

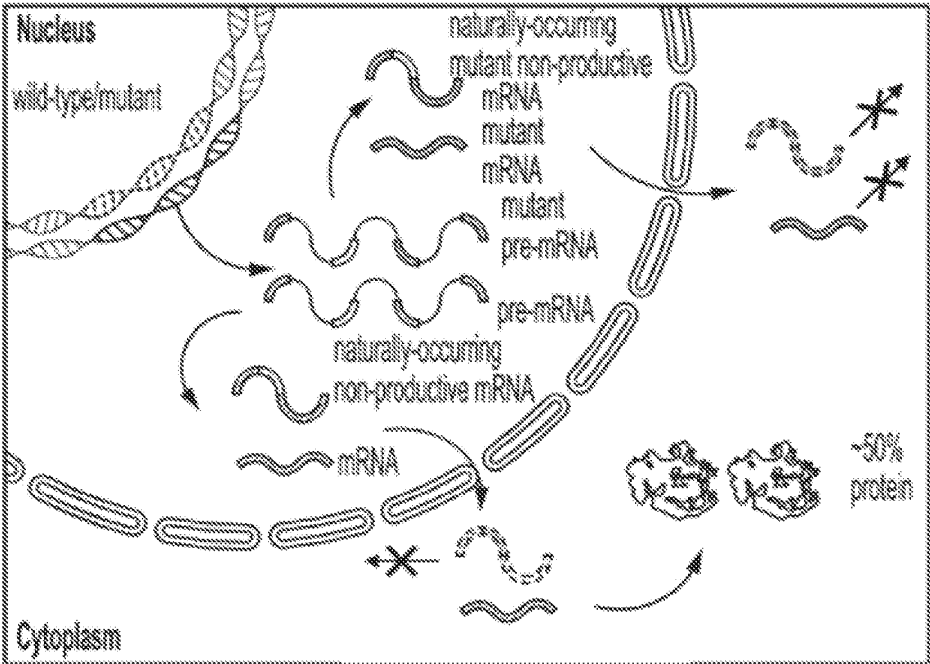


FIG. 1A

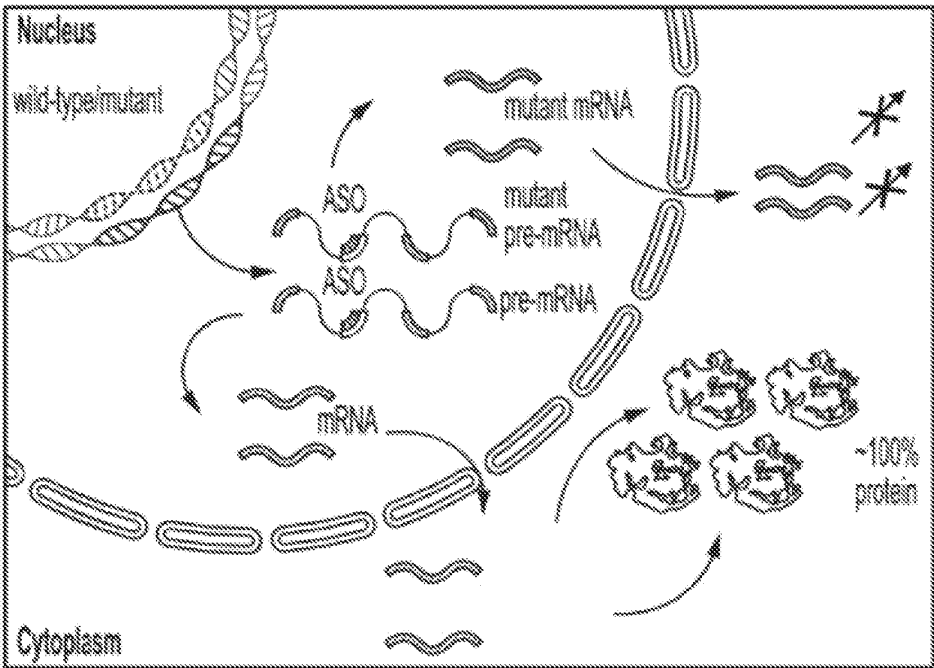


FIG. 1B

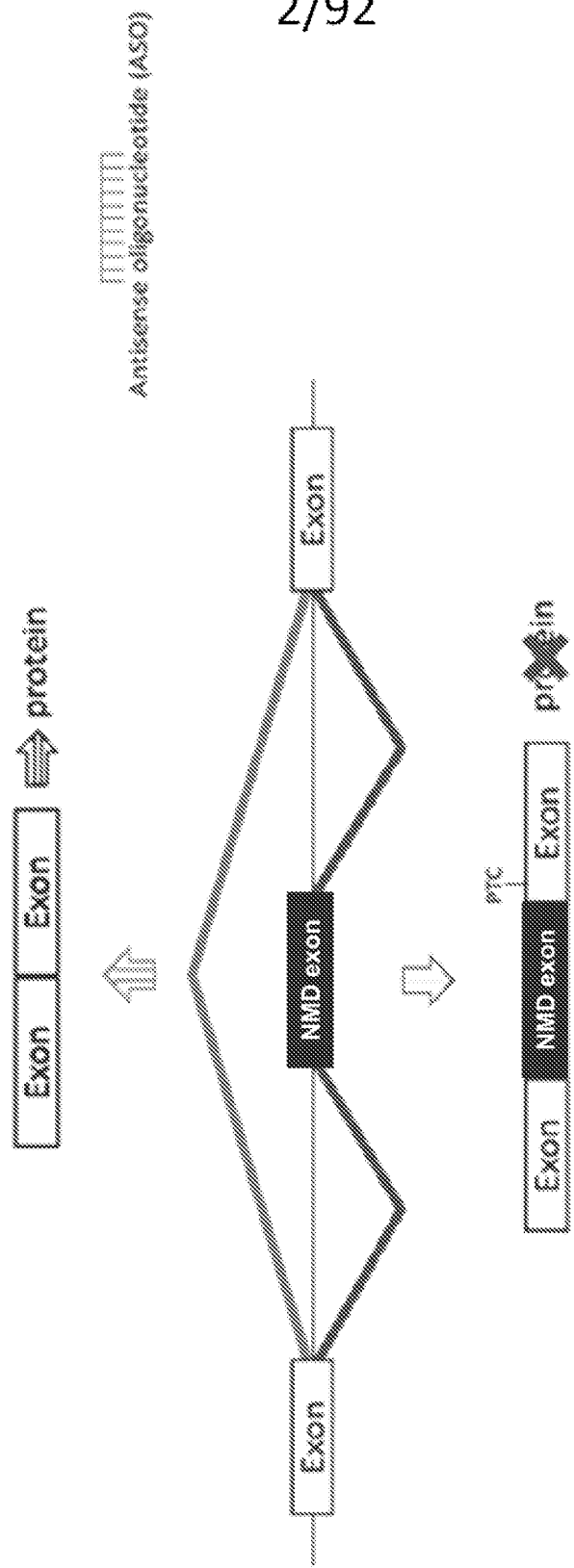


FIG. 1C

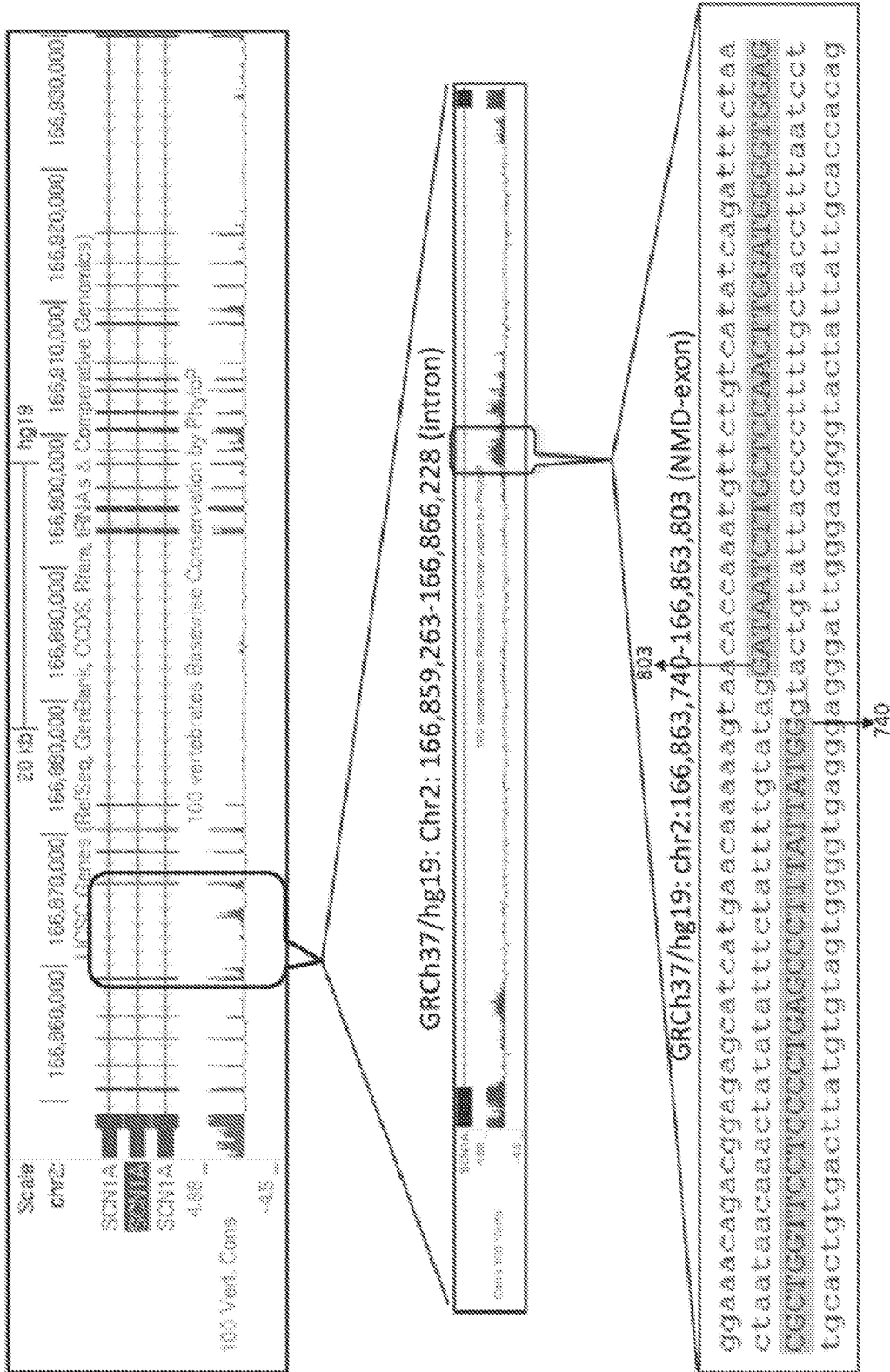


FIG. 1D

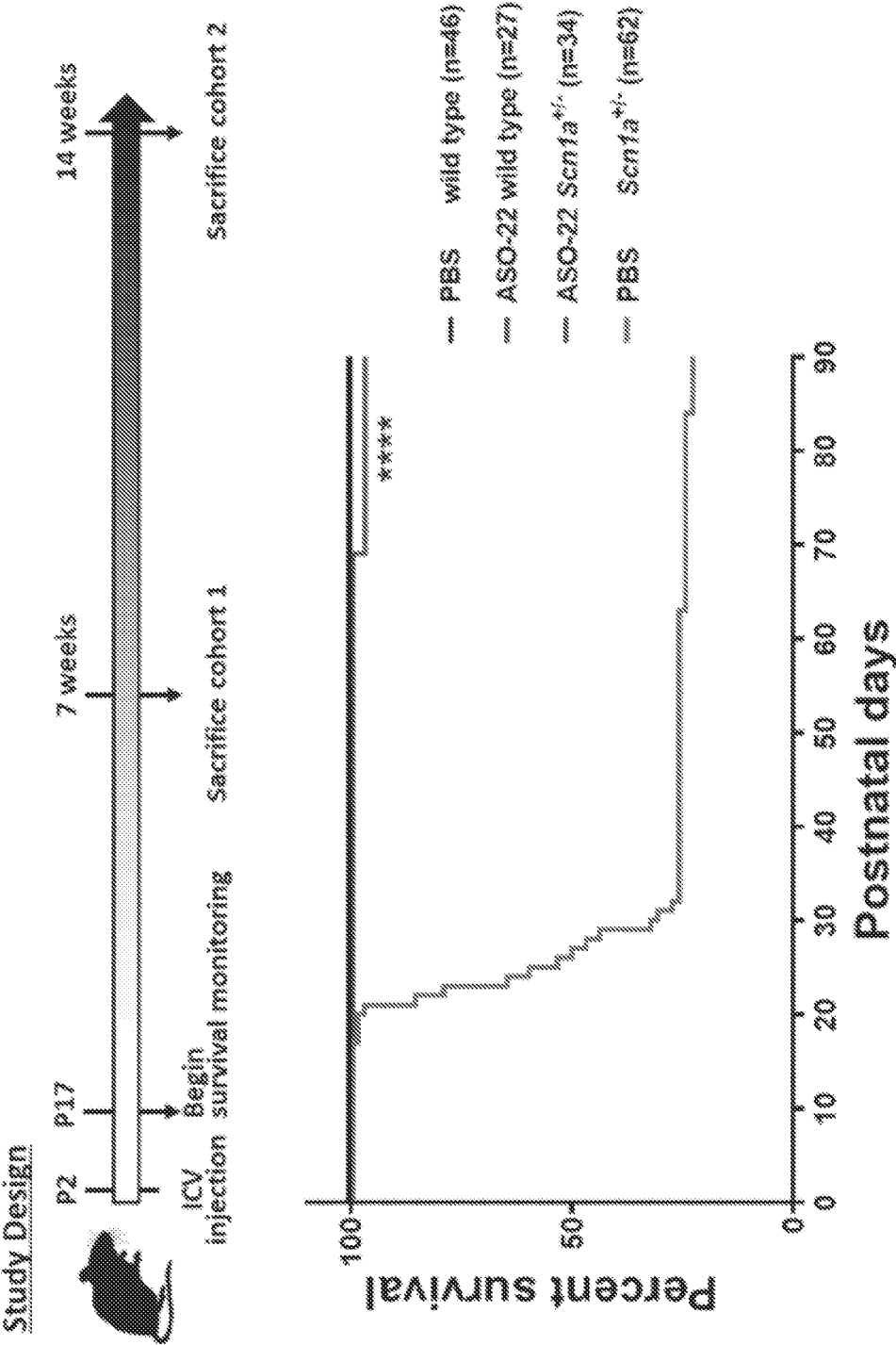


FIG. 2

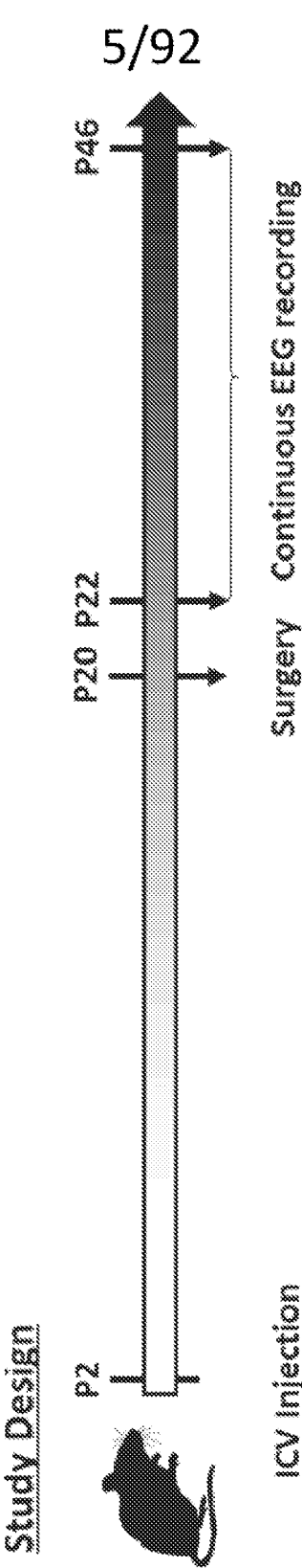


FIG. 3

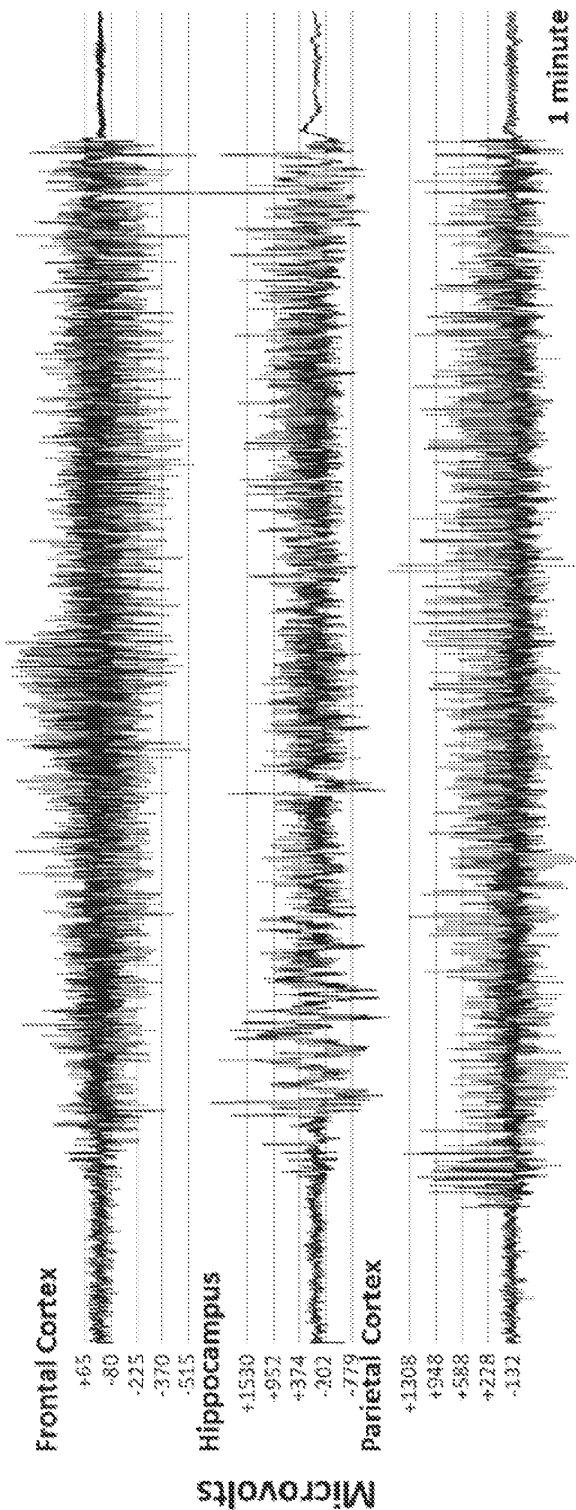


FIG. 4A

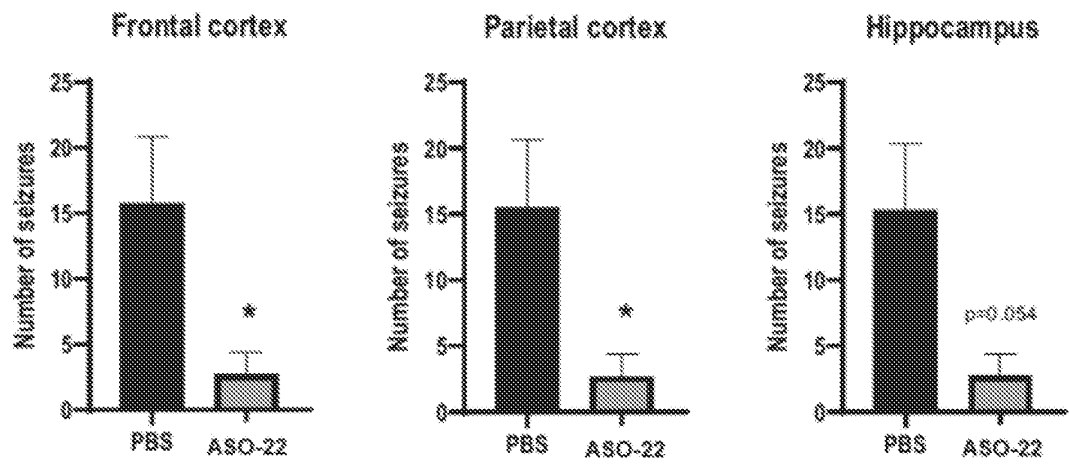


FIG. 4B

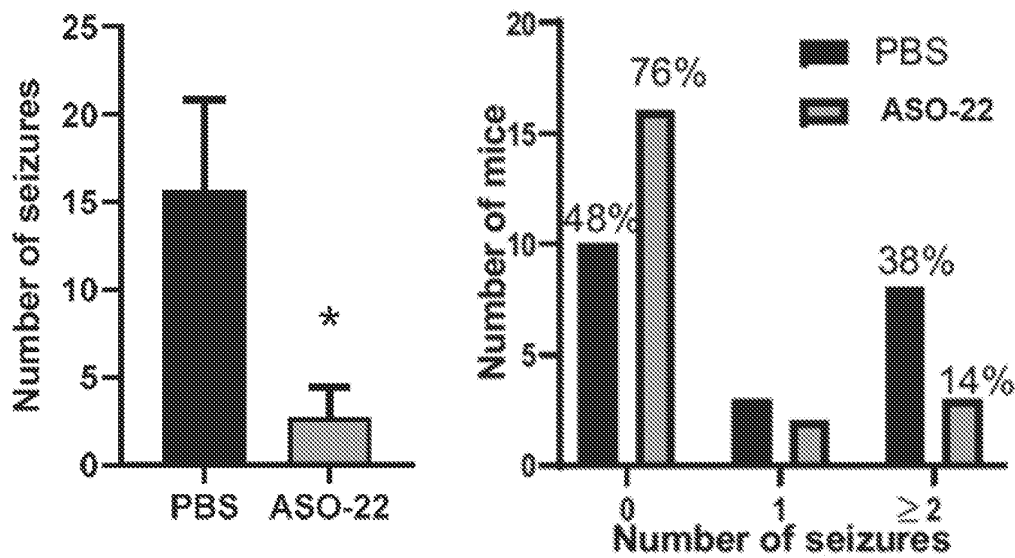


FIG. 4C

FIG. 4D

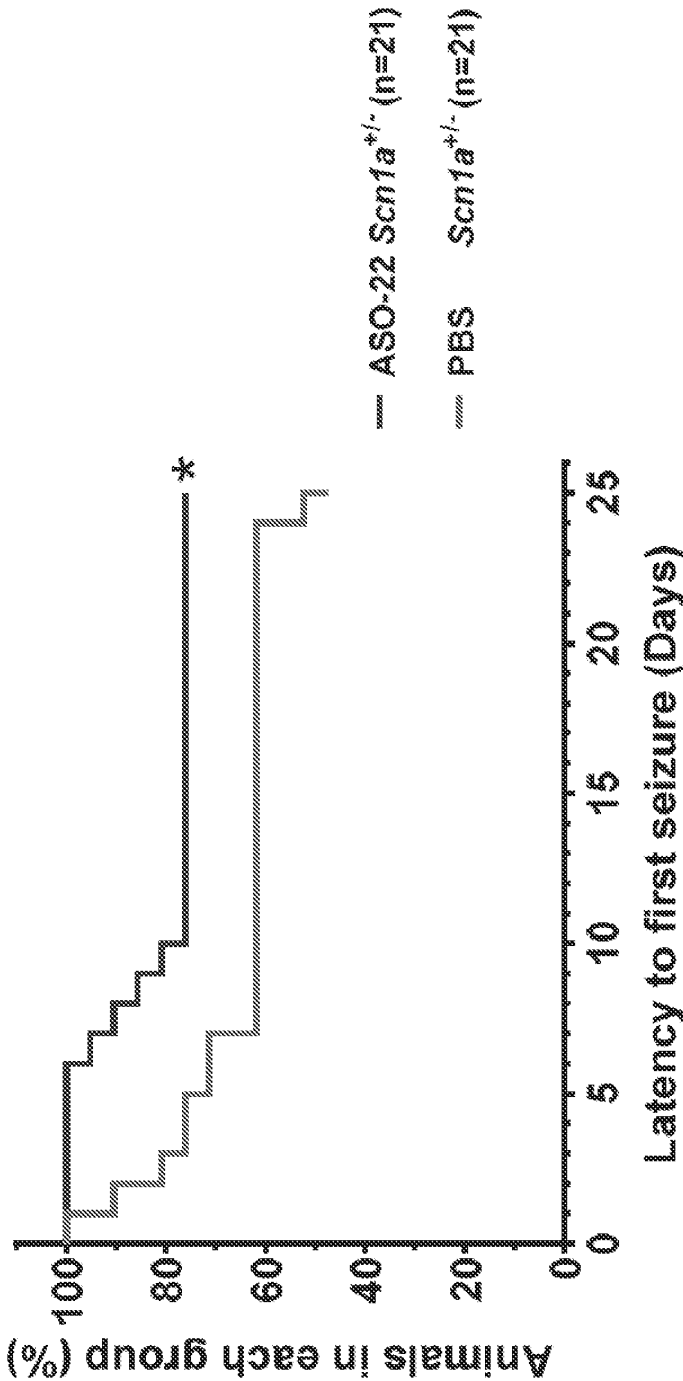


FIG. 4E

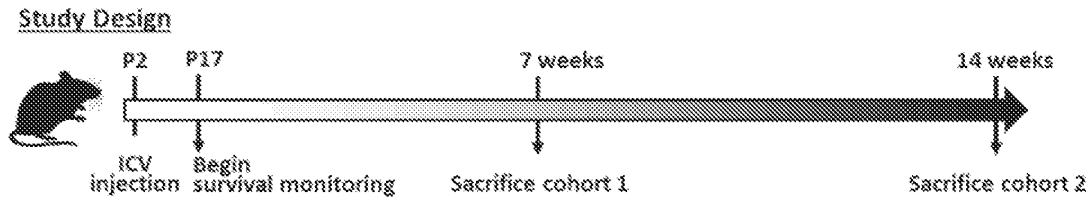


FIG. 5A

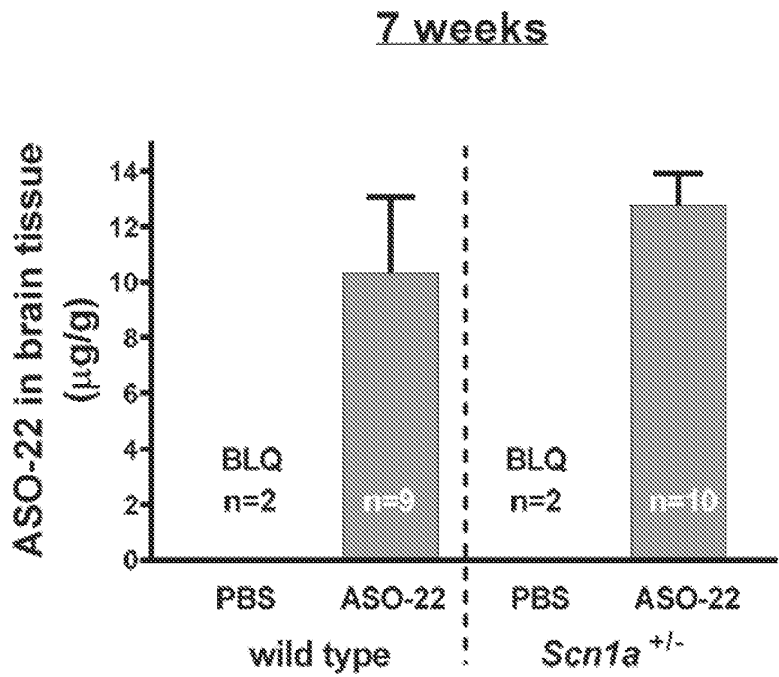


FIG. 5B

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7 weeks

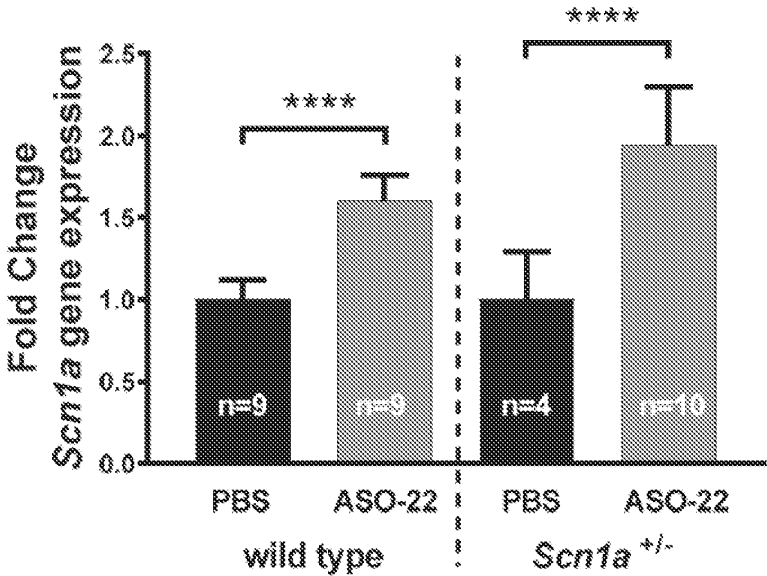


FIG. 5C

7 weeks

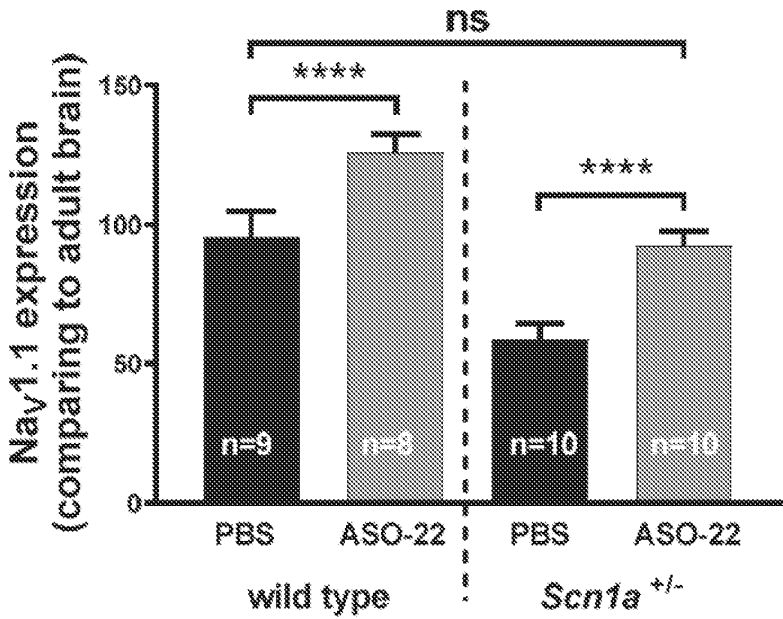


FIG. 5D

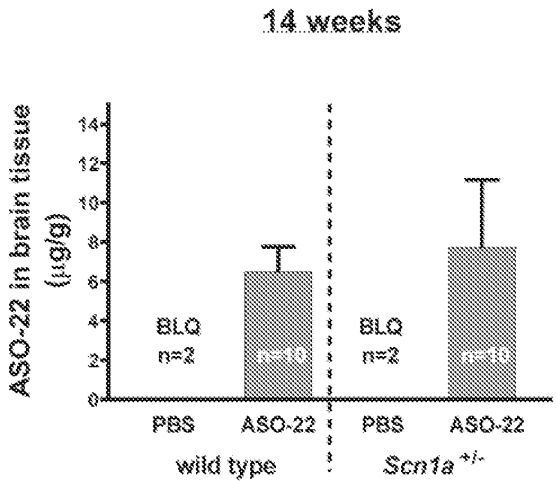


FIG. 5E

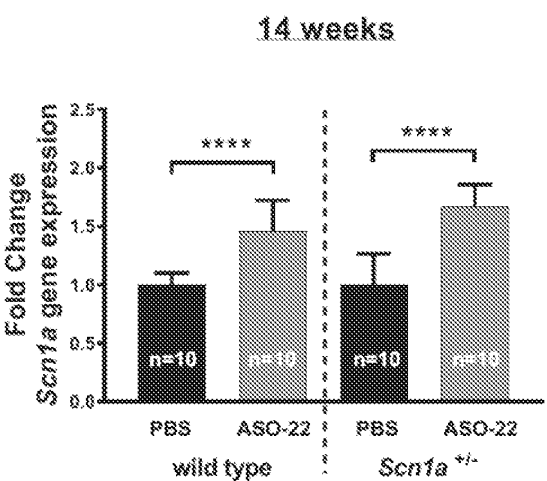


FIG. 5F

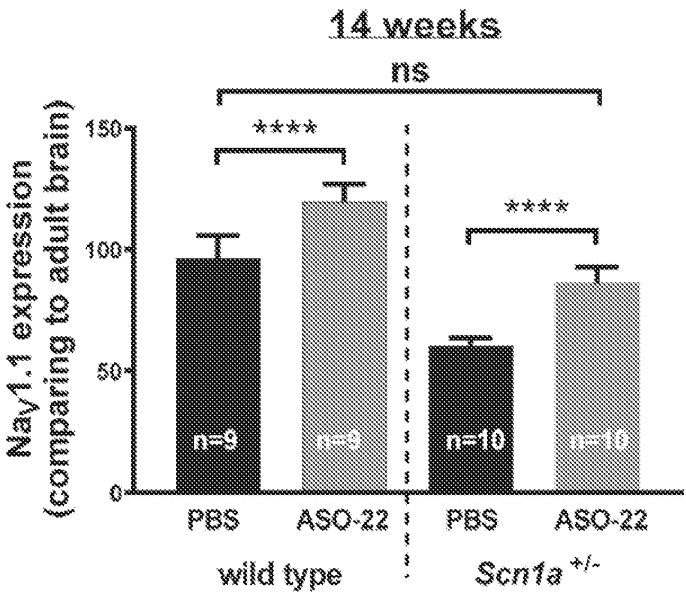
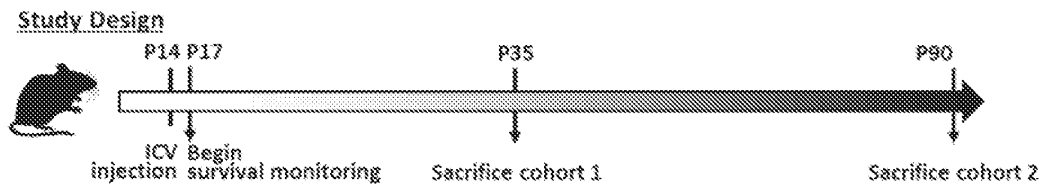
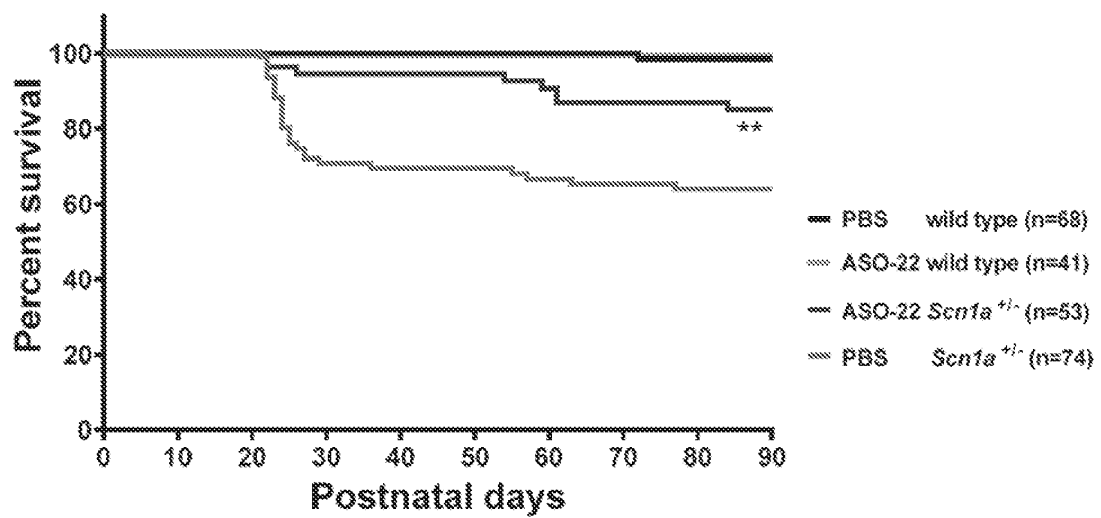


FIG. 5G

**FIG. 6A****FIG. 6B**

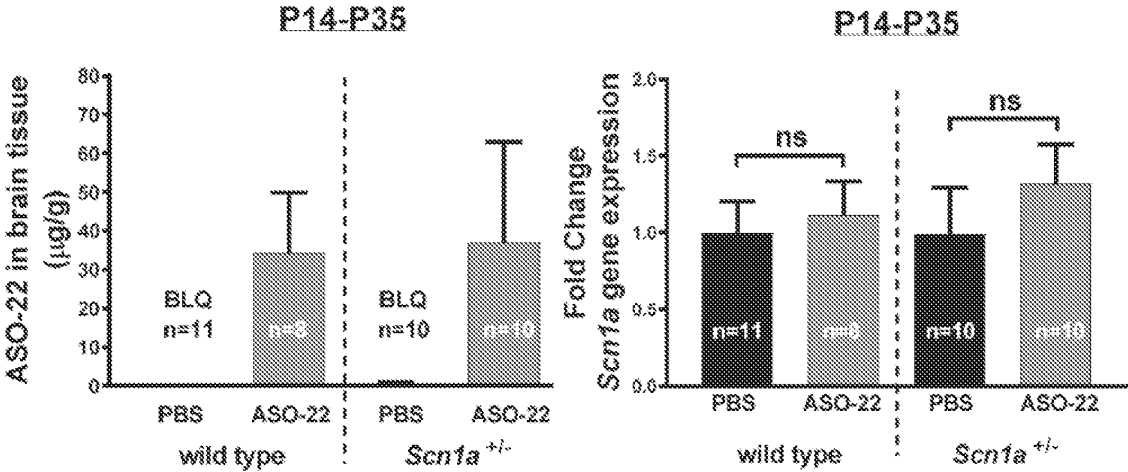


FIG. 7A

FIG. 7B

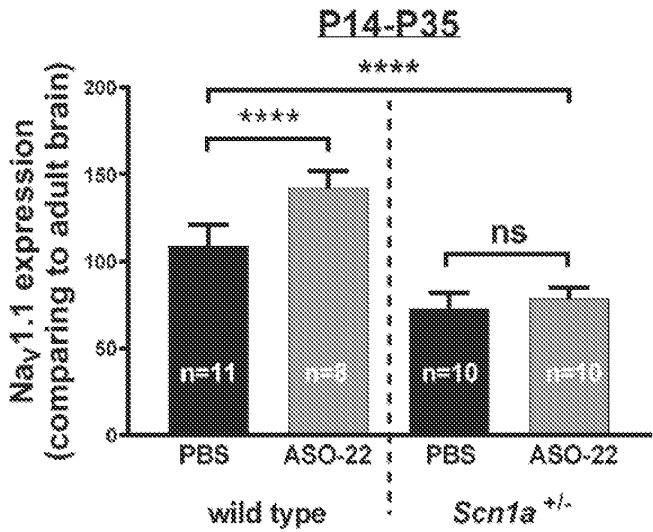


FIG. 7C

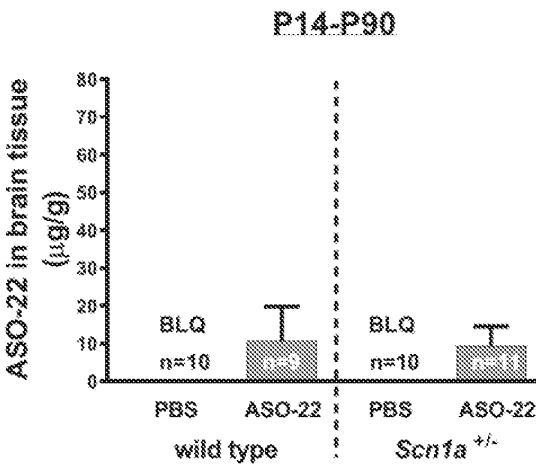


FIG. 7D

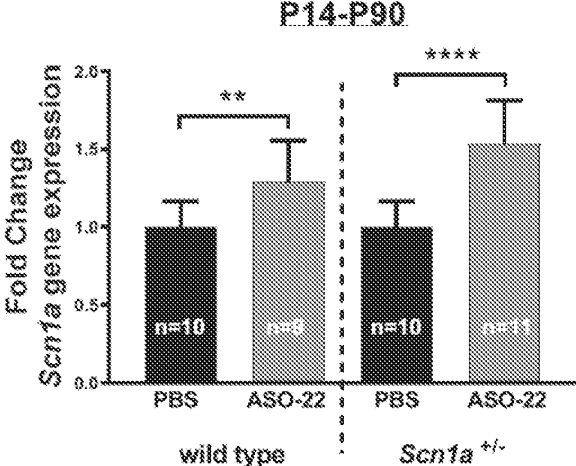


FIG. 7E

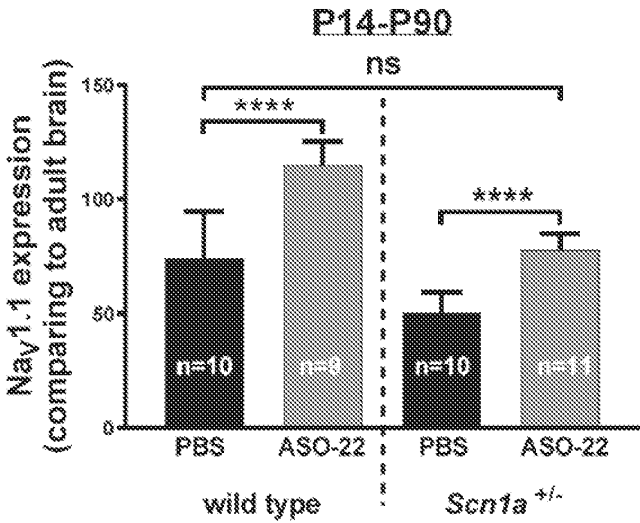


FIG. 7F

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

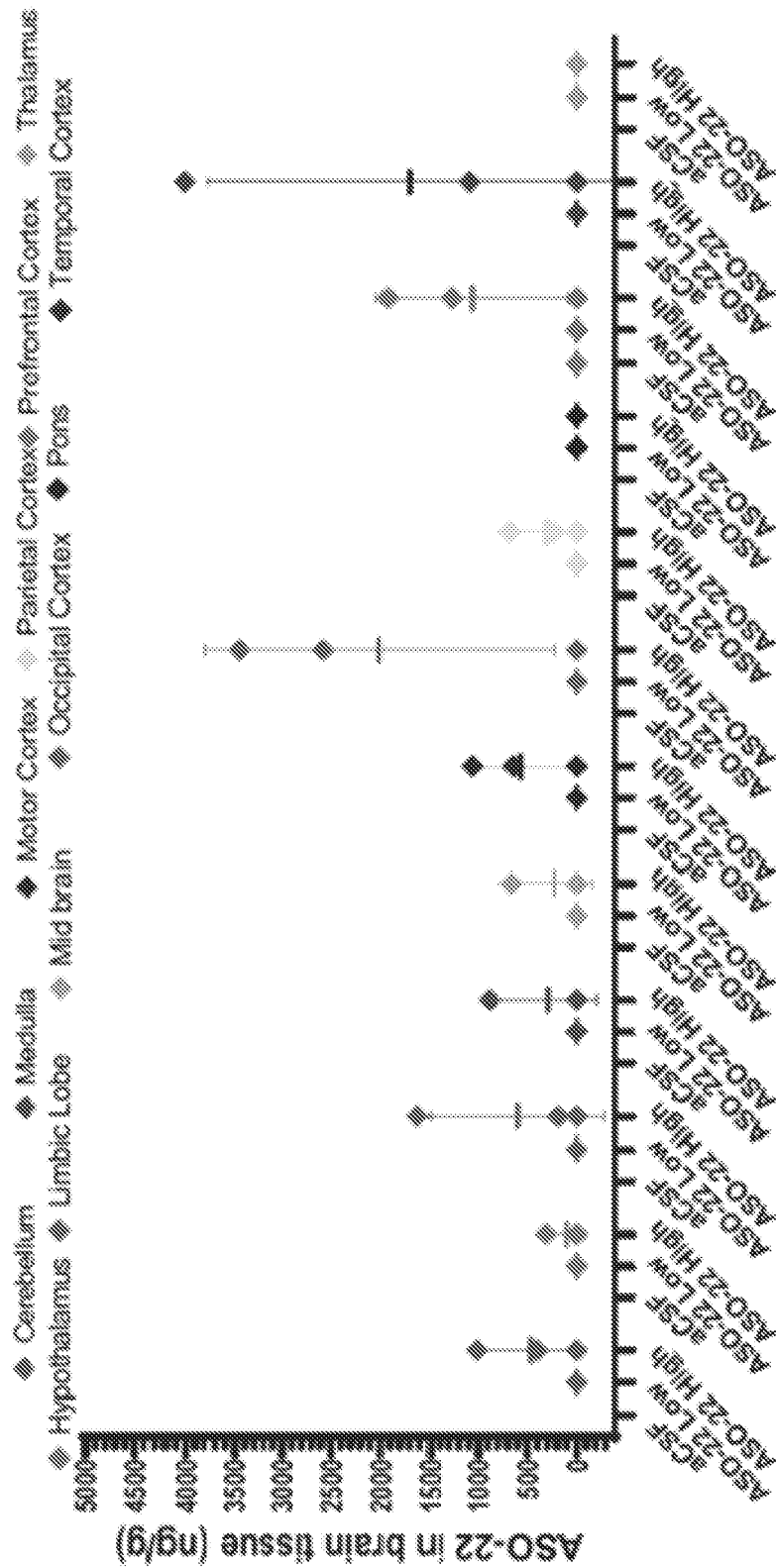


FIG. 9B

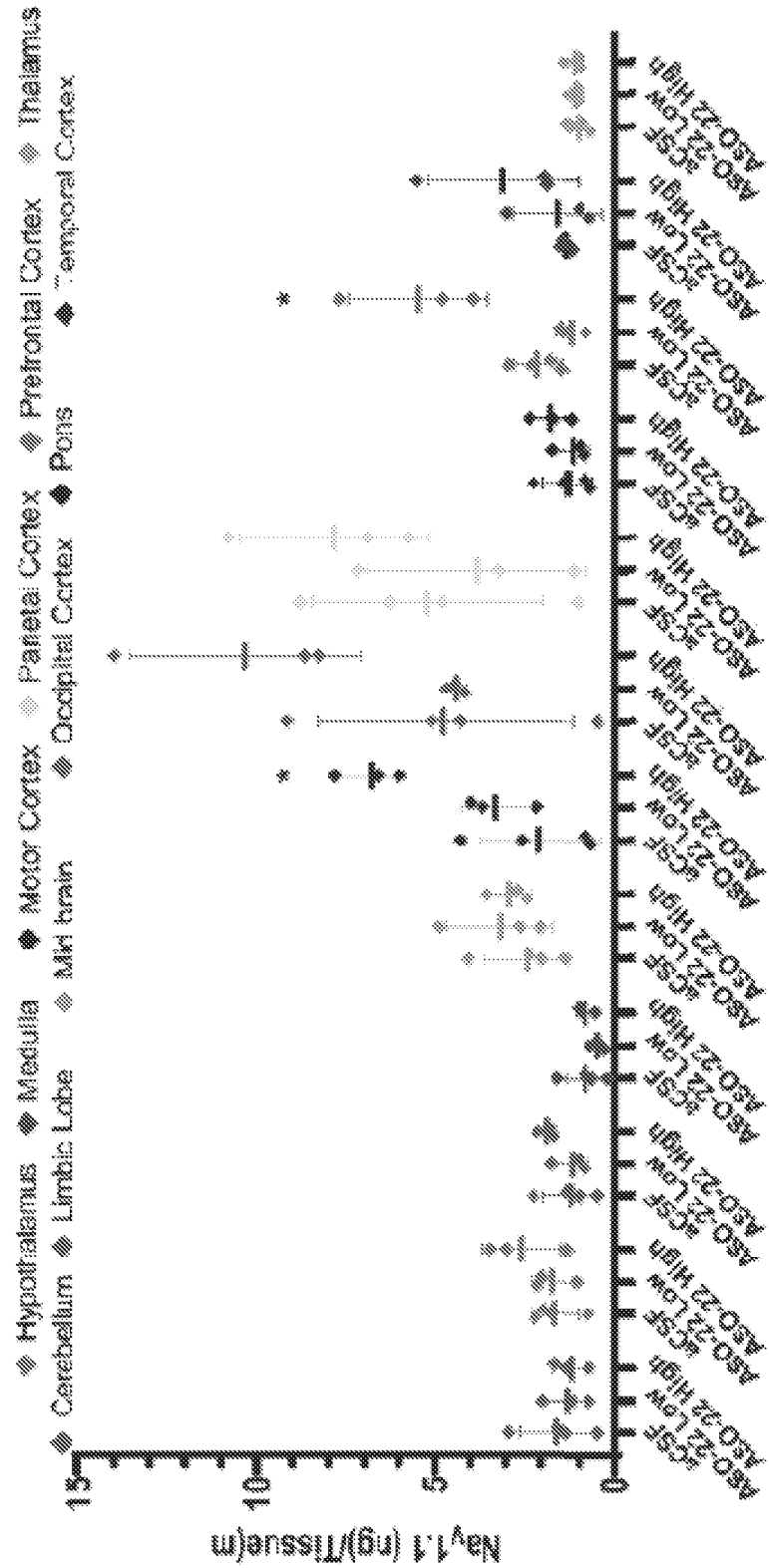


FIG. 10B

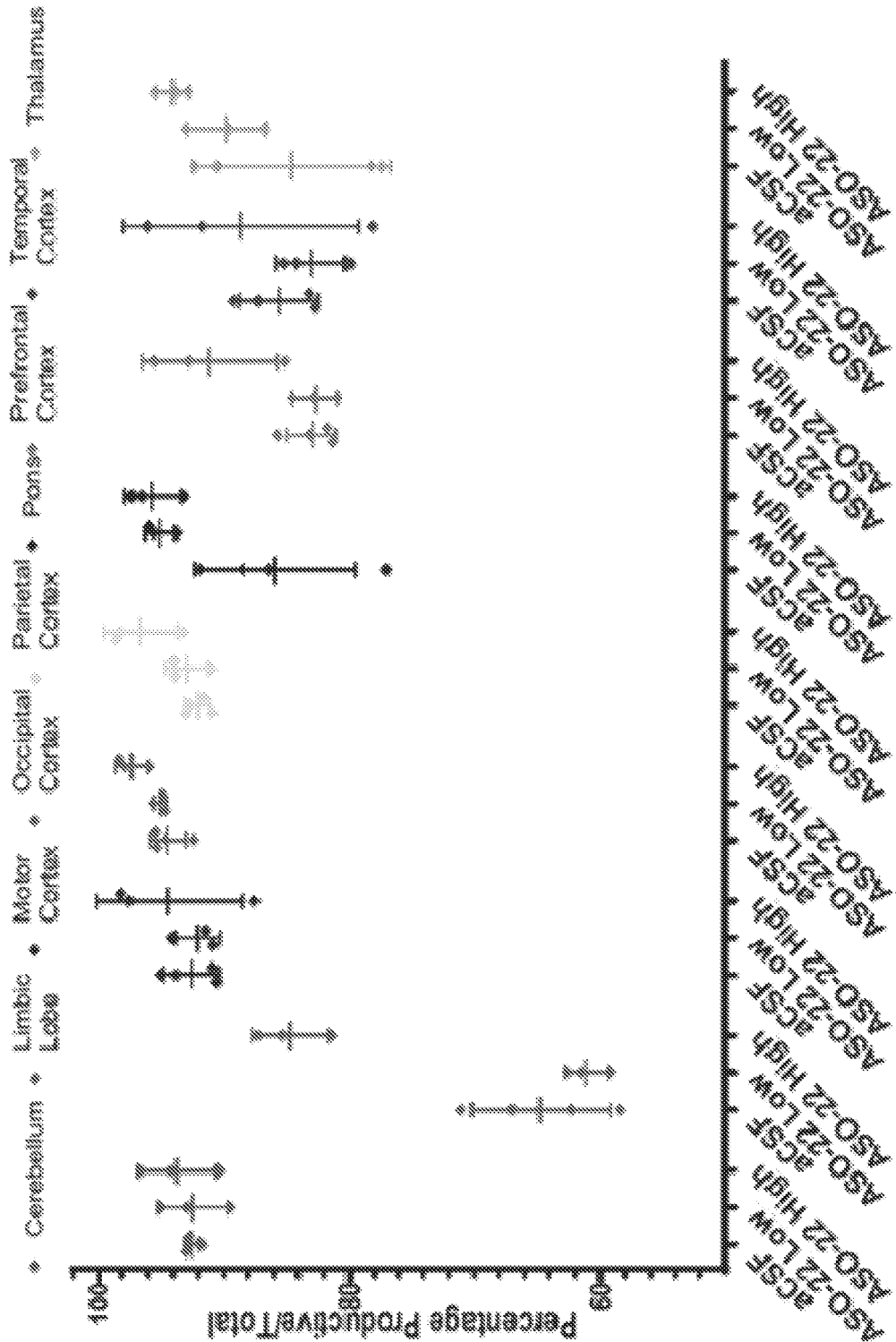


FIG. 11A

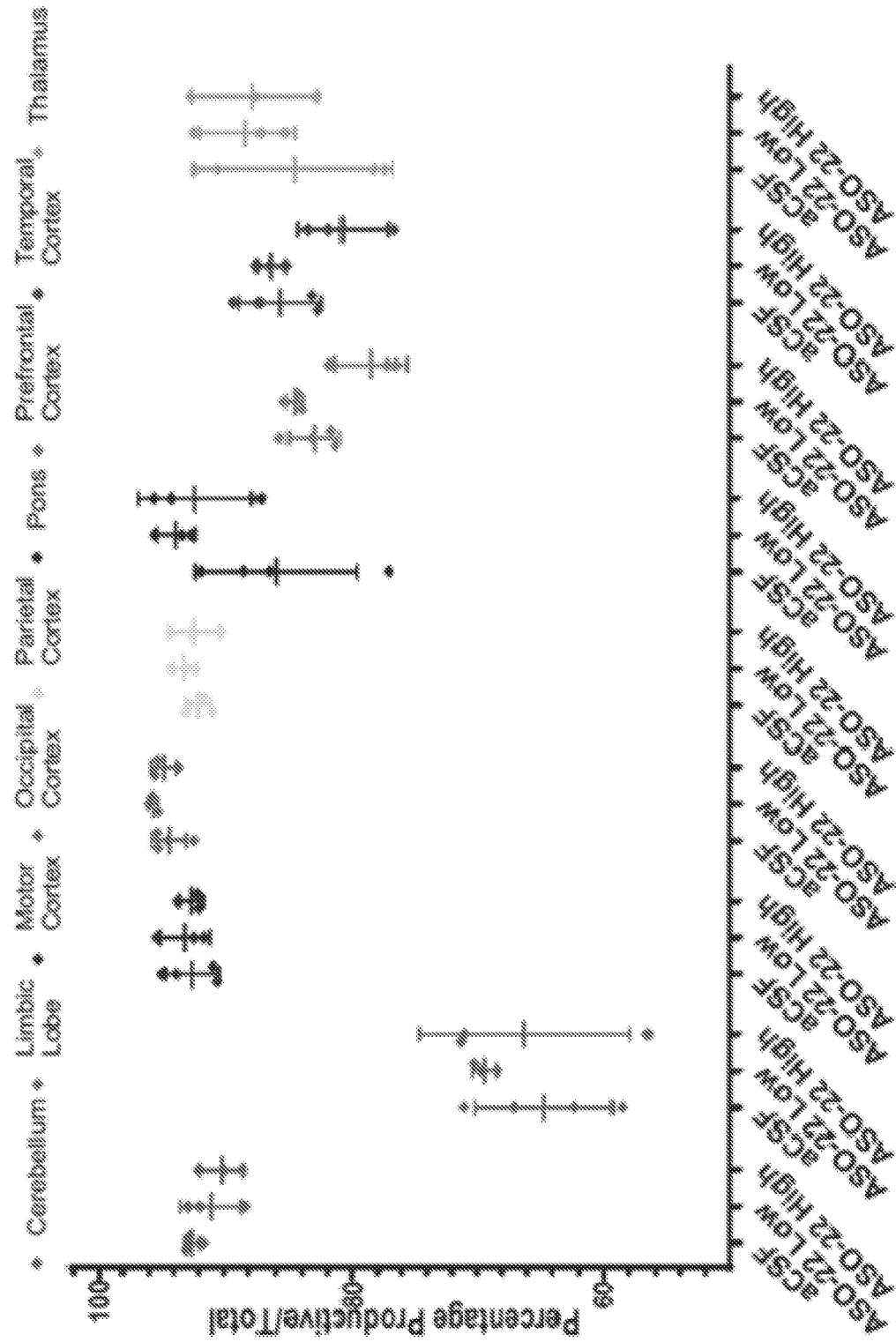


FIG. 11B

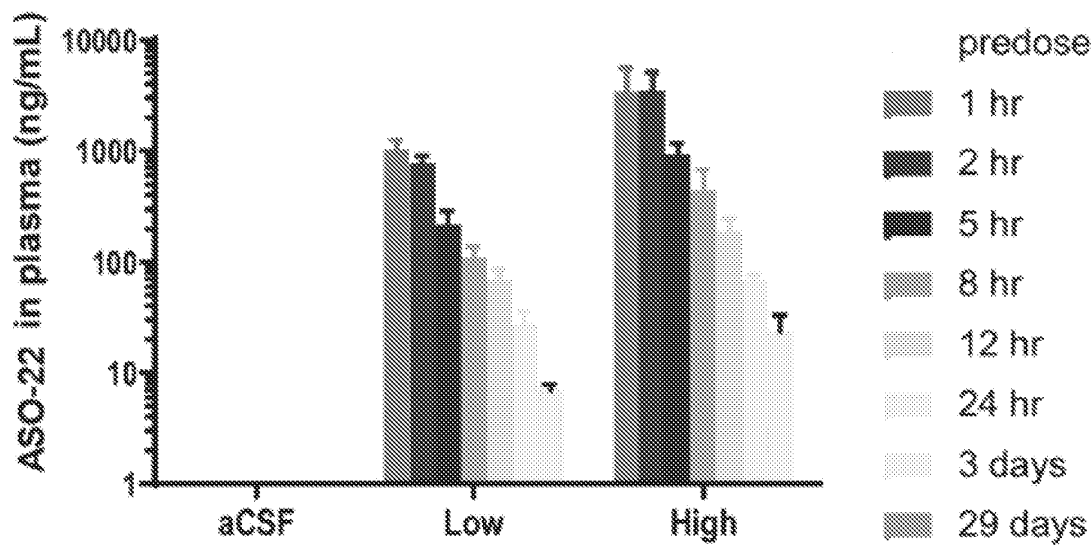


FIG. 12A

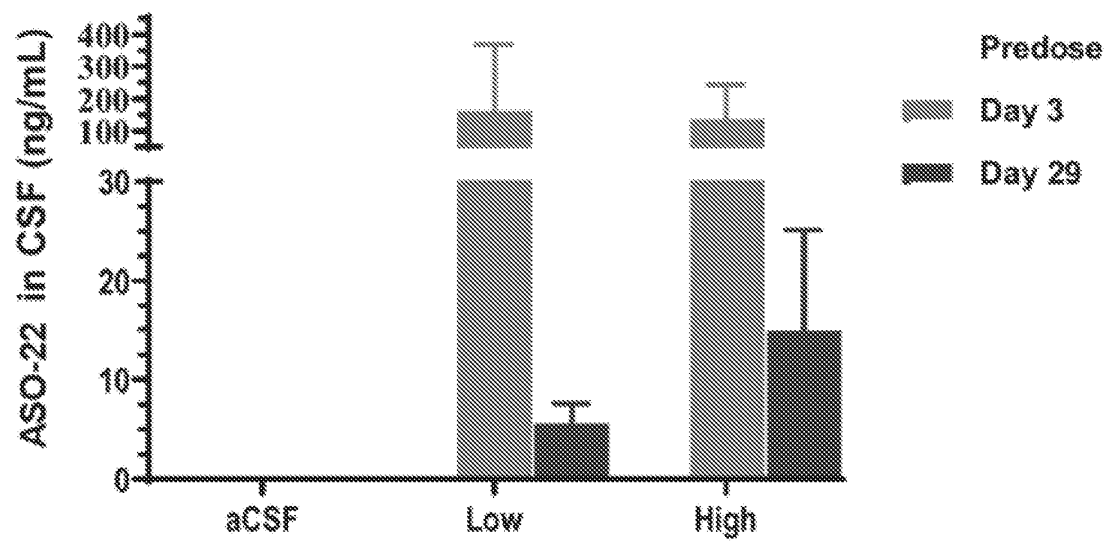


FIG. 12B

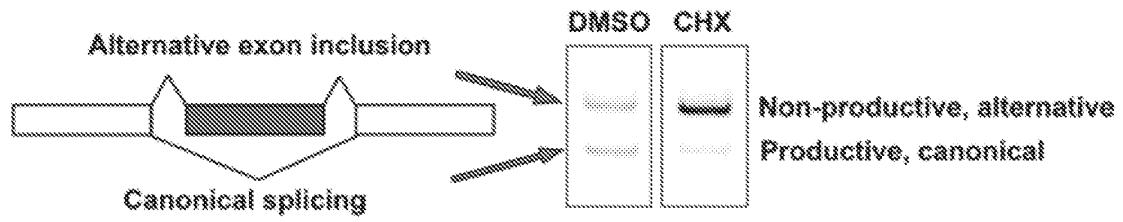


FIG. 13A

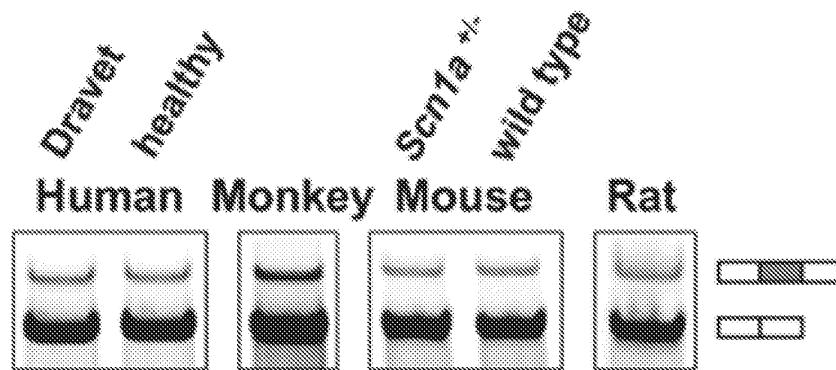


FIG. 13B

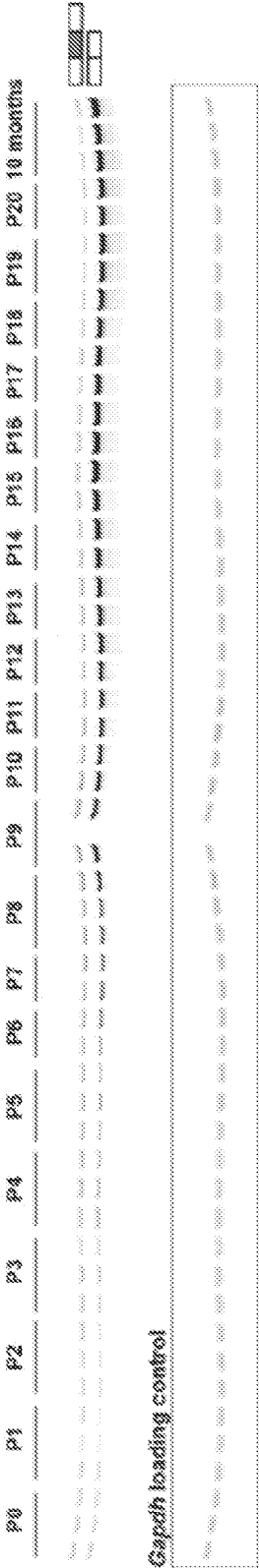


FIG. 13C

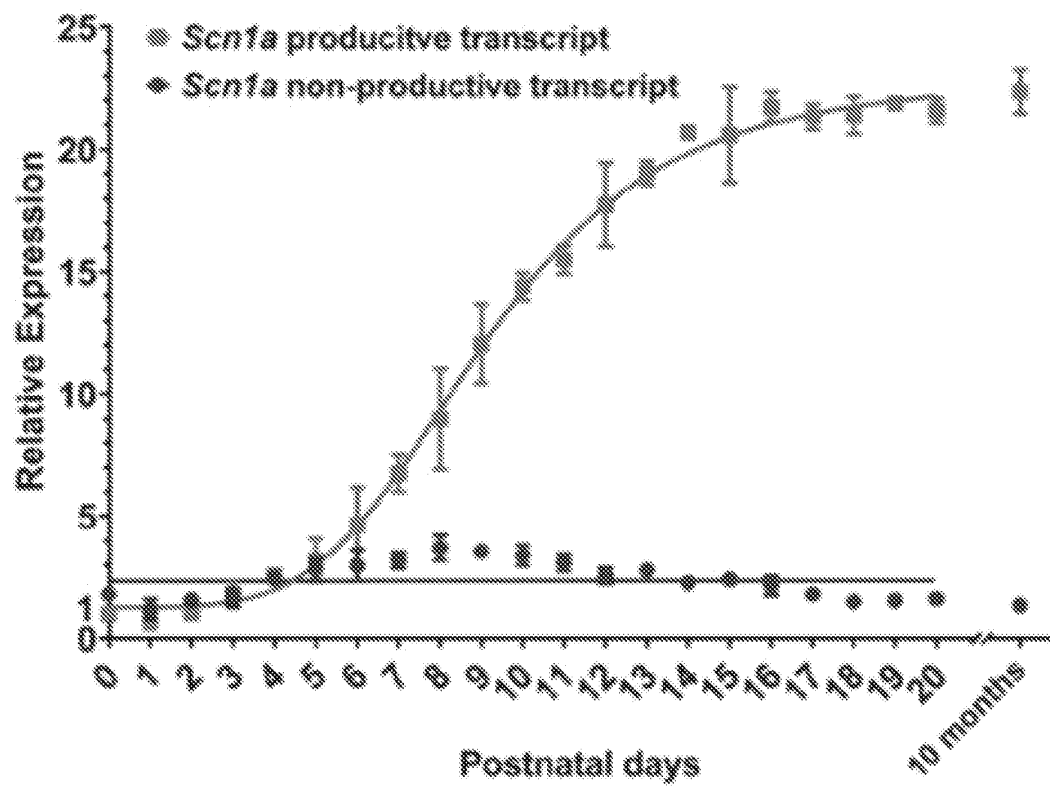


FIG. 13D



FIG. 14B

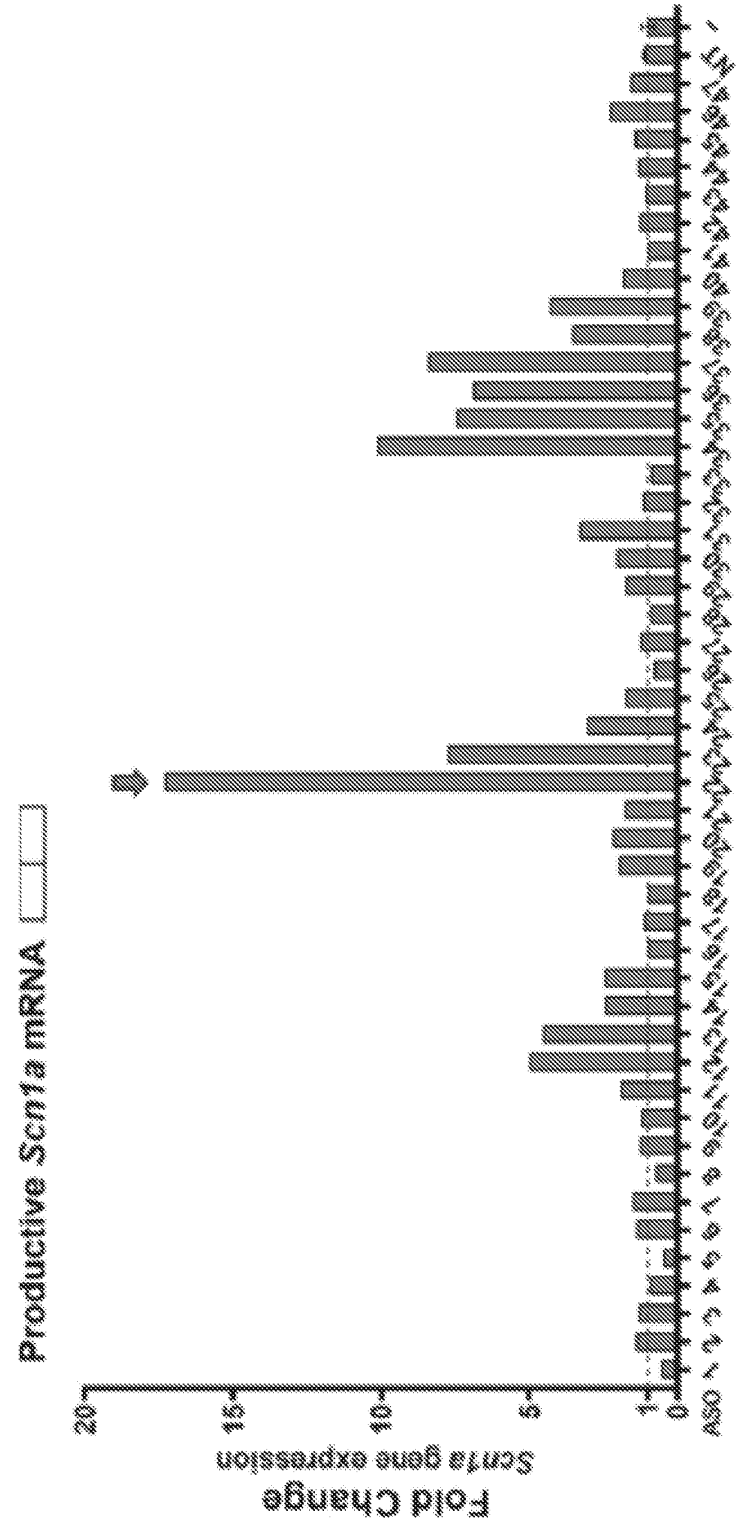


FIG. 14C

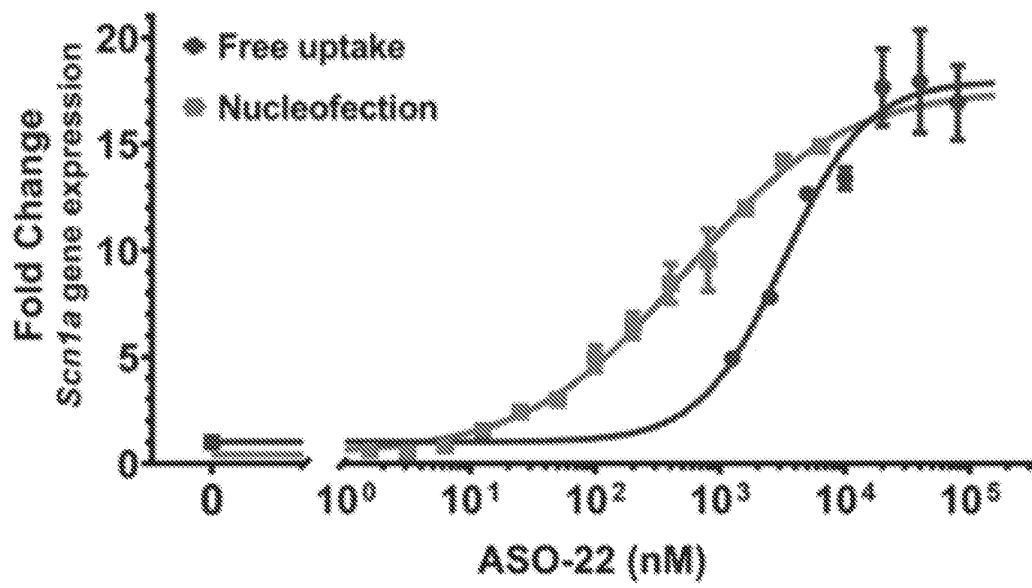


FIG. 14D

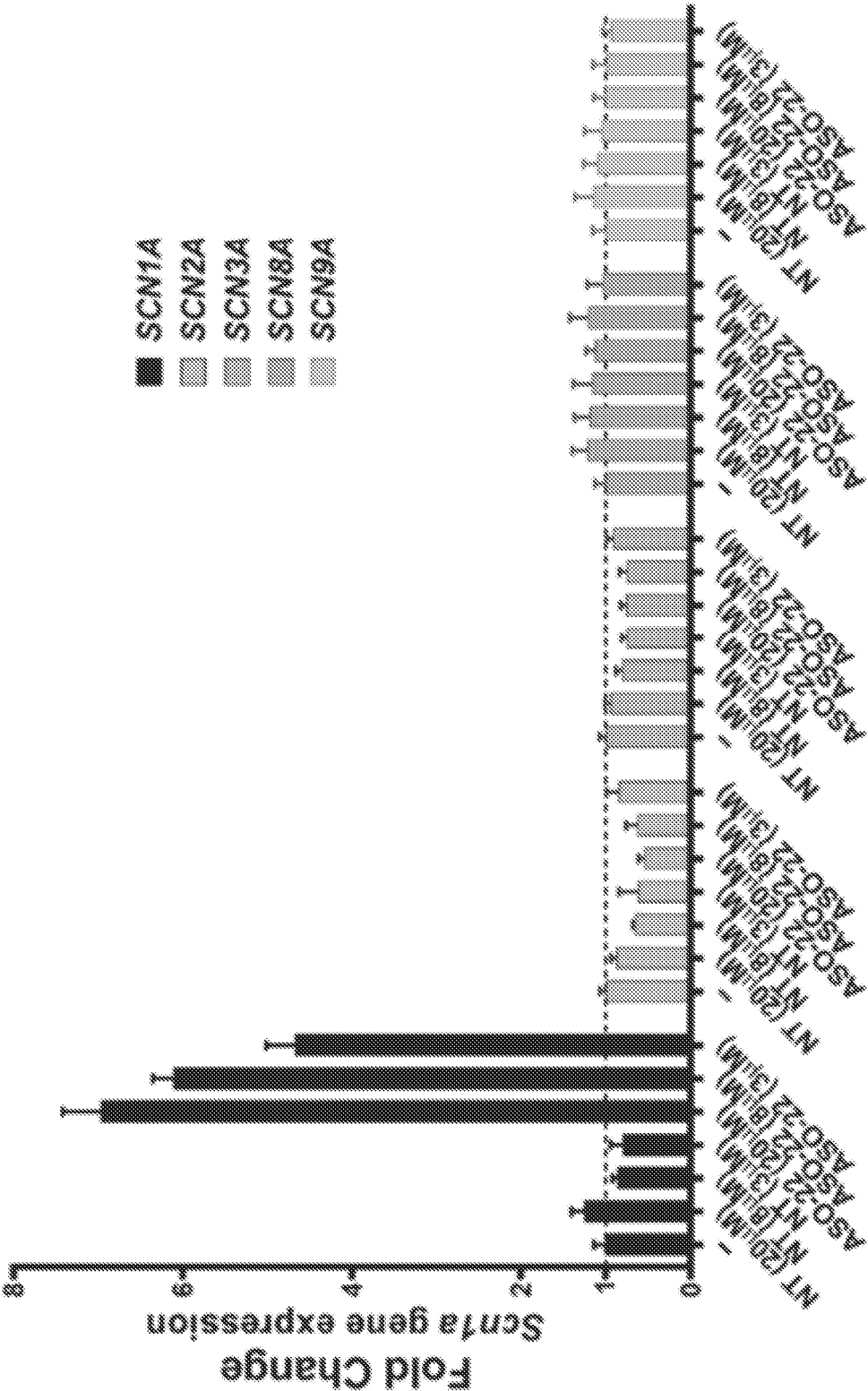


FIG. 14E

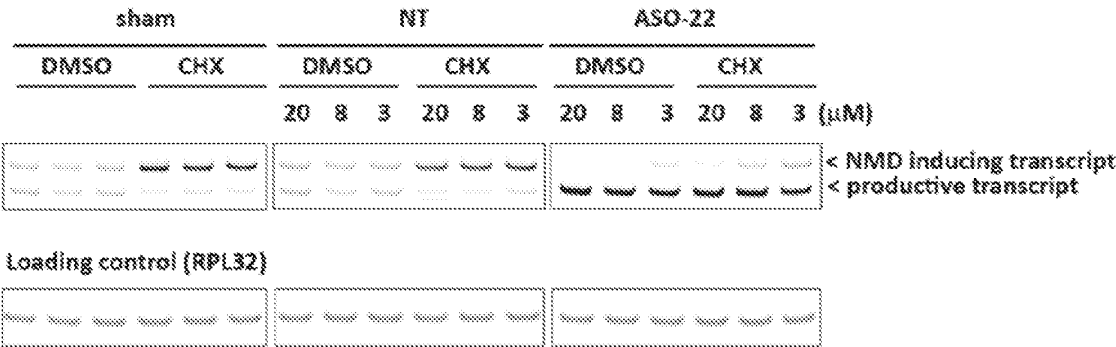


FIG. 15A

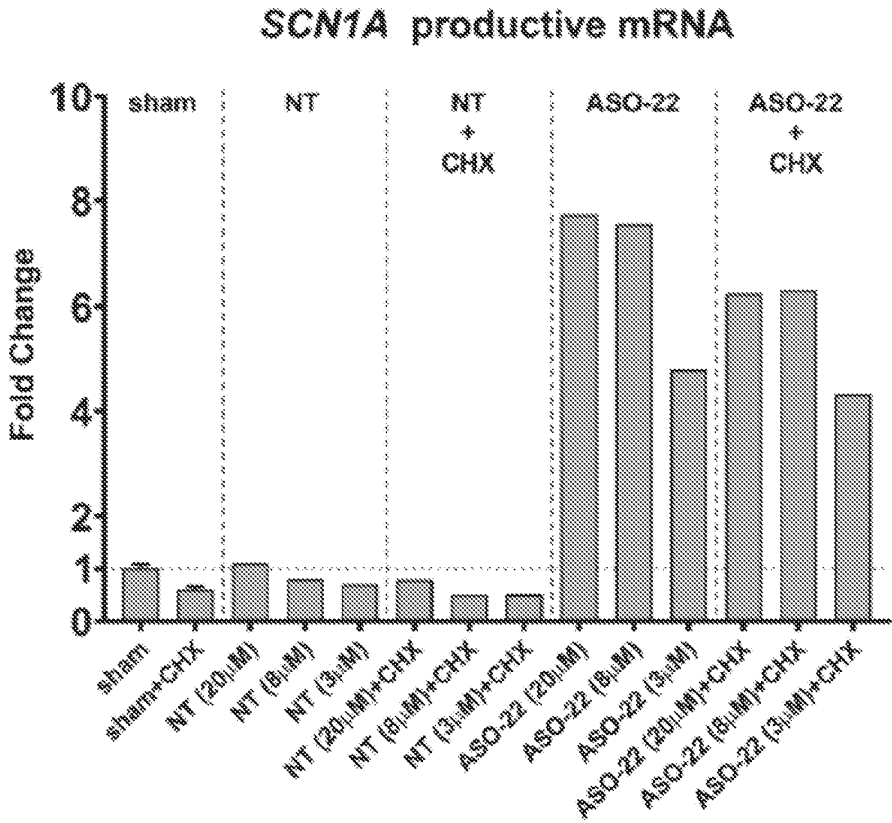


FIG. 15B

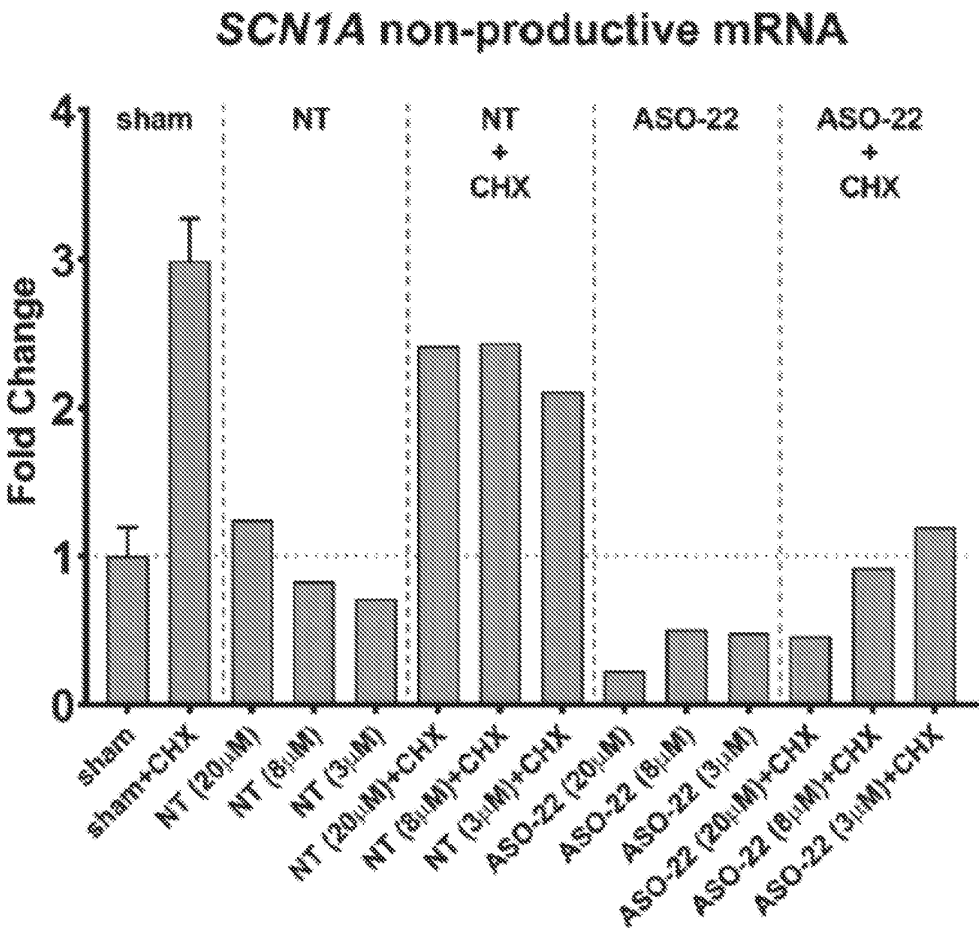


FIG. 15C

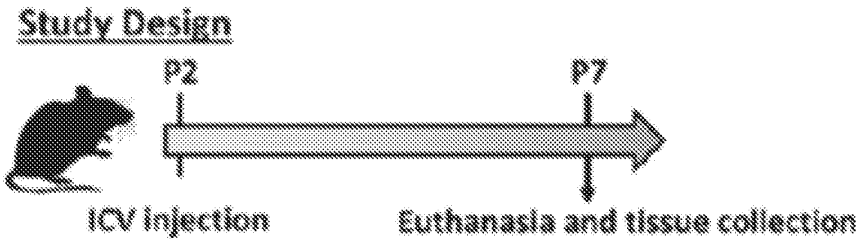


FIG. 16A

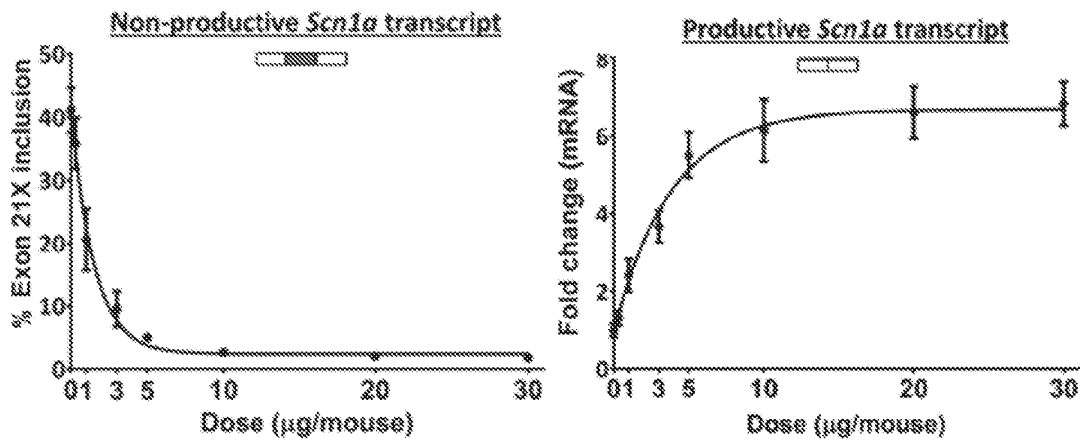


FIG. 16B

FIG. 16C

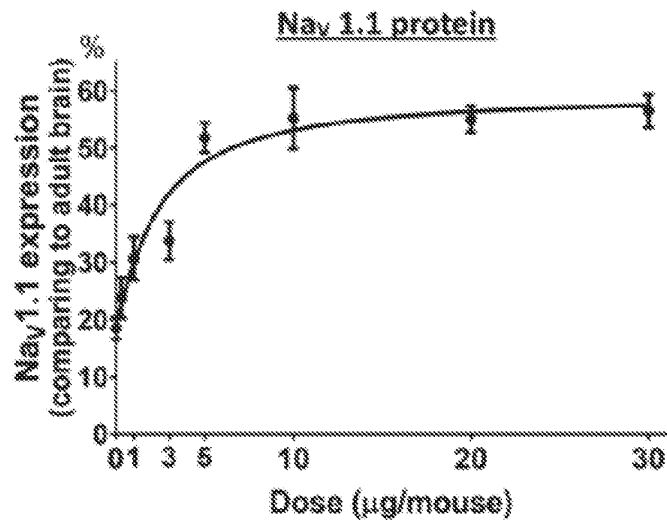


FIG. 16D

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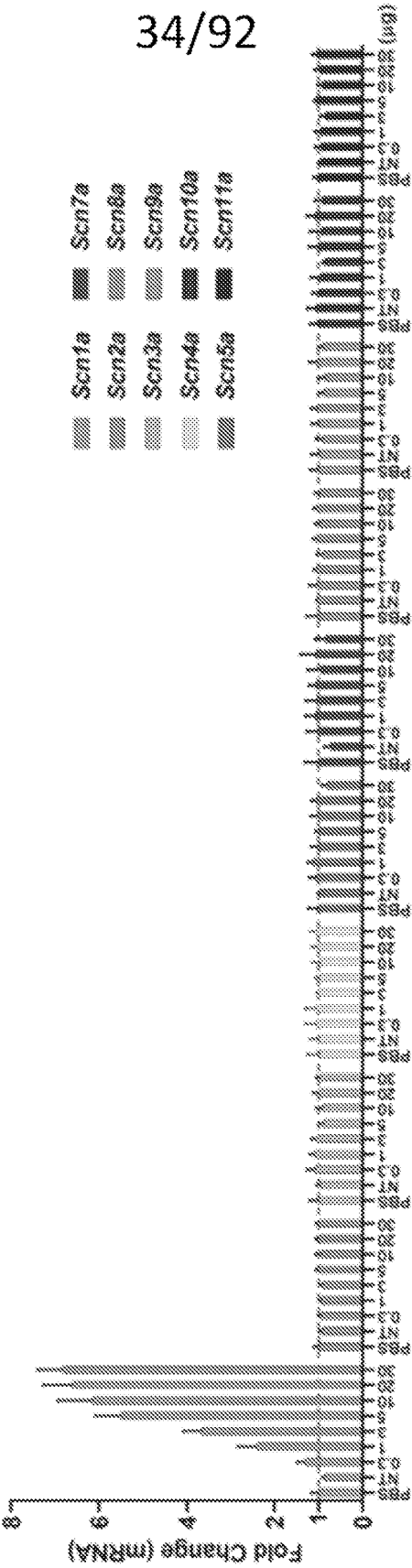


FIG. 16E

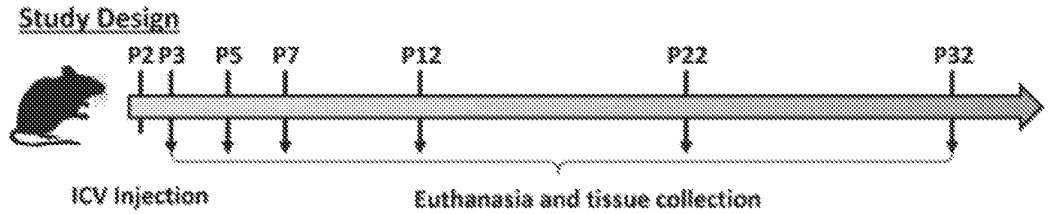


FIG. 16F

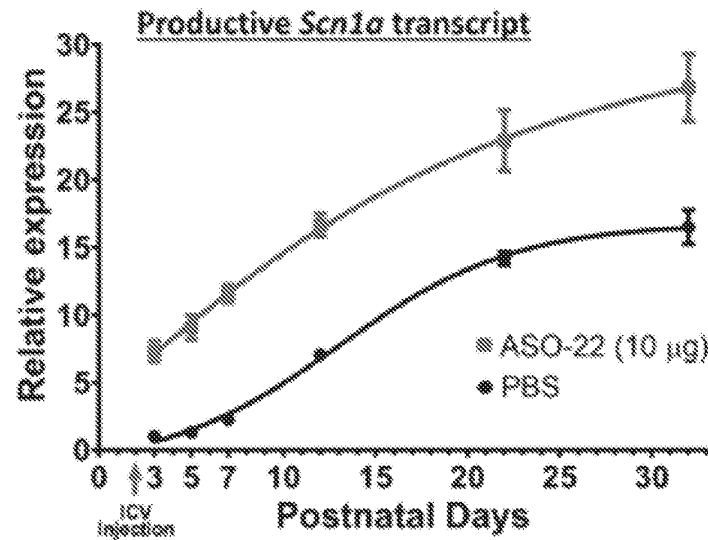


FIG. 16G

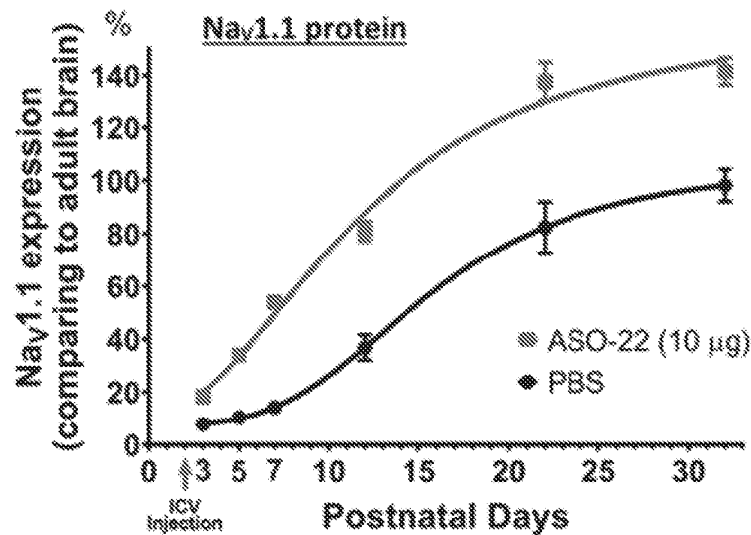


FIG. 16H

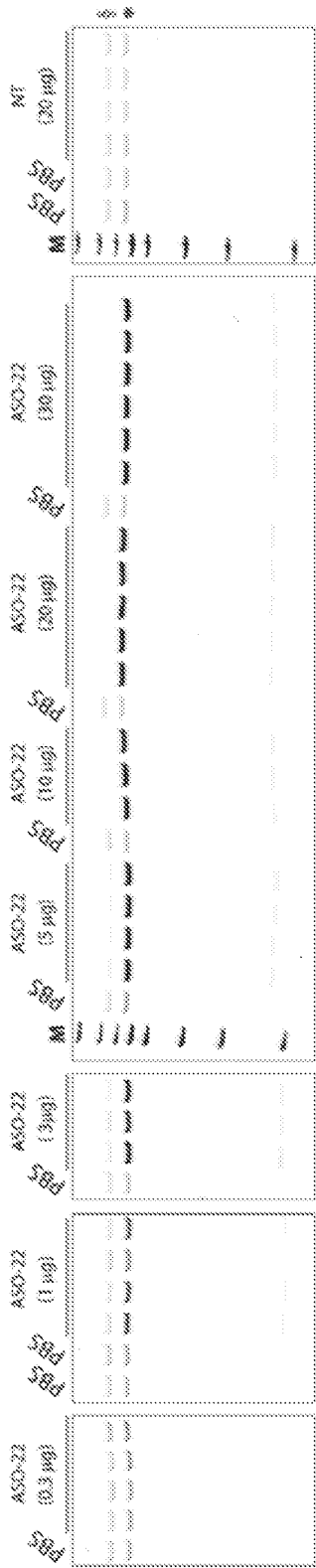


FIG. 17

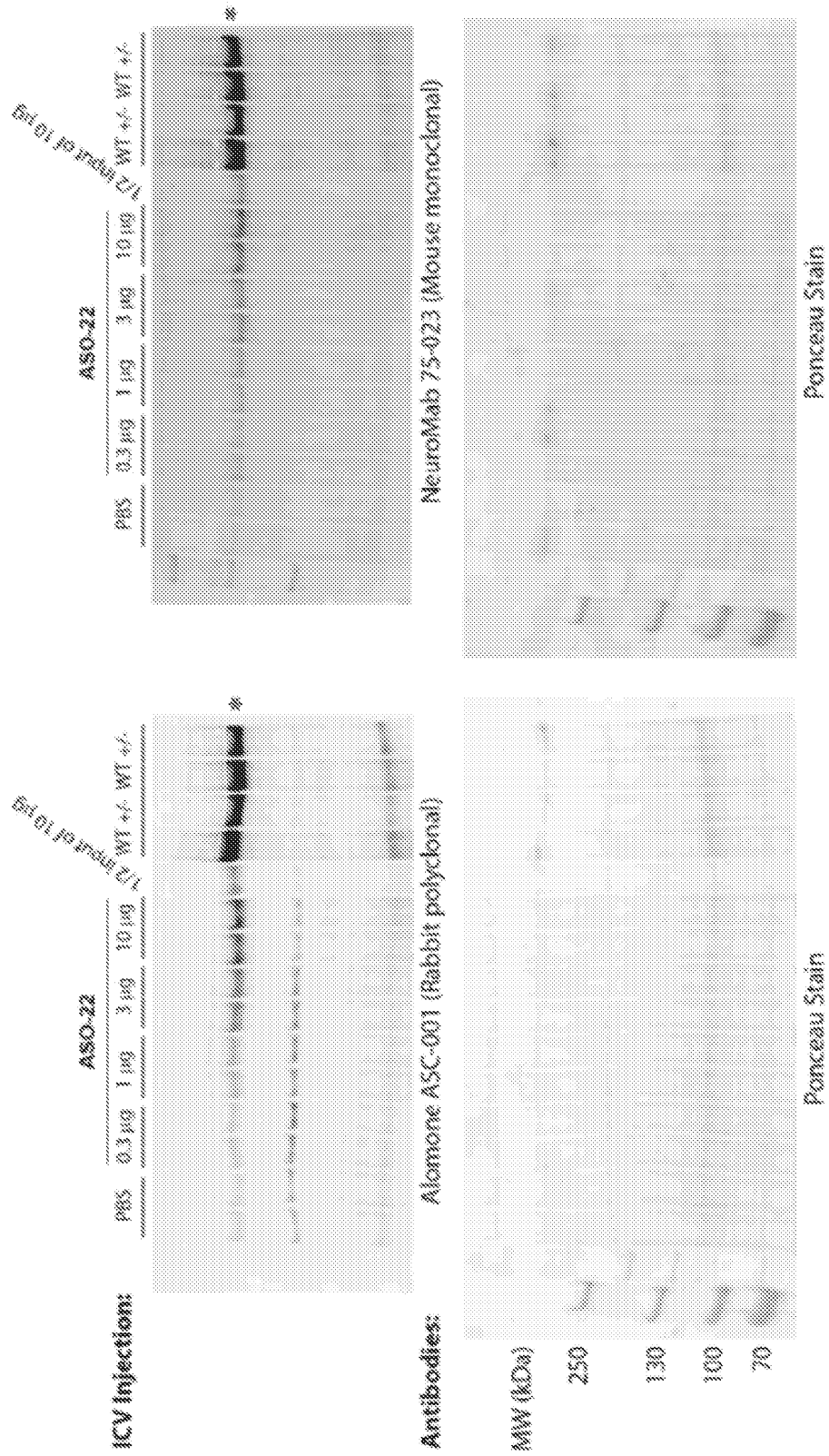


FIG. 18

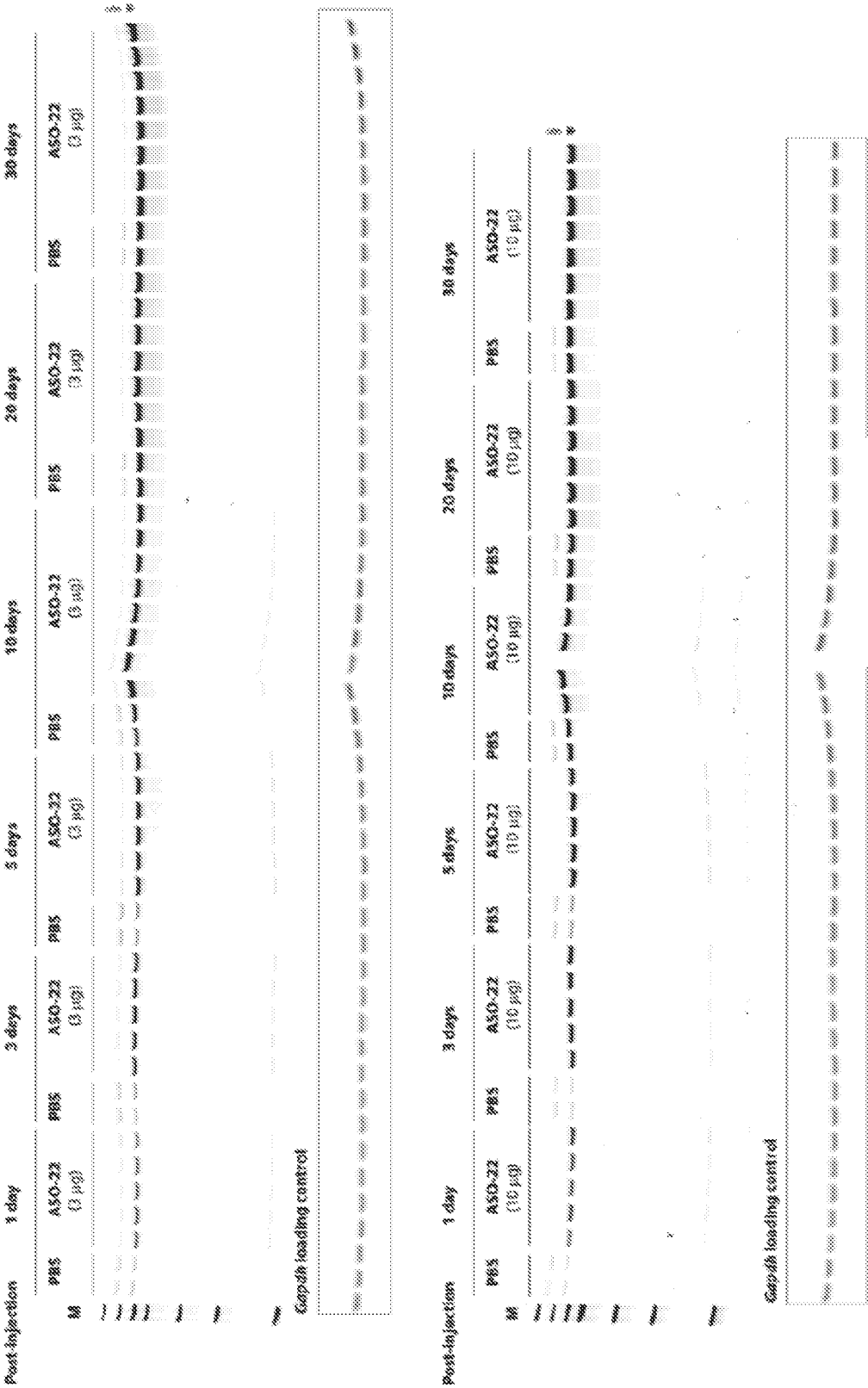
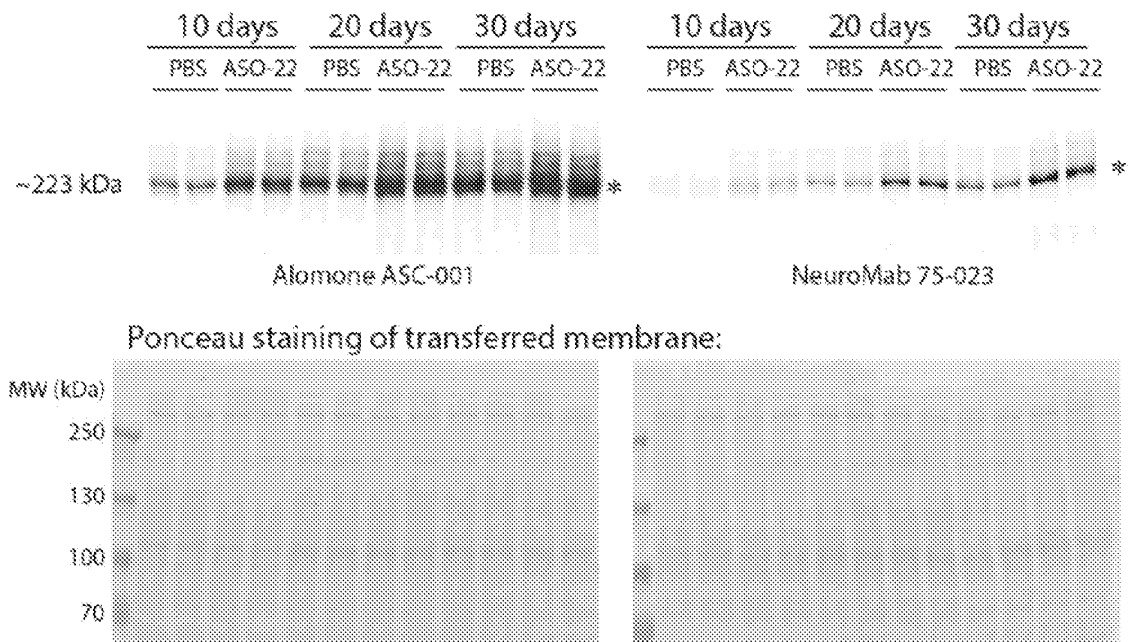


FIG. 19



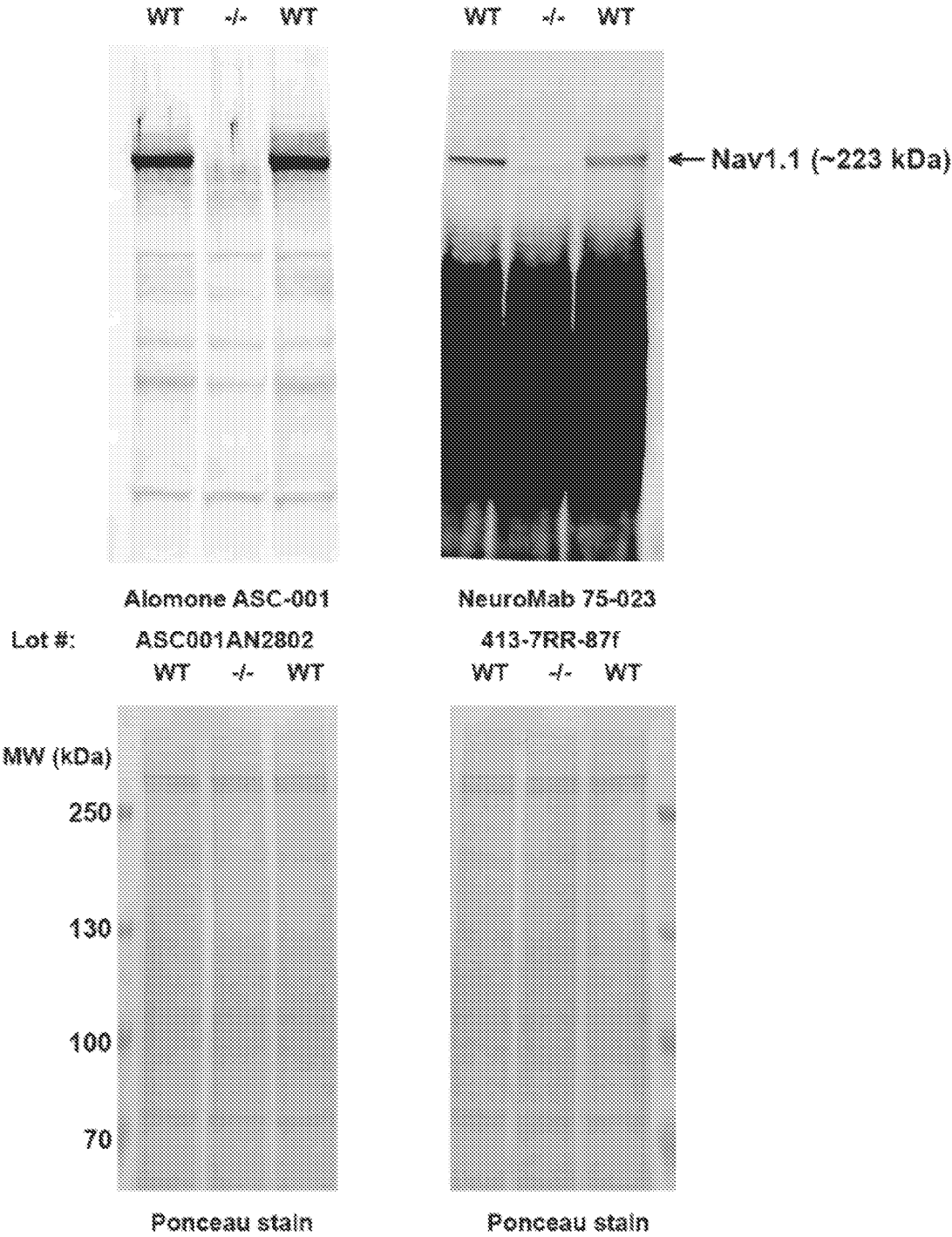


FIG. 21

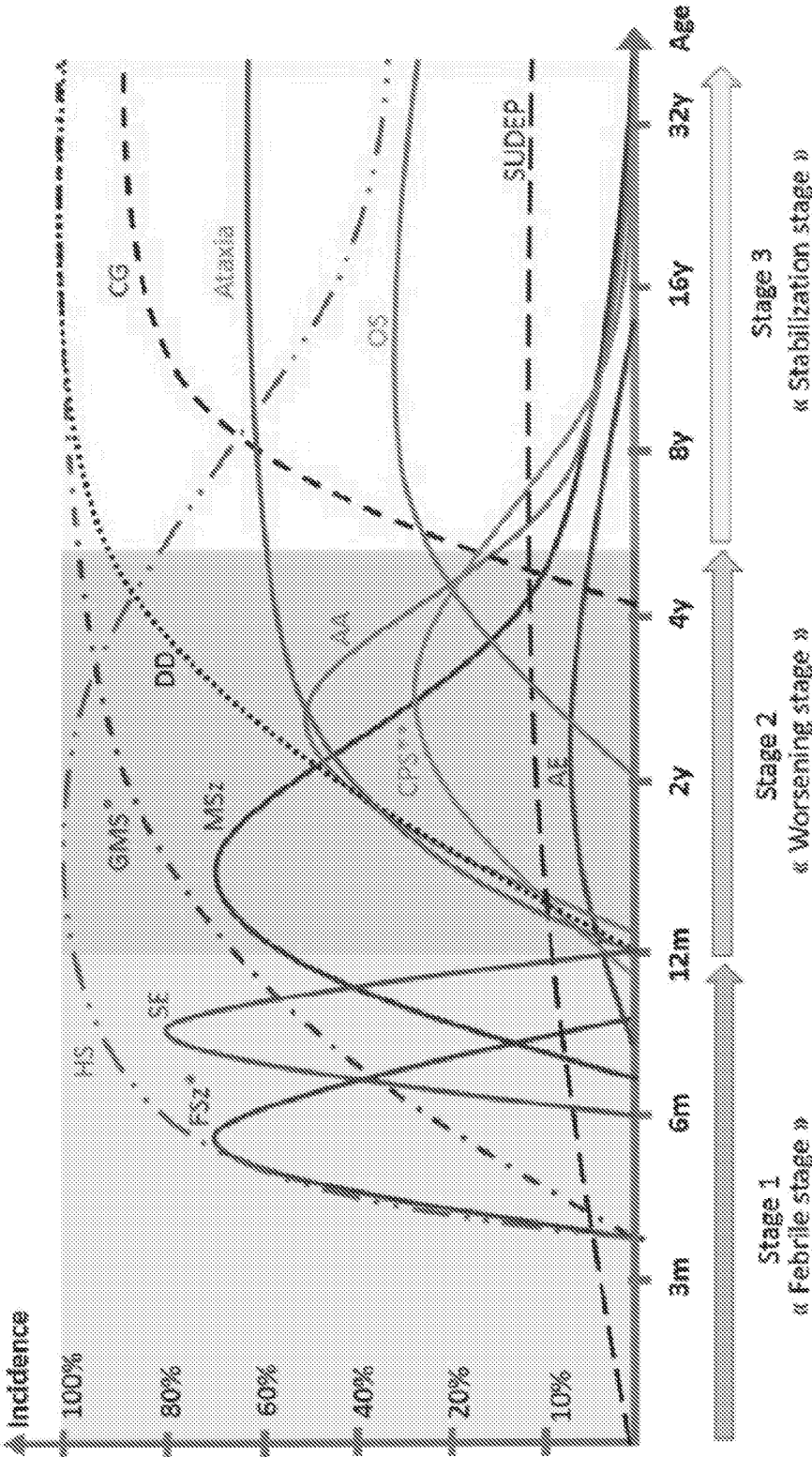


FIG. 22

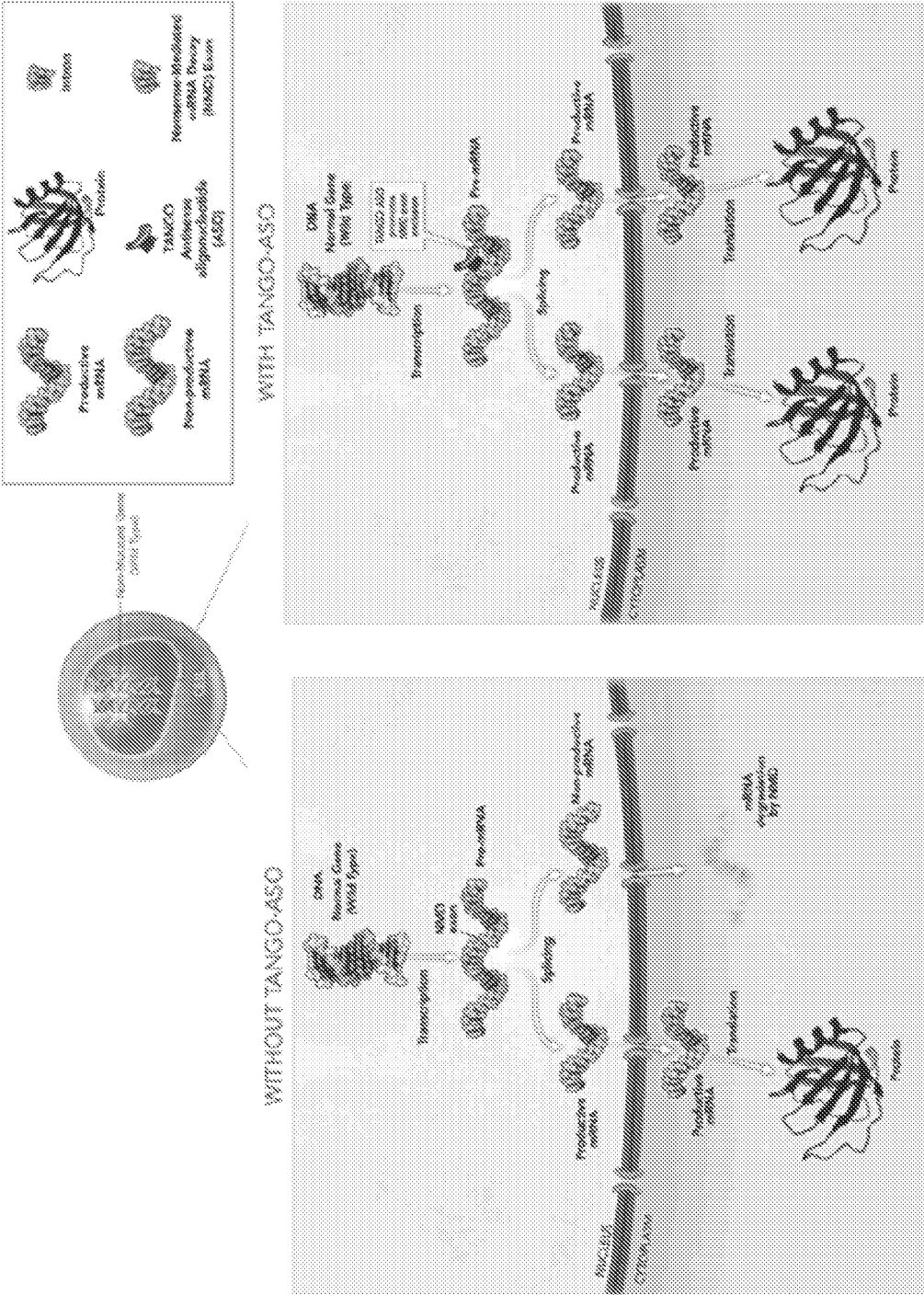


FIG. 23

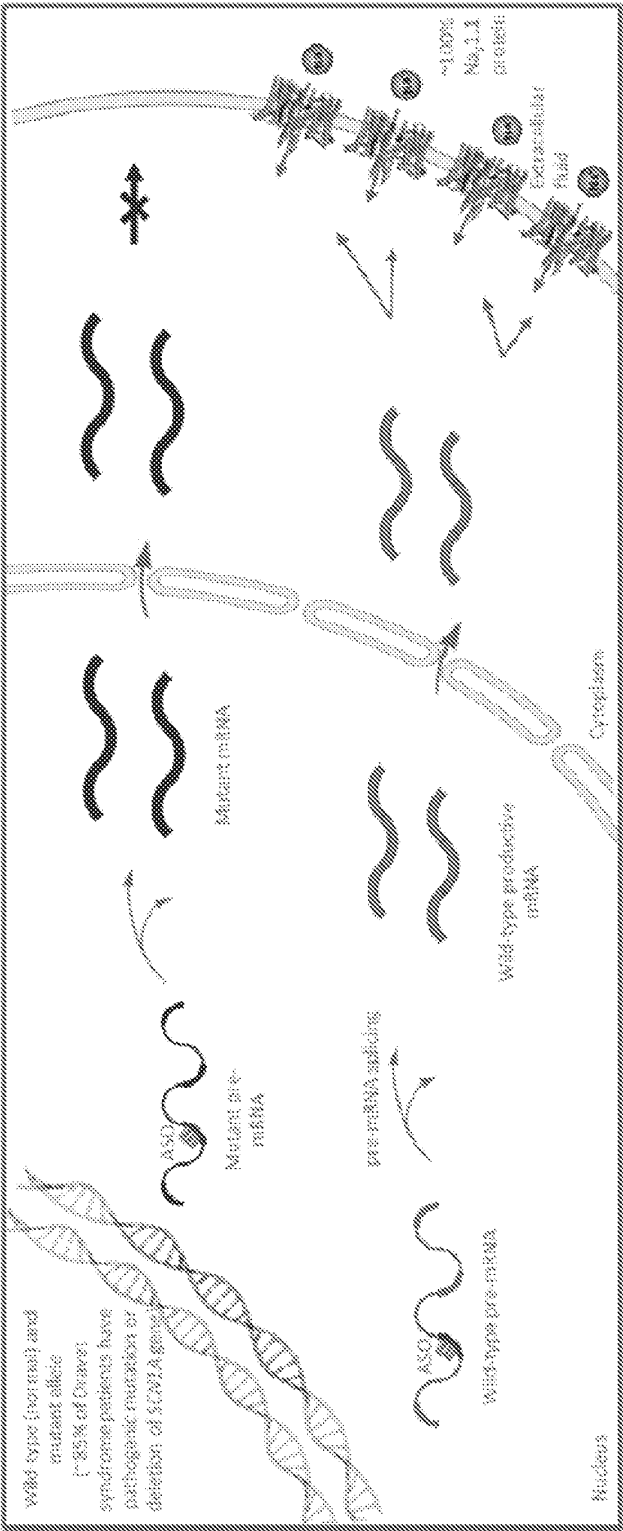


FIG. 24

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

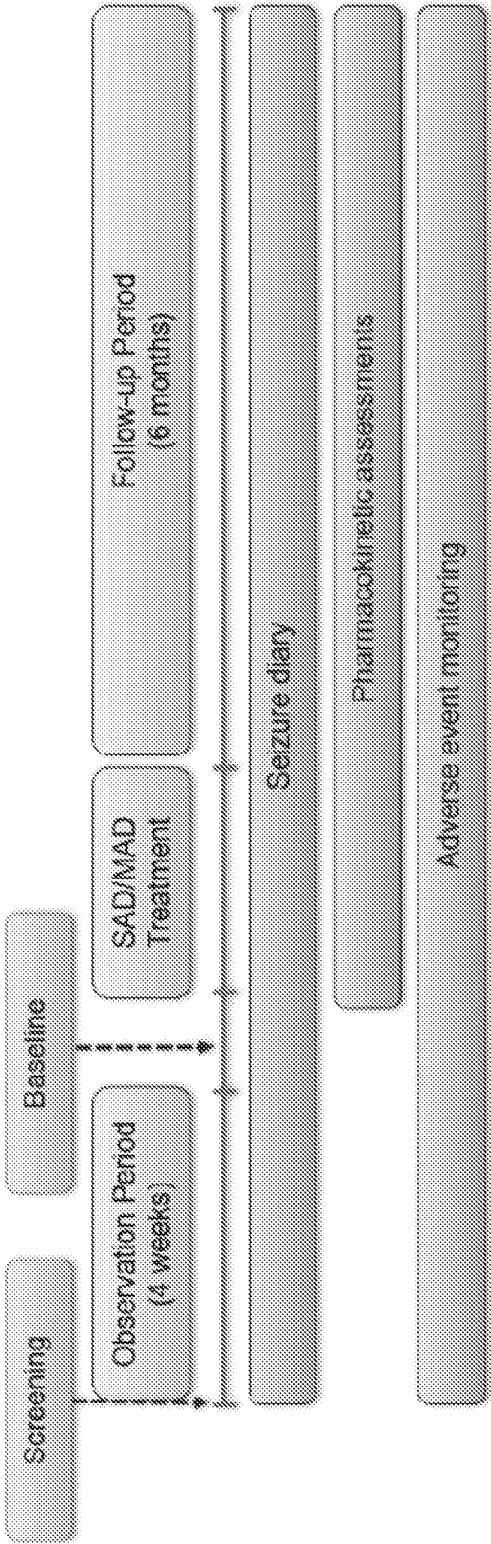


FIG. 26

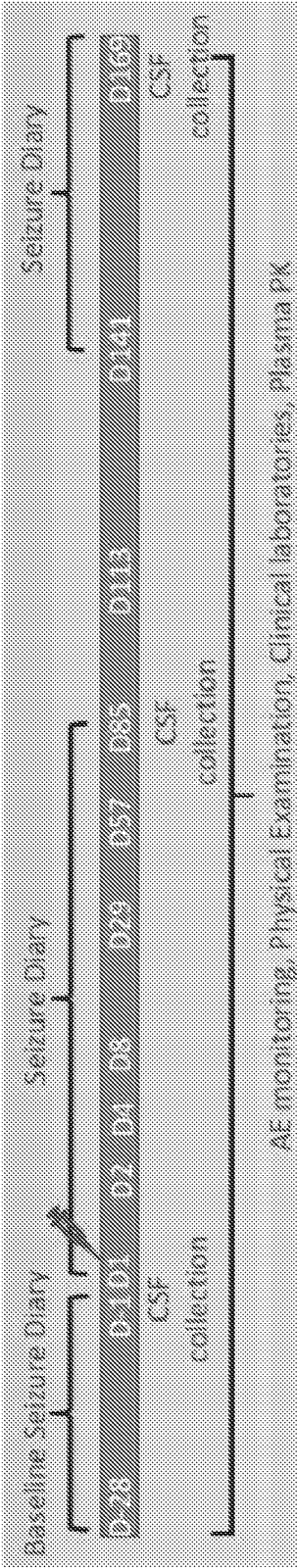
Inclusion Criteria	Exclusion Criteria
Aged 2-18 years (inclusive)	Known pathogenic mutation in another gene that causes epilepsy
DS onset <12 months of age with recurrent seizures (focal motor, hemiconvulsive, or generalized tonic-clonic) - No history of causal MRI lesion (MRI not required) - No other 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



MAD Study Assessments

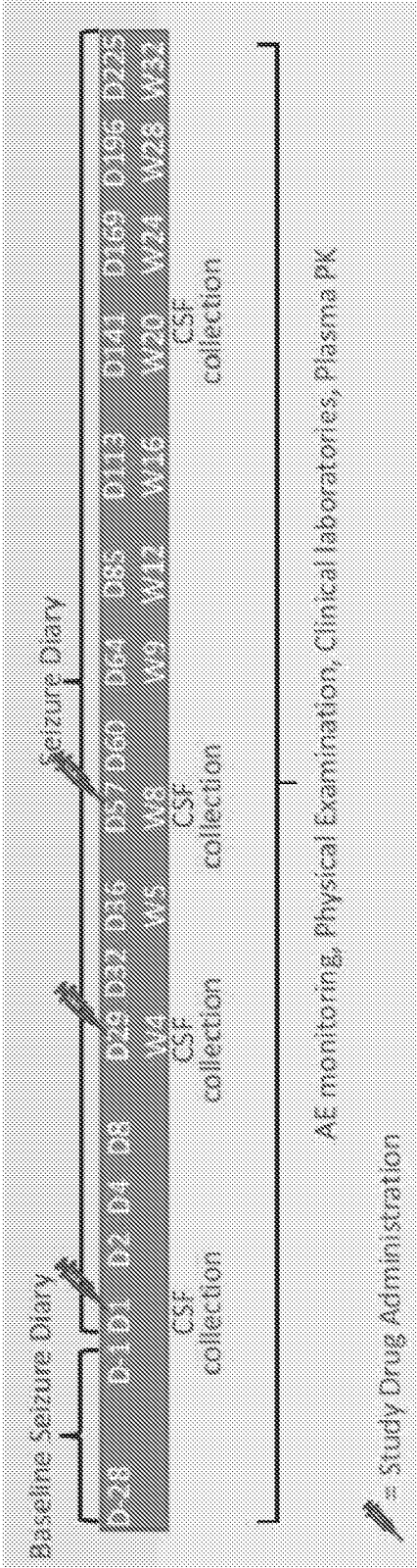


FIG. 29

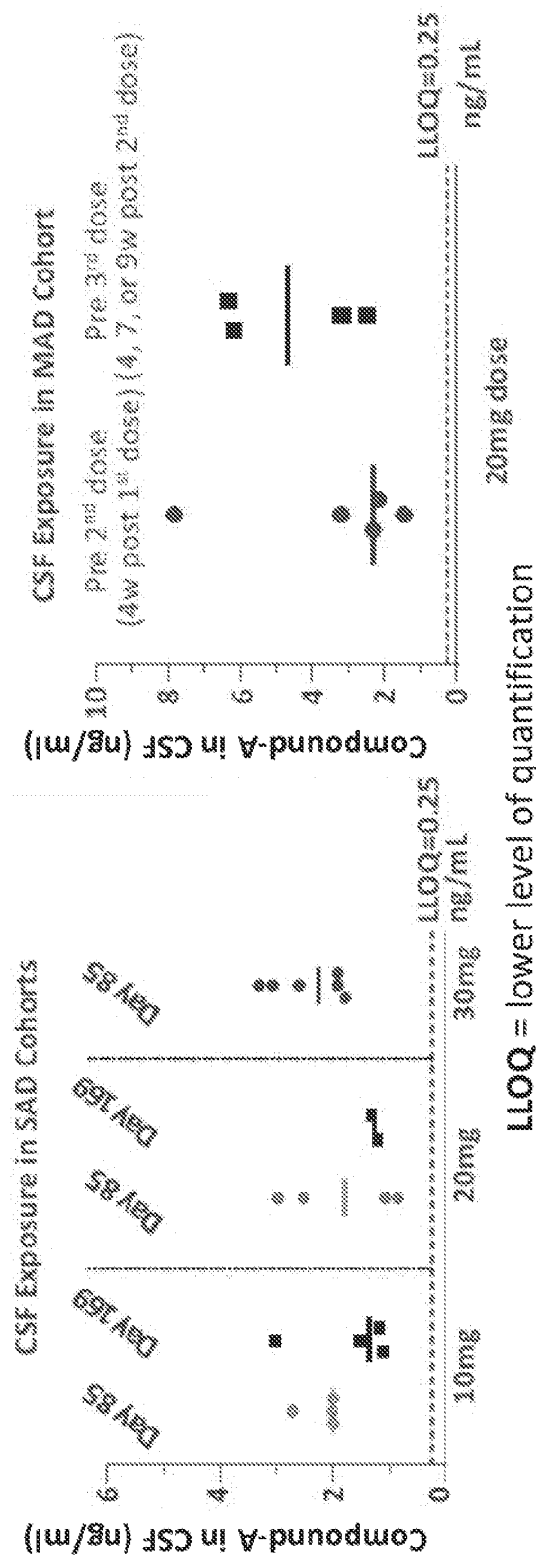


FIG. 30

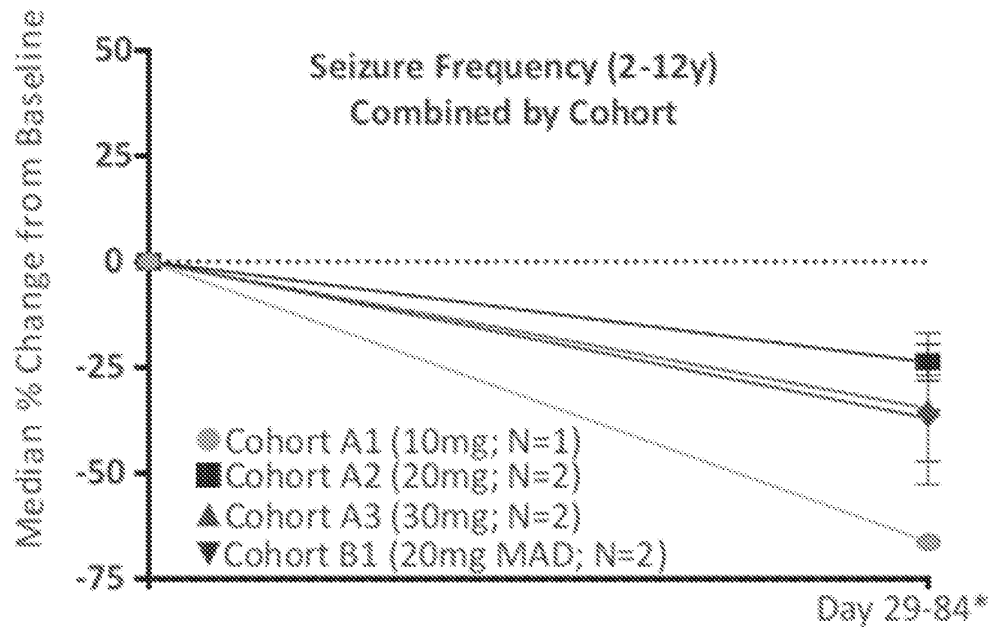


FIG. 31A

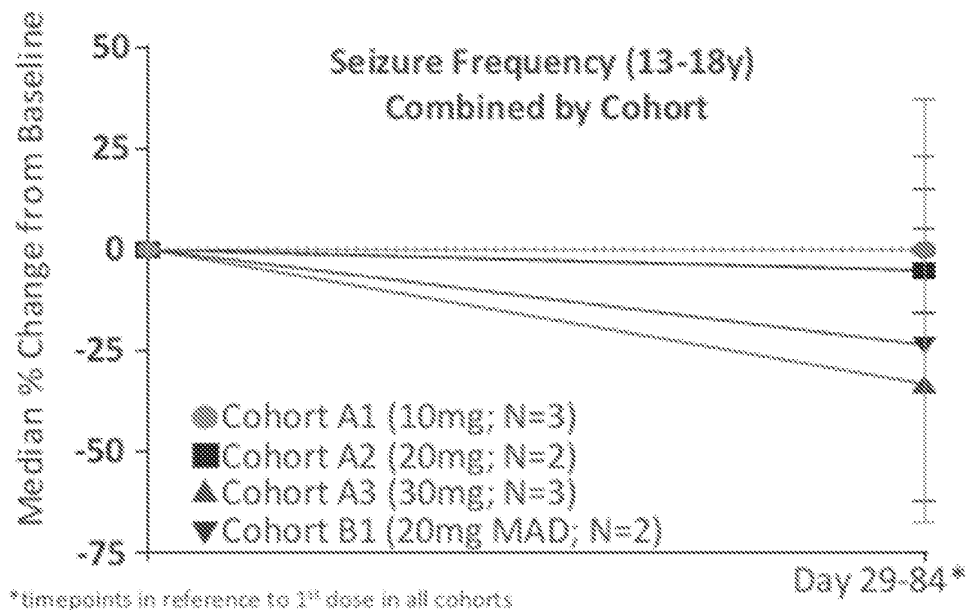


FIG. 31B

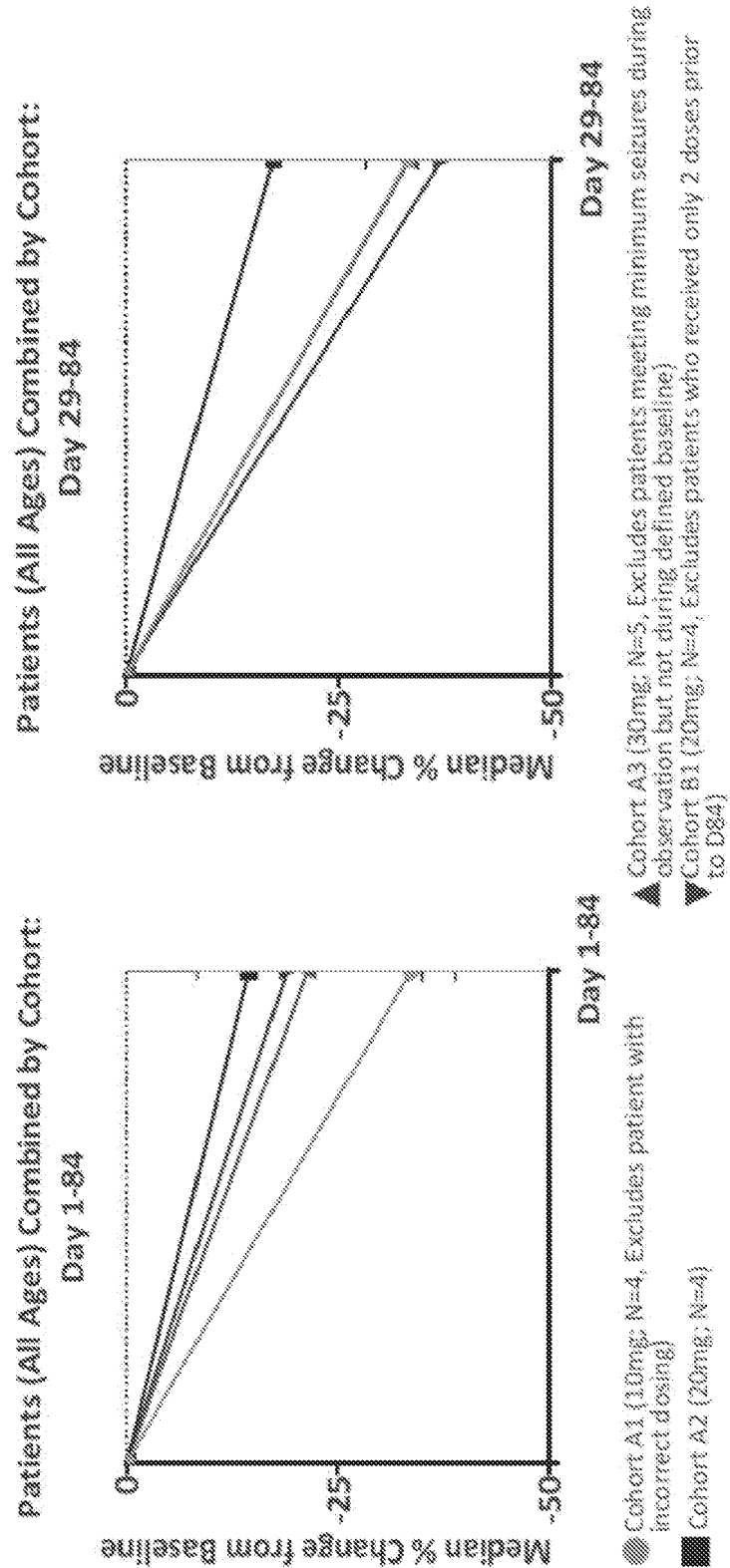


FIG. 32A

FIG. 32B

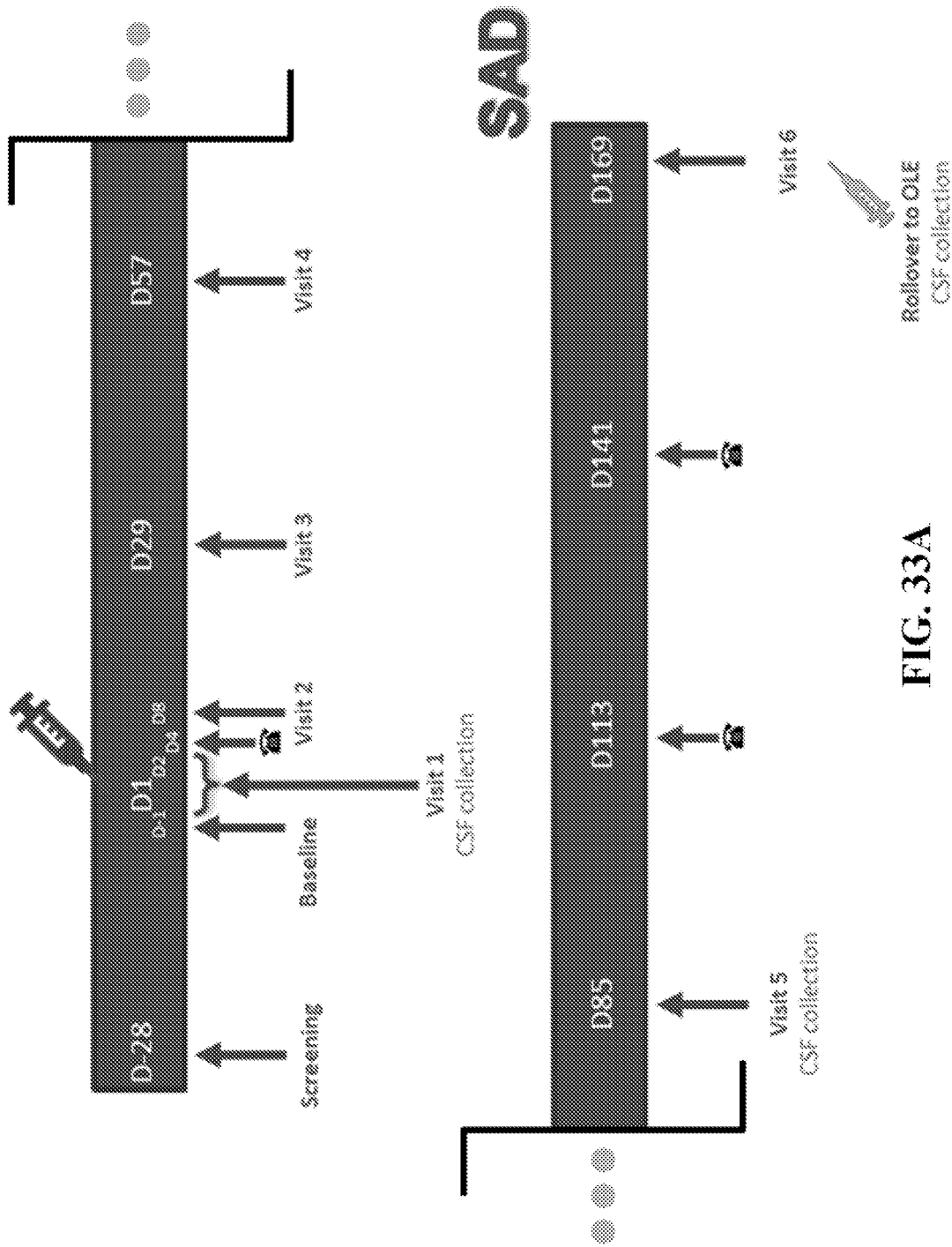


FIG. 33A

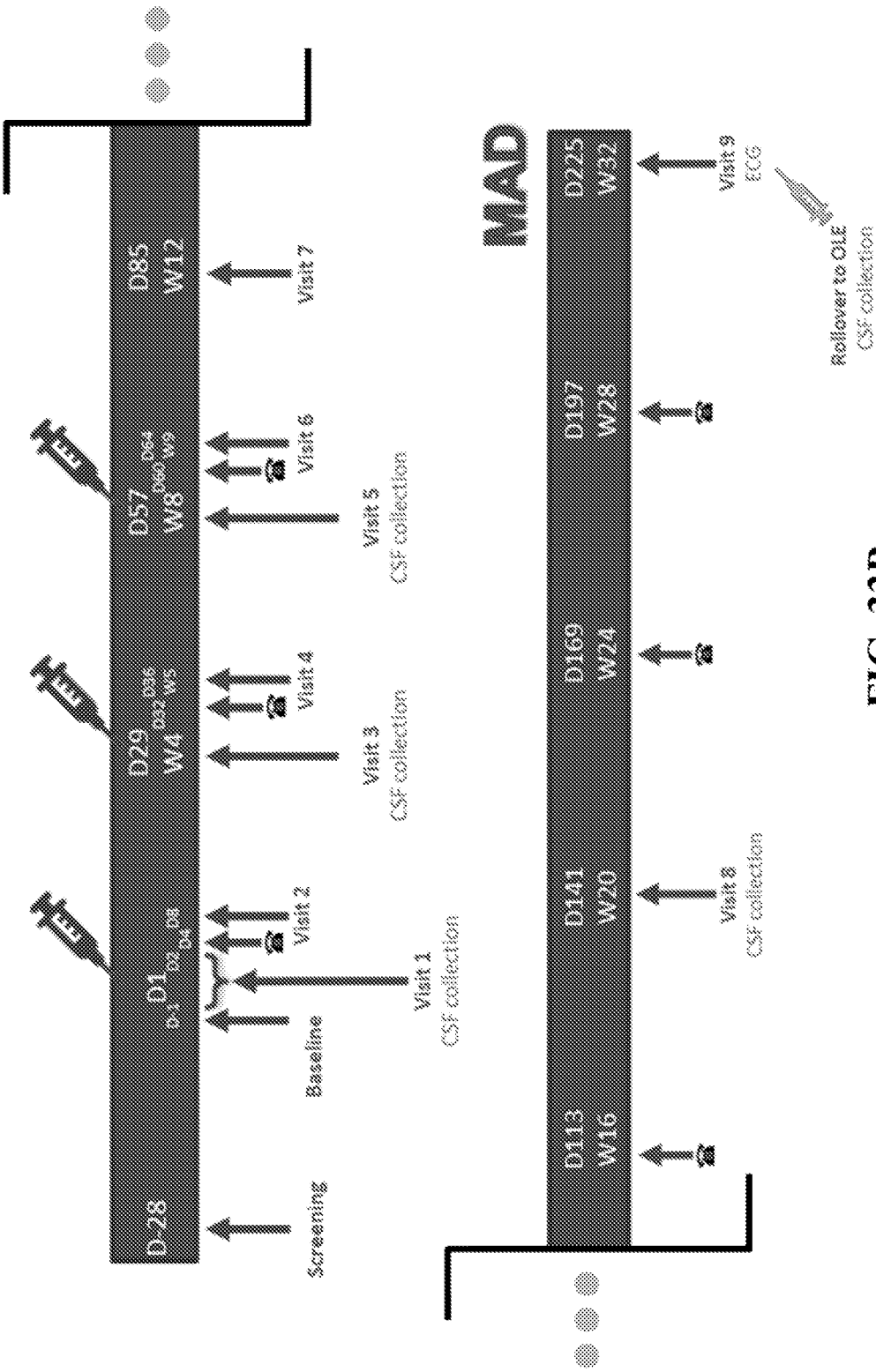


FIG. 33B

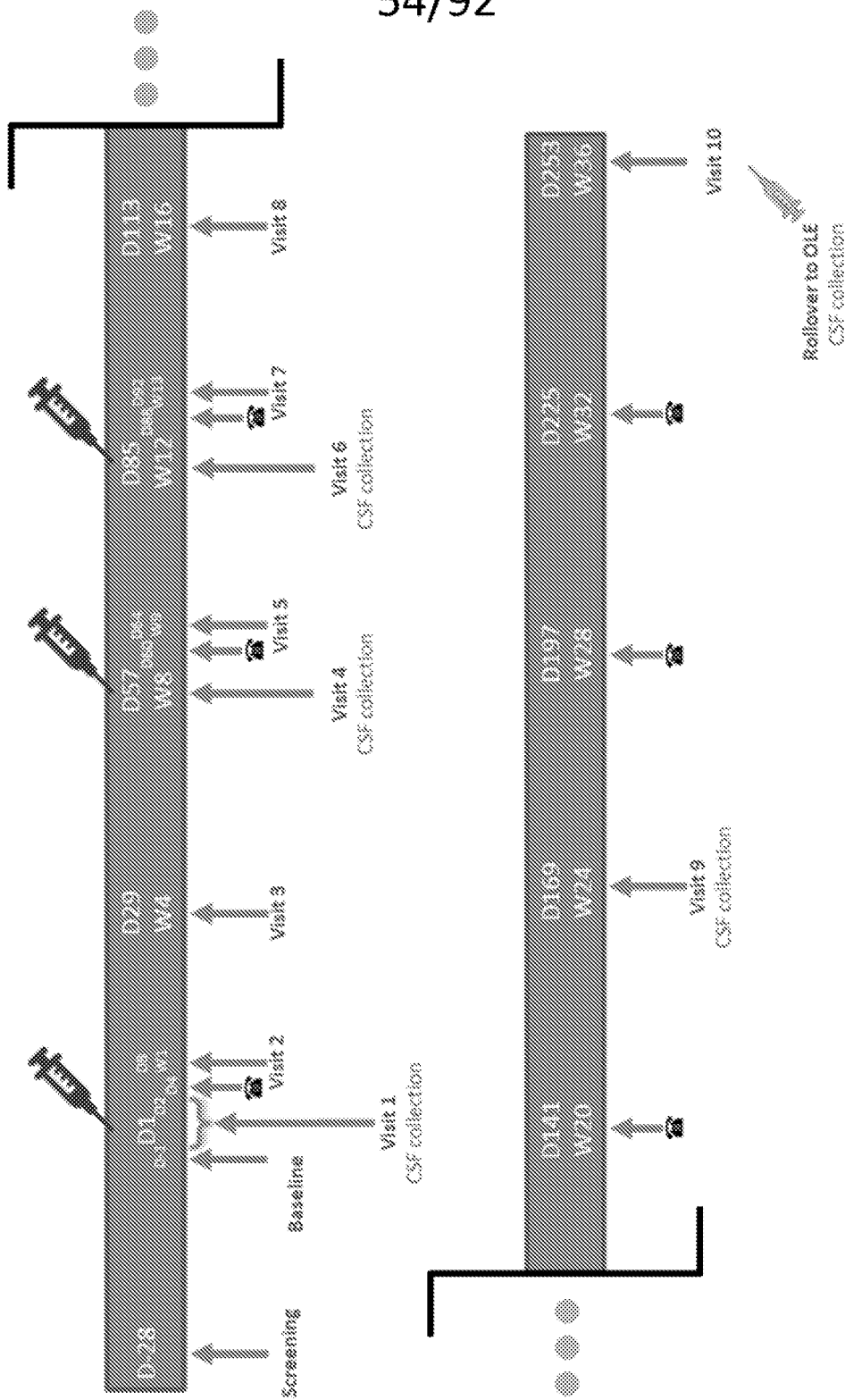


FIG. 33C

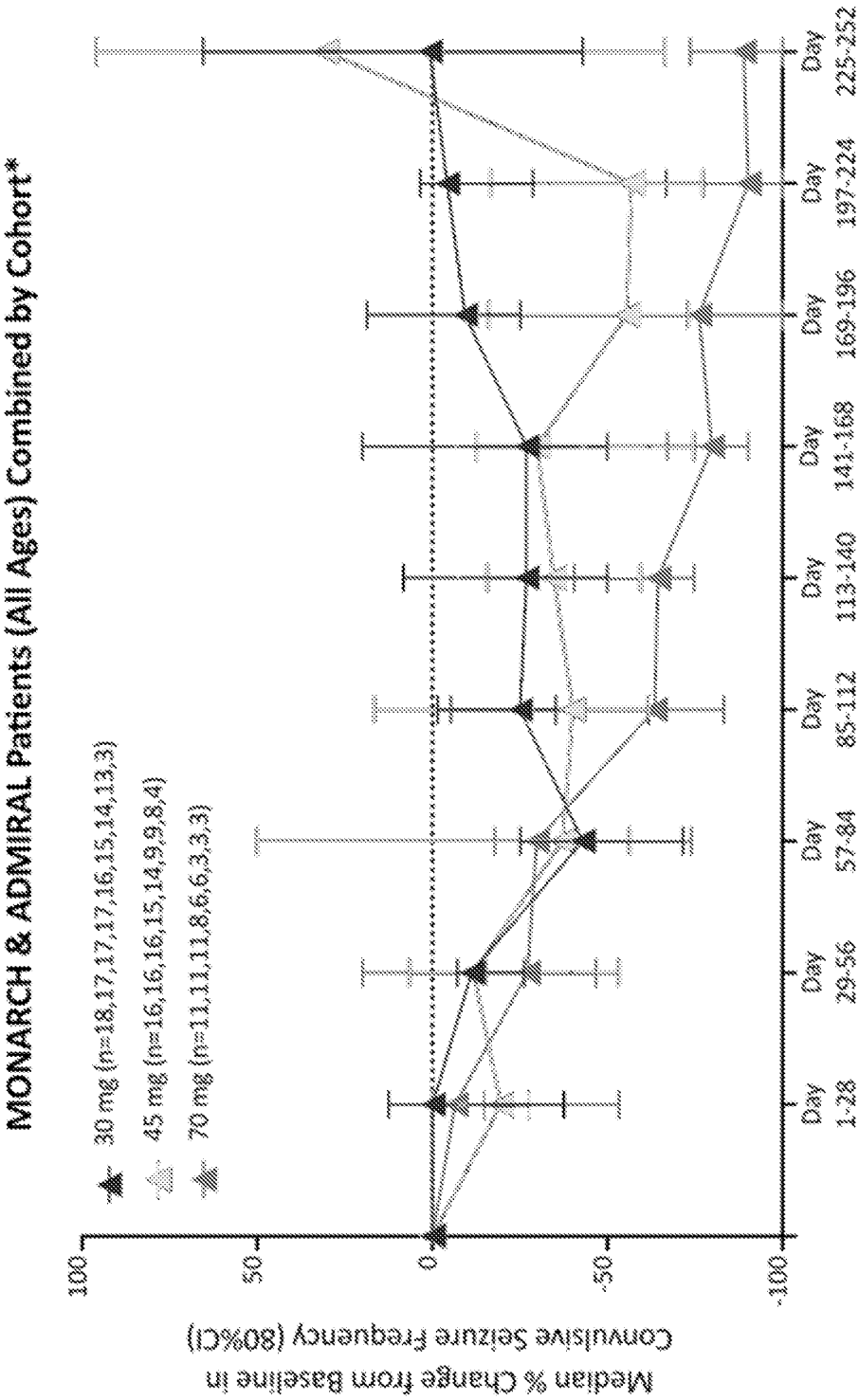


FIG. 34

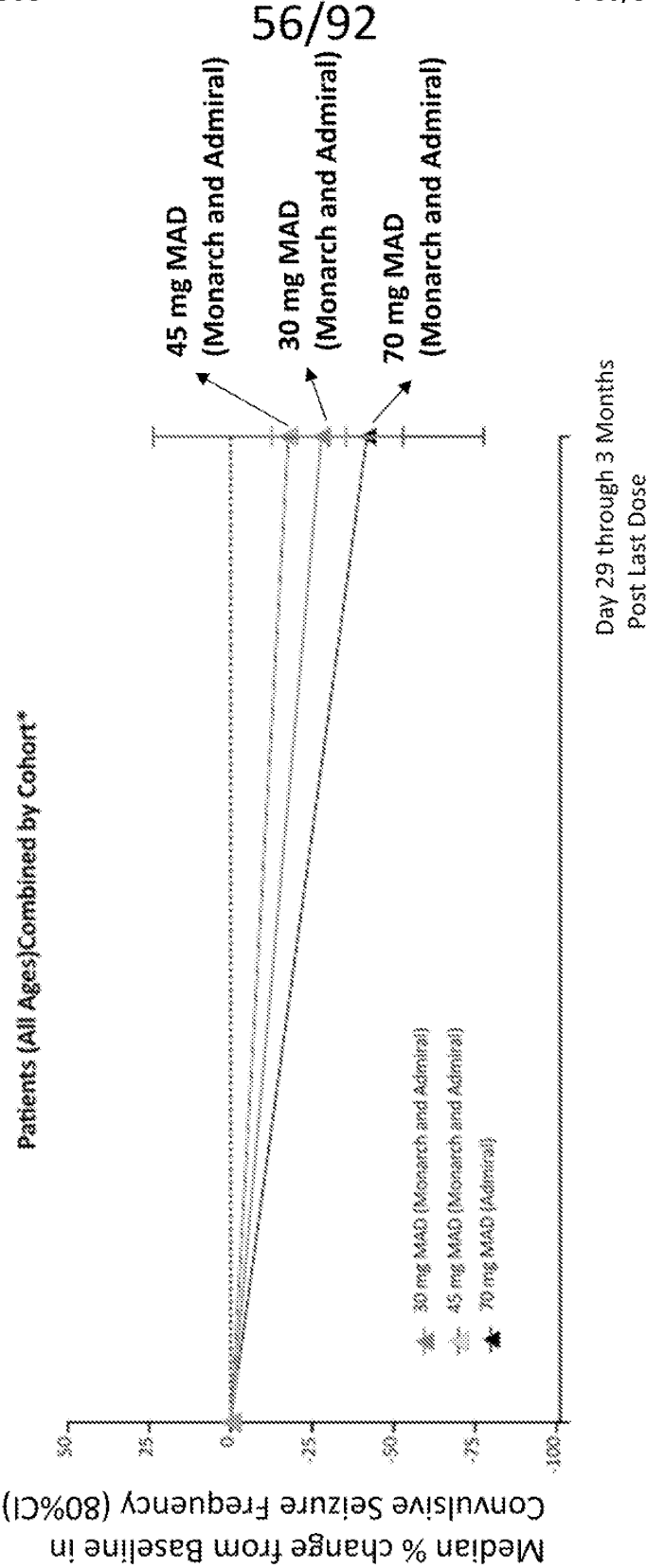


FIG. 35

30 mg MAD (MONARCH)

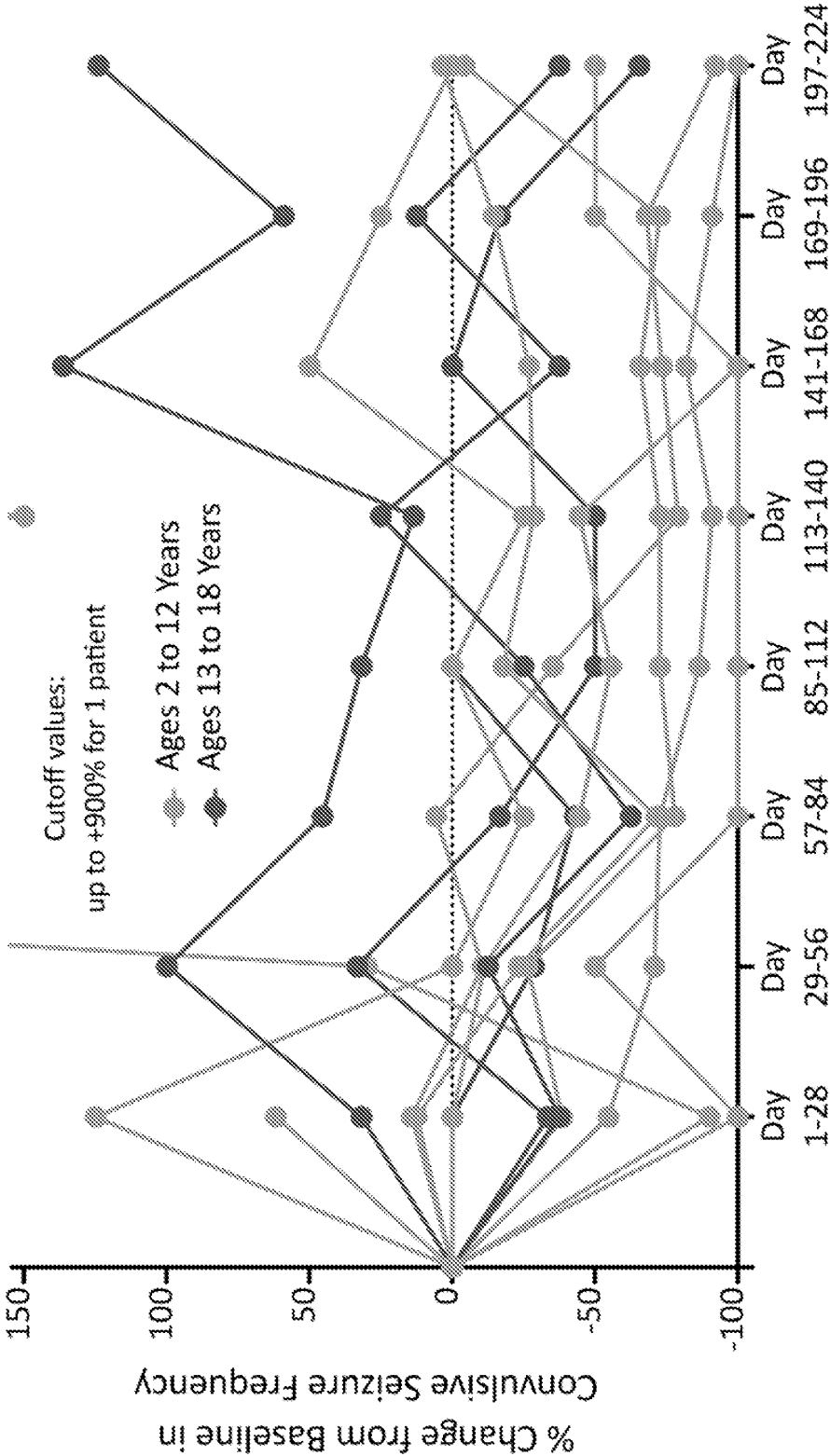


FIG. 36A

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45 mg MAD (MONARCH)

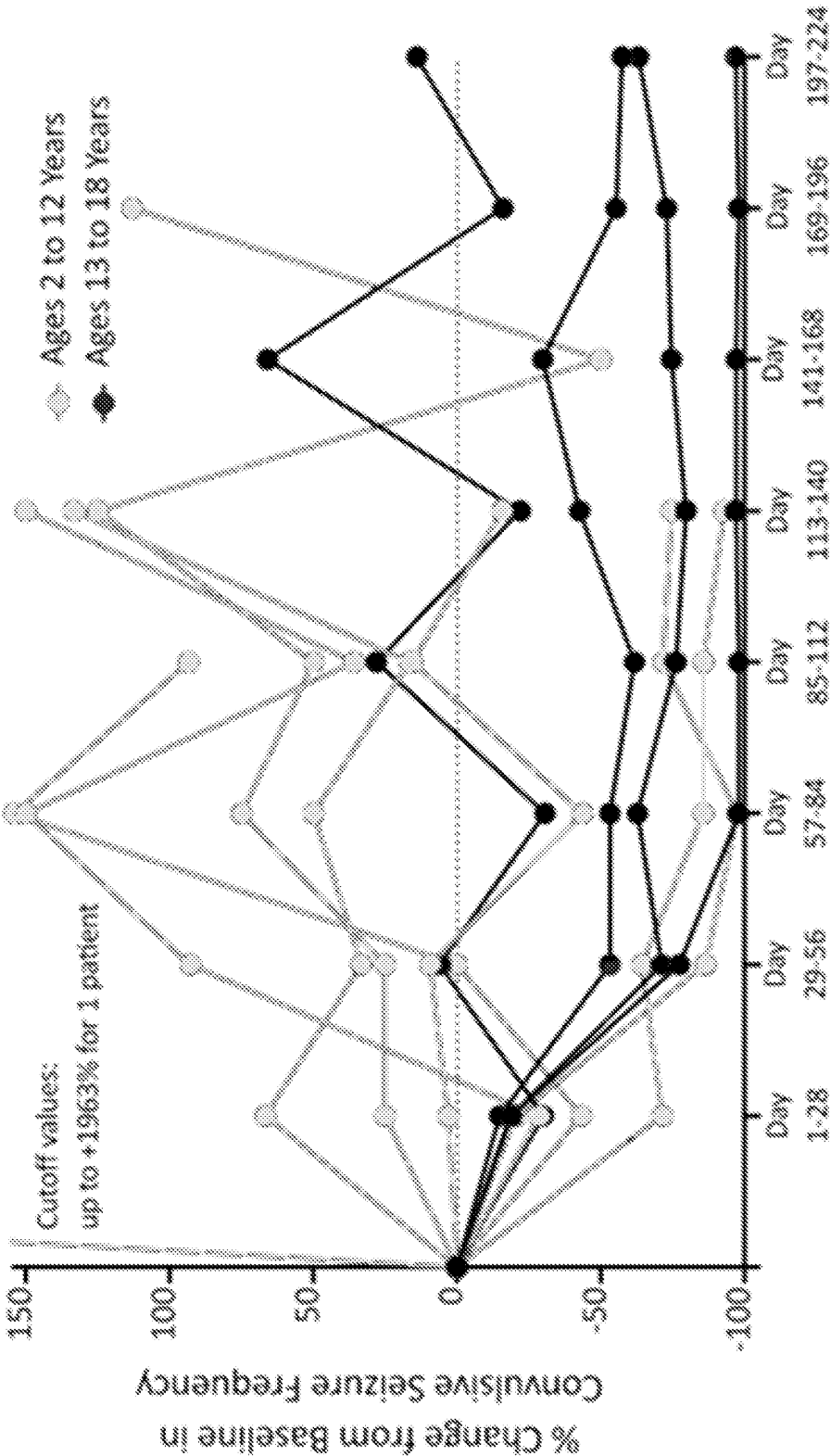


FIG. 36B

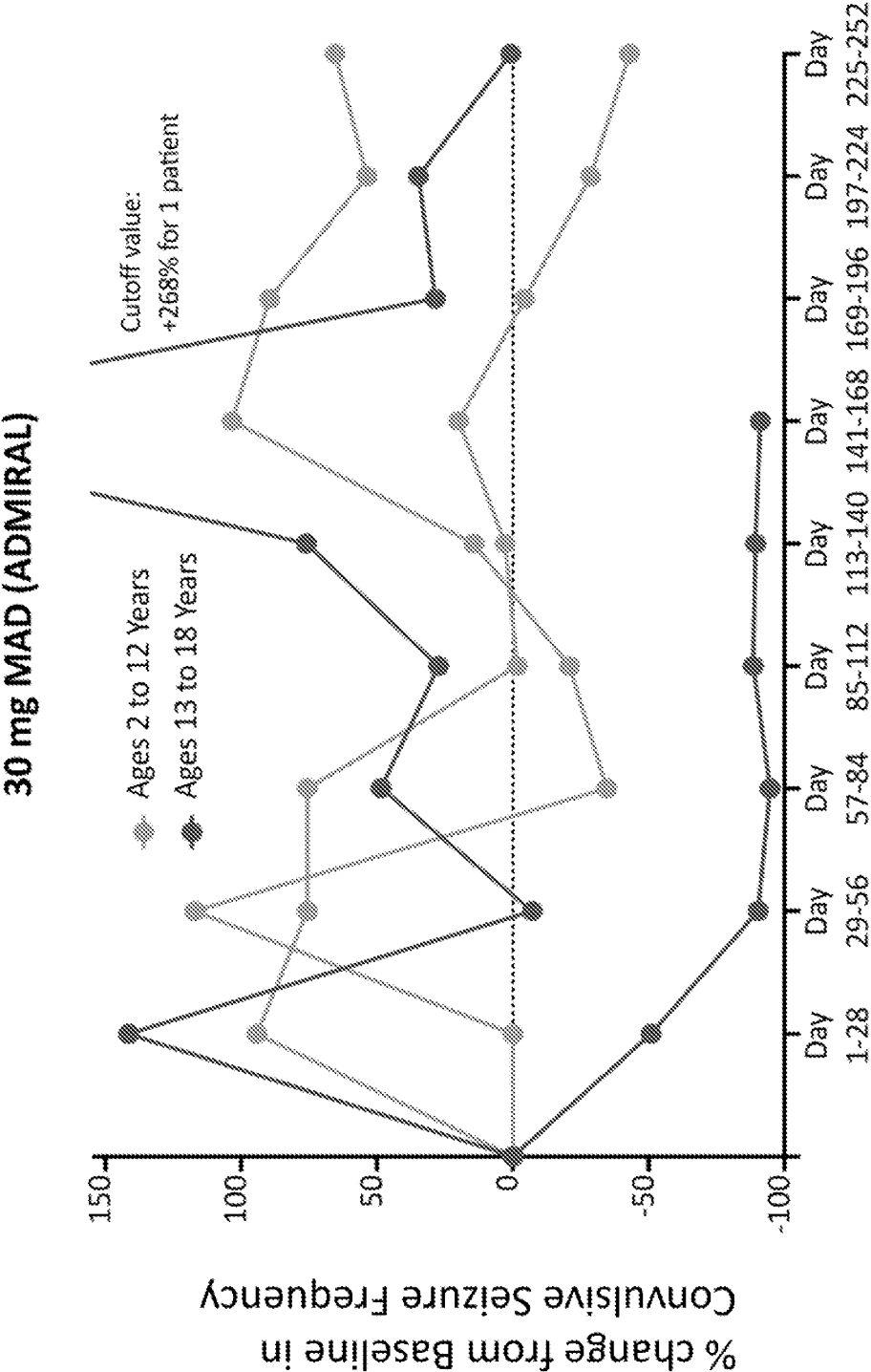


FIG. 37A

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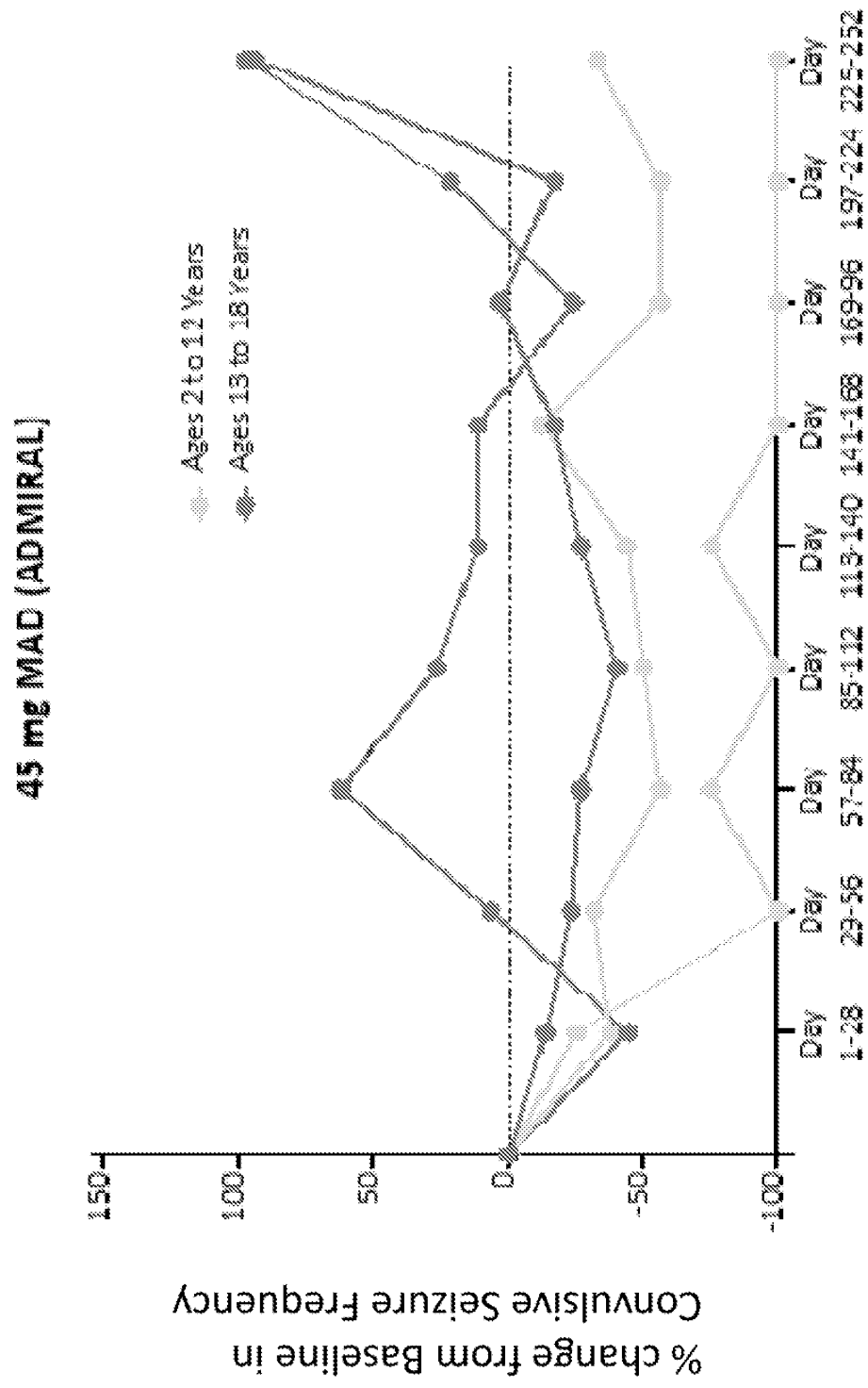


FIG. 37B

70 mg MAD (ADMIRAL)

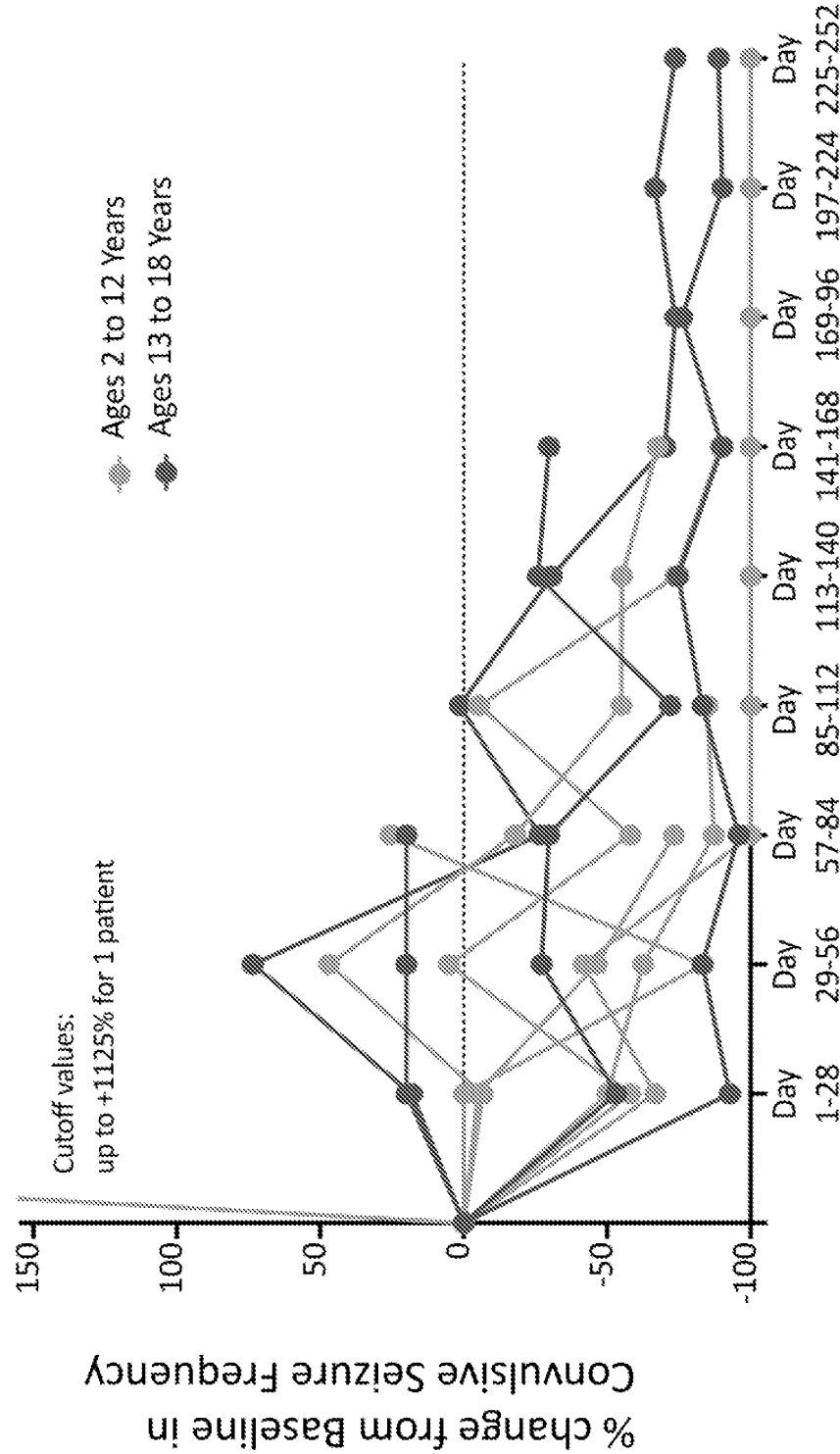


FIG. 37C

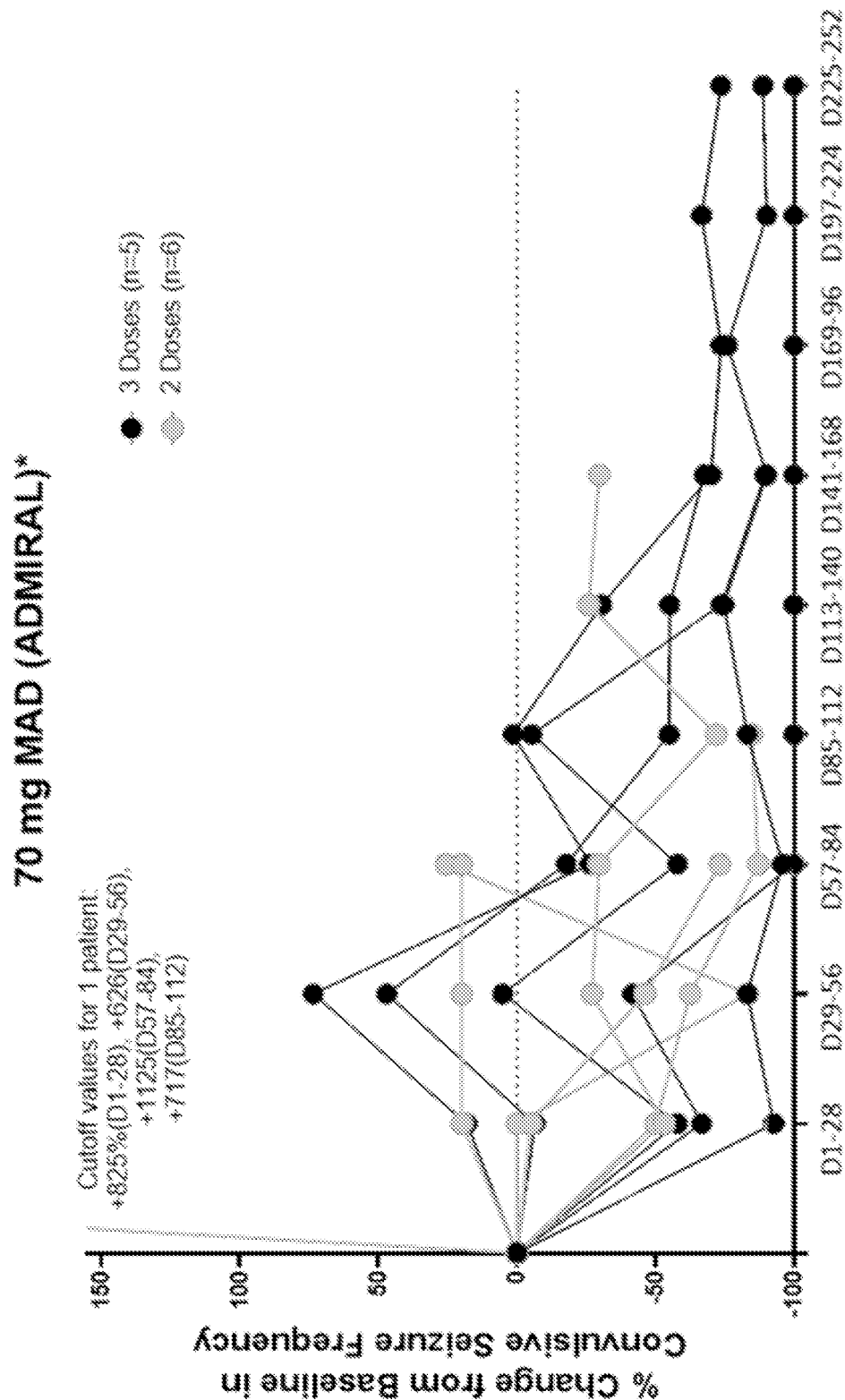


FIG. 38

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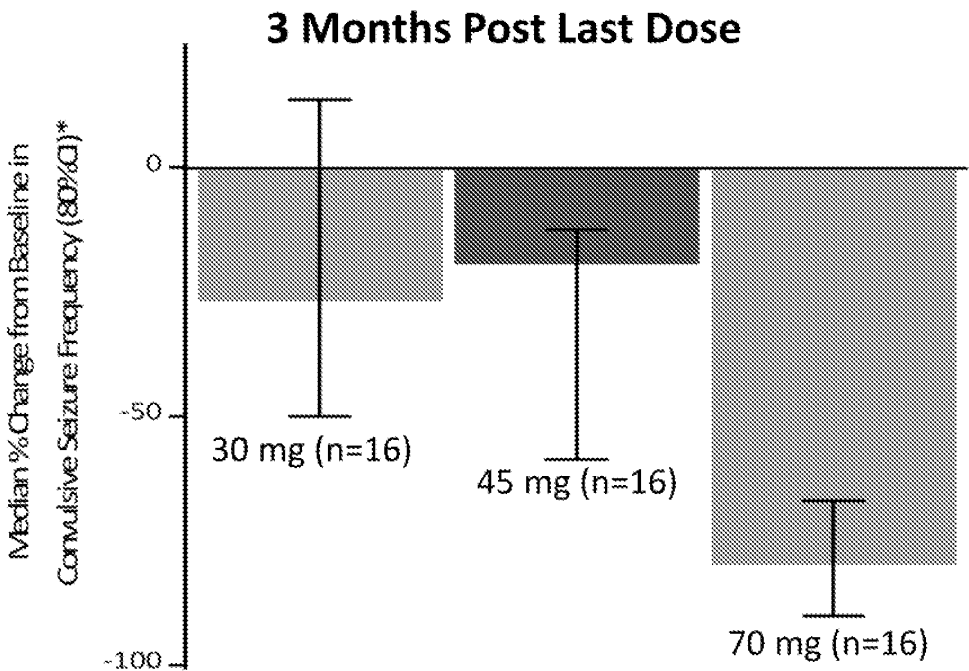


FIG. 39A

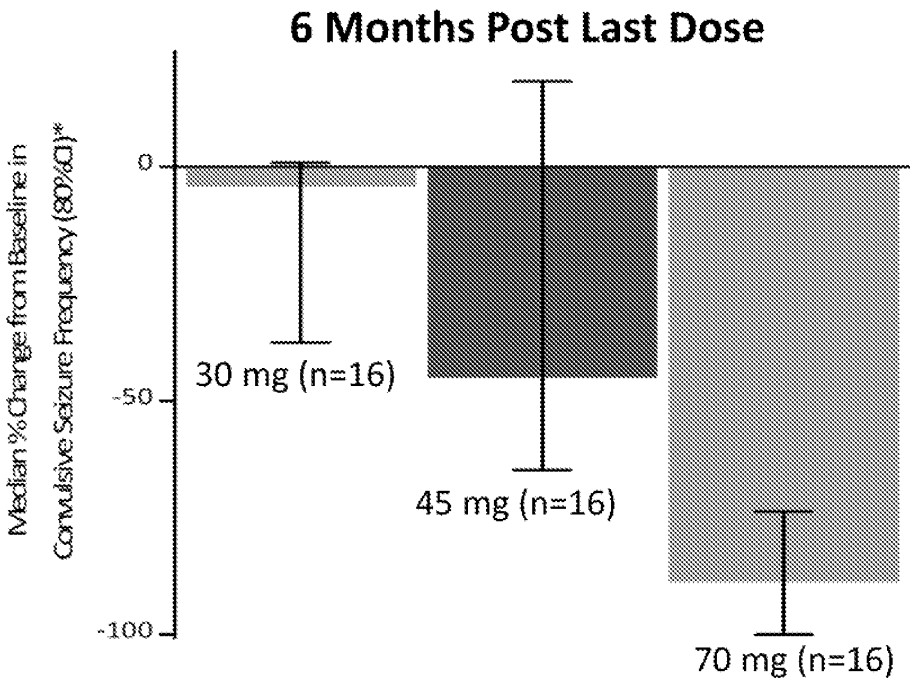


FIG. 39B

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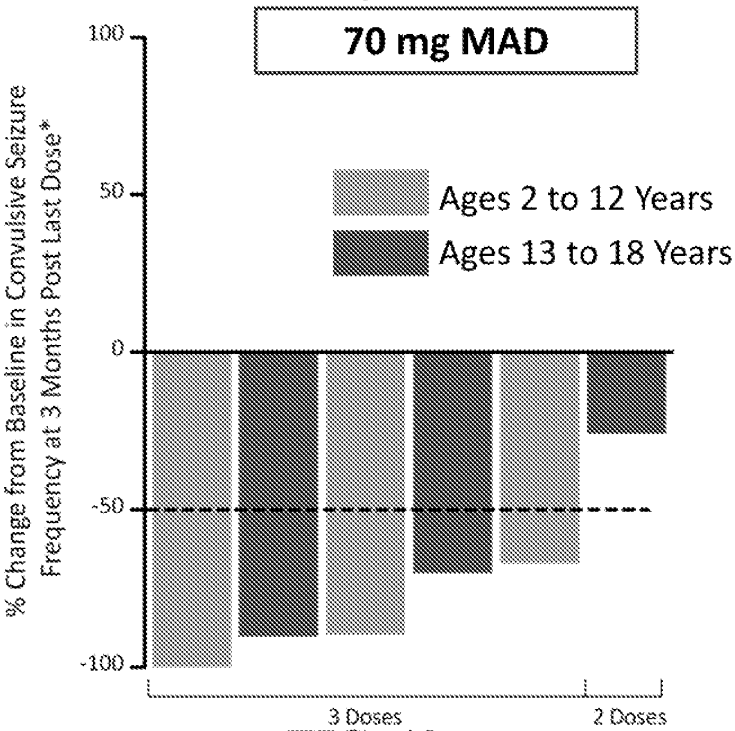


FIG. 40A

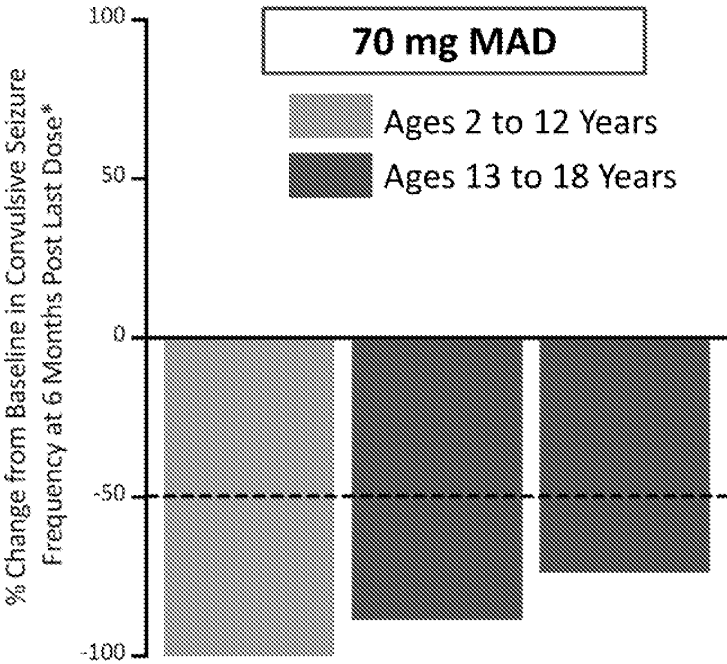


FIG. 40B

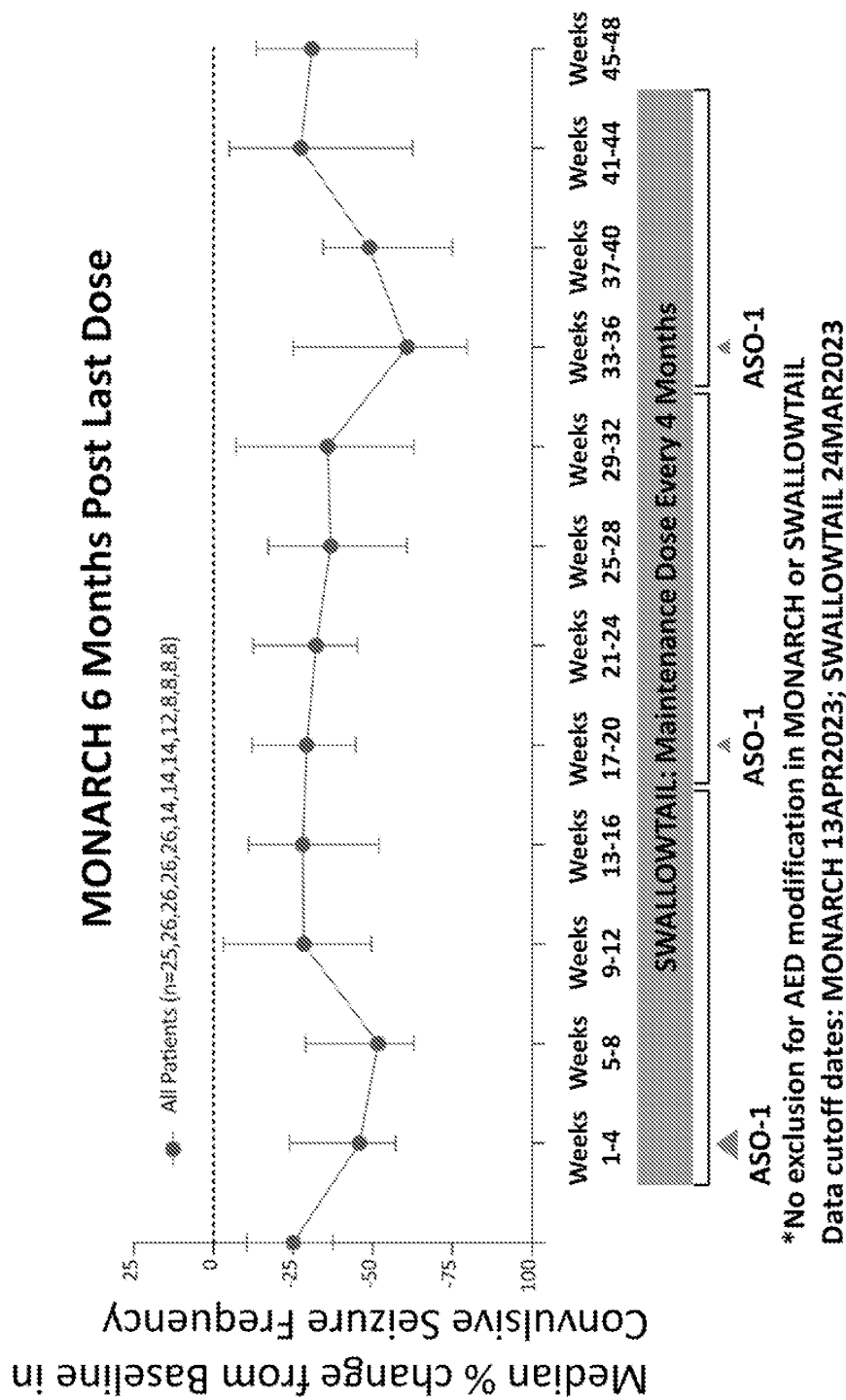


FIG. 41

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Improving

Vineland (VABS-III) Receptive Communication

Worsening

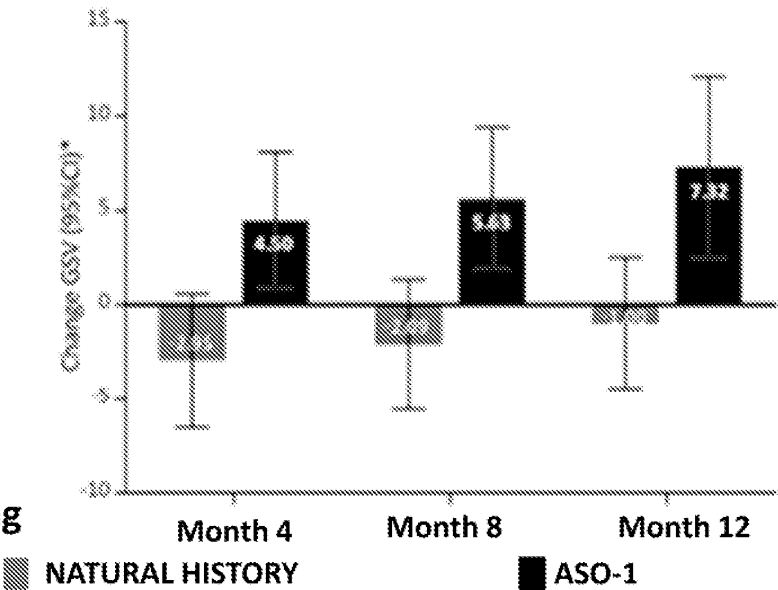


FIG. 42A

Improving

Vineland (VABS-III) Expressive Communication

Worsening

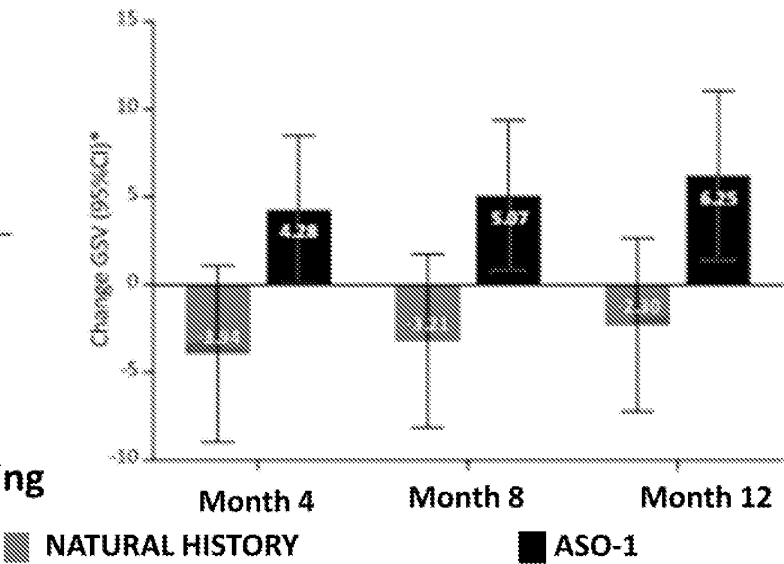
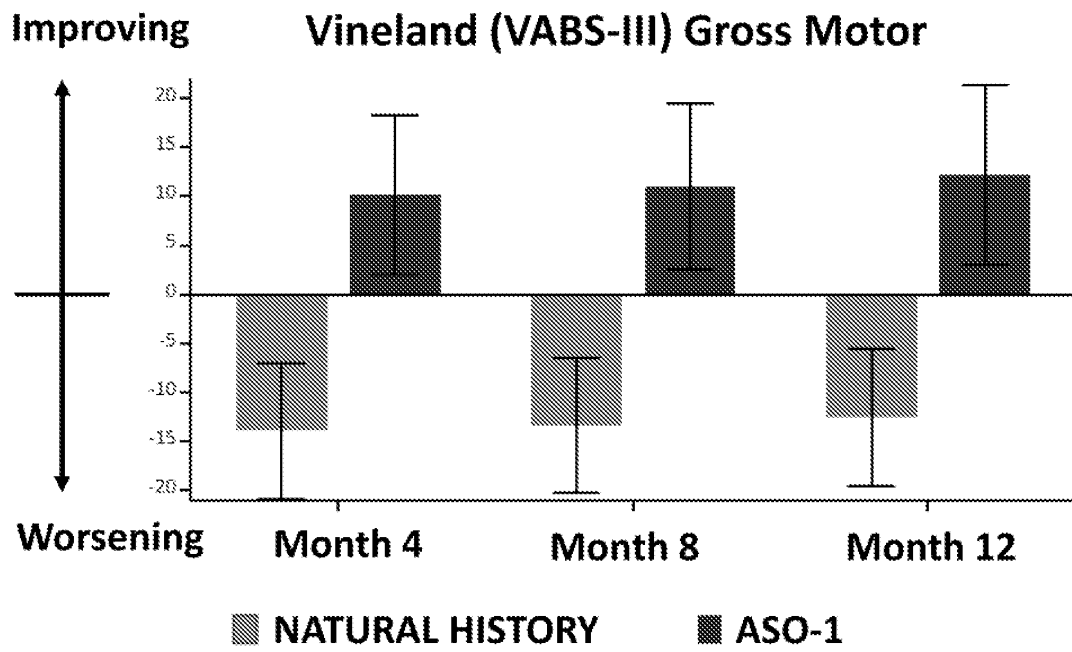
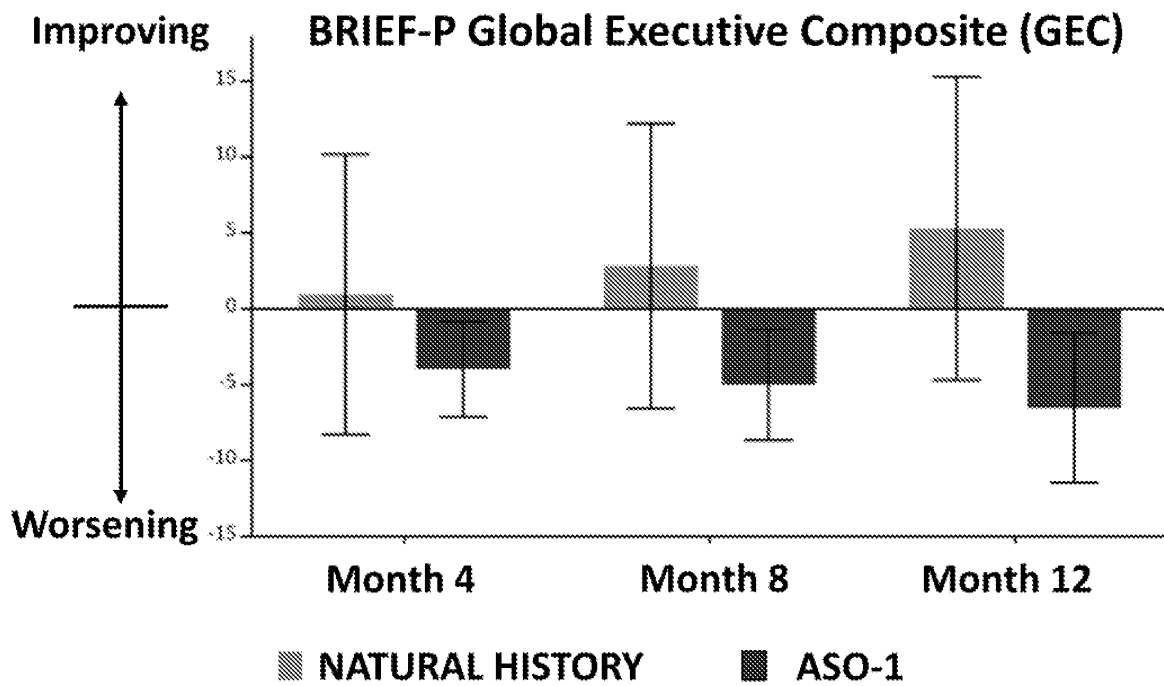


FIG. 42B

**FIG. 43**

**FIG. 44**

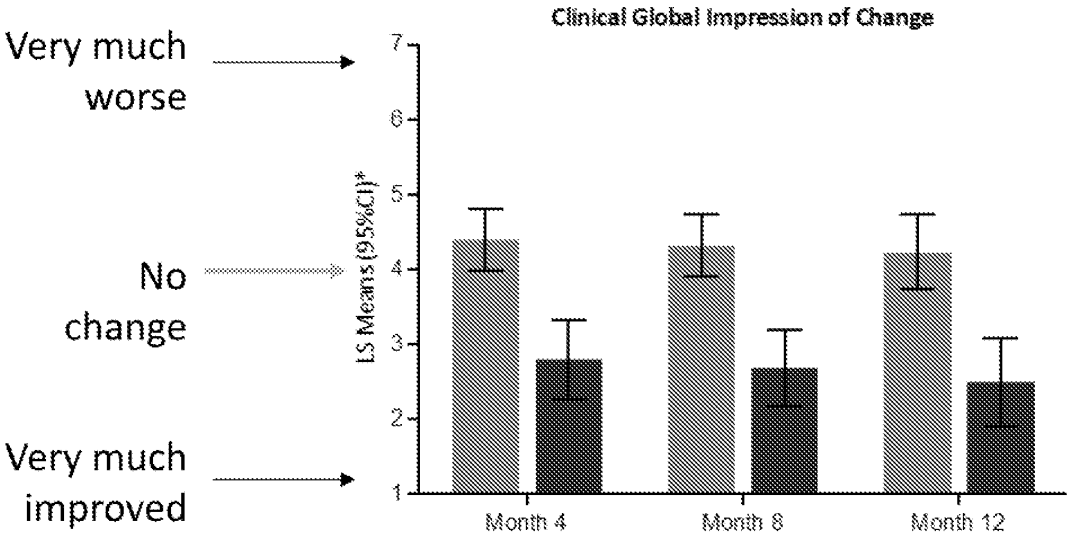


FIG. 45A

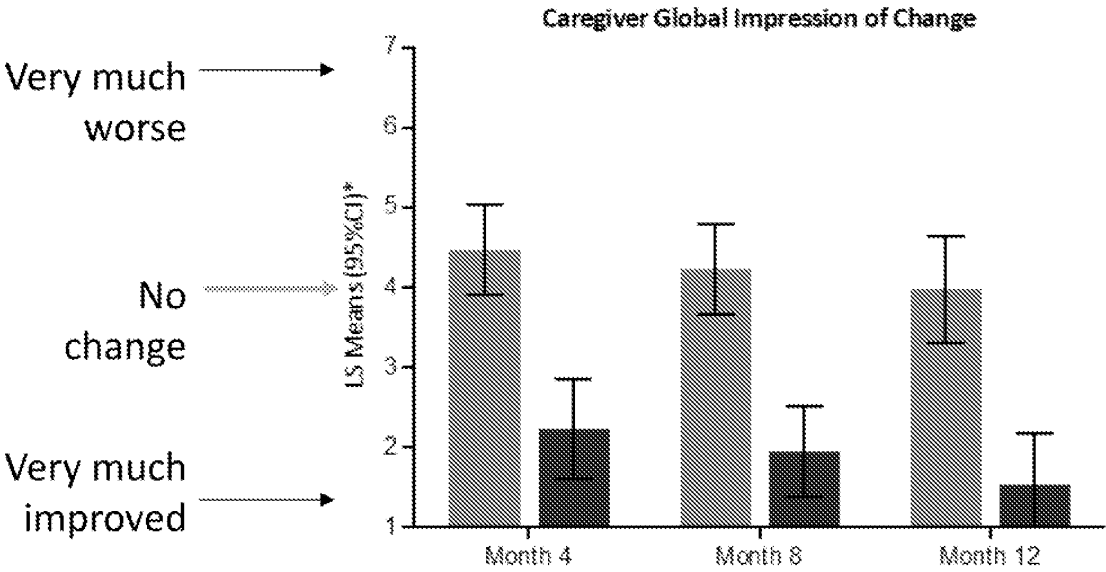


FIG. 45B

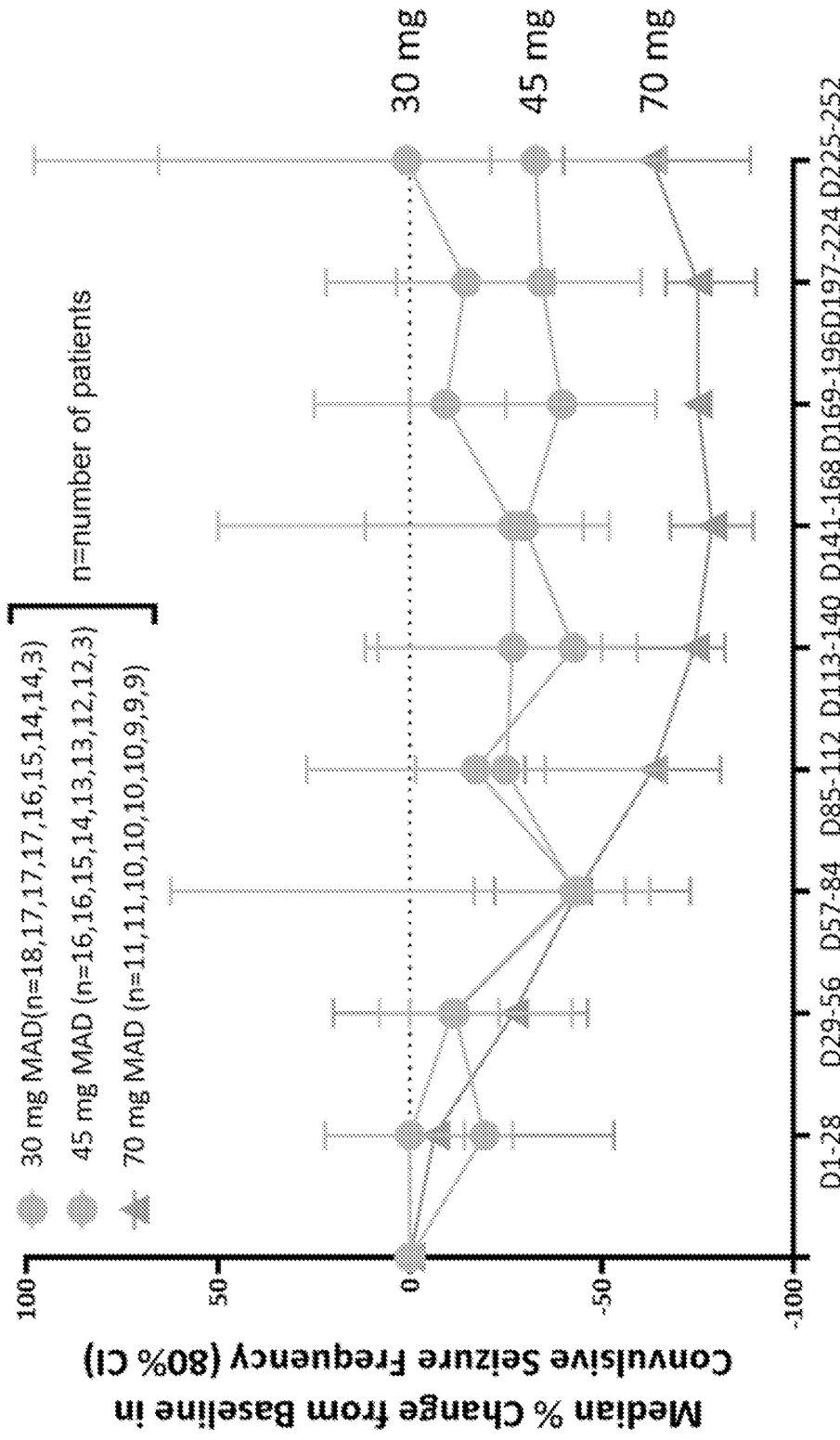


FIG. 46

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3 Months After Last Dose

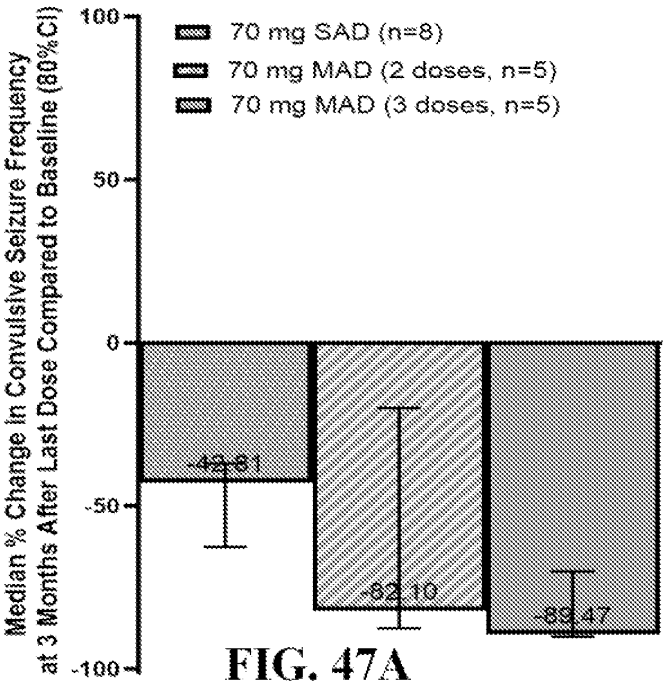


FIG. 47A

4 Months After Last Dose

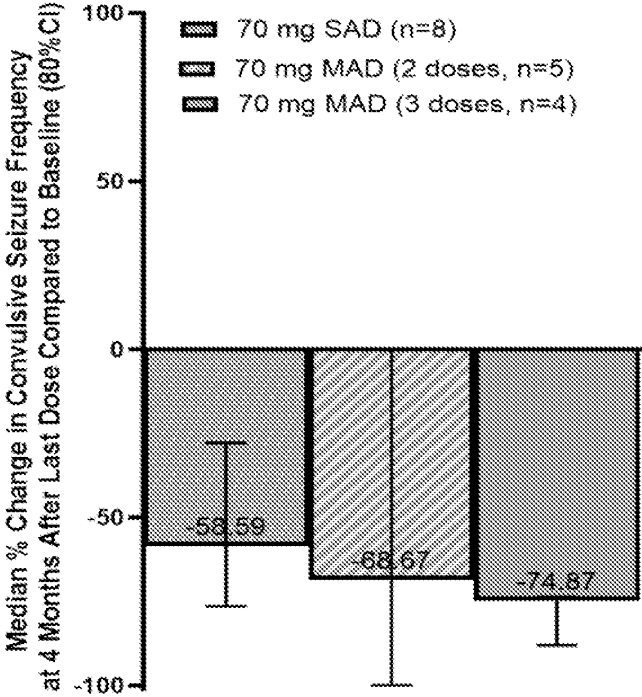


FIG. 47B

6 Months After Last Dose

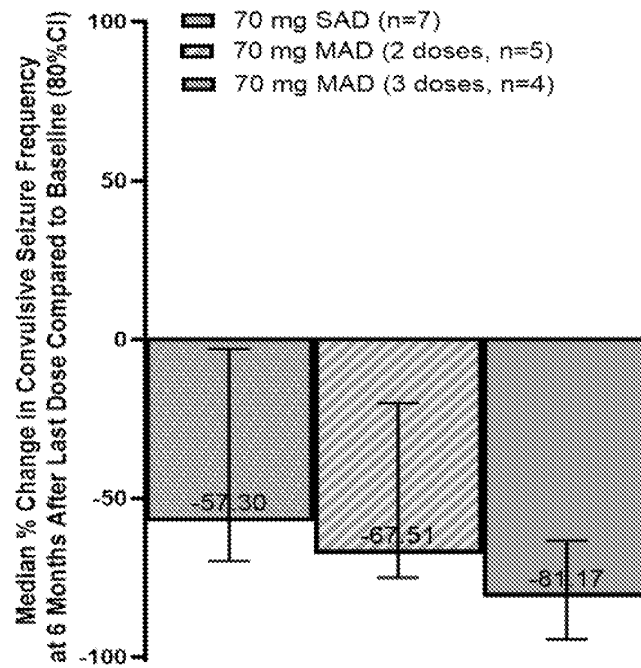


FIG. 47C

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70 mg (1 dose) (n=8, 8, 7)

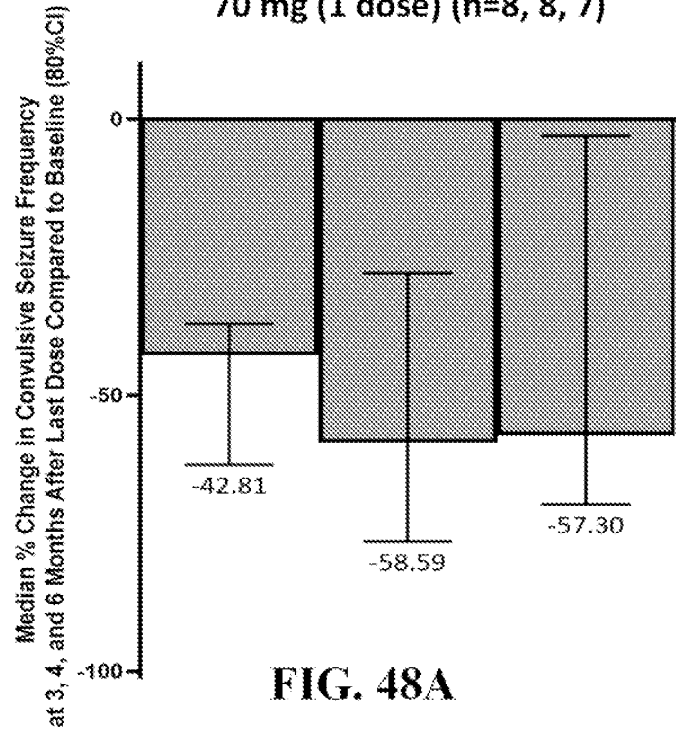


FIG. 48A

70 mg (2 or 3 doses) (n=10, 9, 9)

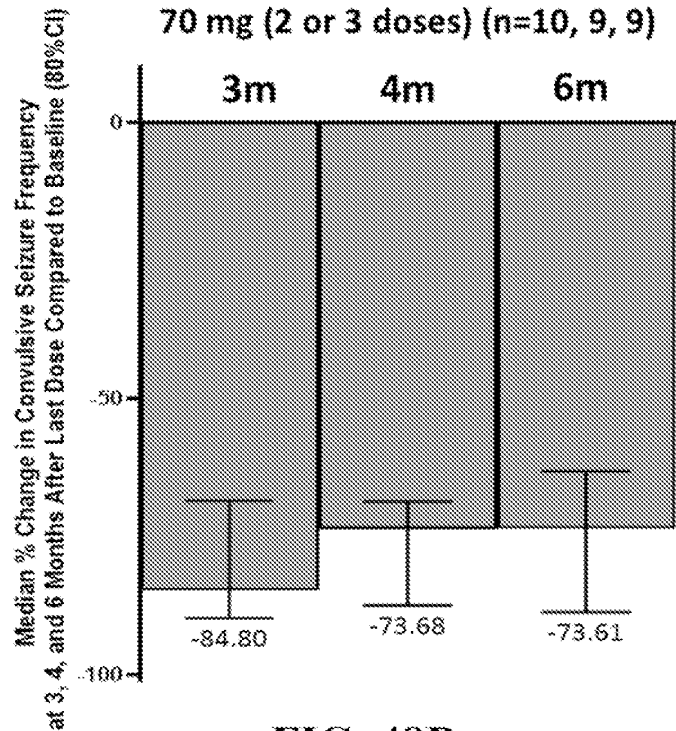


FIG. 48B

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3 Months After Last Dose

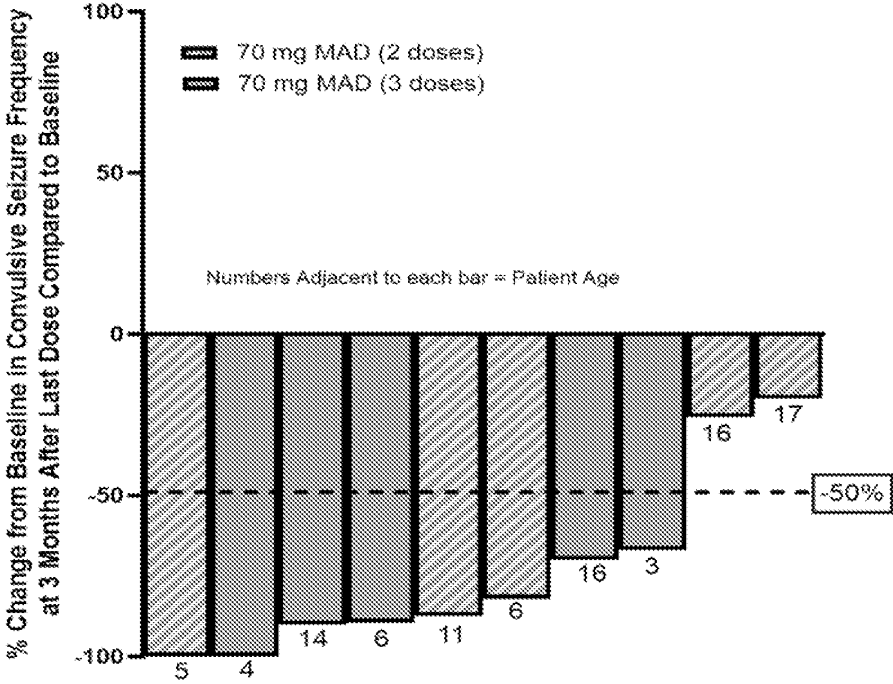


FIG. 49A

6 Months After Last Dose

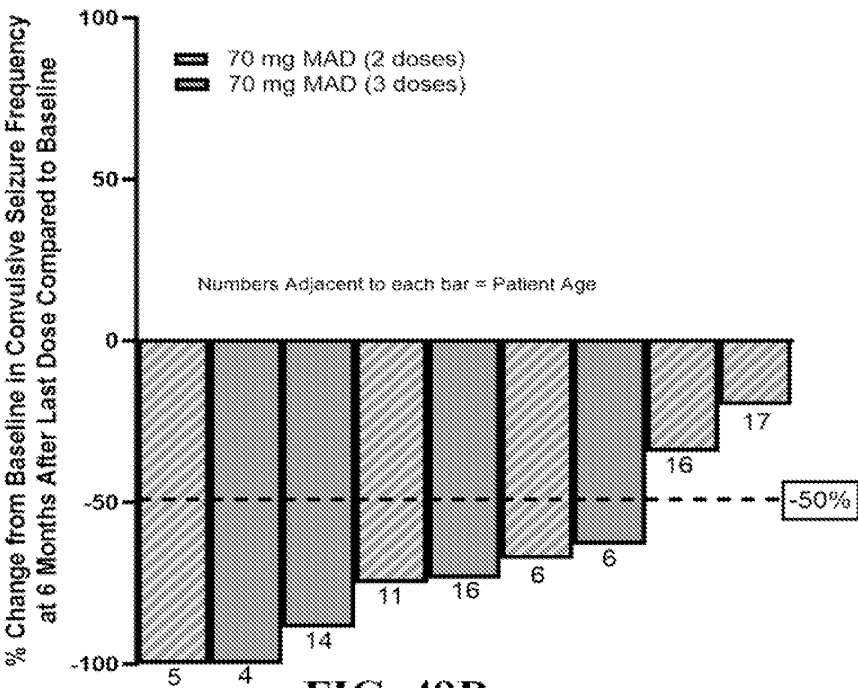


FIG. 49B

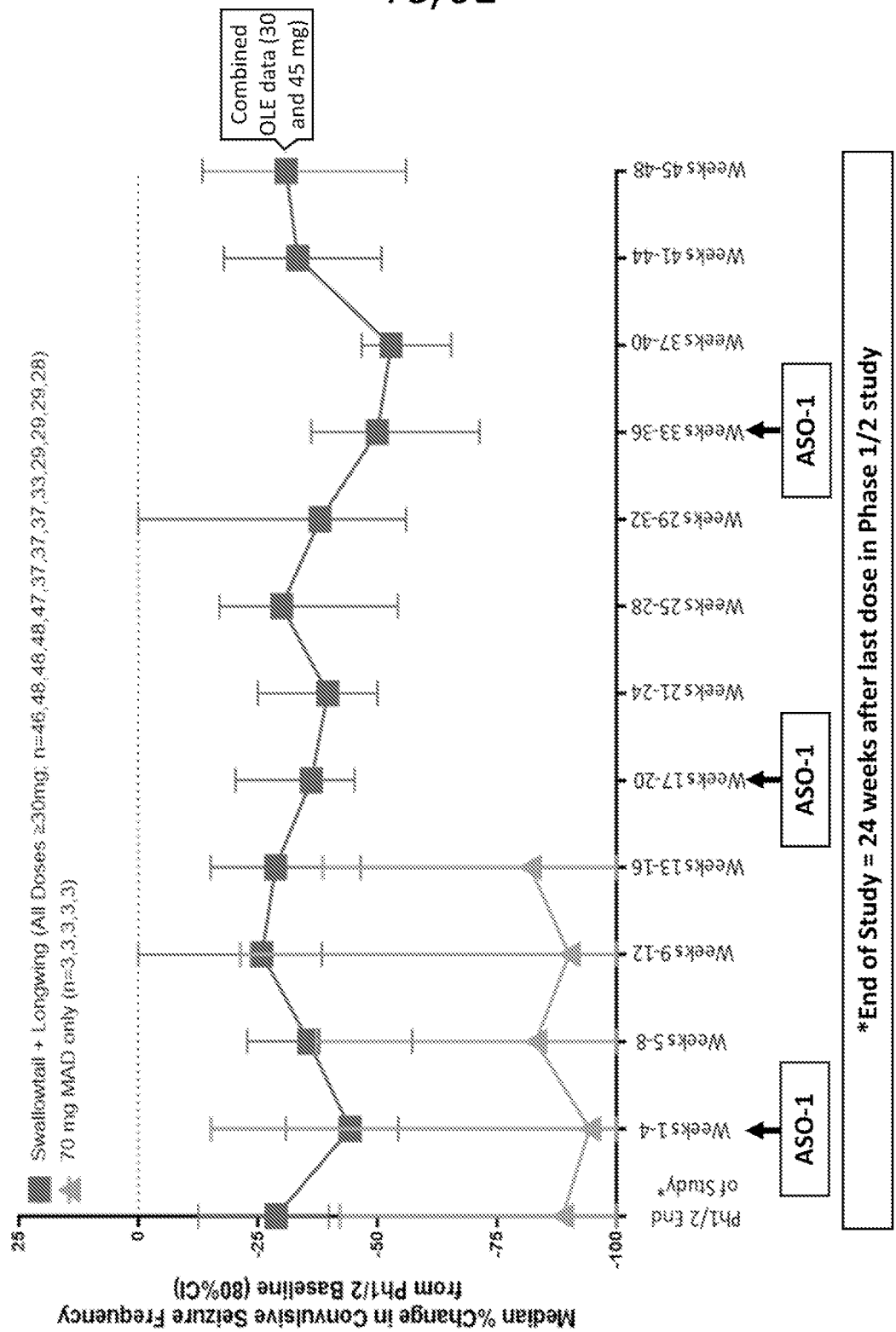


FIG. 50

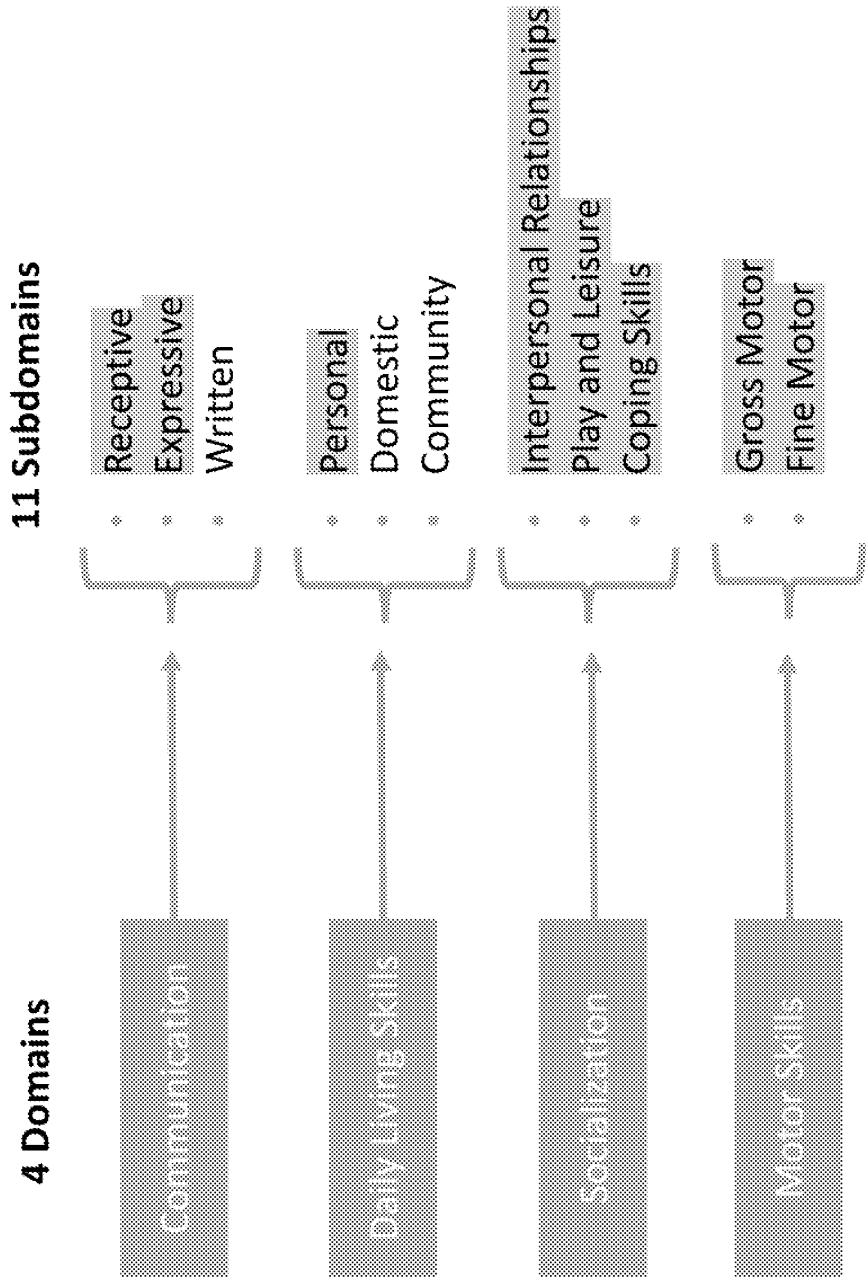
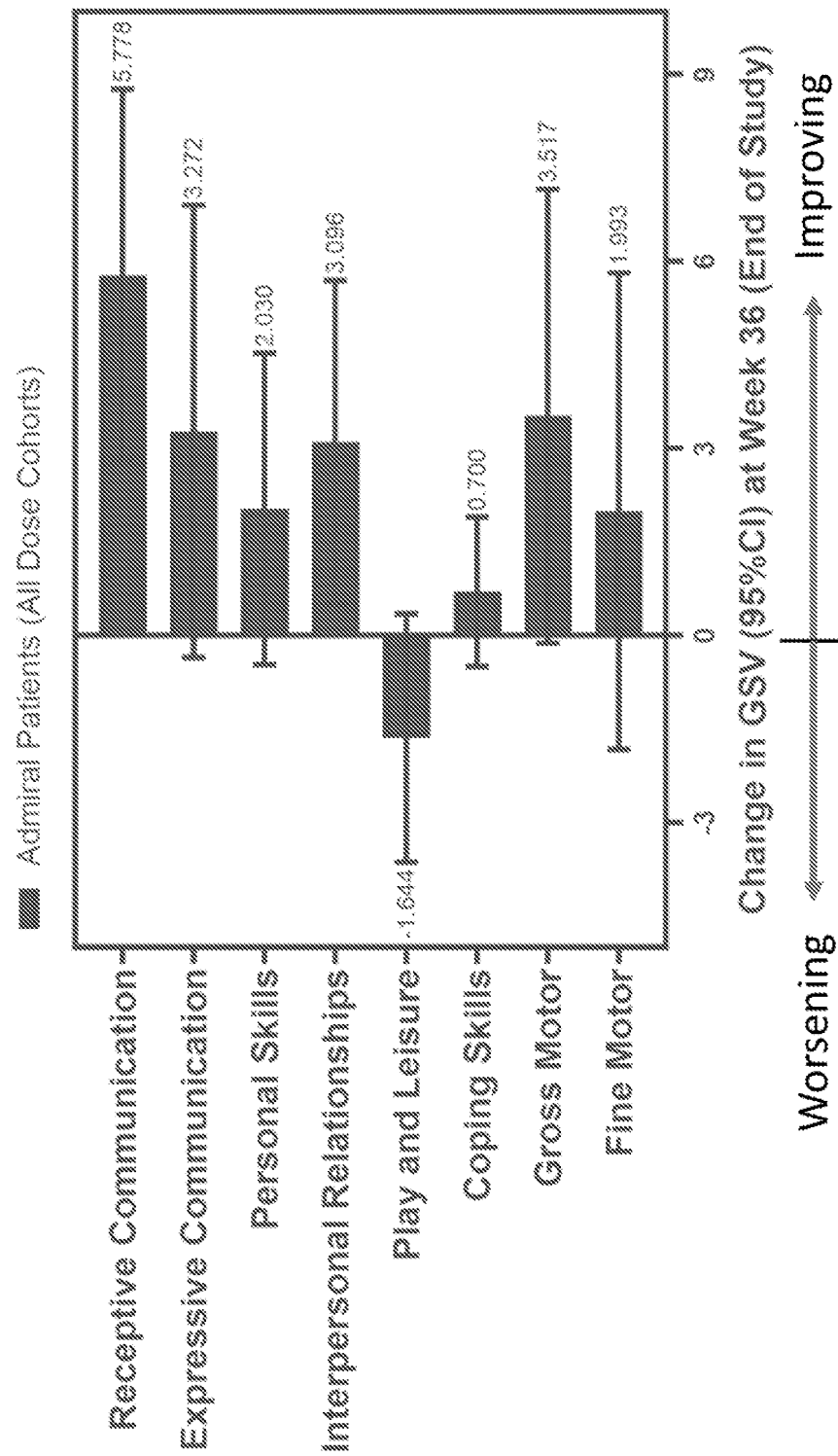


FIG. 51



(n=18 at screen and n=17 at Week 36)

FIG. 52

Clinical Global Impression of Change (CGI-C)

Caregiver Global Impression of Change (CaGI-C)

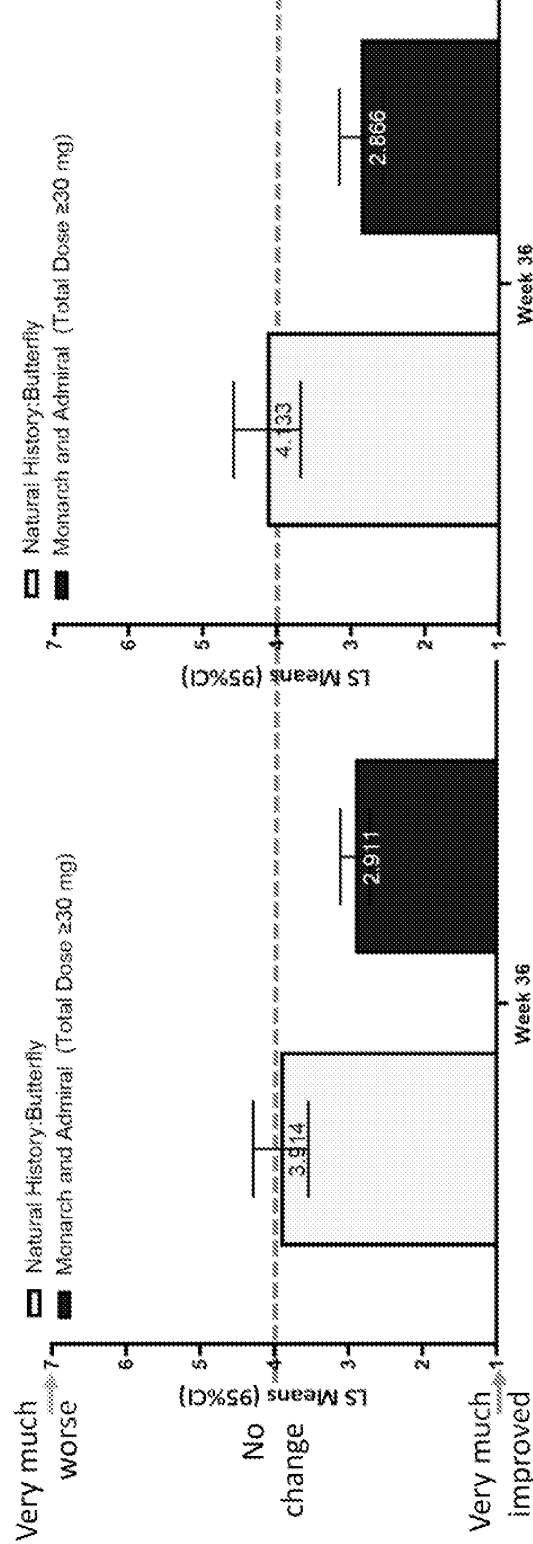


FIG. 53A

FIG. 53B

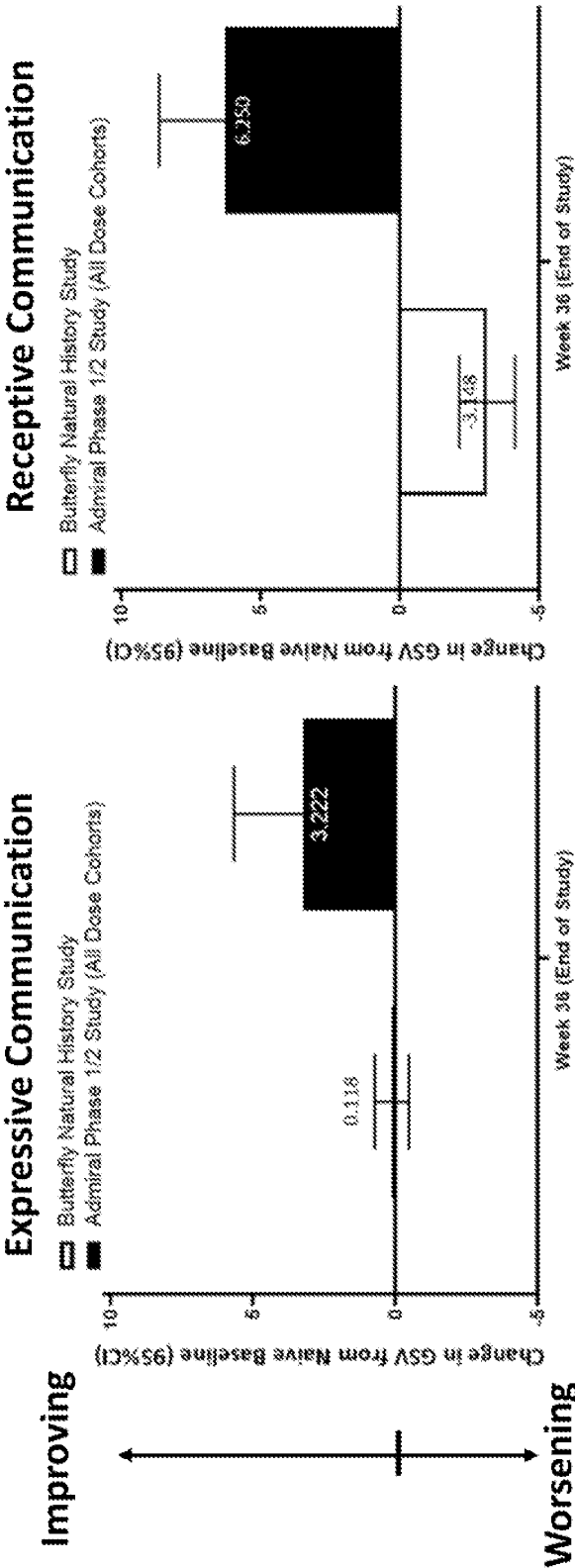


FIG. 54B

FIG. 54A

Interpersonal Relationships

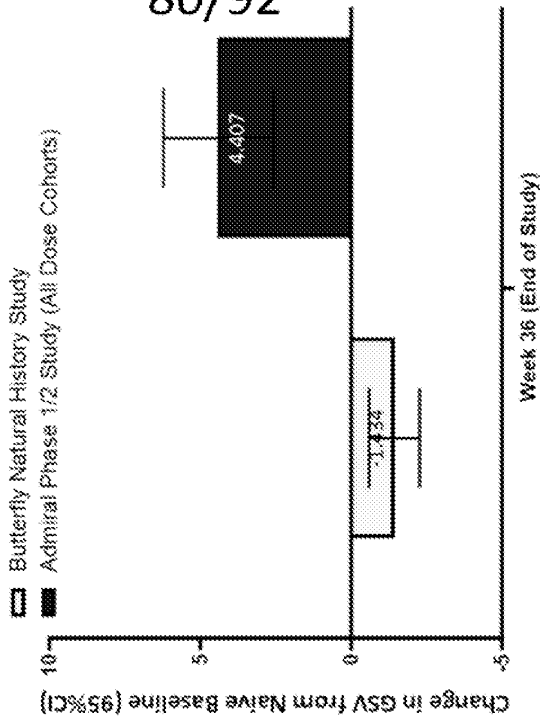


FIG. 55B

Personal Skills

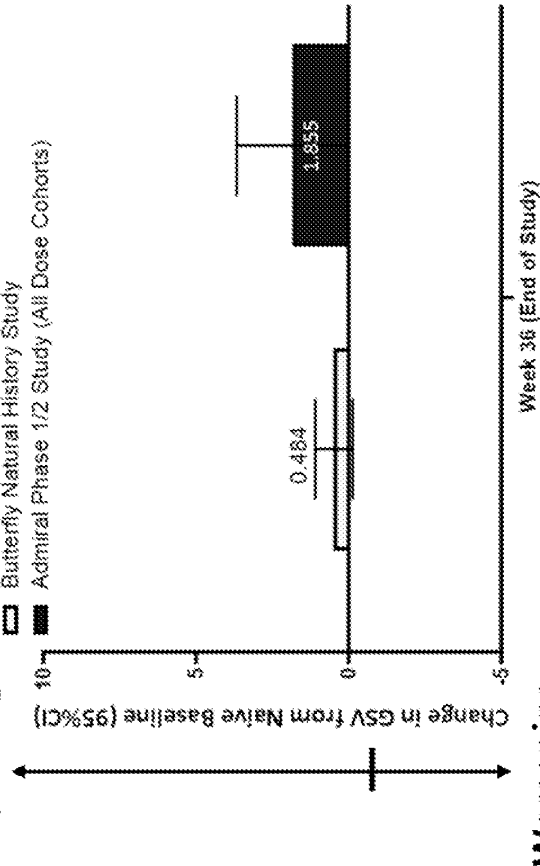


FIG. 55A

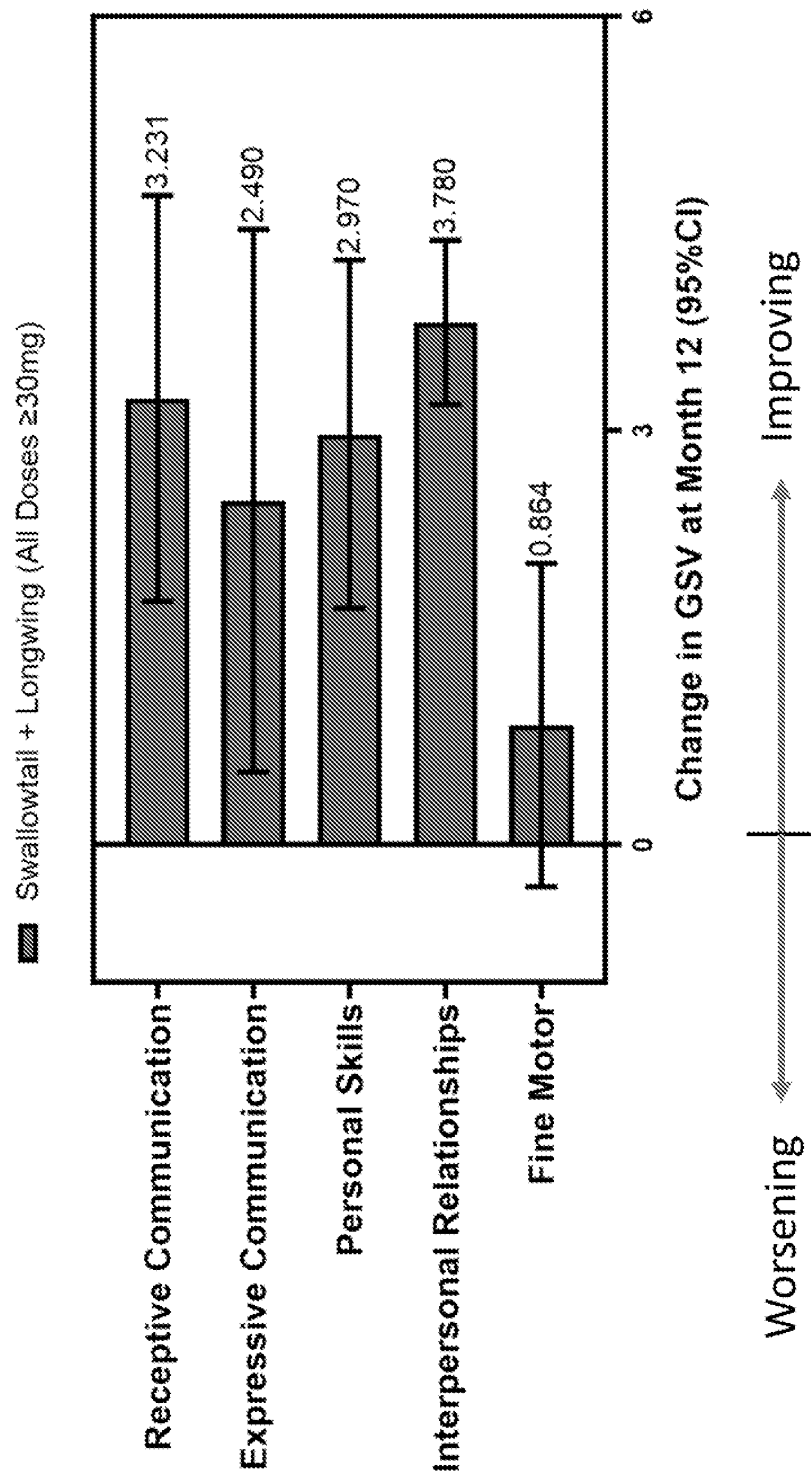


FIG. 56

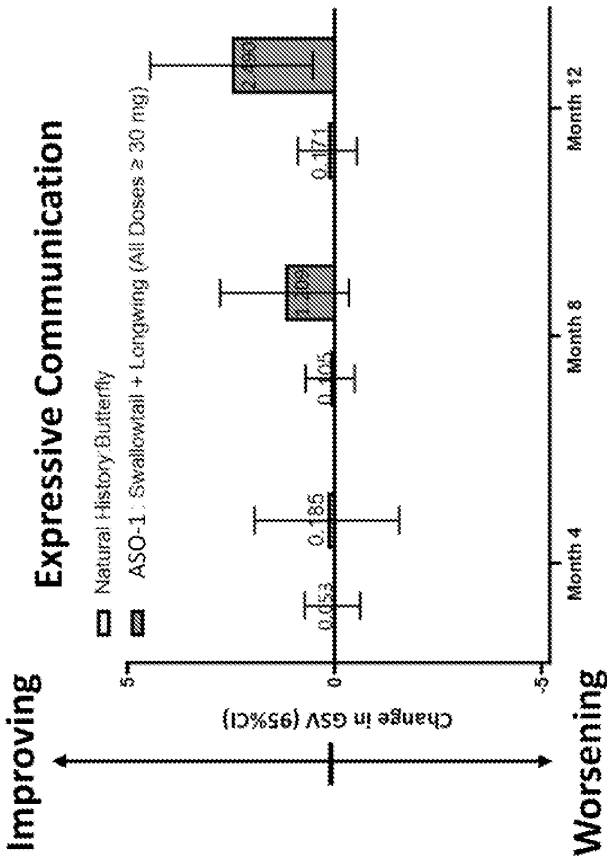


FIG. 57A

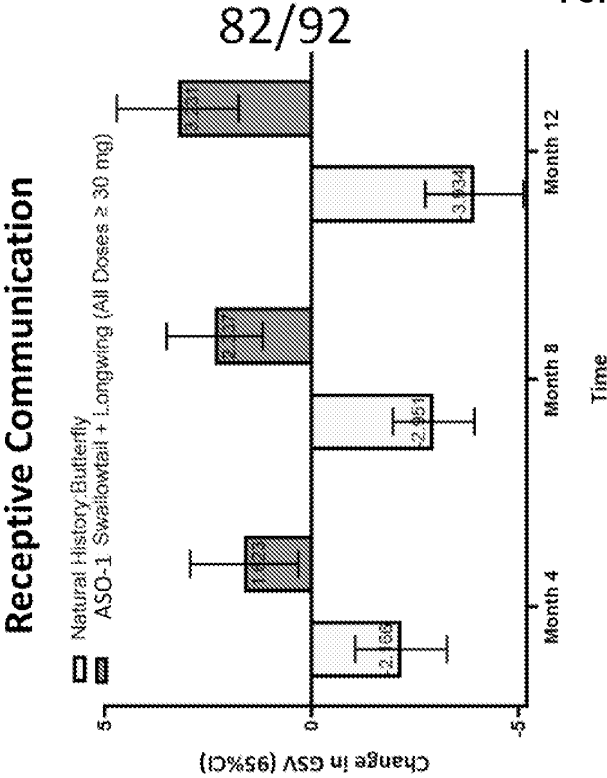


FIG. 57B

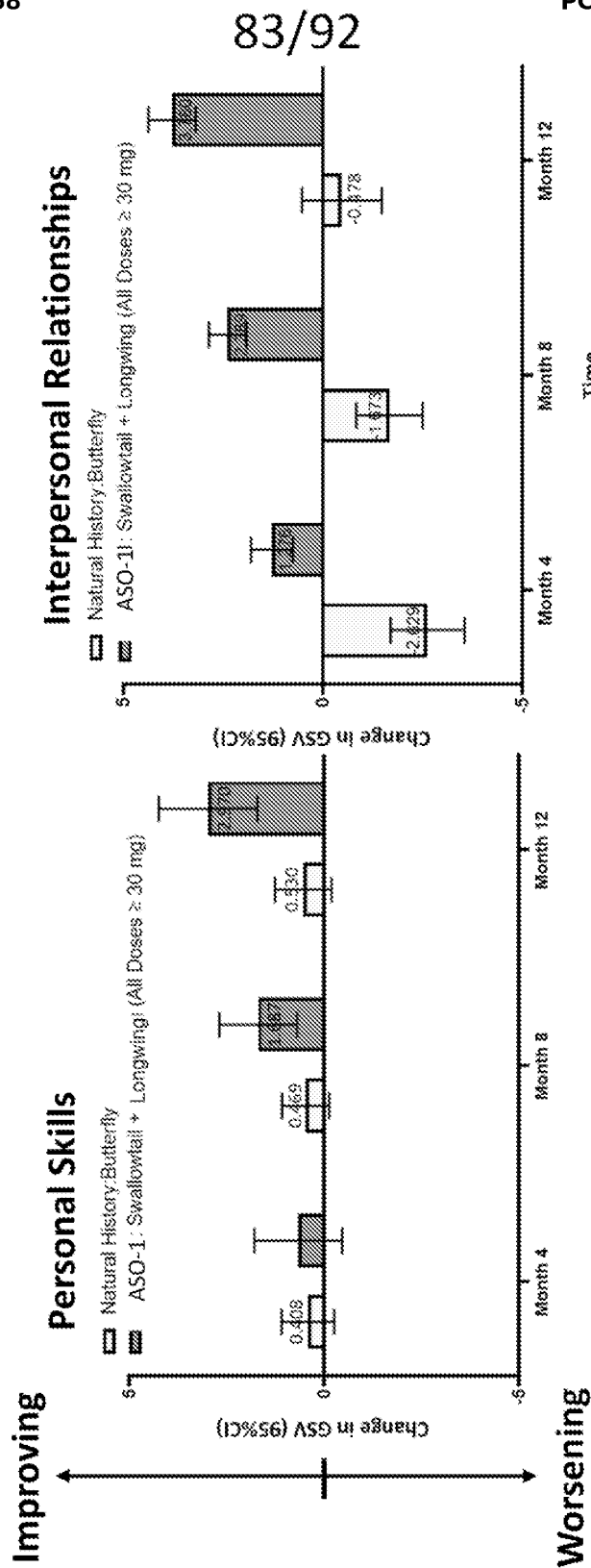
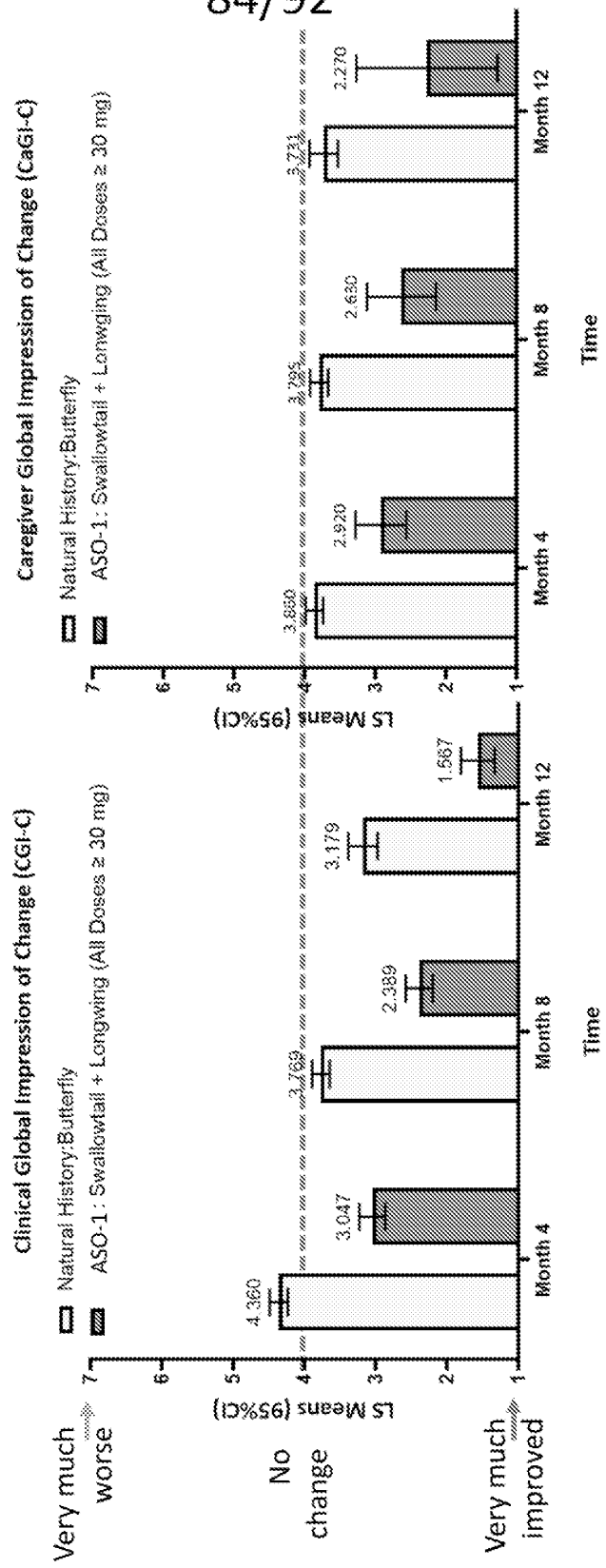
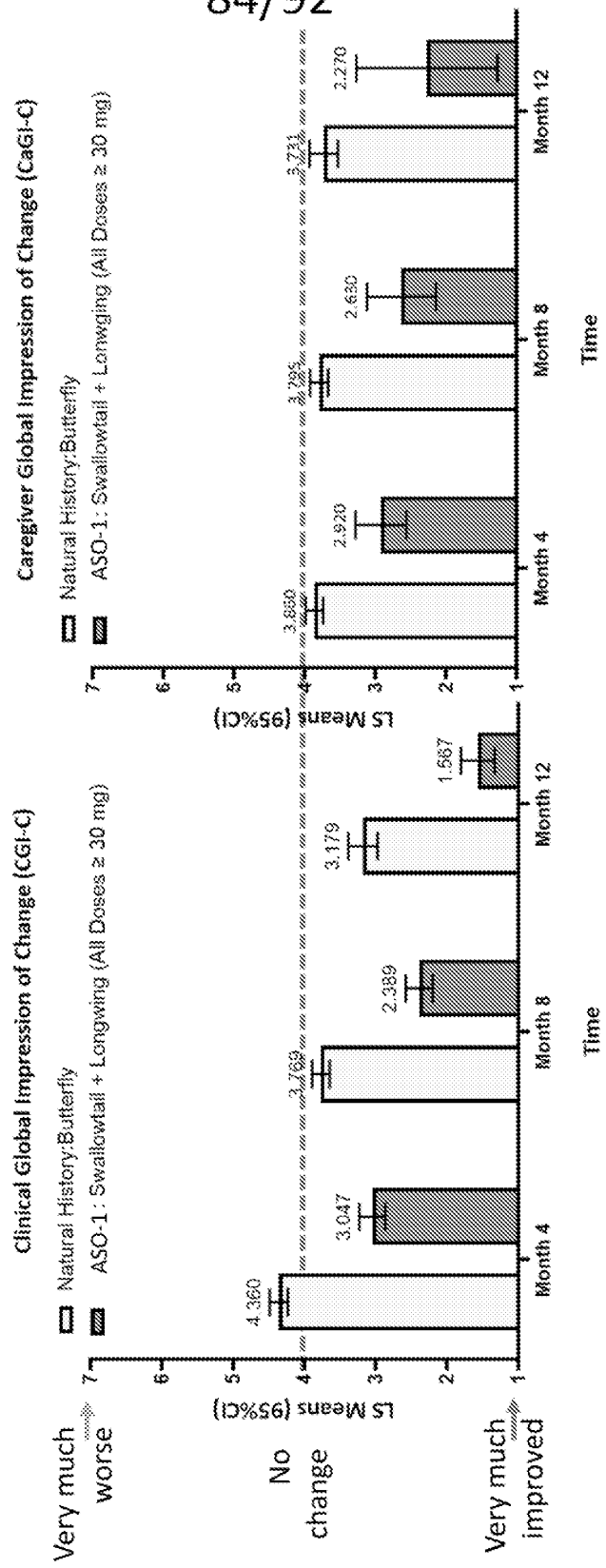


FIG. 58B

FIG. 58A



2 loading doses of 70 mg followed by 70 mg maintenance

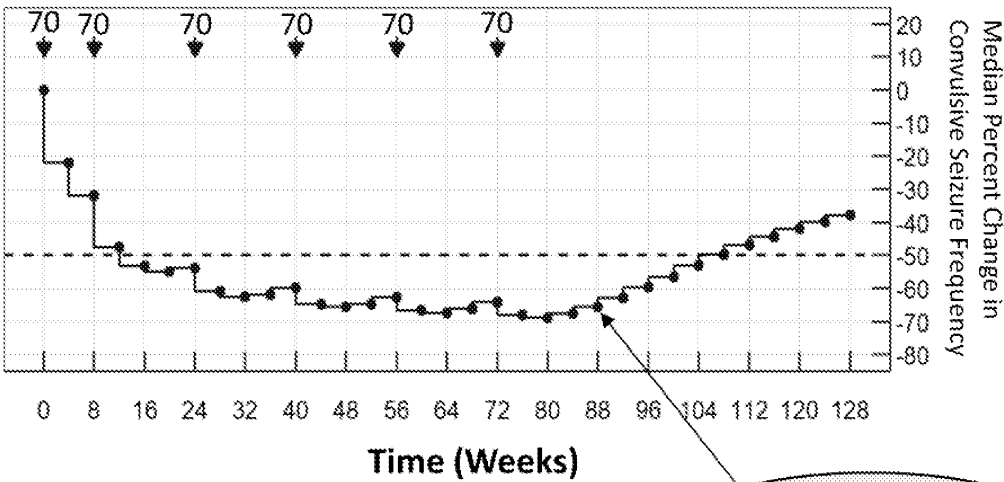


FIG. 60A

-65% seizure reduction

4 months post 4th maintenance dose

3 loading doses of 70 mg followed by 70 mg maintenance

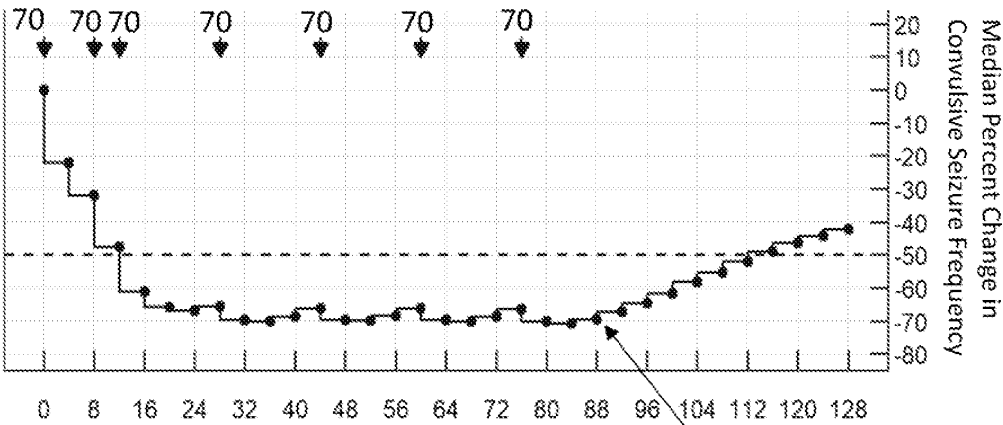
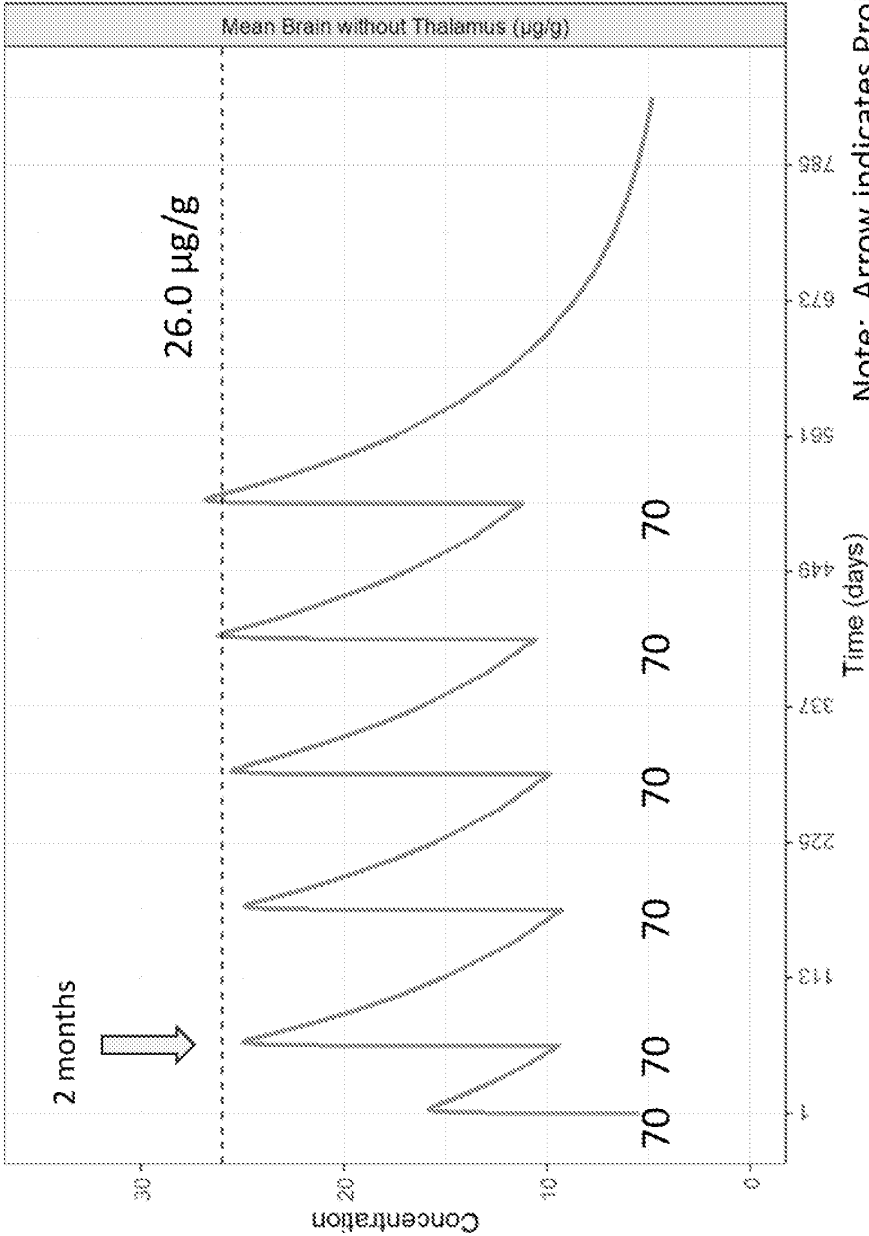


FIG. 60B

-67% seizure reduction

4 months post 4th maintenance dose

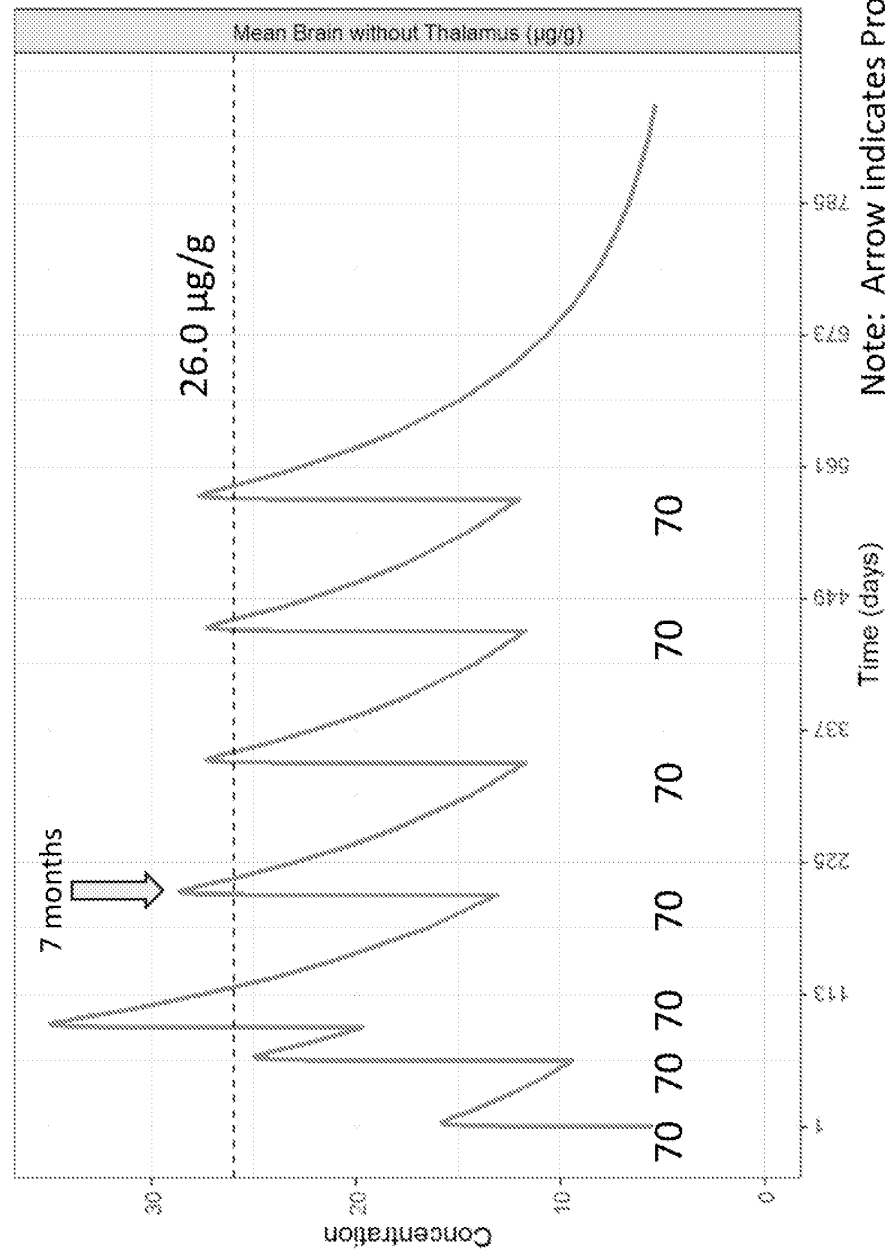
2 loading doses of 70 mg followed by 70 mg maintenance



Note: Arrow indicates Projected Steady State Brain Cmax exposure
Cmax Reference : 26.0 µg/g in Mean Brain without Thalamus

FIG. 61A

3 loading doses of 70 mg followed by 70 mg maintenance



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

2 loading doses of 70 mg followed by 70 mg maintenance

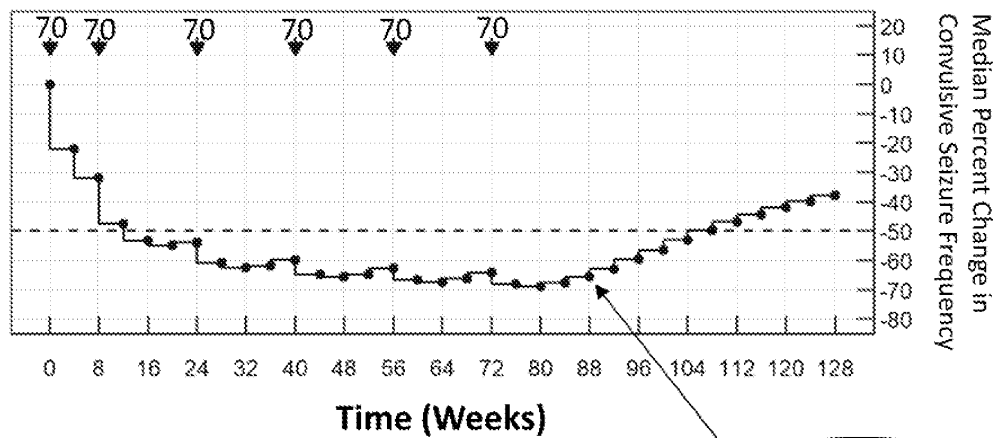


FIG. 62A

-65% seizure reduction
4 months post 4th maintenance dose

2 loading doses of 70 mg followed by 45 mg maintenance

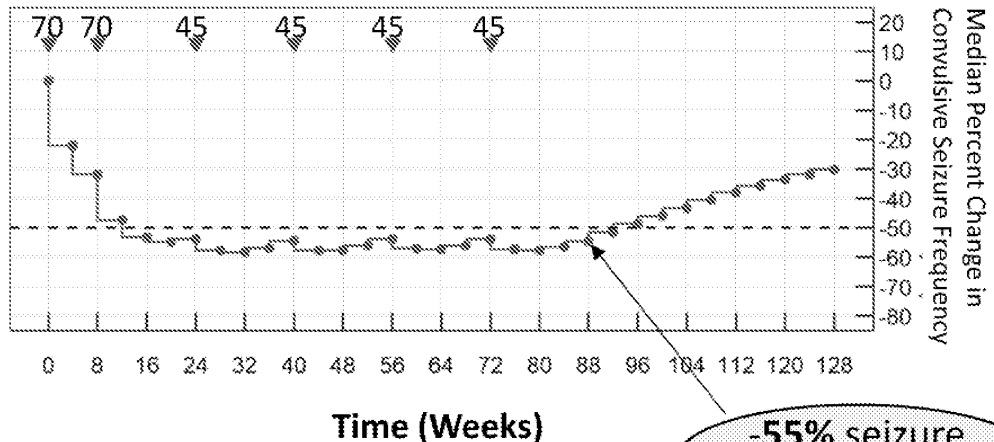


FIG. 62B

-55% seizure reduction
4 months post 4th maintenance dose

2 loading doses of 70 mg followed by 70 mg maintenance

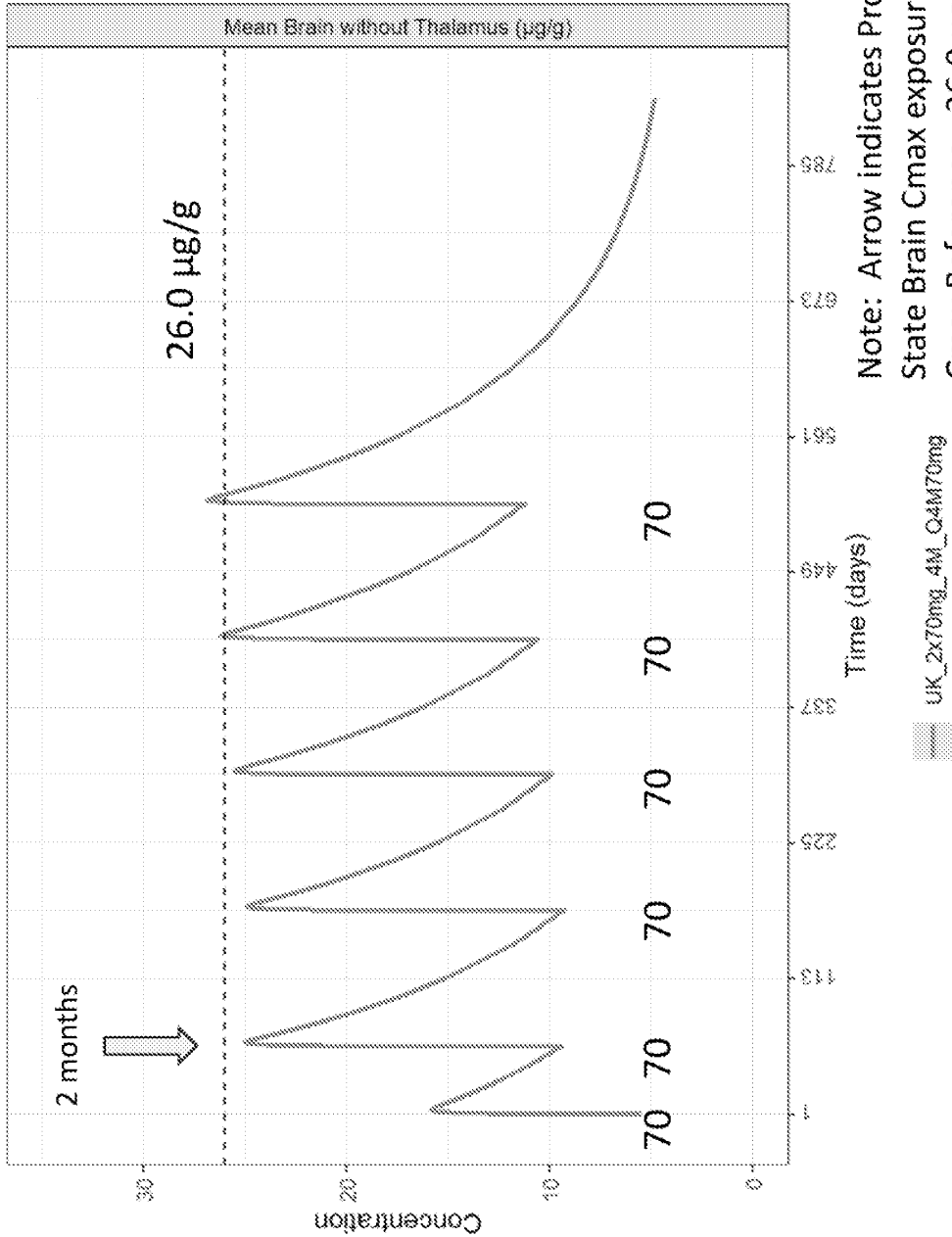
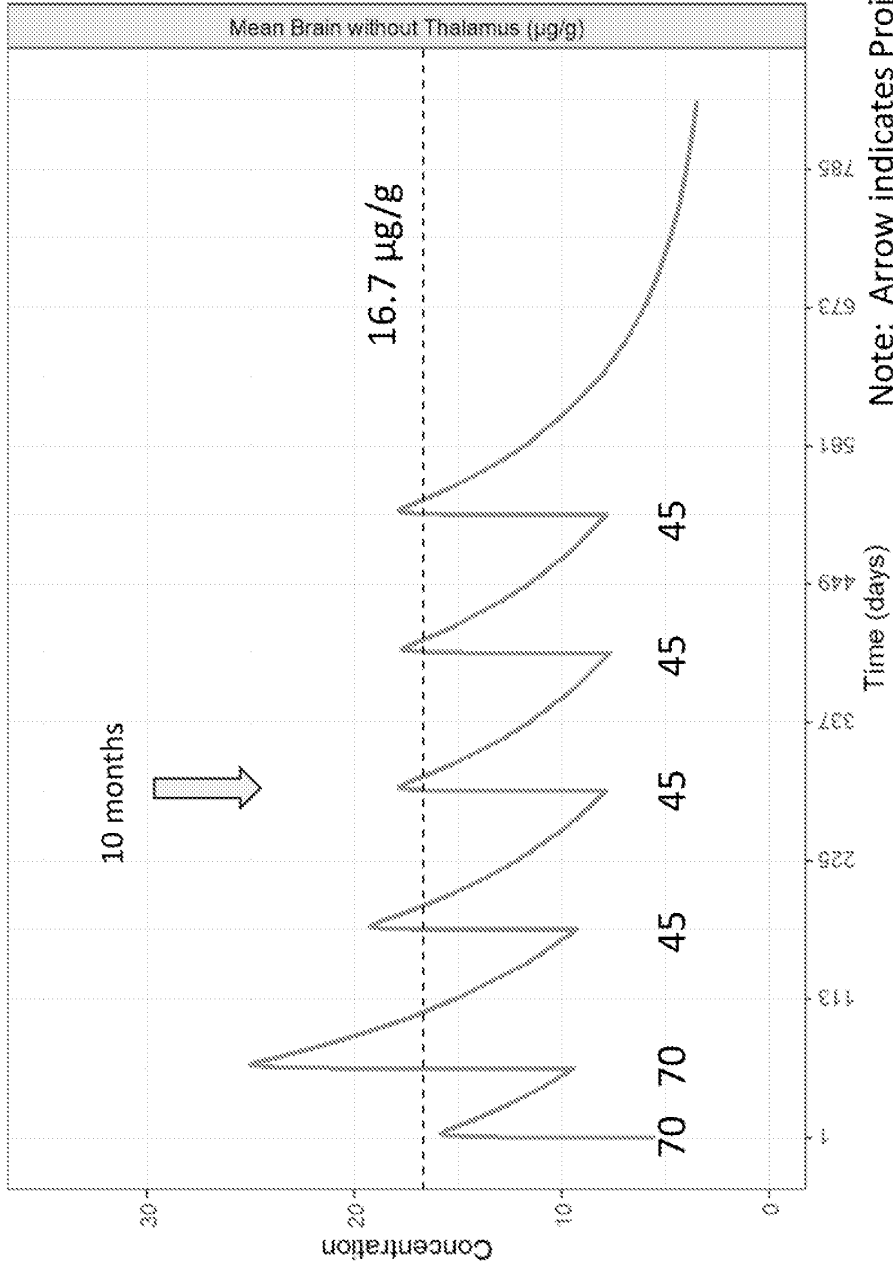


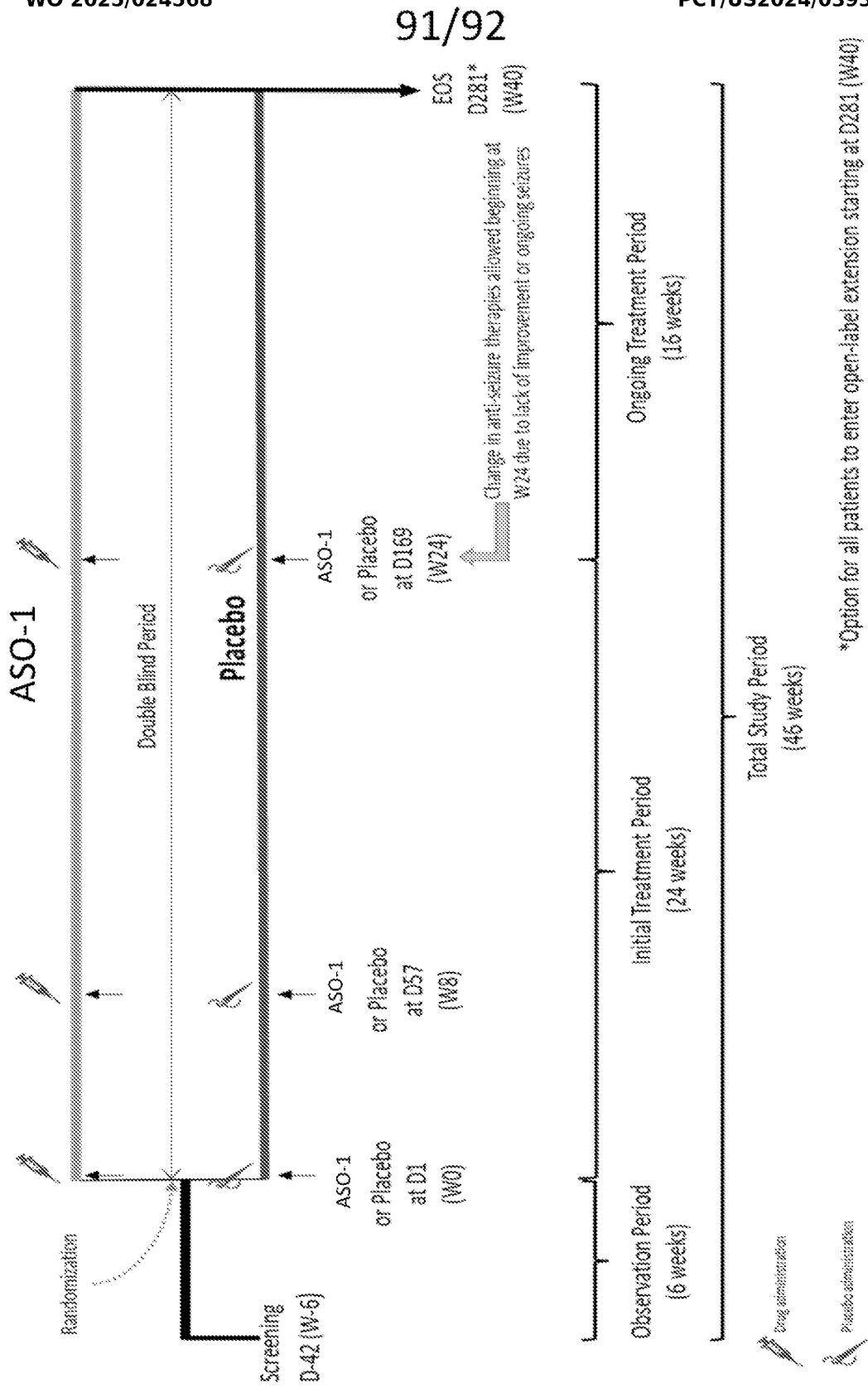
FIG. 63A

2 loading doses of 70 mg followed by 45 mg maintenance



Note: Arrow indicates Projected Steady State Brain Cmax exposure
Cmax Reference : 26.0 $\mu\text{g/g}$ in Mean Brain without Thalamus

FIG. 63B



*Option for all patients to enter open-label extension starting at D281 (W40)

FIG. 64

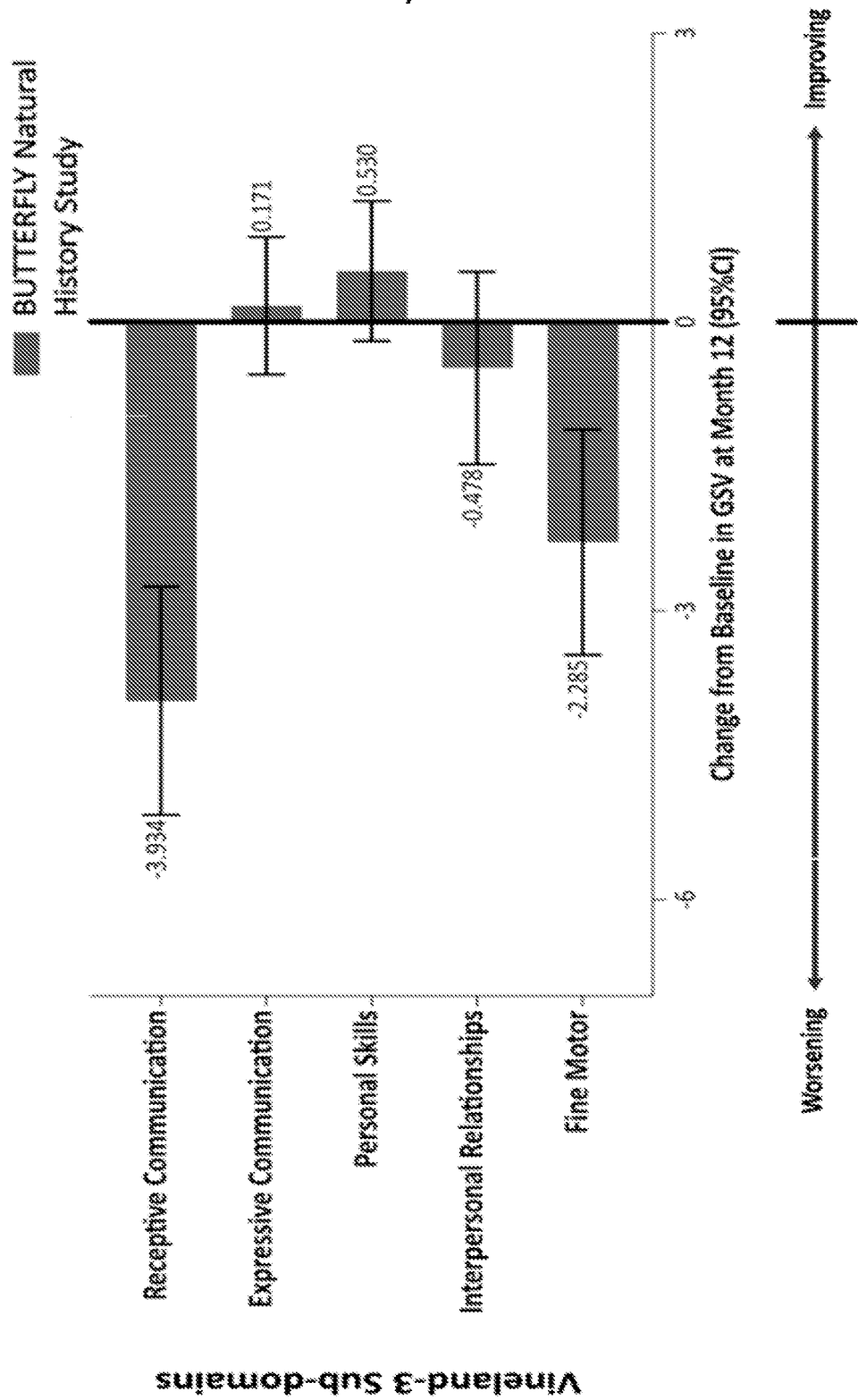


FIG. 65