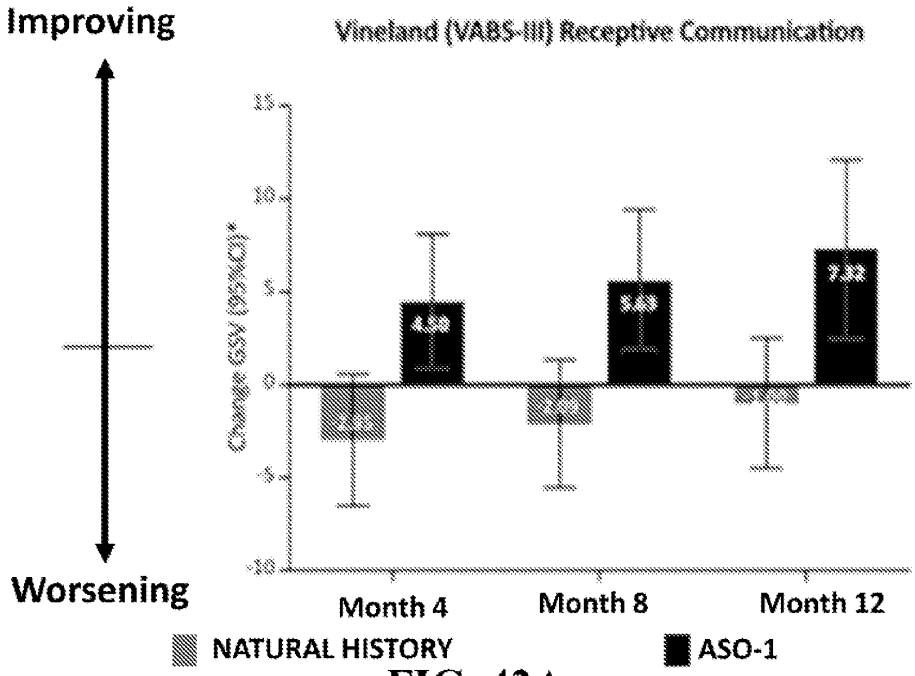

FIG. 42A

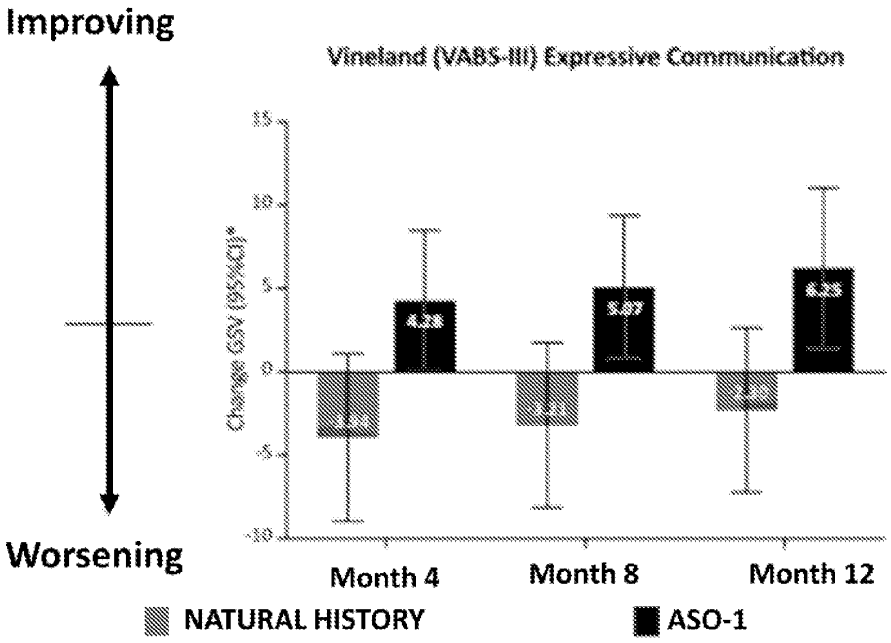

FIG. 42B

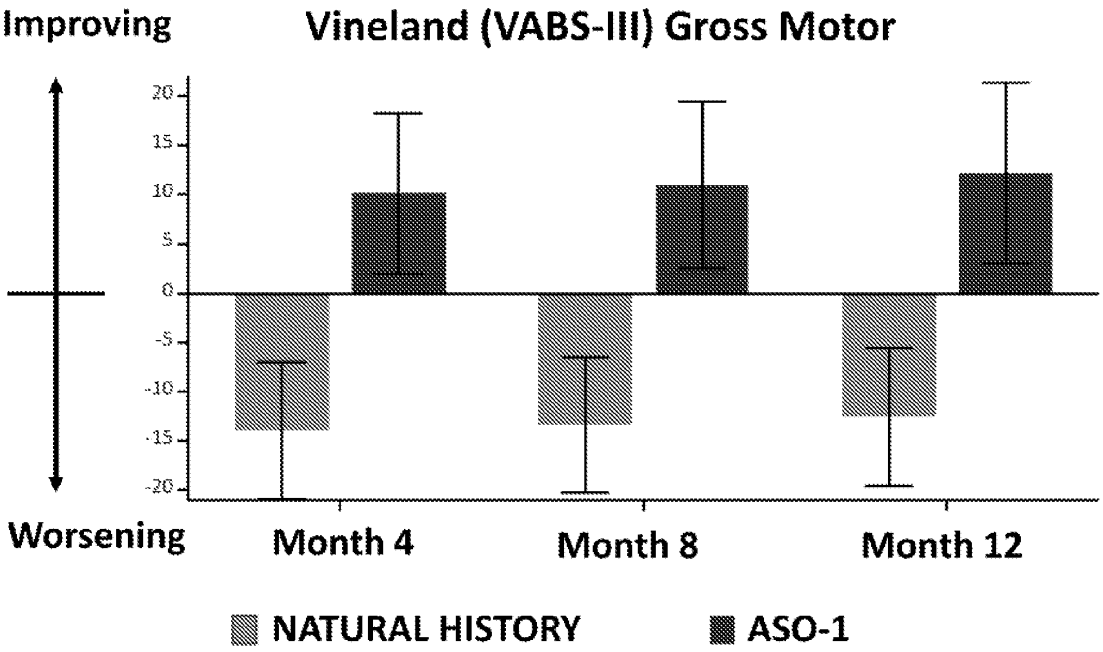
Improving
Vineland (VABS-III) Gross Motor
20
15
10
5
0
-5
-10
-15
-20
Worsening
Month 4
Month 8
Month 12
NATURAL HISTORY
ASO-1

FIG. 43

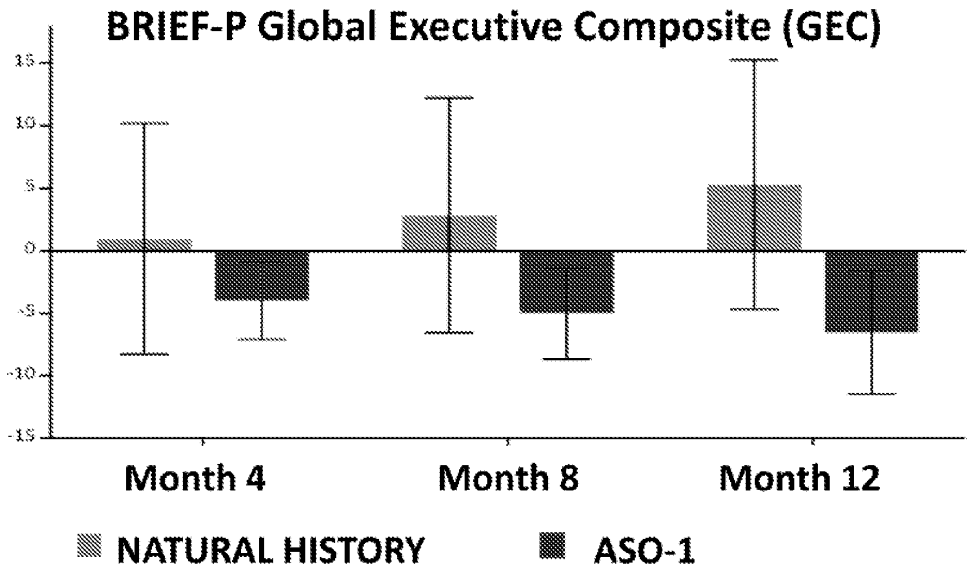
BRIEF-P Global Executive Composite (GEC)
15
10
5
0
-5
-10
-15
Month 4
Month 8
Month 12
NATURAL HISTORY
ASO-1

FIG. 44

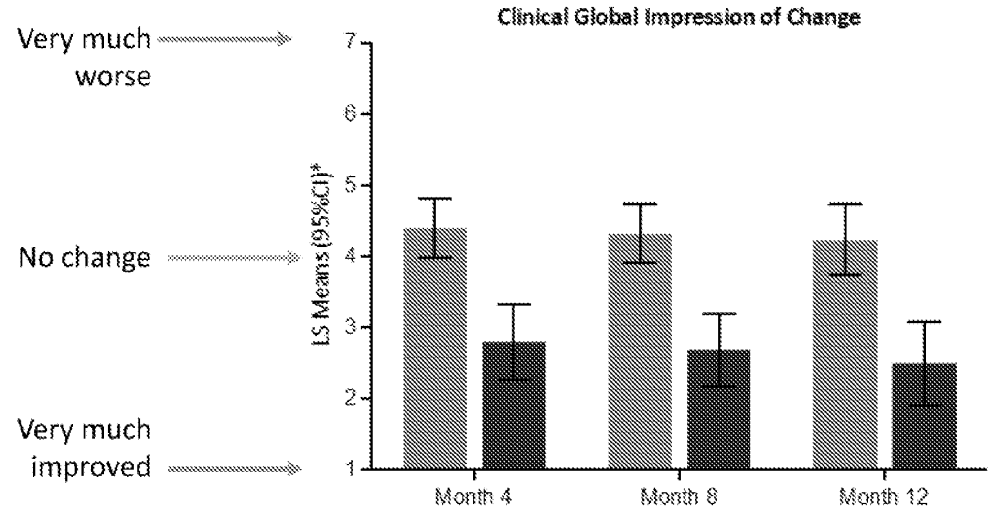

FIG. 45A

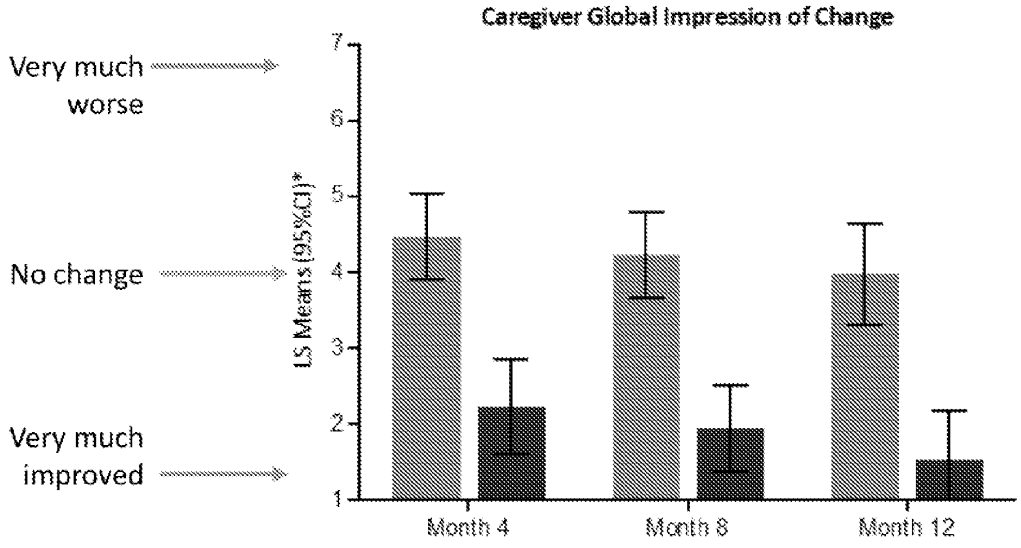

FIG. 45B

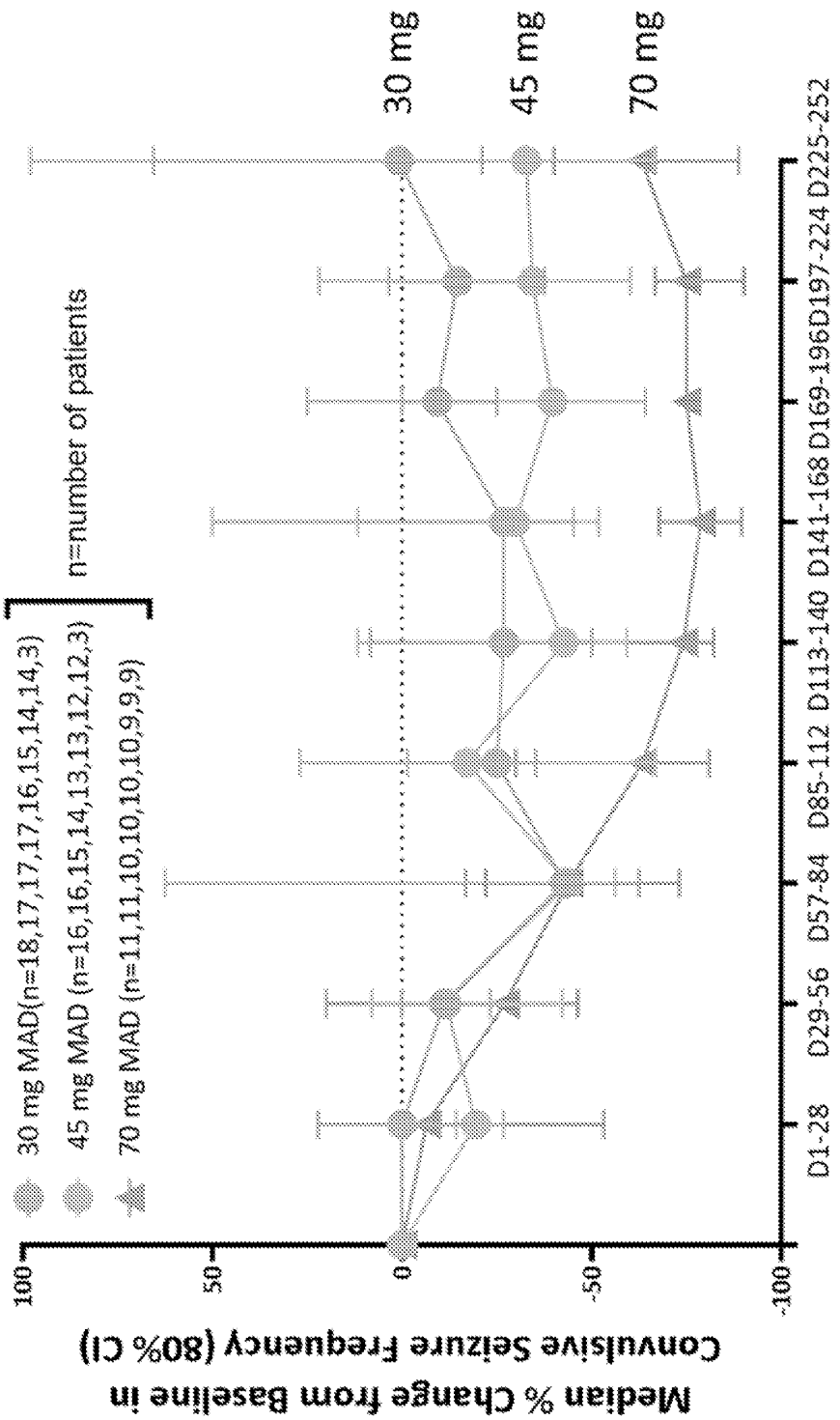
Median % Change from Baseline in Convulsive Seizure Frequency (80% CI)
100
50
0
-50
-100
30 mg
45 mg
70 mg
D1-28
D29-56
D57-84
D85-112
D113-140
D141-168
D169-196
D197-224
D225-252
30 mg MAD(n=18,17,17,17,16,15,14,14,3)
45 mg MAD (n=16,16,15,14,13,13,12,12,3)
70 mg MAD (n=11,11,10,10,10,10,9,9,9)
n=number of patients

FIG. 46

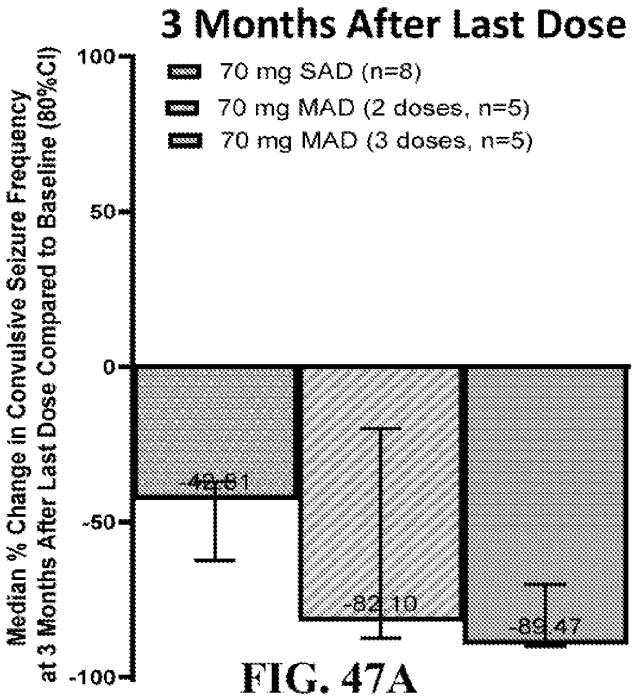

FIG. 47A

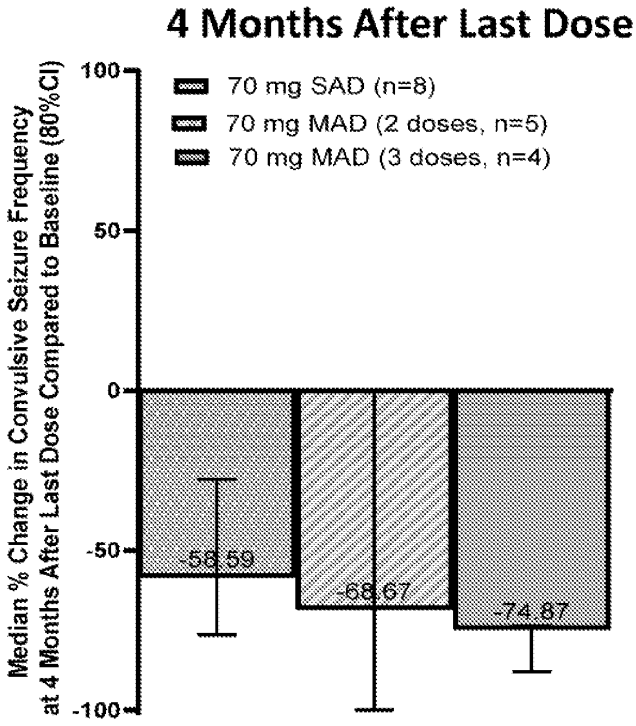

FIG. 47B

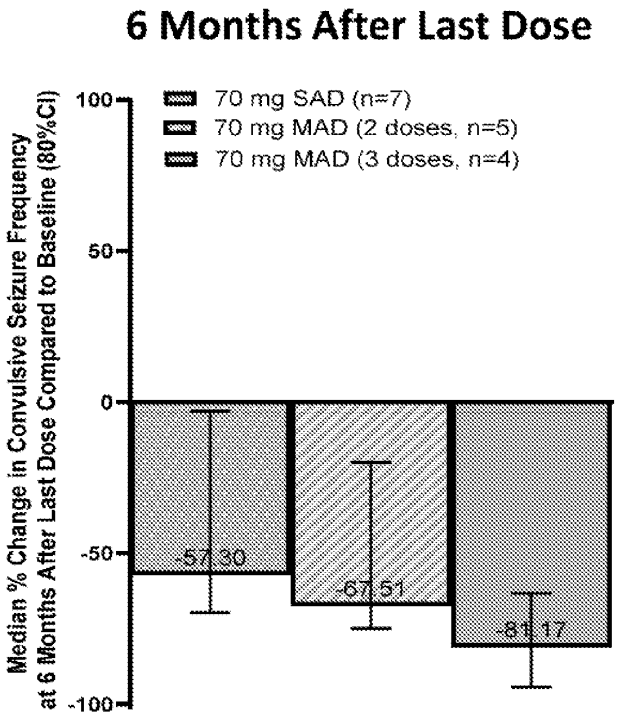
6 Months After Last Dose
70 mg SAD (n=7)
70 mg MAD (2 doses, n=5)
70 mg MAD (3 doses, n=4)
Median % Change in Convulsive Seizure Frequency at 6 Months After Last Dose Compared to Baseline (80%CI)
100
50
0
-50
-100
-57.30
-67.51
-81.17

FIG. 47C

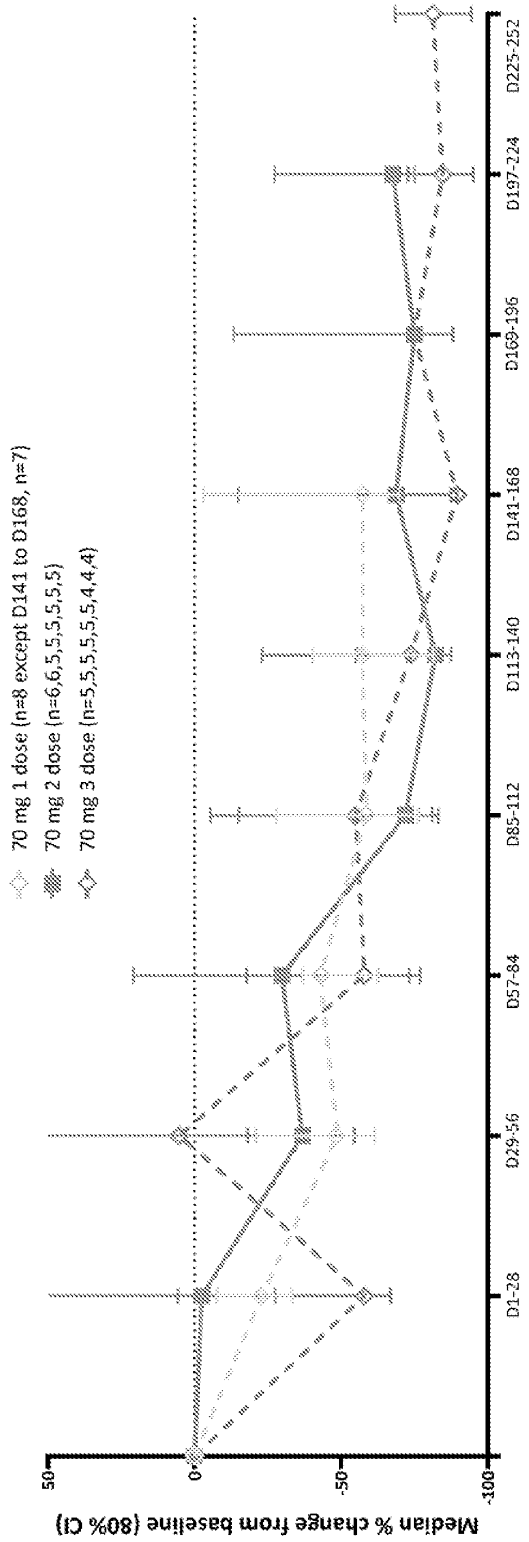
70 mg 1 dose (n=8 except D141 to D168, n=7)
70 mg 2 dose (n=6,6,5,5,5,5,5,5)
70 mg 3 dose (n=5,5,5,5,5,5,4,4,4)
Median % change from baseline (80% CI)
50
0
-50
-100
D1-28
D29-56
D57-84
D85-112
D113-140
D141-168
D169-196
D197-224
D225-252

FIG. 47D

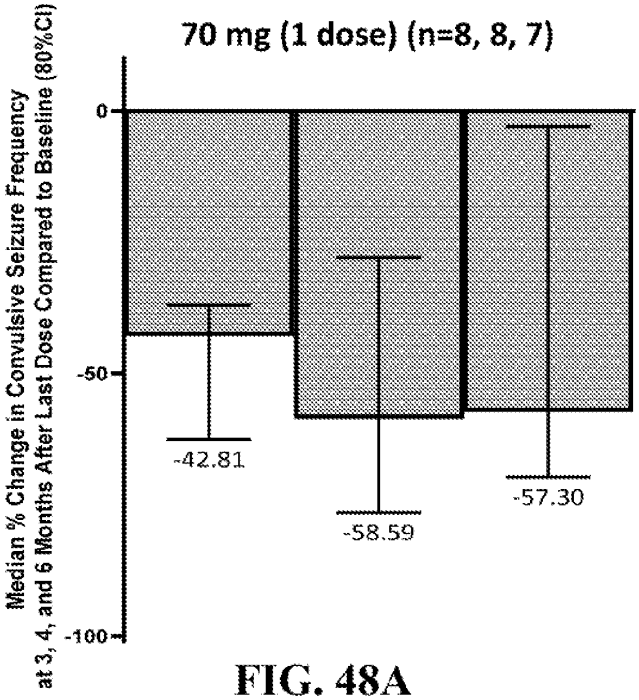

FIG. 48A

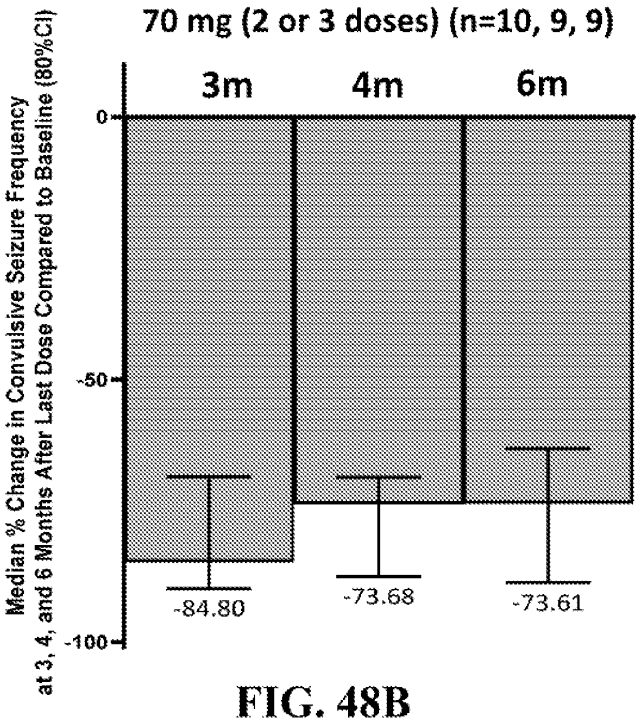

FIG. 48B

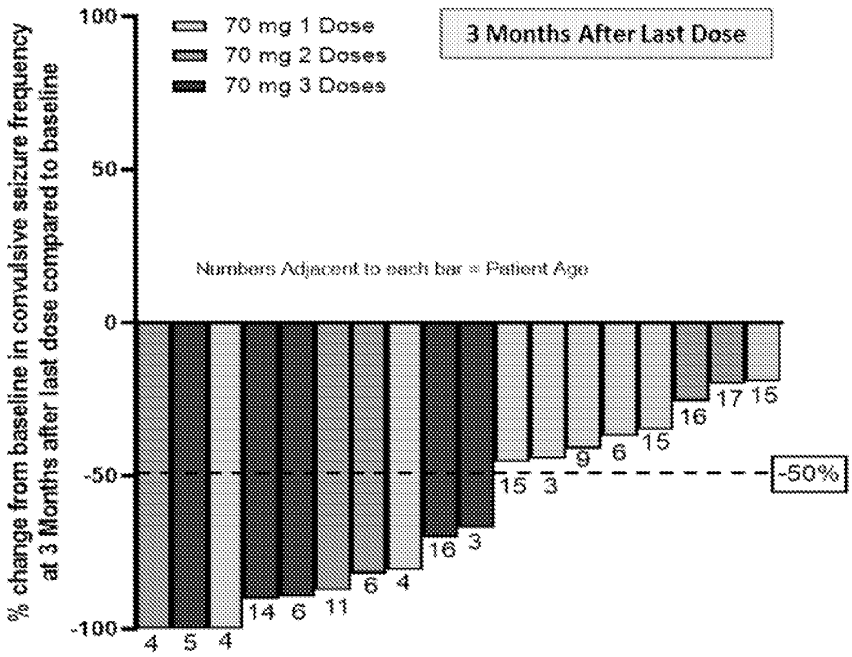

FIG. 49A

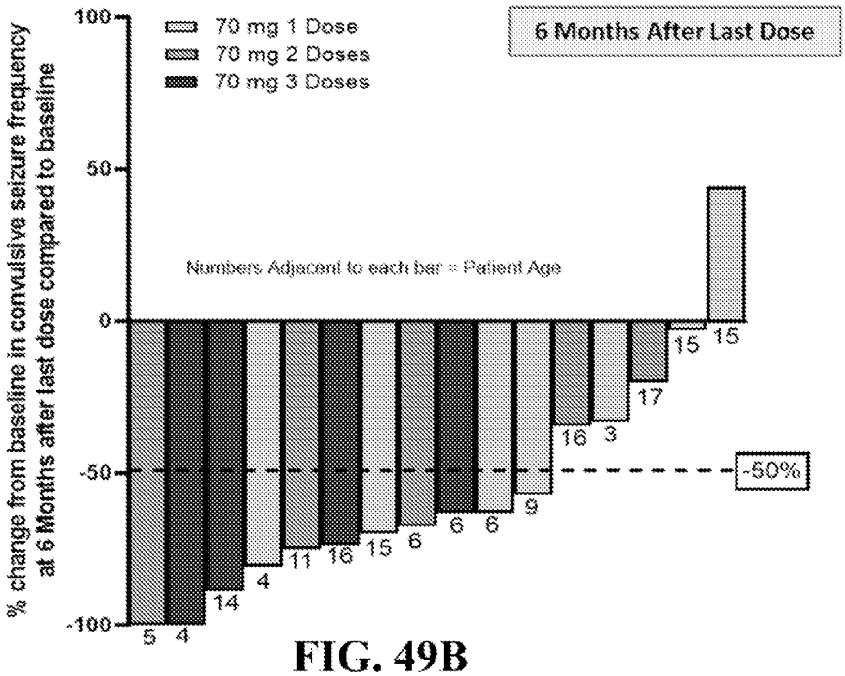

FIG. 49B

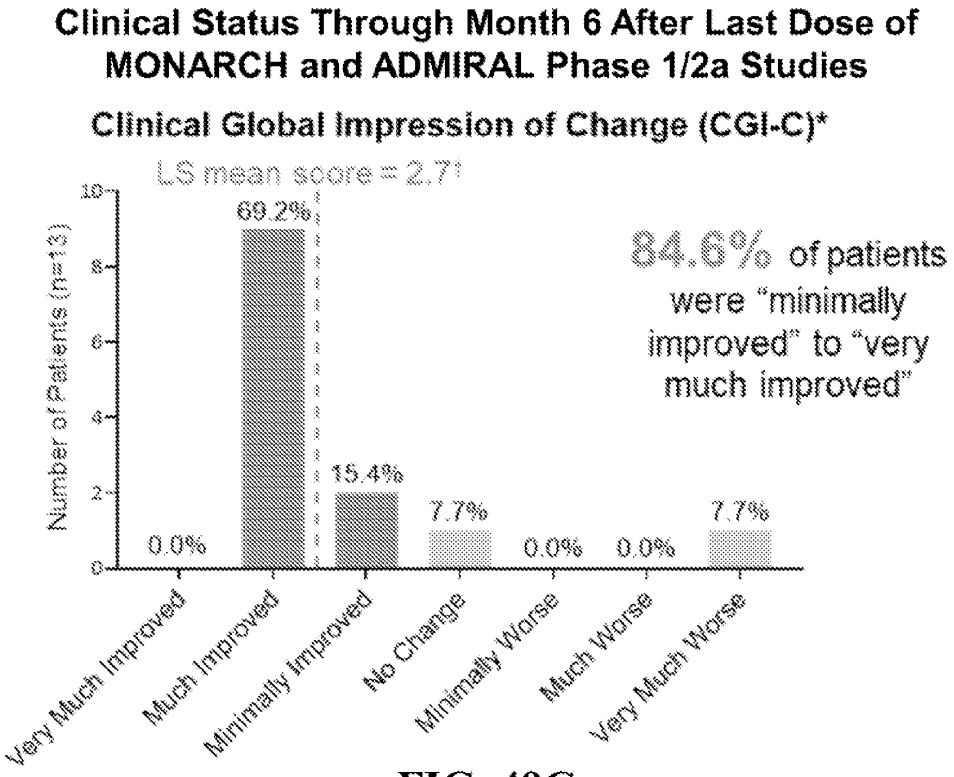

FIG. 49C

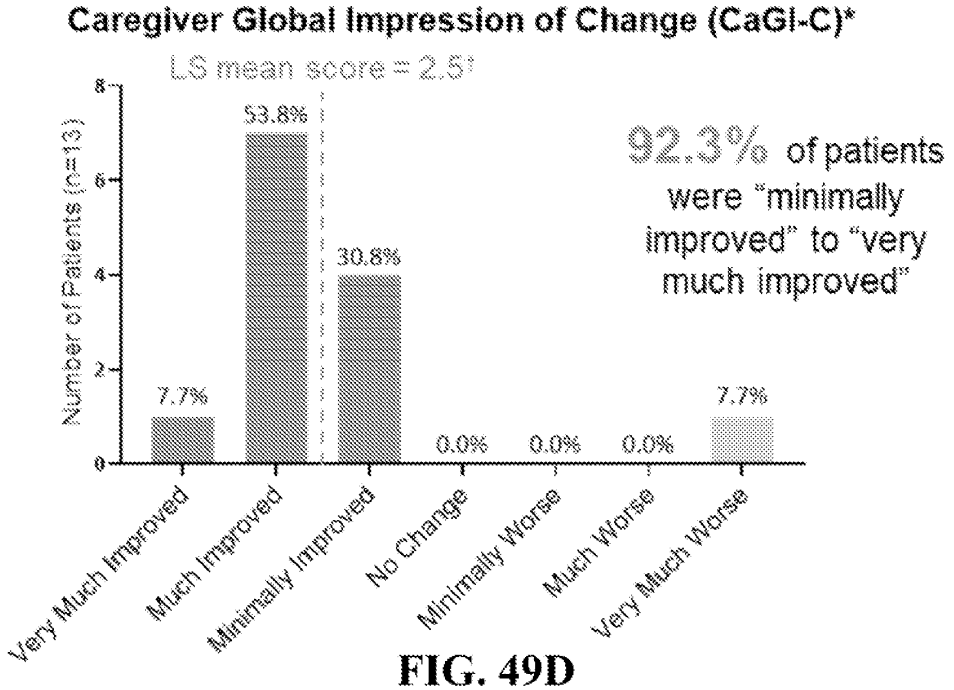

FIG. 49D

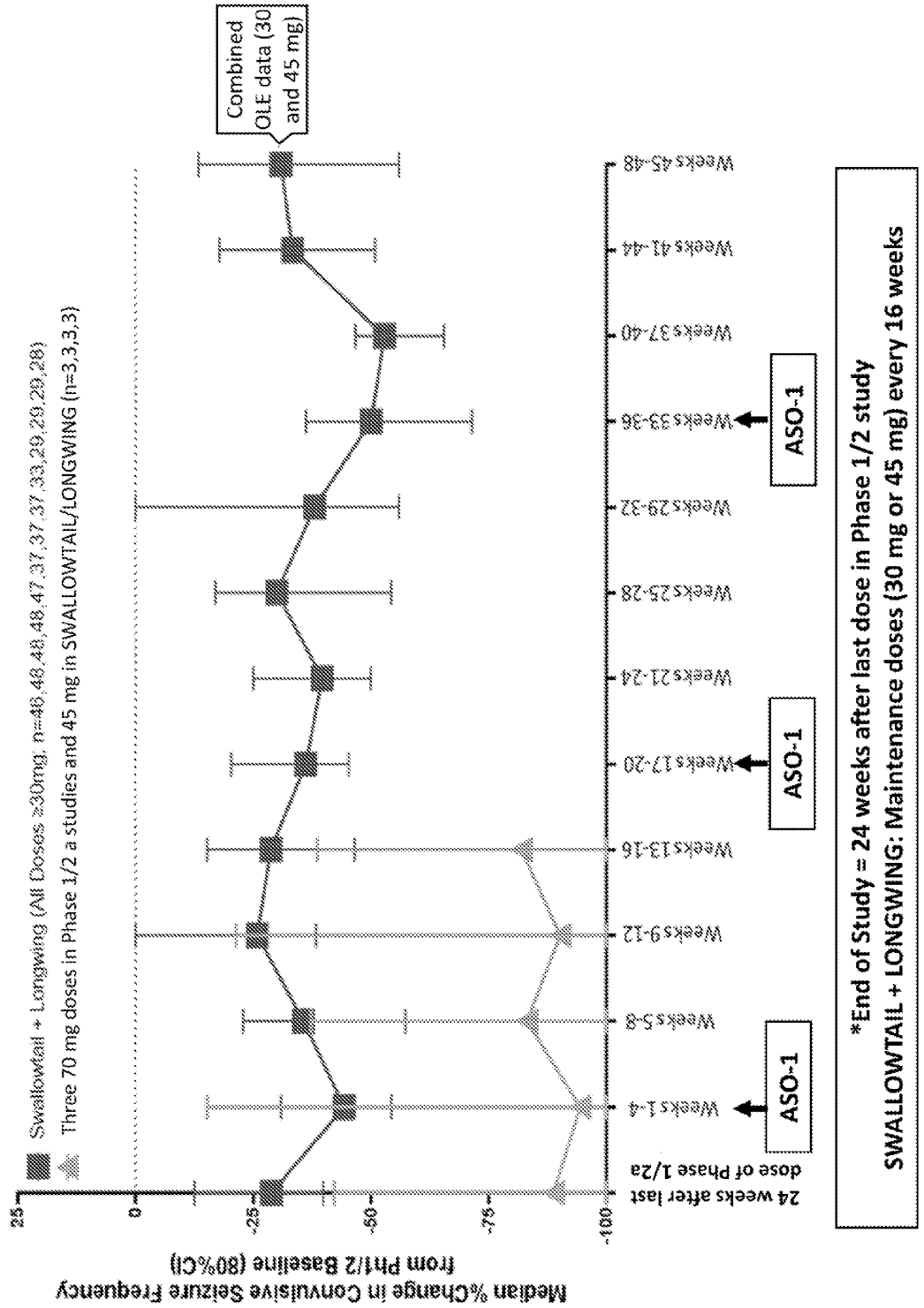
Median %Change in Convulsive Seizure Frequency from Ph1/2 Baseline (80%CI)
25
0
-25
-50
-75
-100
Swallowtail + Longwing (All Doses ≥30mg; n=46,48,48,47,37,37,33,29,29,28)
Three 70 mg doses in Phase 1/2 a studies and 45 mg in SWALLOWTAIL/LONGWING (n=3,3,3)
Combined OLE data (30 and 45 mg)
24 weeks after last dose of Phase 1/2a
Weeks 1-4
Weeks 5-8
Weeks 9-12
Weeks 13-16
Weeks 17-20
Weeks 21-24
Weeks 25-28
Weeks 29-32
Weeks 33-36
Weeks 37-40
Weeks 41-44
Weeks 45-48
ASO-1
ASO-1
ASO-1
*End of Study = 24 weeks after last dose in Phase 1/2 study
SWALLOWTAIL + LONGWING: Maintenance doses (30 mg or 45 mg) every 16 weeks

FIG. 50A

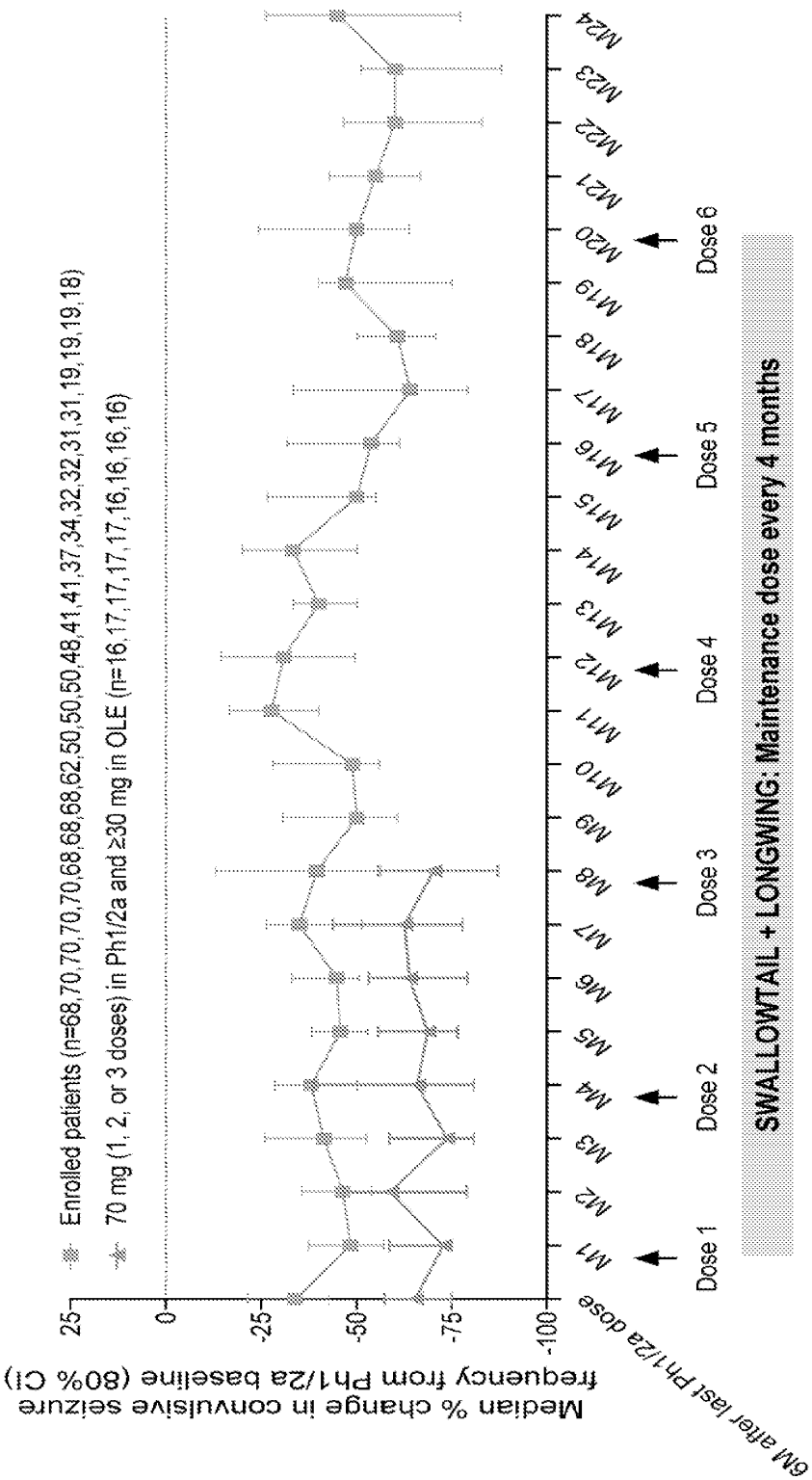
Median % change in convulsive seizure frequency from Ph1/2a baseline (80% CI)
25
0
-25
-50
-75
-100
Enrolled patients (n=68,70,70,70,70,68,68,68,62,50,50,50,48,41,41,37,34,32,32,31,31,19,19,19,18)
70 mg (1, 2, or 3 doses) in Ph1/2a and ≥30 mg in OLE (n=16,17,17,17,17,16,16,16,16)
6M after last Ph1/2a dose
M1
M2
M3
M4
M5
M6
M7
M8
M9
M10
M11
M12
M13
M14
M15
M16
M17
M18
M19
M20
M21
M22
M23
M24
Dose 1
Dose 2
Dose 3
Dose 4
Dose 5
Dose 6
SWALLOWTAIL + LONGWING: Maintenance dose every 4 months

FIG. 50B

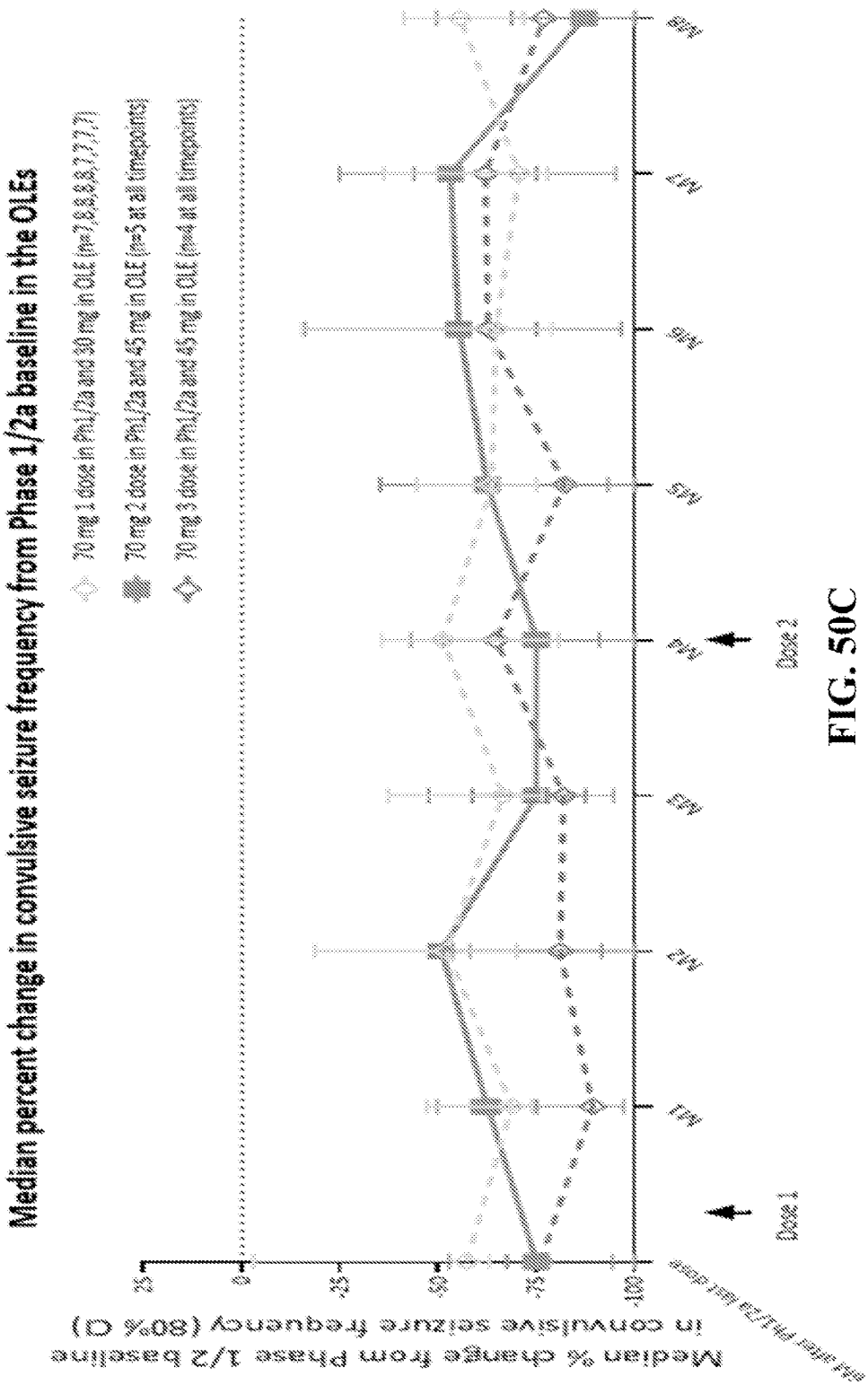
Median percent change in convulsive seizure frequency from Phase 1/2a baseline in the OLEs
70 mg 1 dose in Ph1/2a and 30 mg in OLE (n=7,8,8,8,8,7,7,7,7)
70 mg 2 dose in Ph1/2a and 45 mg in OLE (n=5 at all timepoints)
70 mg 3 dose in Ph1/2a and 45 mg in OLE (n=4 at all timepoints)
Median % change from Phase 1/2 baseline in convulsive seizure frequency (80% CI)
25
0
-25
-50
-75
-100
M1
M2
M3
M4
M5
M6
M7
M8
Dose 1
Dose 2

FIG. 50C

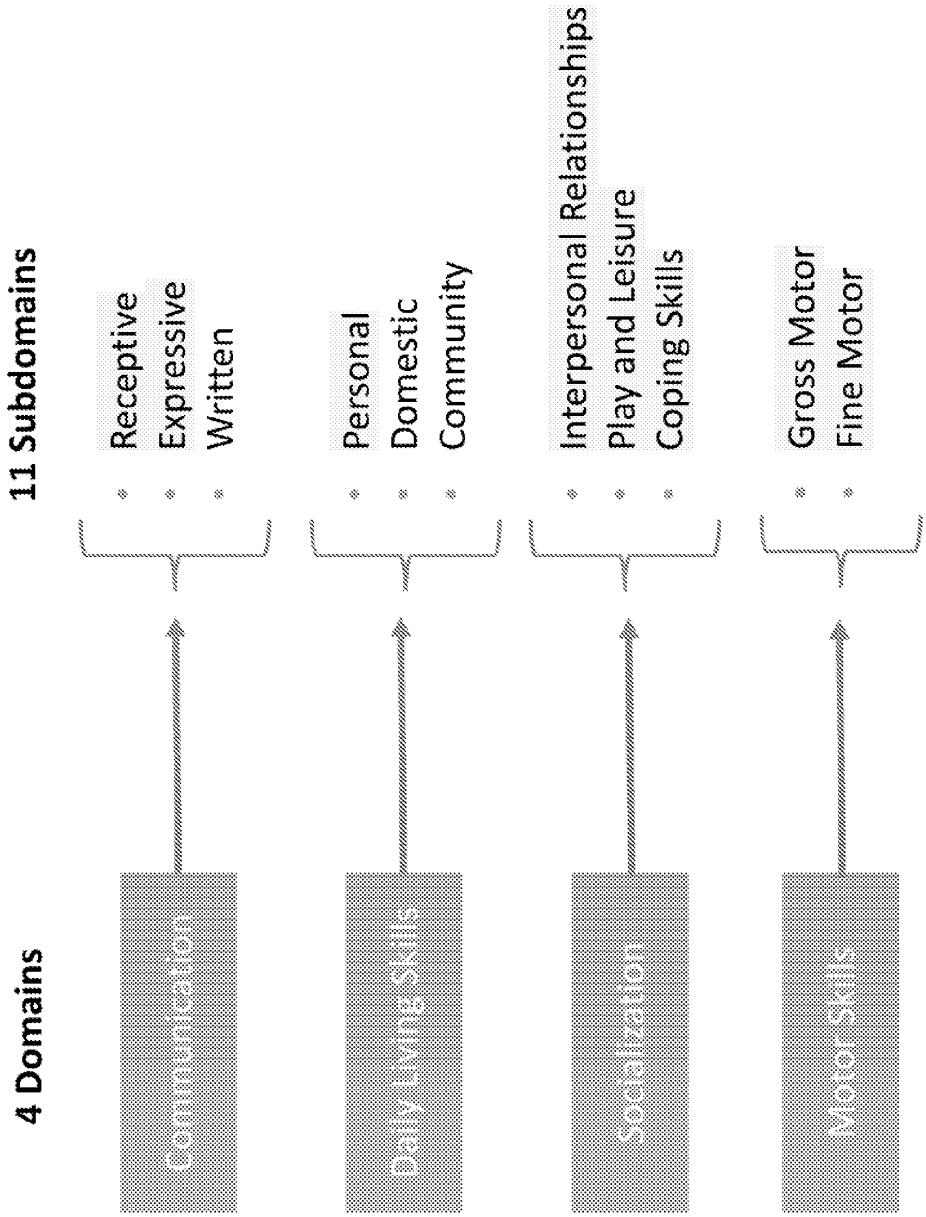
4 Domains
11 Subdomains
Communication
Receptive
Expressive
Written
Daily Living Skills
Personal
Domestic
Community
Socialization
Interpersonal Relationships
Play and Leisure
Coping Skills
Motor Skills
Gross Motor
Fine Motor

FIG. 51

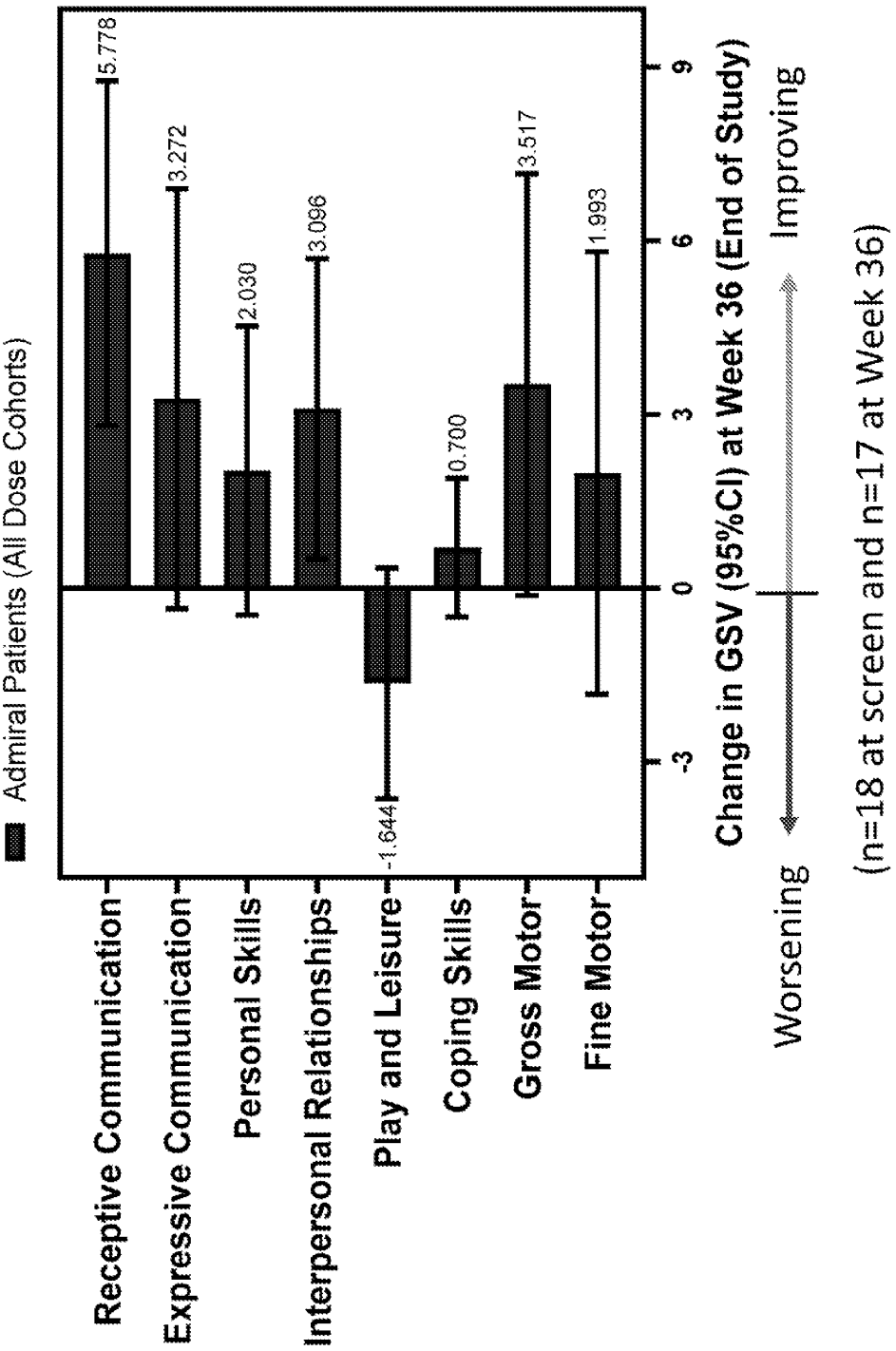
Admiral Patients (All Dose Cohorts)
Receptive Communication
Expressive Communication
Personal Skills
Interpersonal Relationships
Play and Leisure
Coping Skills
Gross Motor
Fine Motor
5.778
3.272
2.030
3.096
-1.644
0.700
3.517
1.993
-3
0
3
6
9
Change in GSV (95%CI) at Week 36 (End of Study)
Worsening
Improving
(n=18 at screen and n=17 at Week 36)

FIG. 52

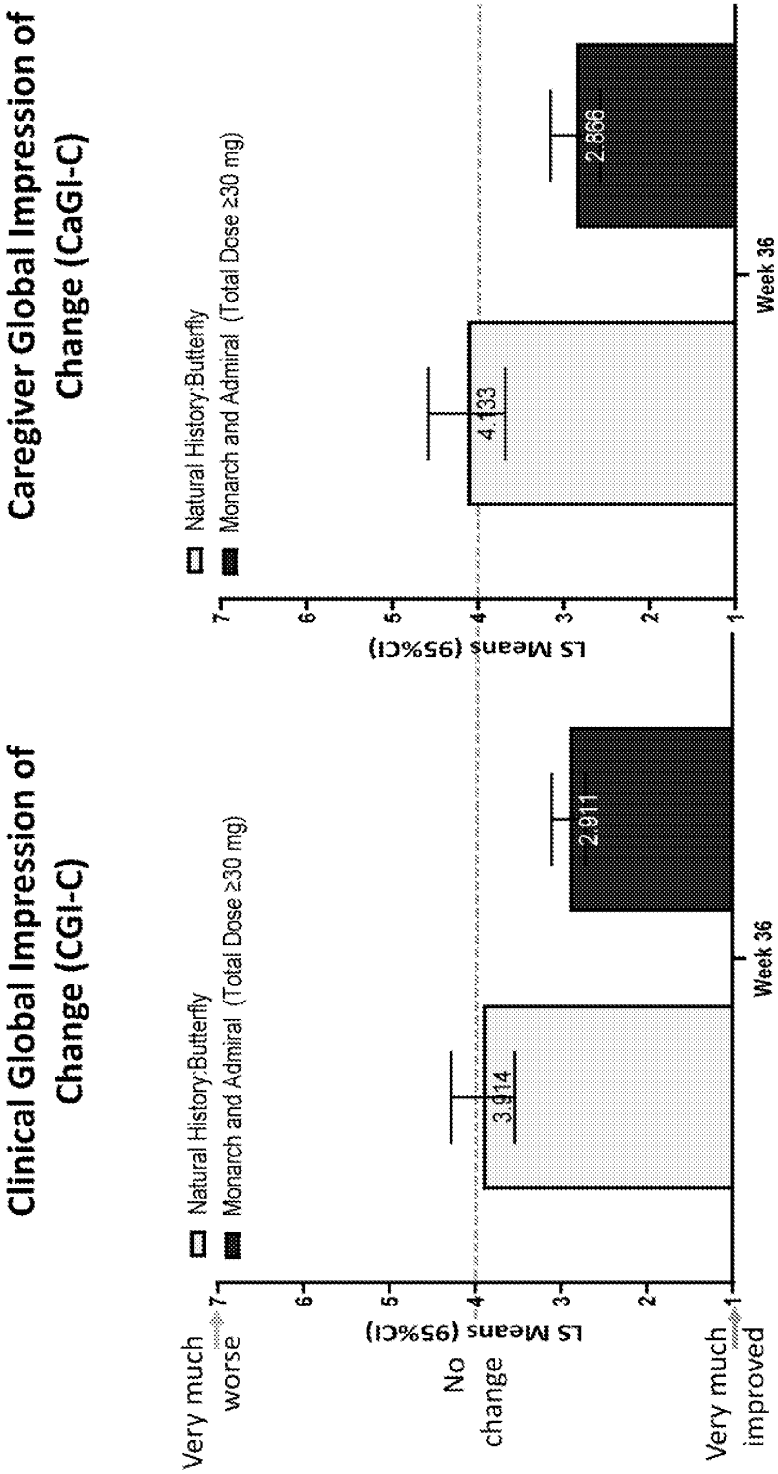

FIG. 53A

FIG. 53B

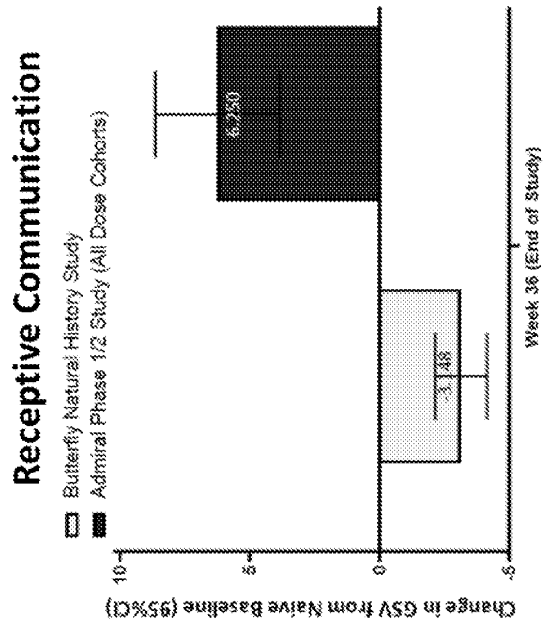

FIG. 54B

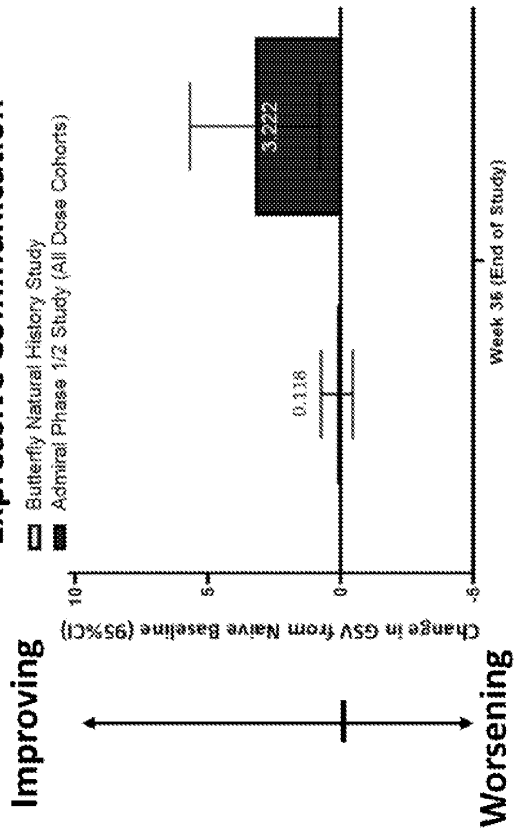

FIG. 54A

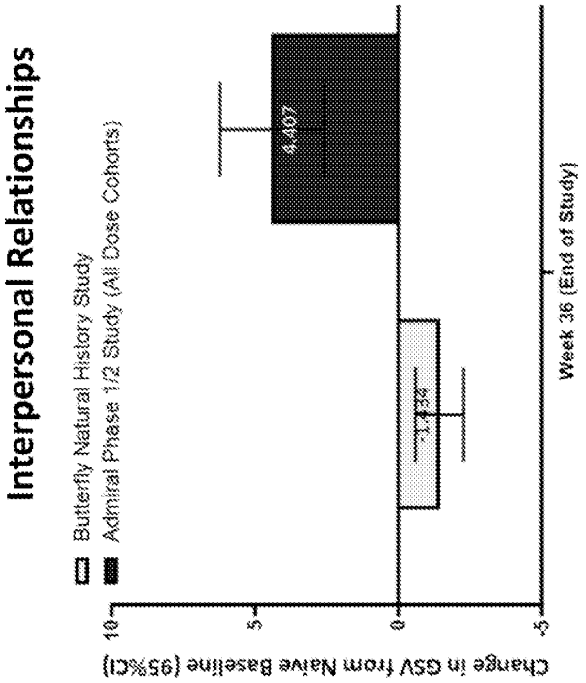

FIG. 55B

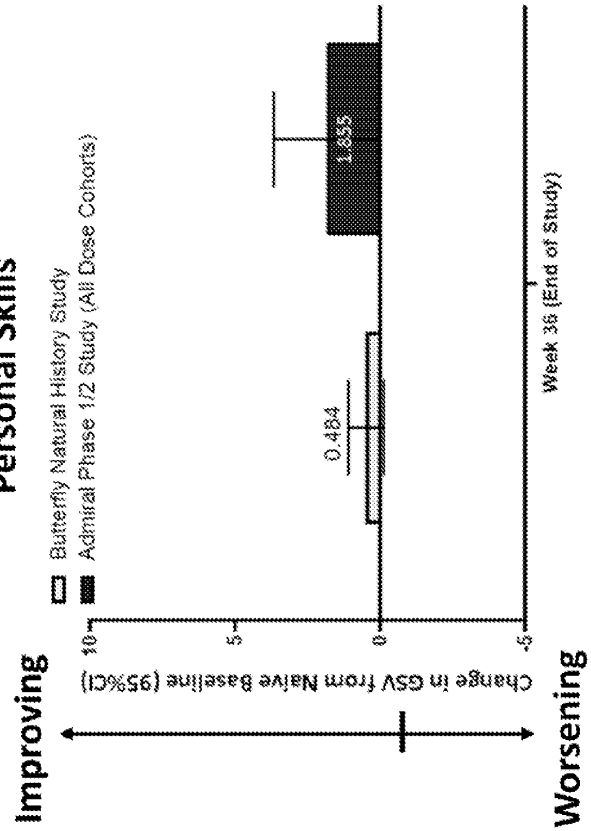

FIG. 55A

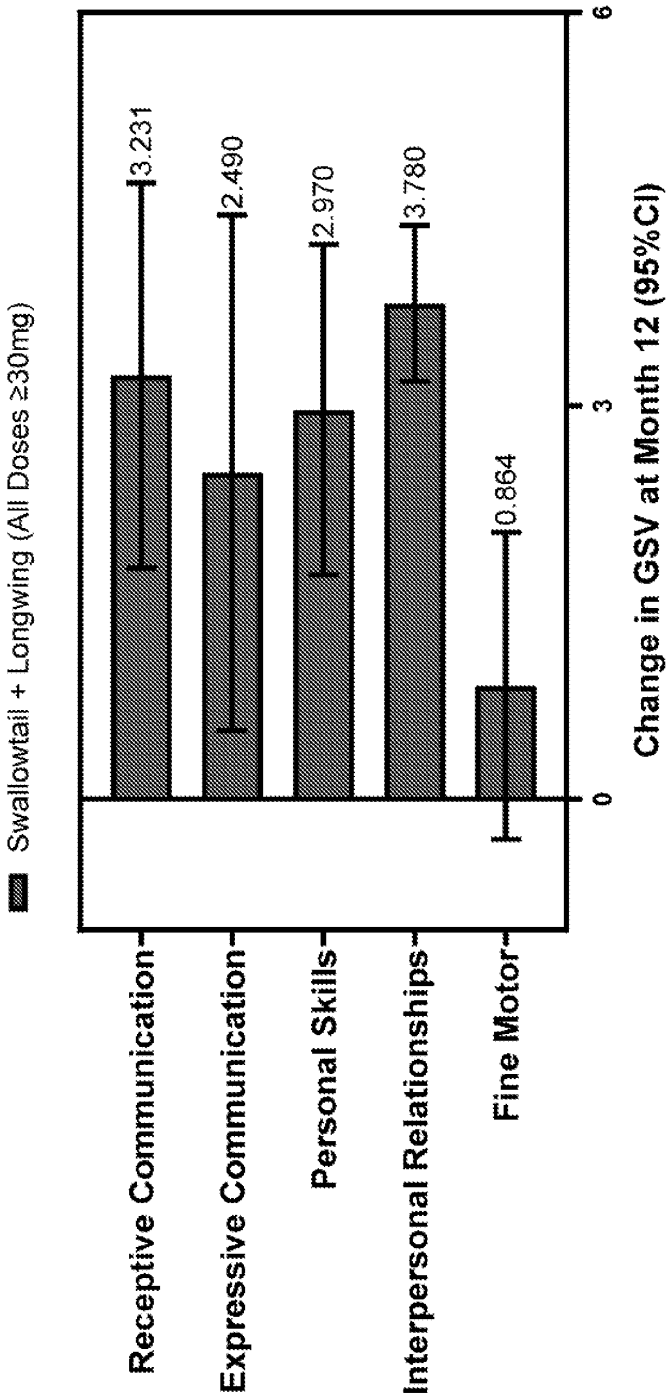
Swallowtail + Longwing (All Doses ≥30mg)
Receptive Communication
Expressive Communication
Personal Skills
Interpersonal Relationships
Fine Motor
3.231
2.490
2.970
3.780
0.864
0
3
6
Change in GSV at Month 12 (95%CI)
Worsening
Improving

FIG. 56A

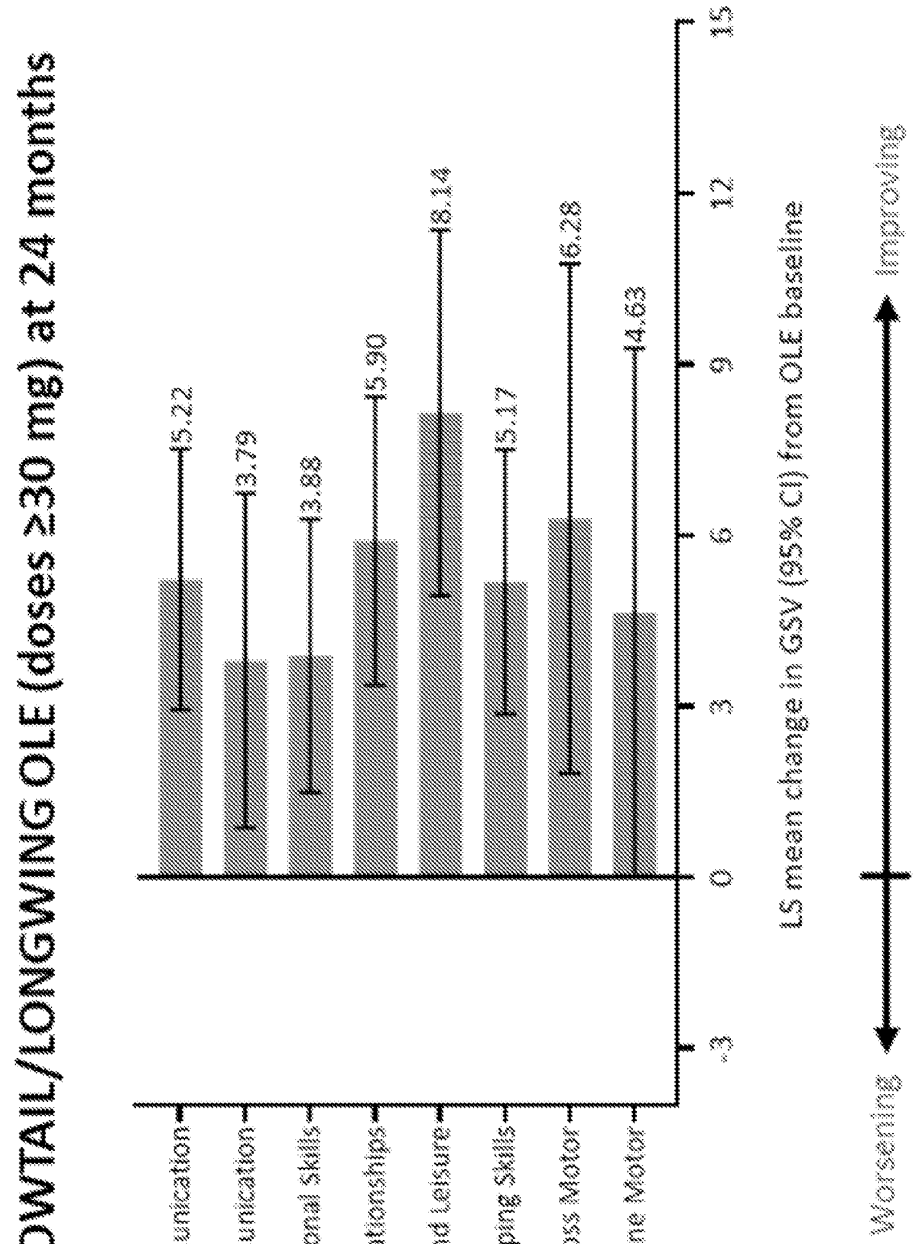
SWALLOWTAIL/LONGWING OLE (doses ≥30 mg) at 24 months
Receptive Communication
Expressive Communication
Personal Skills
Interpersonal Relationships
Play and Leisure
Coping Skills
Gross Motor
Fine Motor
5.22
3.79
3.88
5.90
8.14
5.17
6.28
4.63
-3
0
3
6
9
12
15
LS mean change in GSV (95% CI) from OLE baseline
Worsening
Improving

FIG. 56B

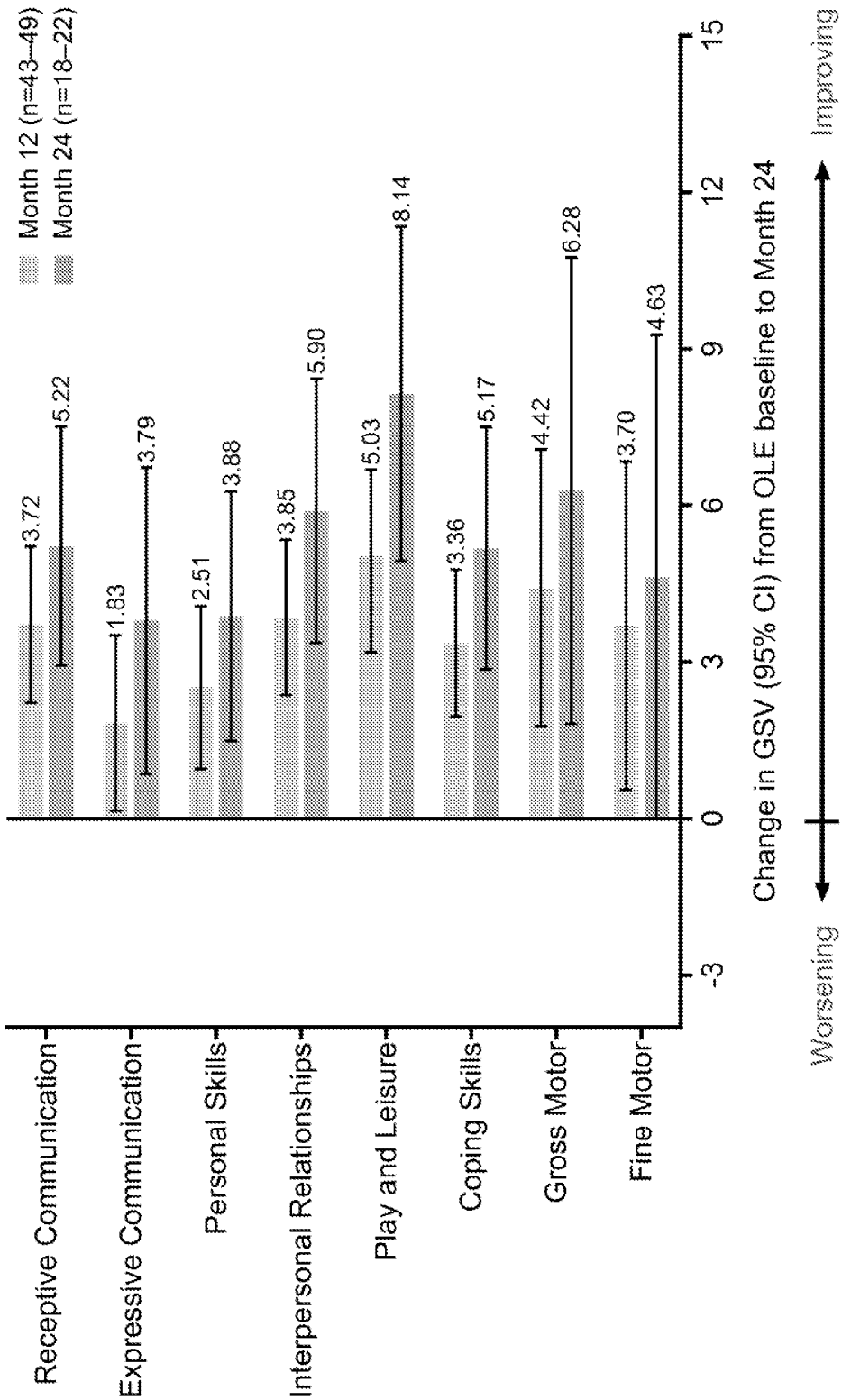
Month 12 (n=43–49)
Month 24 (n=18–22)
Receptive Communication
Expressive Communication
Personal Skills
Interpersonal Relationships
Play and Leisure
Coping Skills
Gross Motor
Fine Motor
3.72
5.22
1.83
3.79
2.51
3.88
3.85
5.90
5.03
8.14
3.36
5.17
4.42
6.28
3.70
4.63
-3
0
3
6
9
12
15
Change in GSV (95% CI) from OLE baseline to Month 24
Worsening
Improving

FIG. 56C

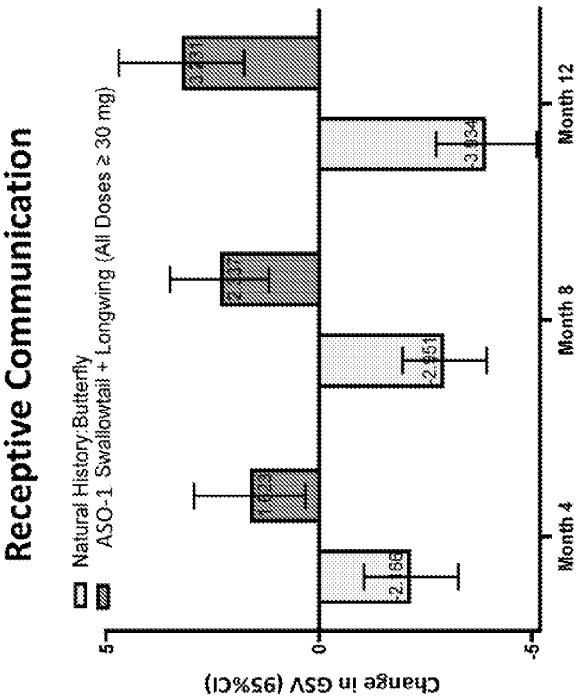

FIG. 57B

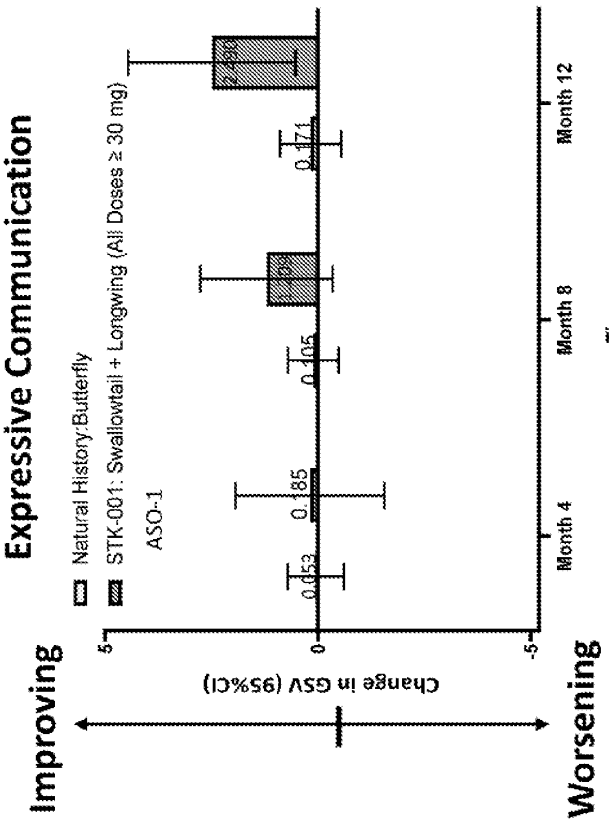

FIG. 57A

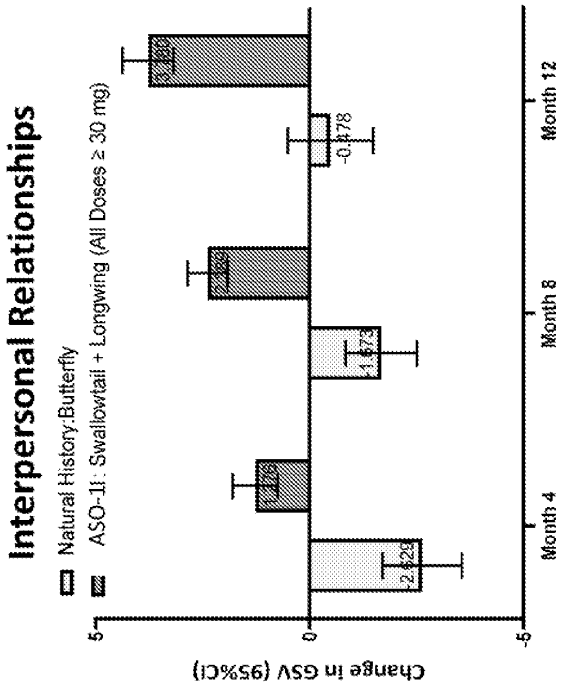

FIG. 58B

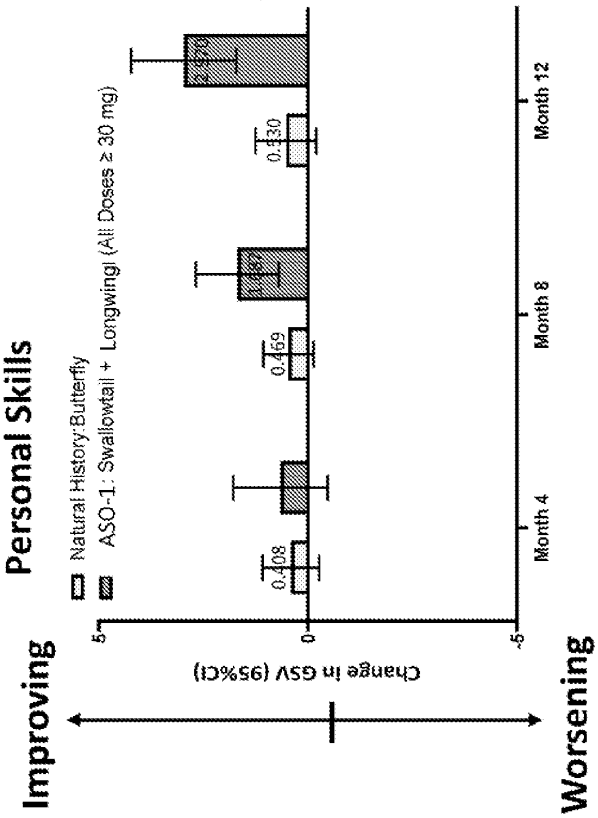

FIG. 58A

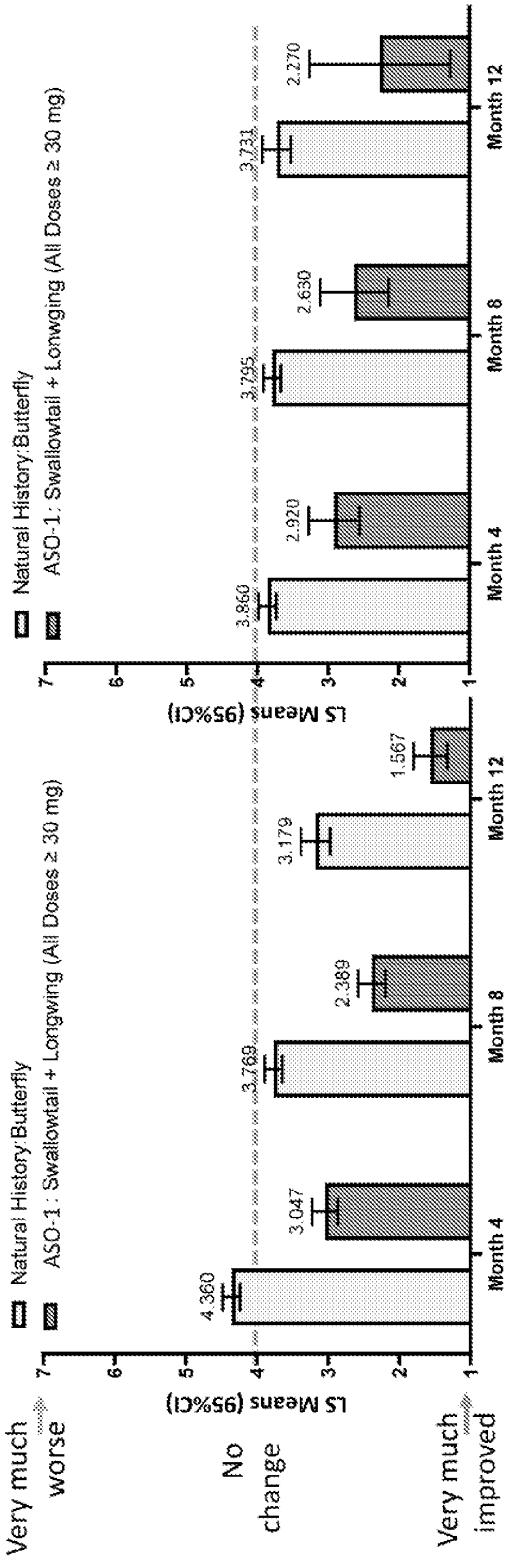

FIG. 59A

FIG. 59B

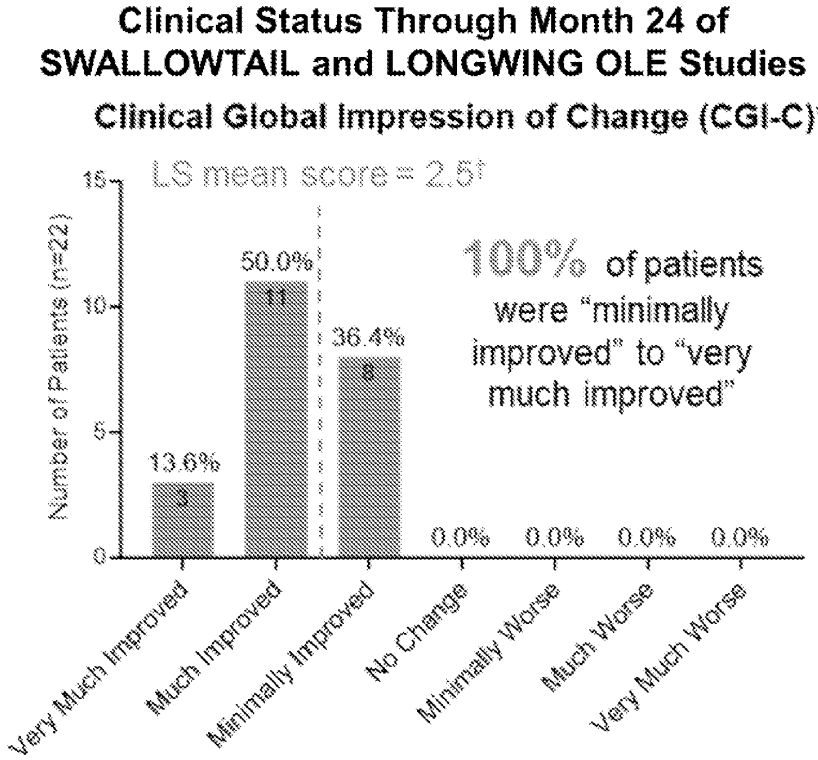

FIG. 59C

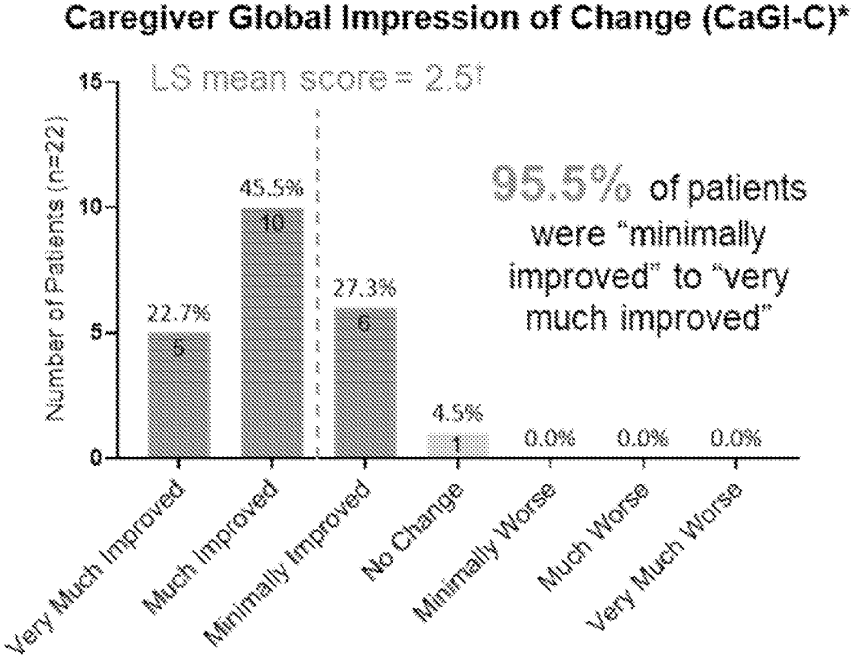

FIG. 59D

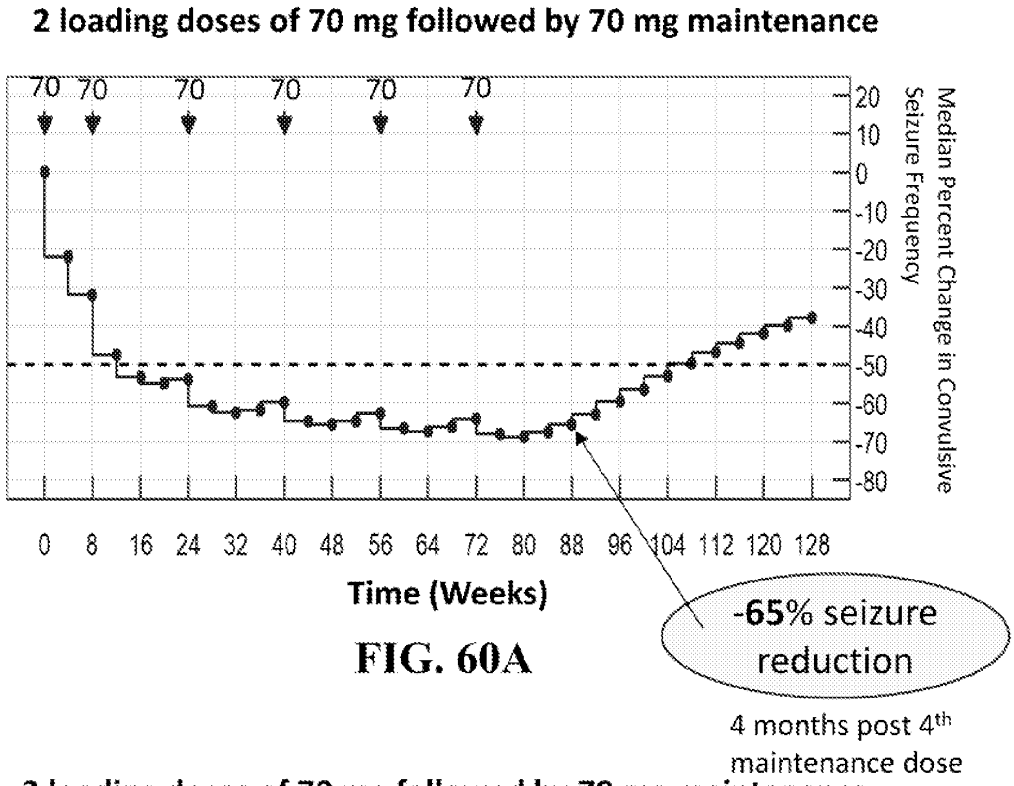

FIG. 60A

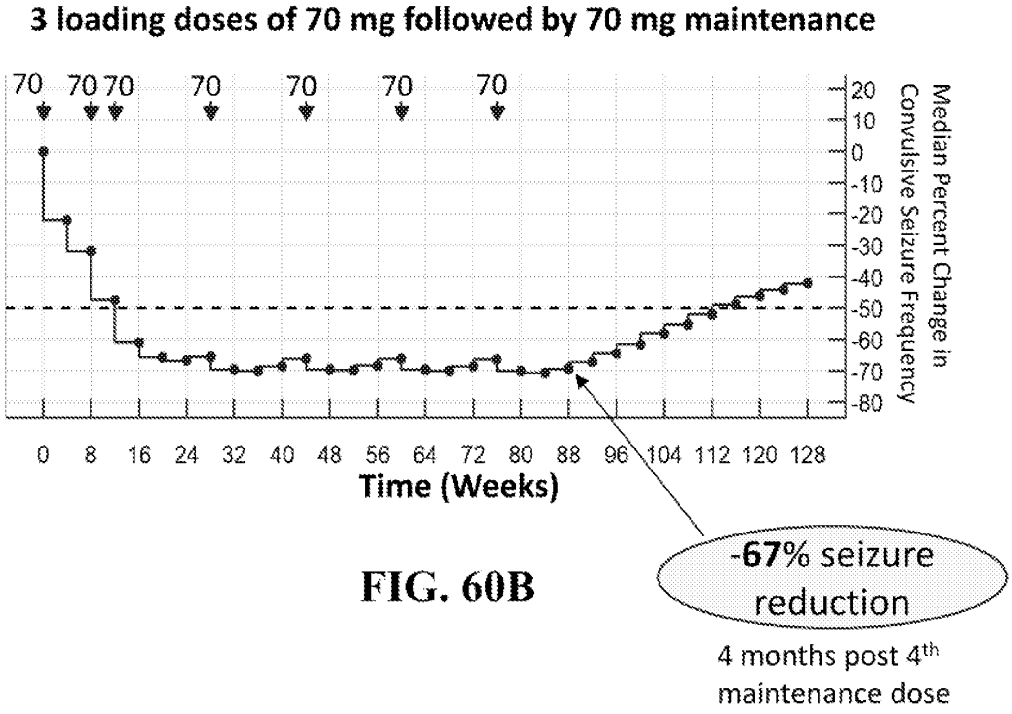

FIG. 60B

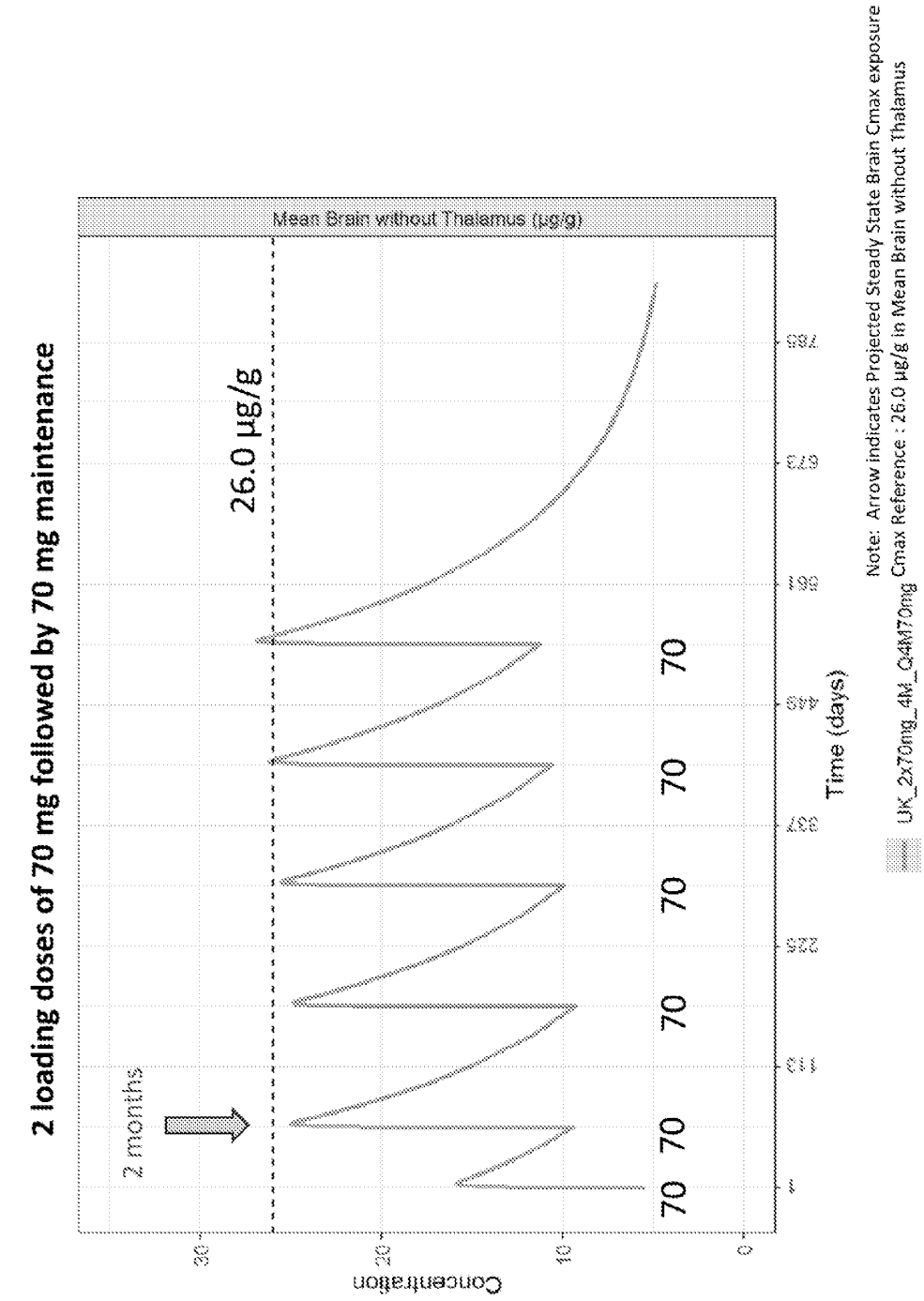
2 loading doses of 70 mg followed by 70 mg maintenance
Mean Brain without Thalamus (µg/g)
26.0 µg/g
2 months
70
Concentration
0
10
20
30
Time (days)
1
113
225
337
449
561
673
785
Note: Arrow indicates Projected Steady State Brain Cmax exposure
Cmax Reference : 26.0 µg/g in Mean Brain without Thalamus
UK_2x70mg_4M_Q4M70mg

FIG. 61A

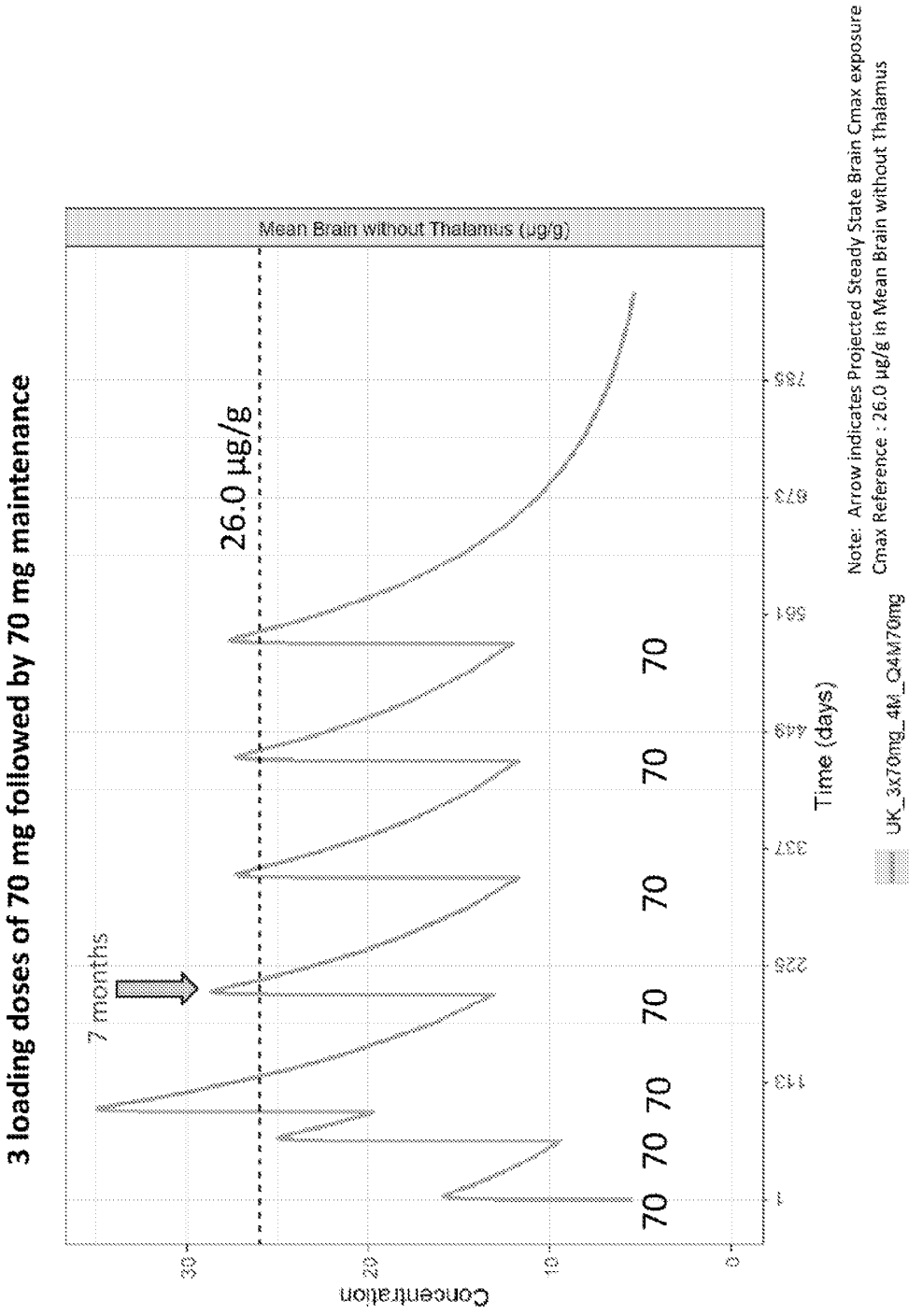
3 loading doses of 70 mg followed by 70 mg maintenance
Mean Brain without Thalamus (ug/g)
26.0 µg/g
7 months
70
70
70
70
70
70
Concentration
0
10
20
30
Time (days)
1
113
225
337
449
561
673
785
Note: Arrow indicates Projected Steady State Brain Cmax exposure
Cmax Reference : 26.0 µg/g in Mean Brain without Thalamus
UK_3x70mg_4M_Q4M70mg

FIG. 61B

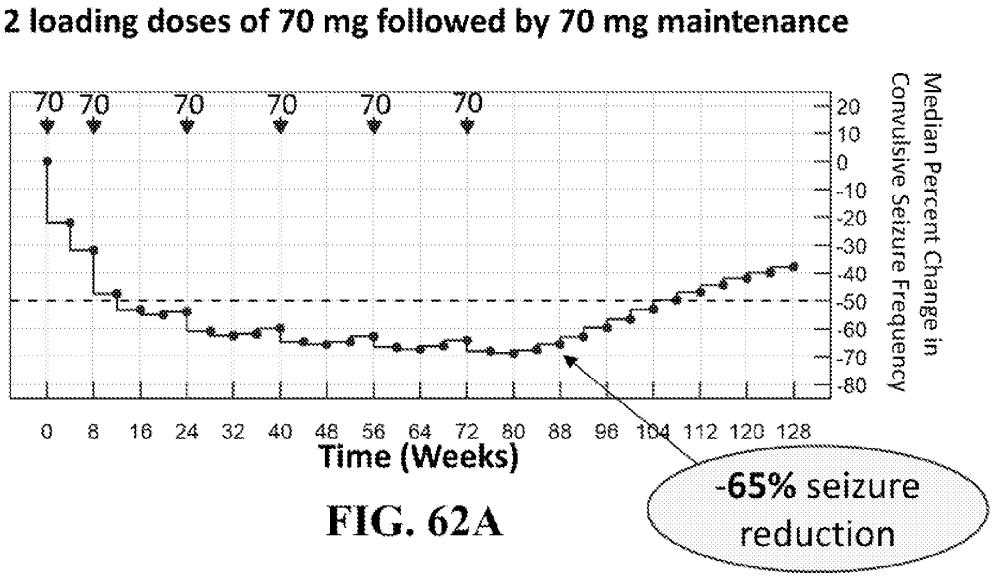

FIG. 62A

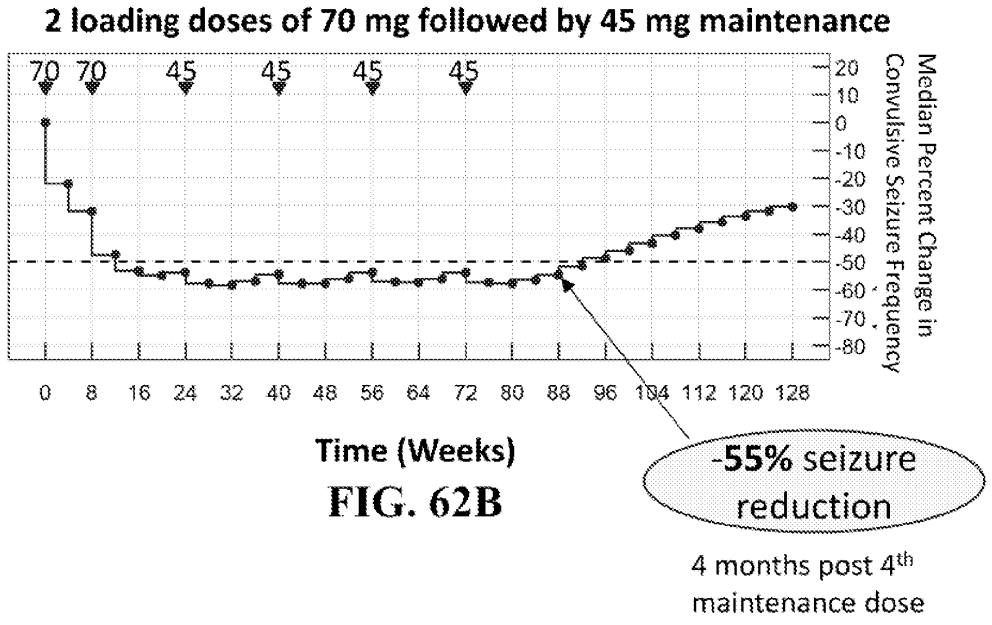

FIG. 62B

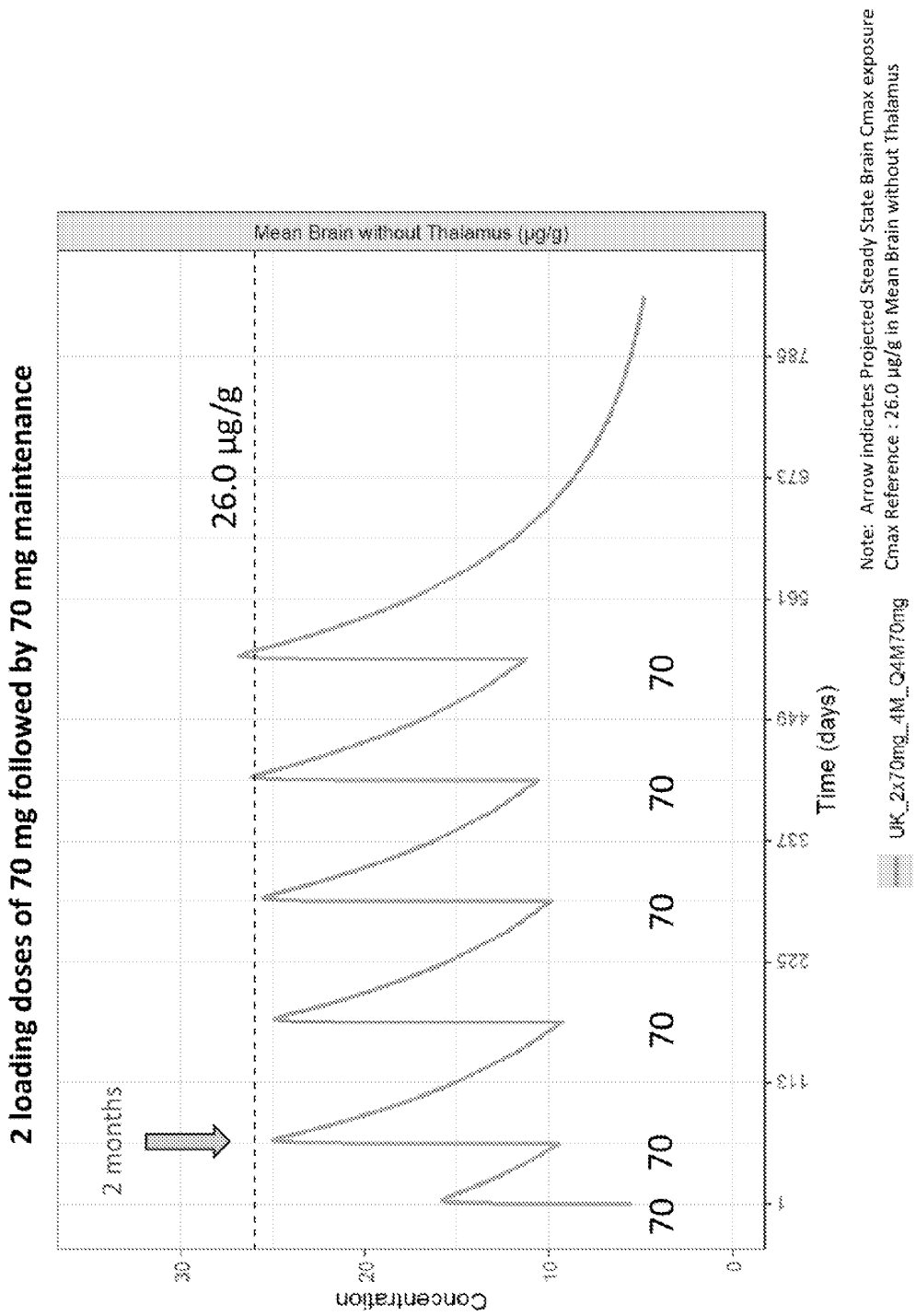
2 loading doses of 70 mg followed by 70 mg maintenance
Mean Brain without Thalamus (µg/g)
26.0 µg/g
2 months
70
Concentration
Time (days)
UK_2x70mg_4M_Q4M70mg
Note: Arrow indicates Projected Steady State Brain Cmax exposure
Cmax Reference : 26.0 µg/g in Mean Brain without Thalamus

FIG. 63A

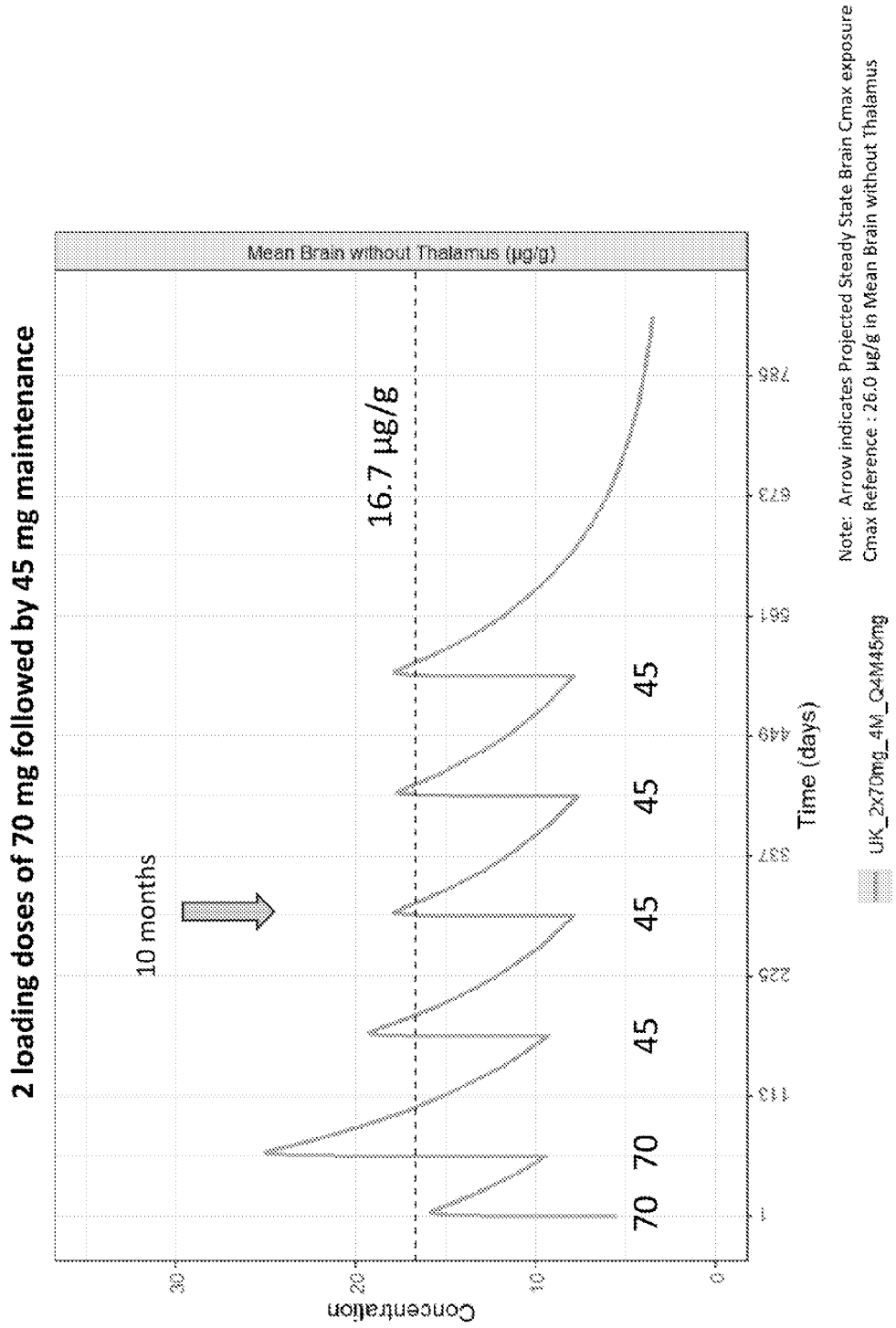
2 loading doses of 70 mg followed by 45 mg maintenance
Mean Brain without Thalamus (µg/g)
16.7 µg/g
10 months
70 70 45 45 45 45 45
Concentration
Time (days)
0
10
20
30
1
113
225
337
449
561
673
785
UK_2x70mg_4M_Q4M45mg
Note: Arrow indicates Projected Steady State Brain Cmax exposure
Cmax Reference : 26.0 µg/g in Mean Brain without Thalamus

FIG. 63B

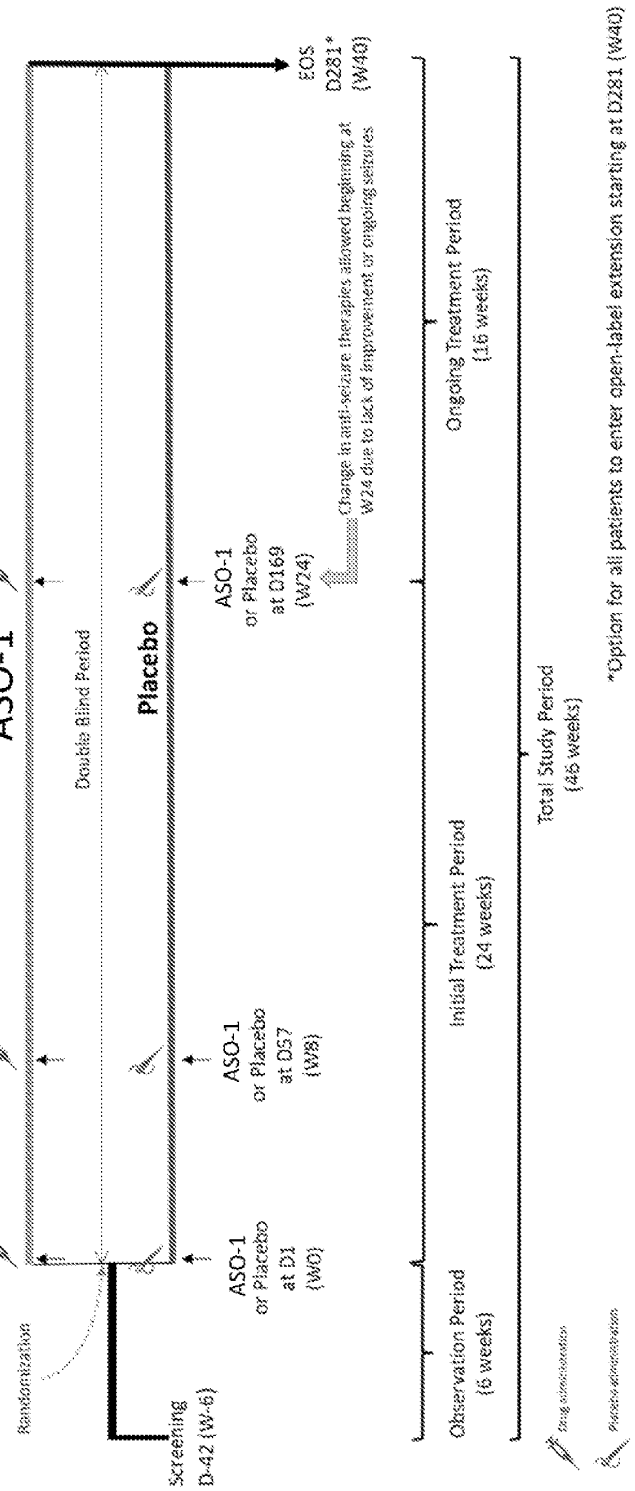
ASO-1
Placebo
Double Blind Period
Randomization
Screening
D-42 (W-6)
ASO-1
or Placebo
at D1
(W0)
ASO-1
or Placebo
at D57
(W8)
ASO-1
or Placebo
at D169
(W24)
Change in anti-seizure therapies allowed beginning at W24 due to lack of improvement or ongoing seizures
EOS
D281*
(W40)
Observation Period
(6 weeks)
Initial Treatment Period
(24 weeks)
Ongoing Treatment Period
(16 weeks)
Total Study Period
(46 weeks)
*Option for all patients to enter open-label extension starting at D281 (W40)

FIG. 64

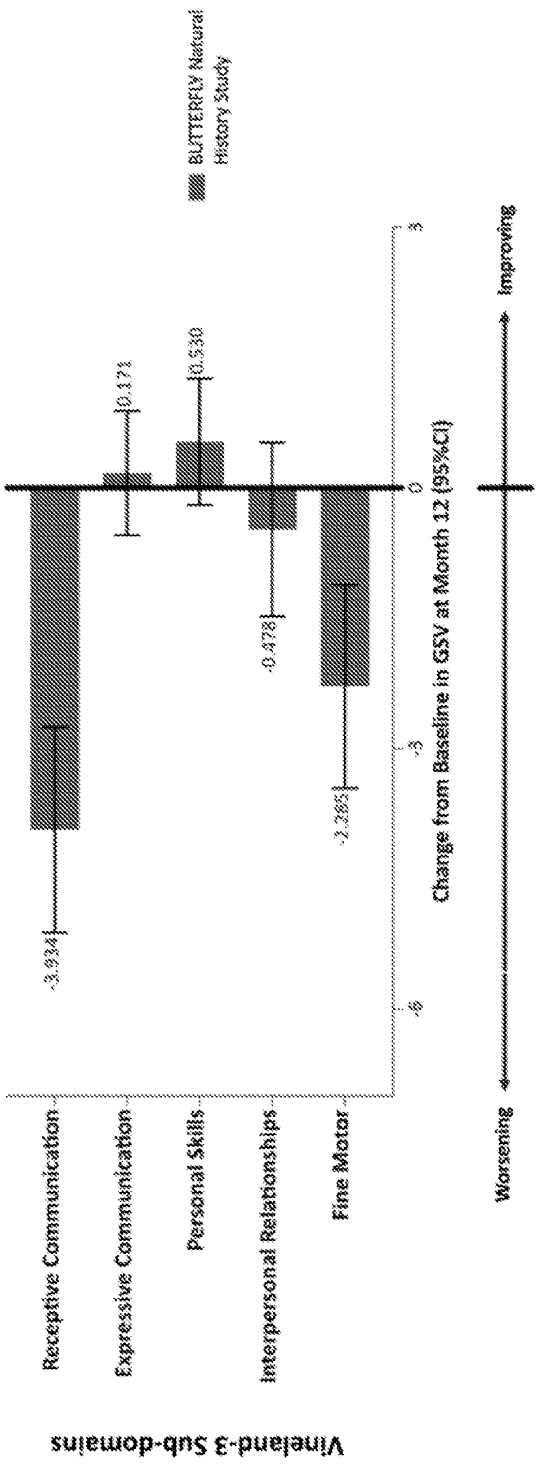
BLITTERFLY Natural History Study
Vineland-3 Sub-domains
Receptive Communication
Expressive Communication
Personal Skills
Interpersonal Relationships
Fine Motor
-3.934
0.171
0.530
-0.478
-3.265
-6
-3
0
3
Change from Baseline in GSV at Month 12 (95%CI)
Worsening
Improving

FIG. 65

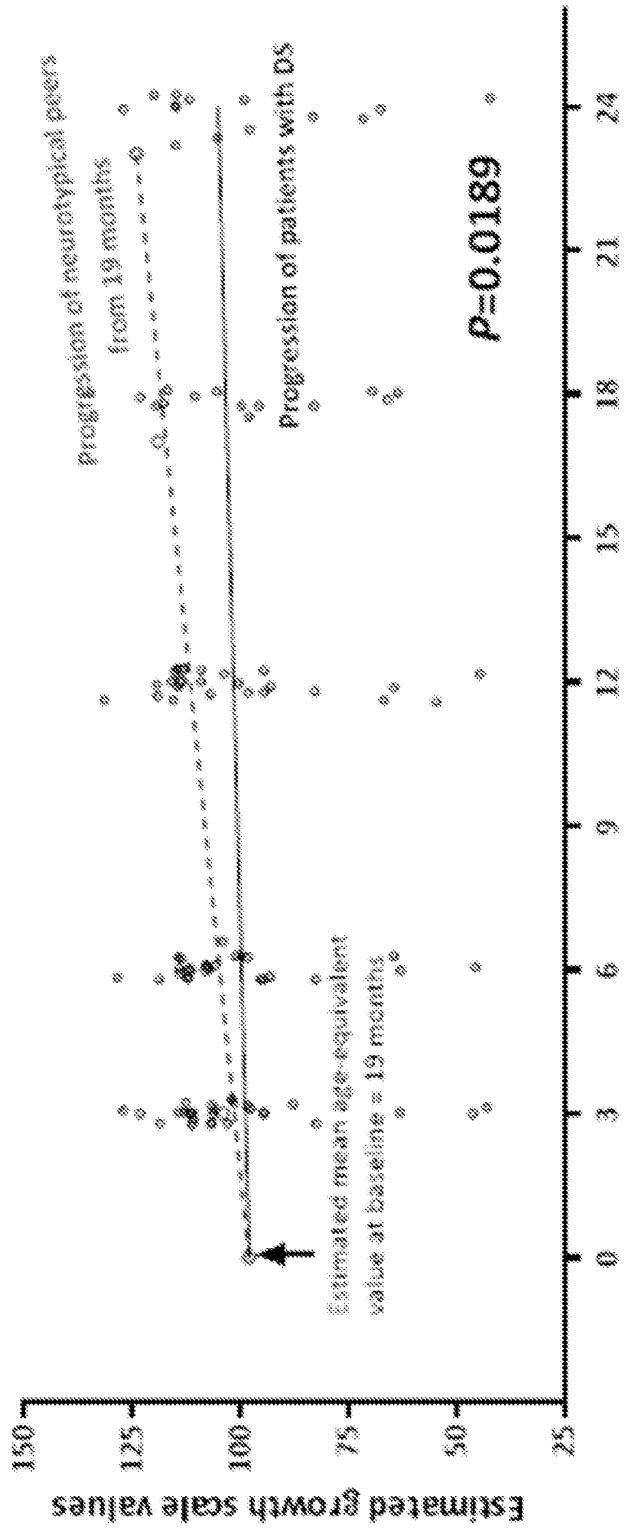
Receptive Communication
Estimated growth scale values
150
125
100
75
50
25
0
3
6
9
12
15
18
21
24
Month in study
Progression of neurotypical peers
from 19 months
Progression of patients with DS
Estimated mean age-equivalent
value at baseline = 19 months
P=0.0189

FIG. 66A

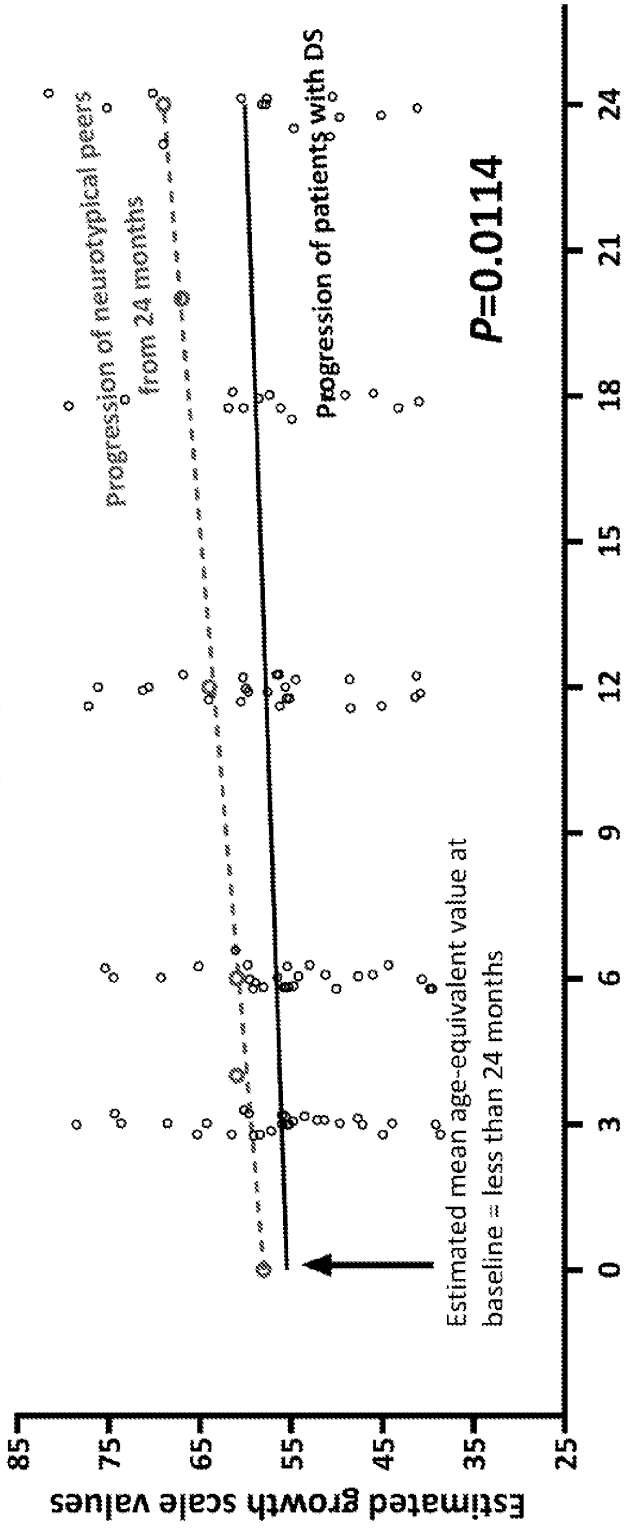
Coping Skills
Estimated growth scale values
85
75
65
55
45
35
25
0
3
6
9
12
15
18
21
24
Month in study
Progression of neurotypical peers from 24 months
Progression of patients with DS
P=0.0114
Estimated mean age-equivalent value at baseline = less than 24 months

FIG. 66B

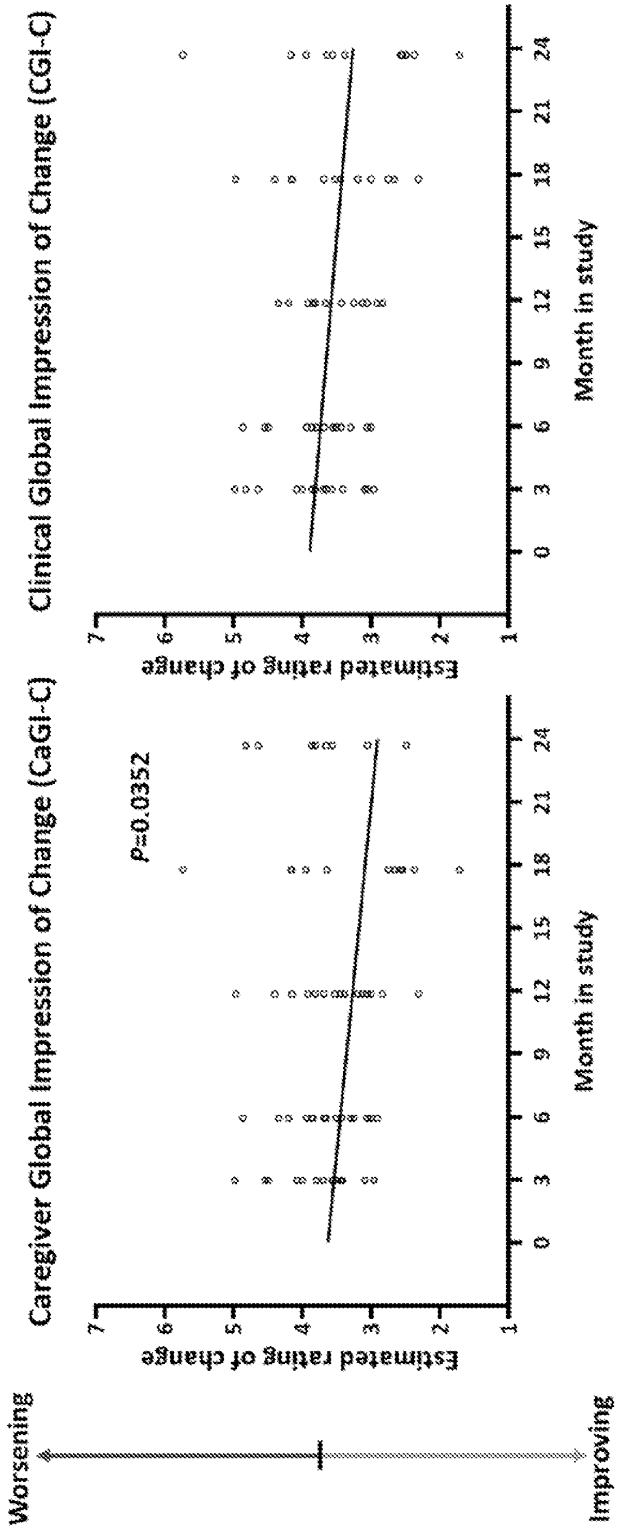

FIG. 67B

FIG. 67A

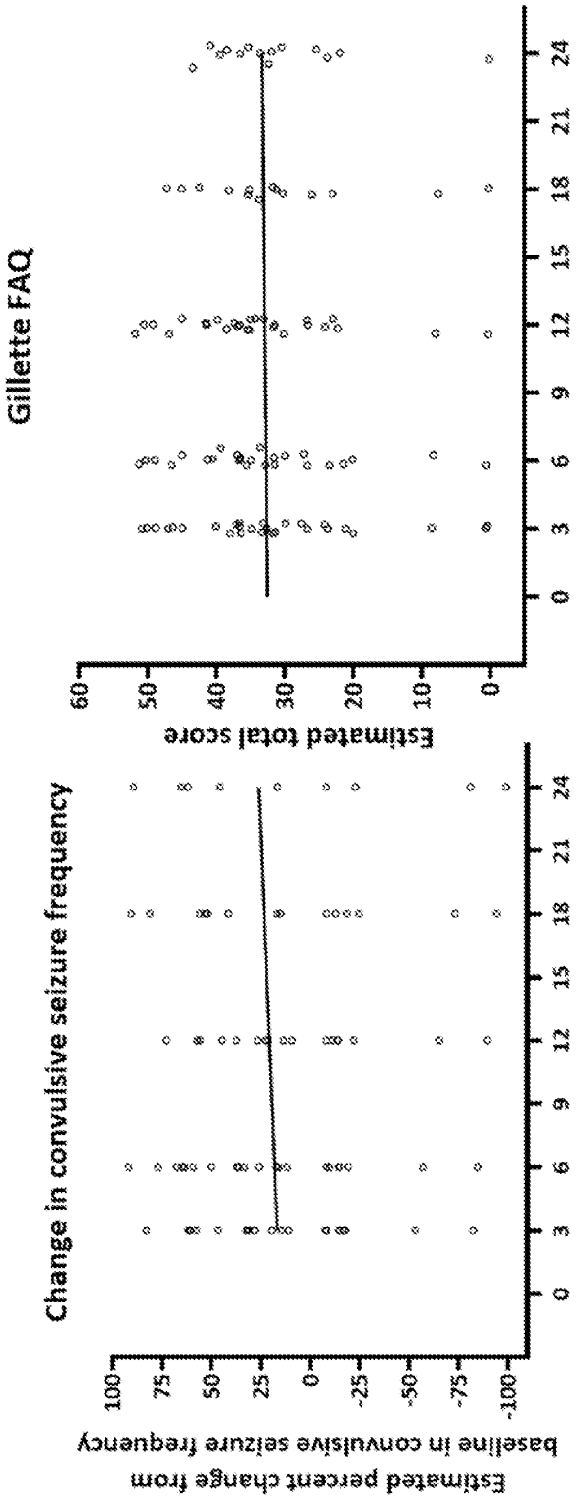

FIG. 68B

FIG. 68A

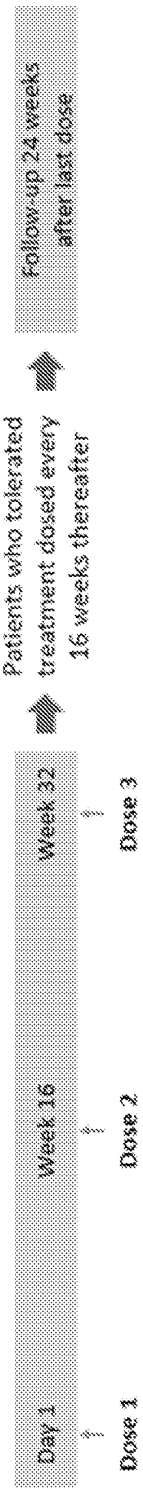
Day 1
Dose 1
Week 16
Dose 2
Week 32
Dose 3
Patients who tolerated treatment dosed every 16 weeks thereafter
Follow-up 24 weeks after last dose

FIG. 69

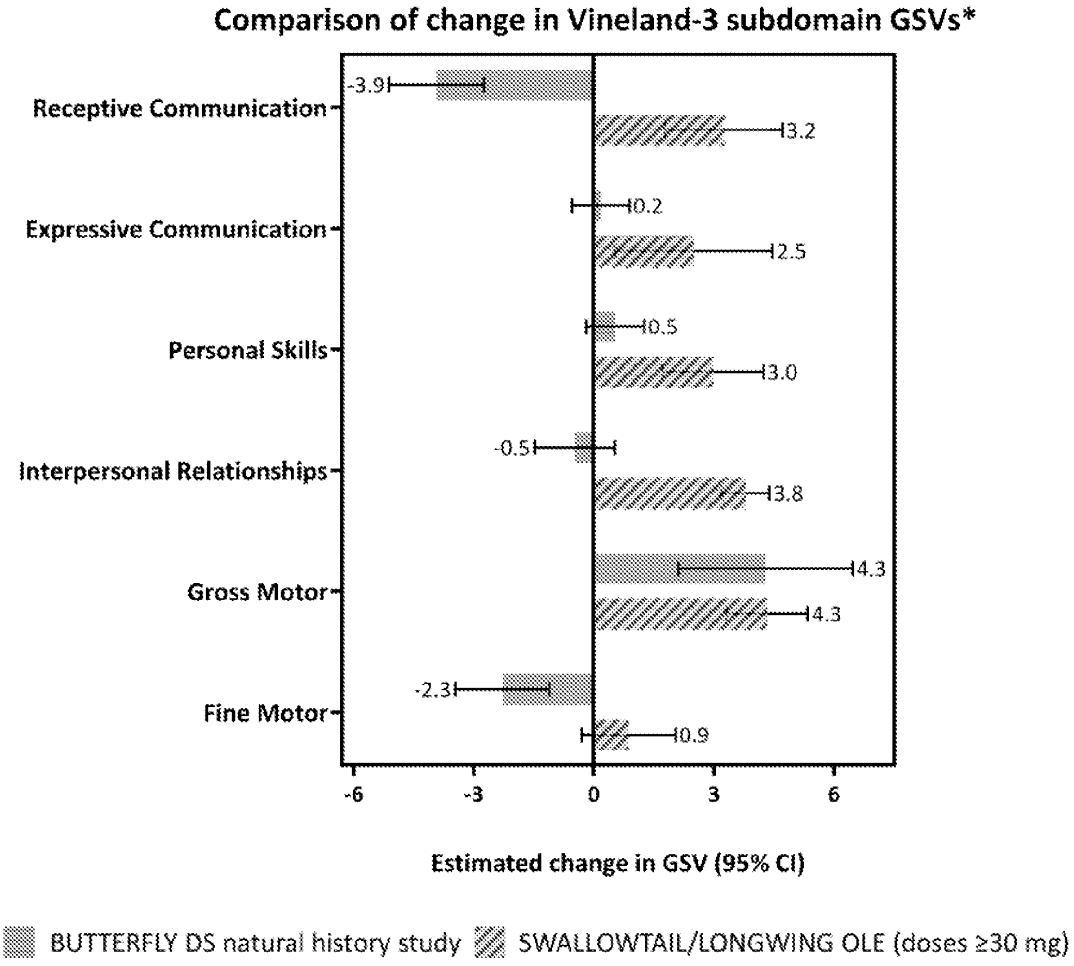
Comparison of change in Vineland-3 subdomain GSVs*
Receptive Communication
Expressive Communication
Personal Skills
Interpersonal Relationships
Gross Motor
Fine Motor
-3.9
3.2
0.2
2.5
0.5
3.0
-0.5
3.8
4.3
4.3
-2.3
0.9
-6
-3
0
3
6
Estimated change in GSV (95% CI)
BUTTERFLY DS natural history study
SWALLOWTAIL/LONGWING OLE (doses ≥30 mg)

FIG. 70A

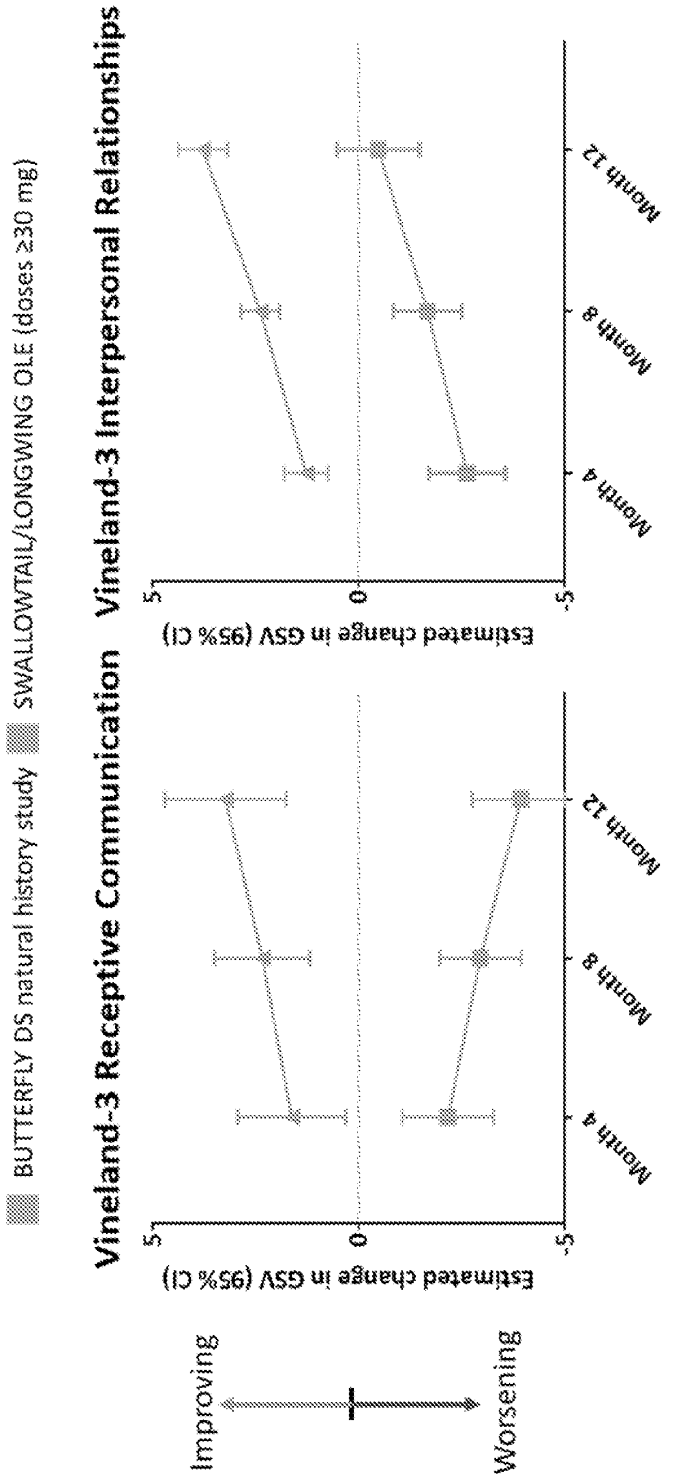

FIG. 70B

FIG. 70C

Clinical Status Within First 9 Months of Phase 1/2a Treatment, Continuing Through Ongoing Treatment in SWALLOWTAIL and LONGWING OLE Studies

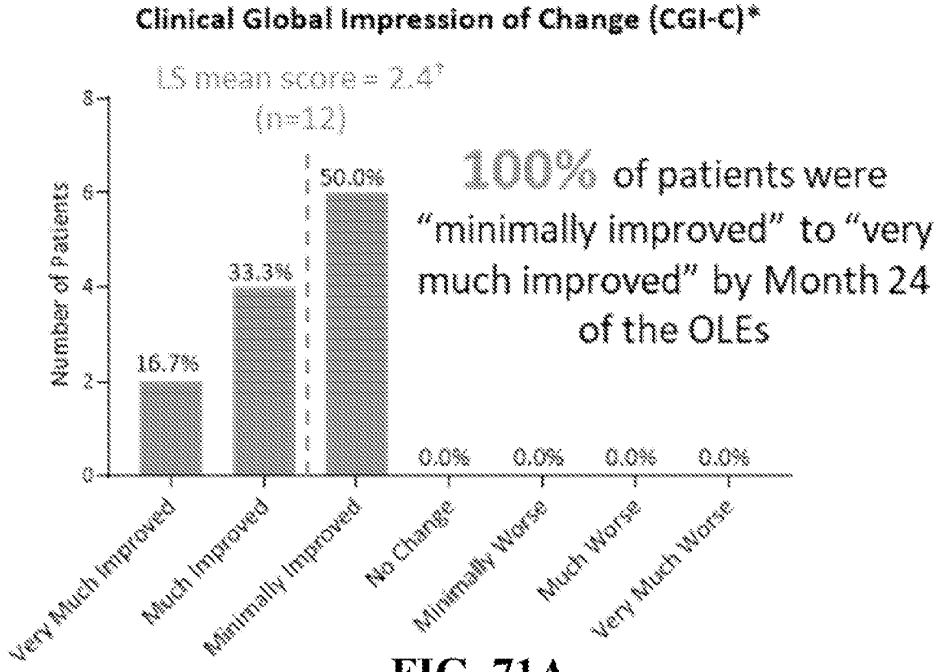

FIG. 71A

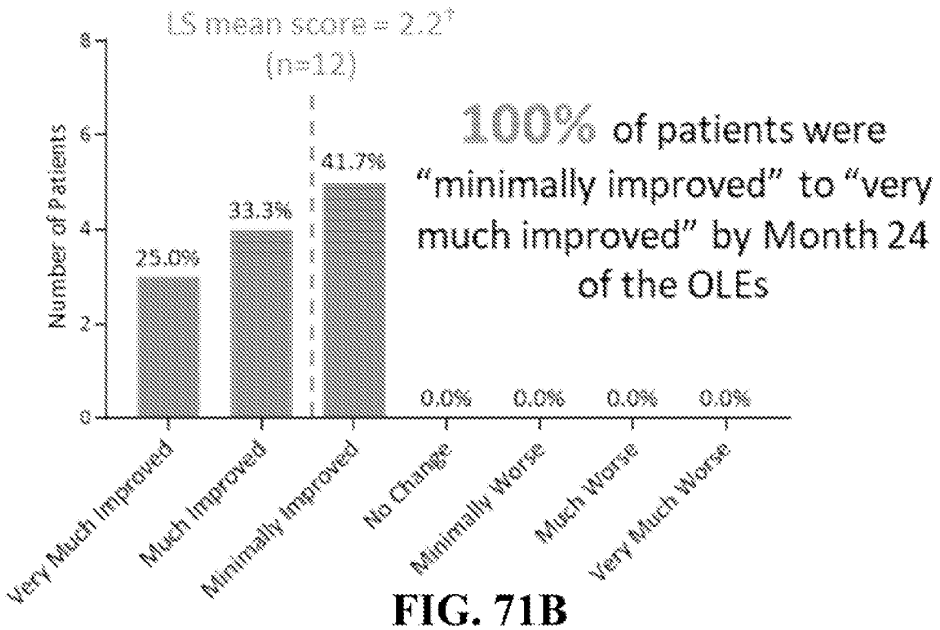

FIG. 71B

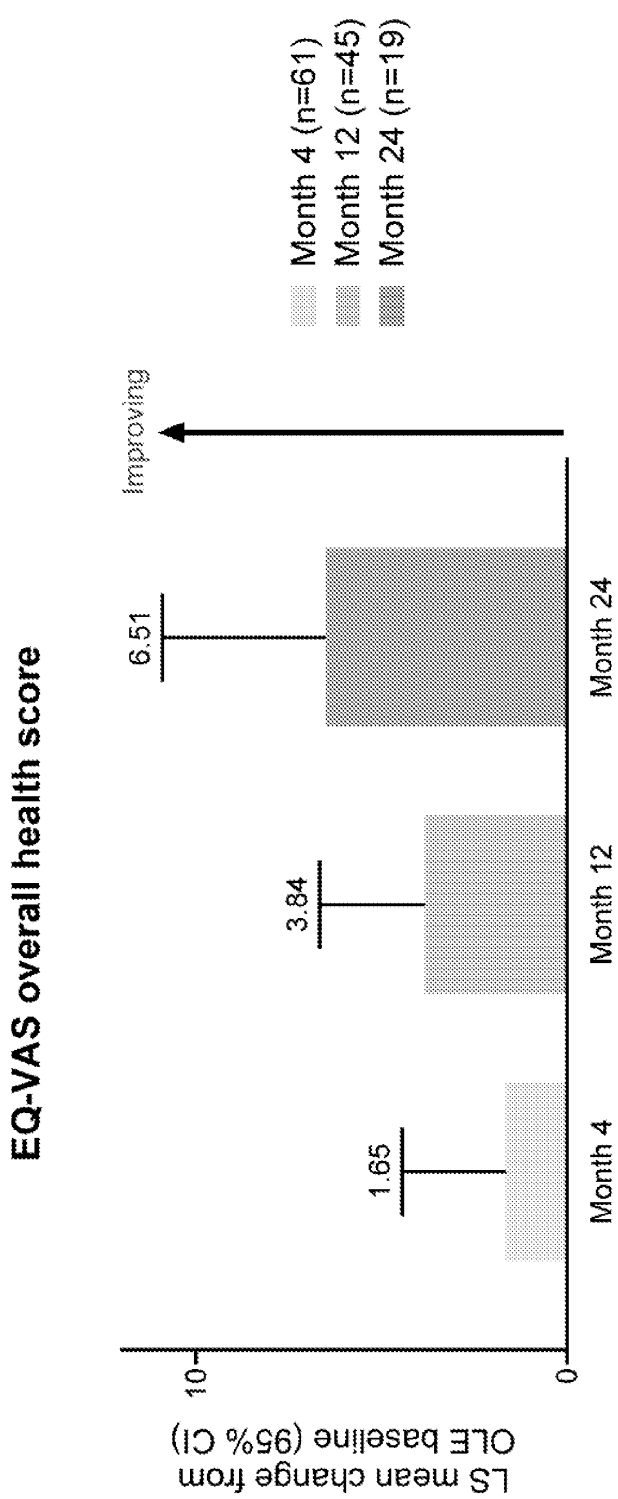
EQ-VAS overall health score
LS mean change from OLE baseline (95% CI)
10
0
improving
Month 4 (n=61)
Month 12 (n=45)
Month 24 (n=19)
1.65
3.84
6.51
Month 4
Month 12
Month 24

FIG. 72