

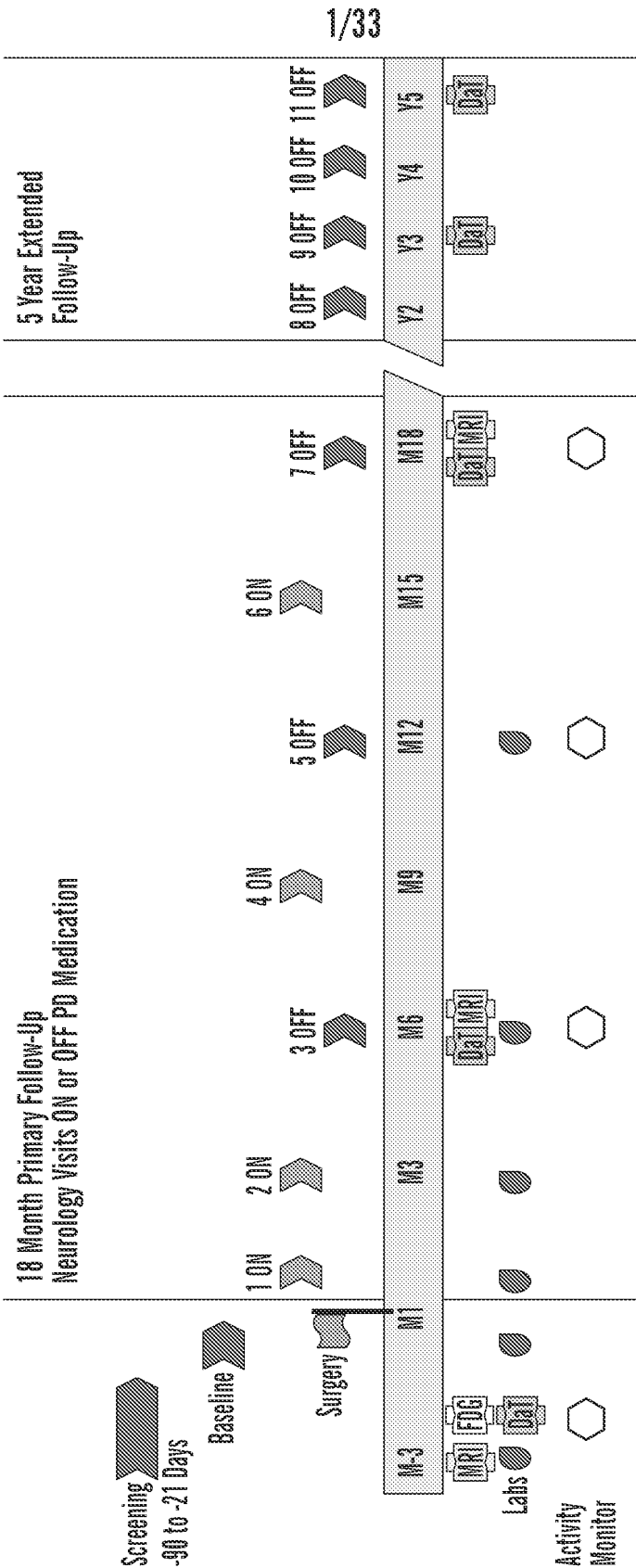


FIG. 1

Cohort A

Subject	Dx Duration	Screening UPDRS III (OFF → ON)	Screening UDysRS	Levodopa Equivalent Dose At Screening	AEs/Comments
A-1	1.5 years	15 → 10 (33.3%)	0	1575 mg	AEs: R shoulder pain, hypotension
A-2	1.5 years	15 → 7 (53%)	0	400 mg	AEs: Transient increase tremors
A-3	3 years	27 → 14 (48.1%)	0	300 mg	AEs: Transient increase tremors, low back pain, cold fingers, fatigue
A-4	3 years	27 → 8 (70%)	5	748 mg	AEs: Incision pain, transient tongue numbness, anxious episode, thigh numbness, headache
A-5	9 months	15 → 7 (53%)	0	400 mg	AEs: None
A-6	2 years	11 → 5 (55%)	0	850 mg	AEs: emesis, headache

FIG. 2

Cohort B

Subject	Dx Duration	Screening UPDRS III (OFF → ON)	Screening UDyRS	Levodopa Equivalent Dose At Screening	AEs/Comments
B-1	6 years	51 → 32 (37%)	5	825 mg	AEs: HA, RLE pain, rib pain
B-2	8 years	45 → 27 (37%)	4	2505 mg	SAE: L2 fx from fall off ladder, delayed hemorrhage/infarct AEs: None
B-3	9 years	40 → 21 (48%)	0	650 mg	AEs: Shoulder pain, nausea, headache, rib pain
B-4	9 years	35 → 13 (63%)	23	600 mg	AEs: Scratchy throat, IV site bruise, fatigue

FIG. 3

Surgical Infusion and Coverage Data									
Subject ID	Left Putamen			Right Putamen			Mean Coverage		
	Putamen Vol.	Infusion Vol.	Coverage	Putamen Vol.	Infusion Vol.	Coverage			
A-1	3905	1400	66%	3248	1400	70%	68%		
A-2	3019	1573	63%	3073	1571	61%	62%		
A-3	4159	1530	55%	4060	1800	64%	59%		
A-4	4118	1437	59%	4011	1435	53%	65%		
A-5	3121	1500	69%	3238	1500	61%	66%		
A-6	4120	1140	55%	3970	1286	63%	59%		
B-1	3775	1634	53%	3490	1602	40%	47%		
B-2	3255	955	60%	3460	1402	81%	70%		
B-3	3246	1500	68%	3242	1500	73%	71%		
B-4	4356	1797	71%	4461	1797	64%	60%		
							Avg 63%		

FIG. 4

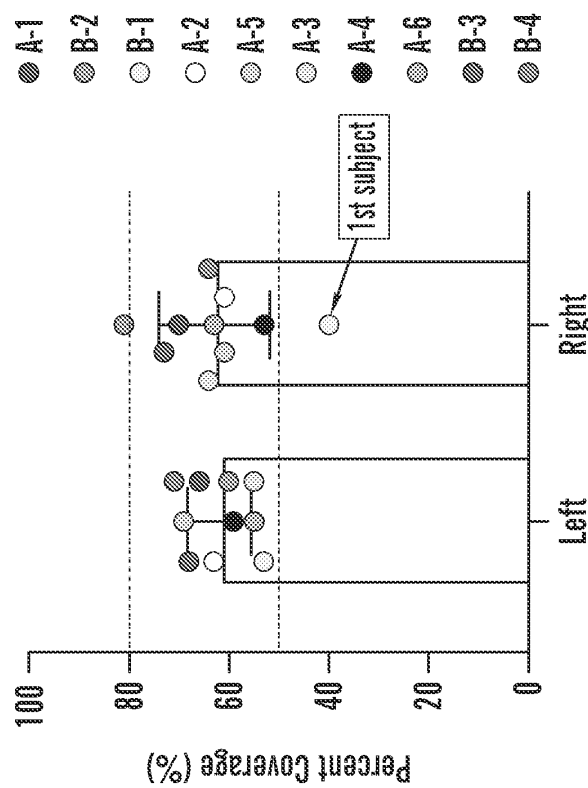


FIG. 5

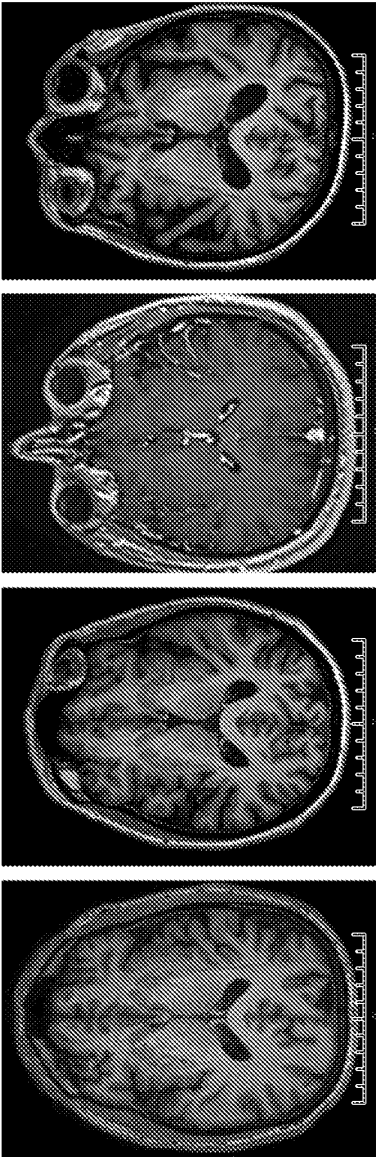


FIG. 6A

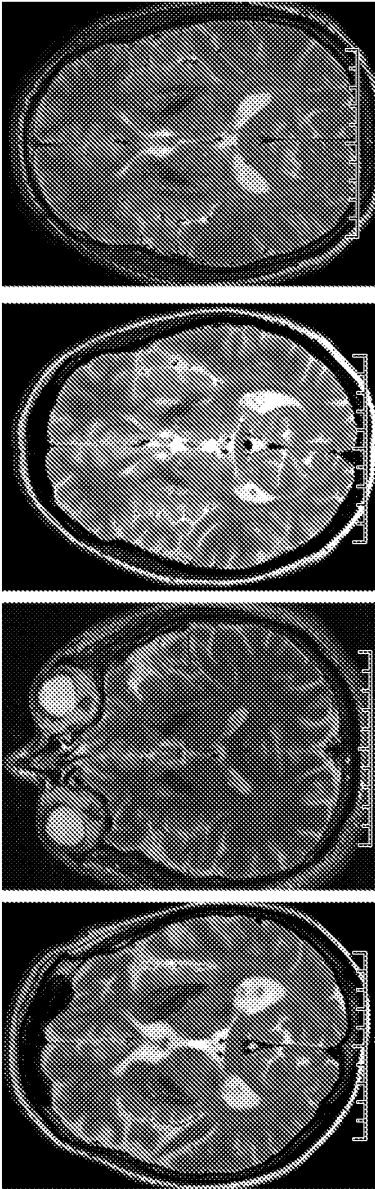


FIG. 6B

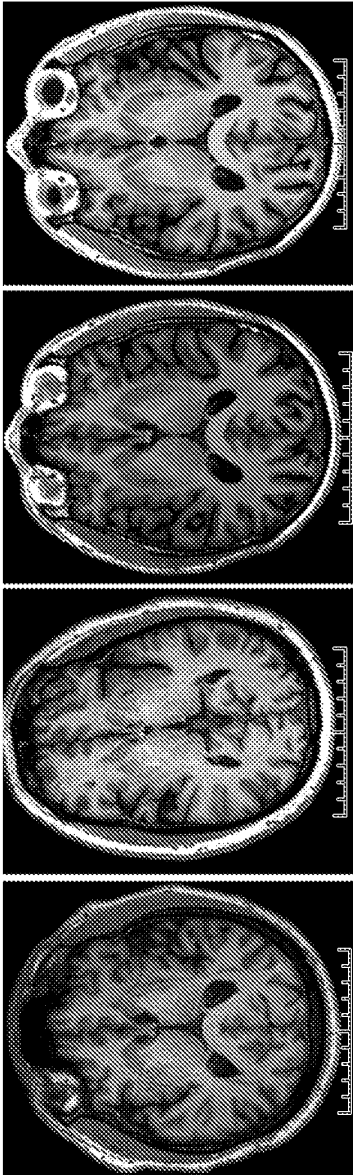


FIG. 7A

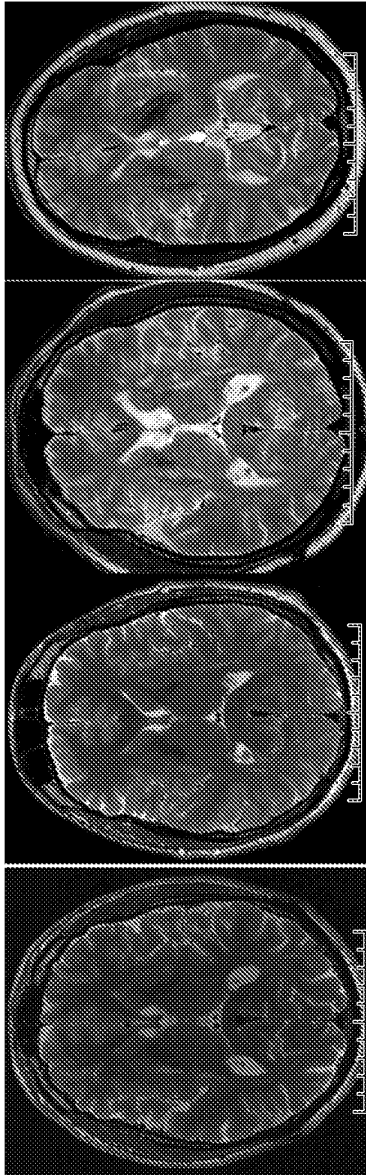


FIG. 7B

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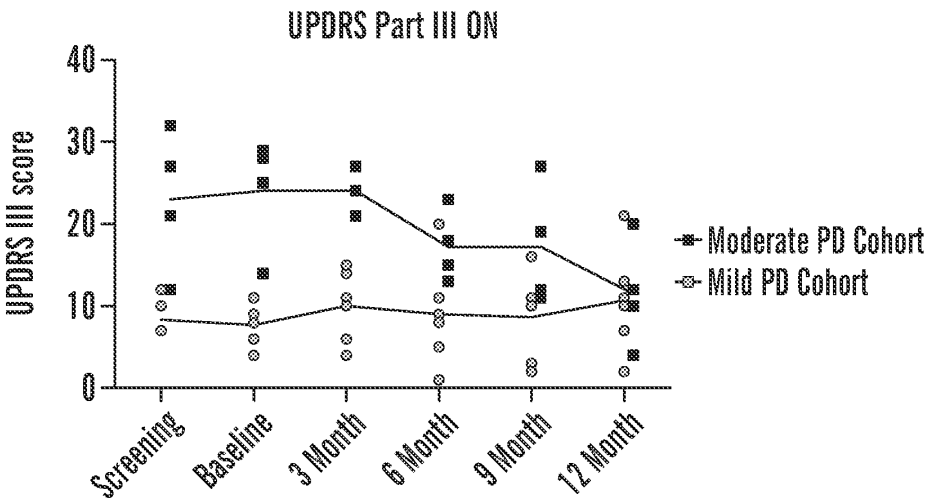


FIG. 8A

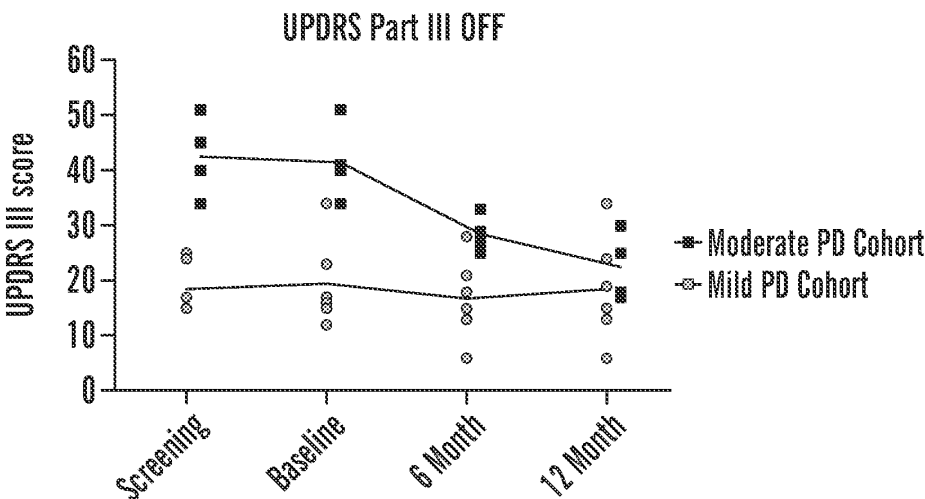
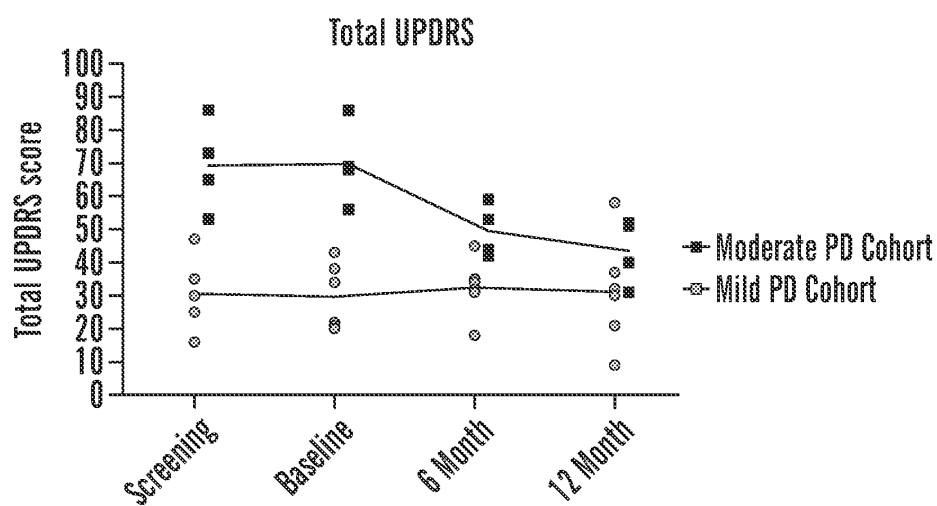
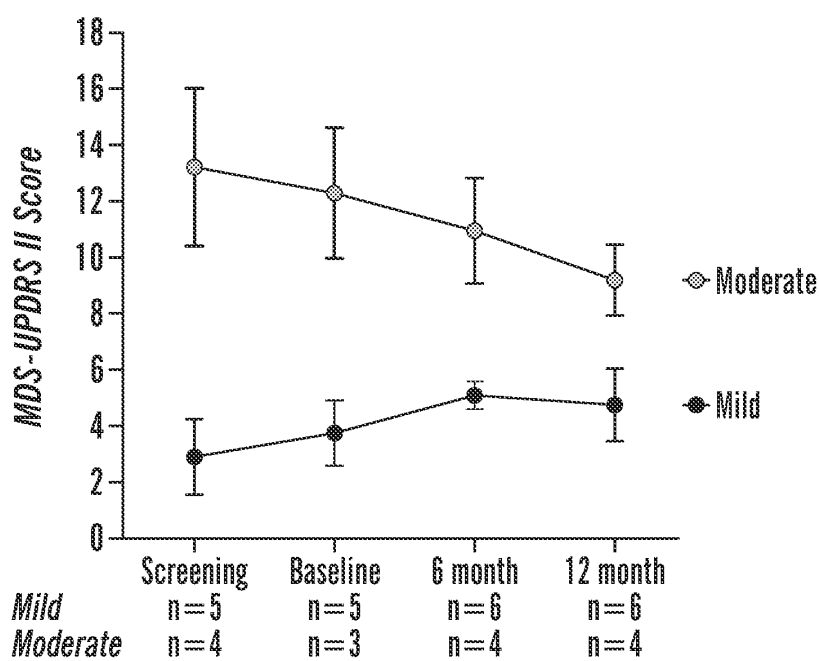


FIG. 8B

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**FIG. 8C****FIG. 8D**

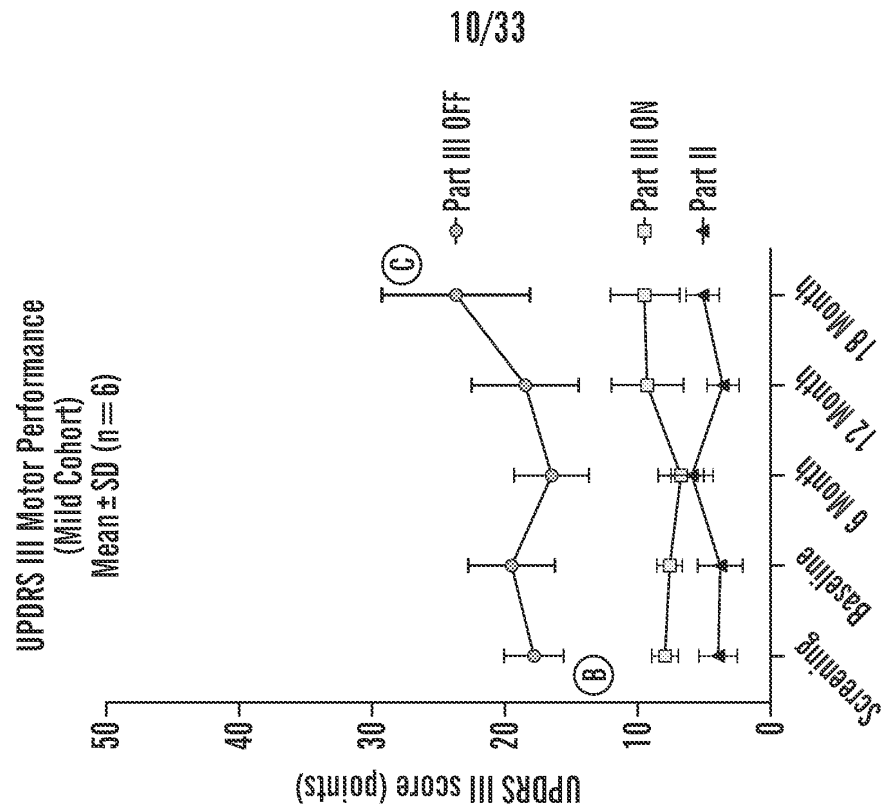


FIG. 8F

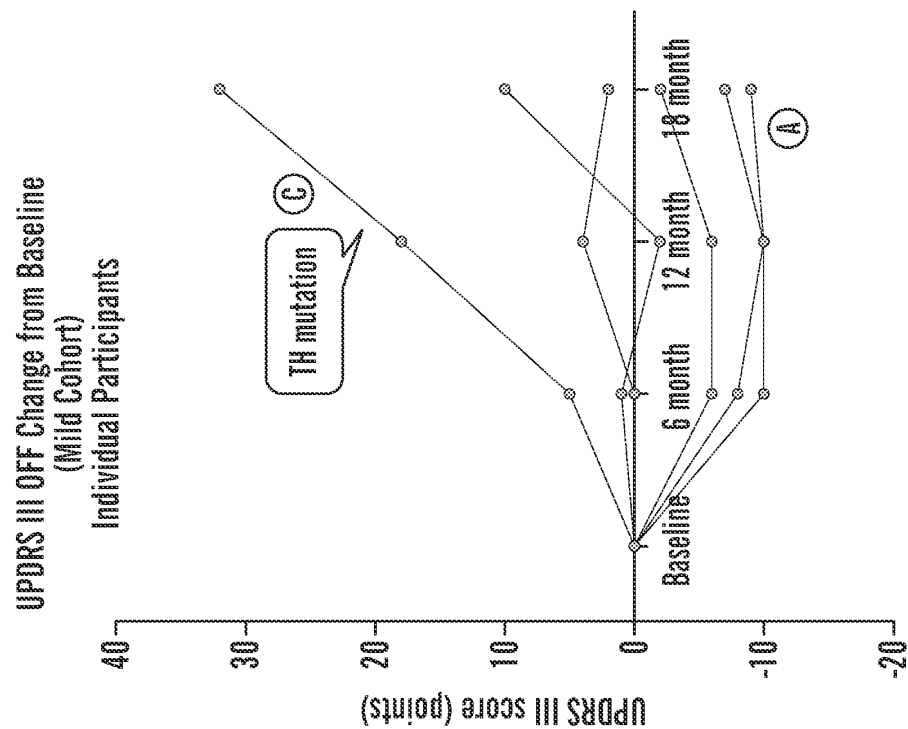


FIG. 8E

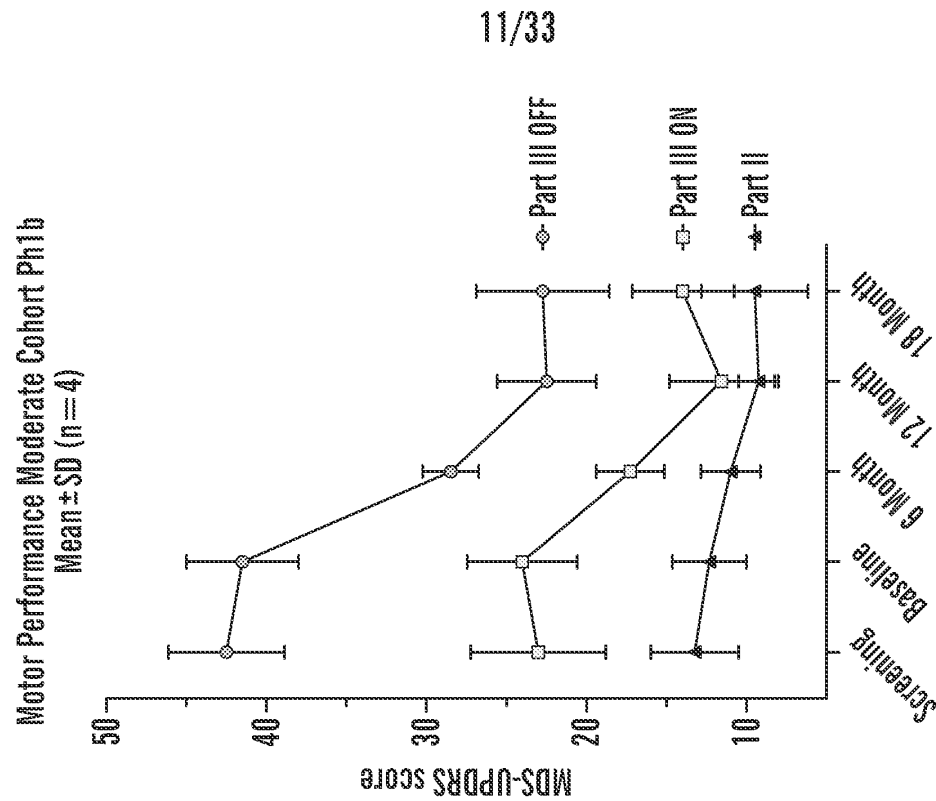


FIG. 8H

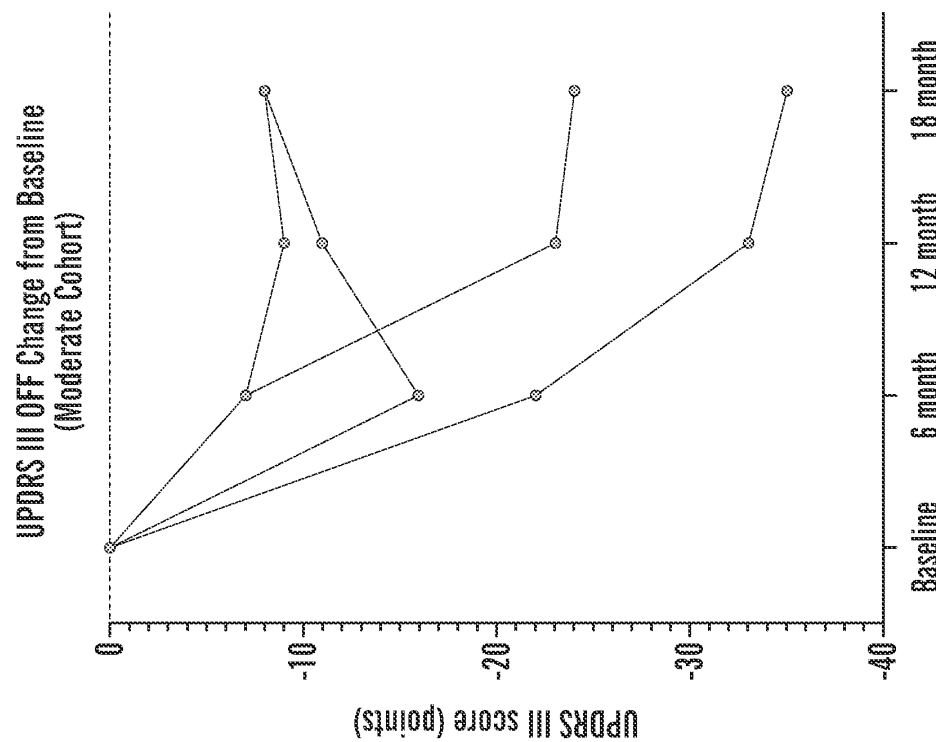


FIG. 8G

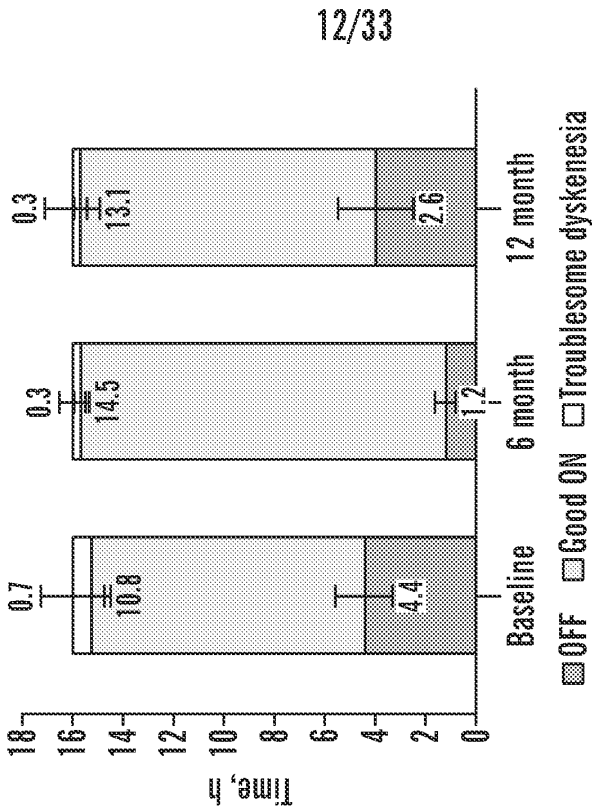


FIG. 9B

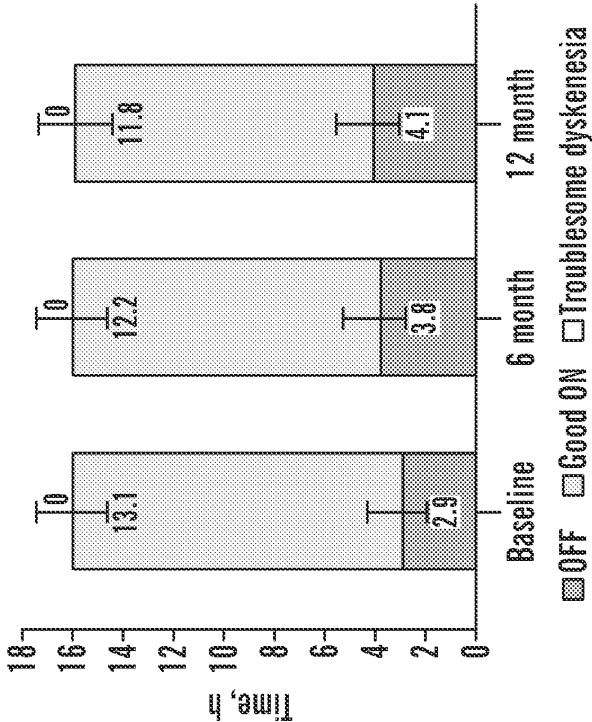


FIG. 9A

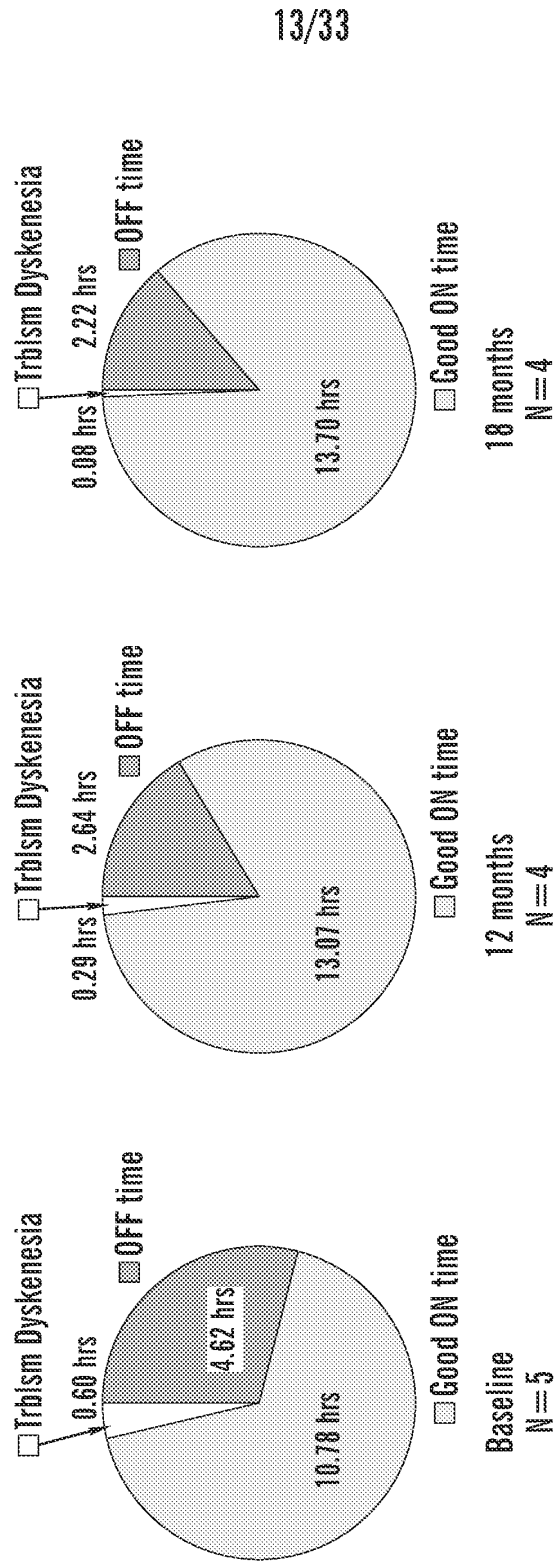


FIG. 9C

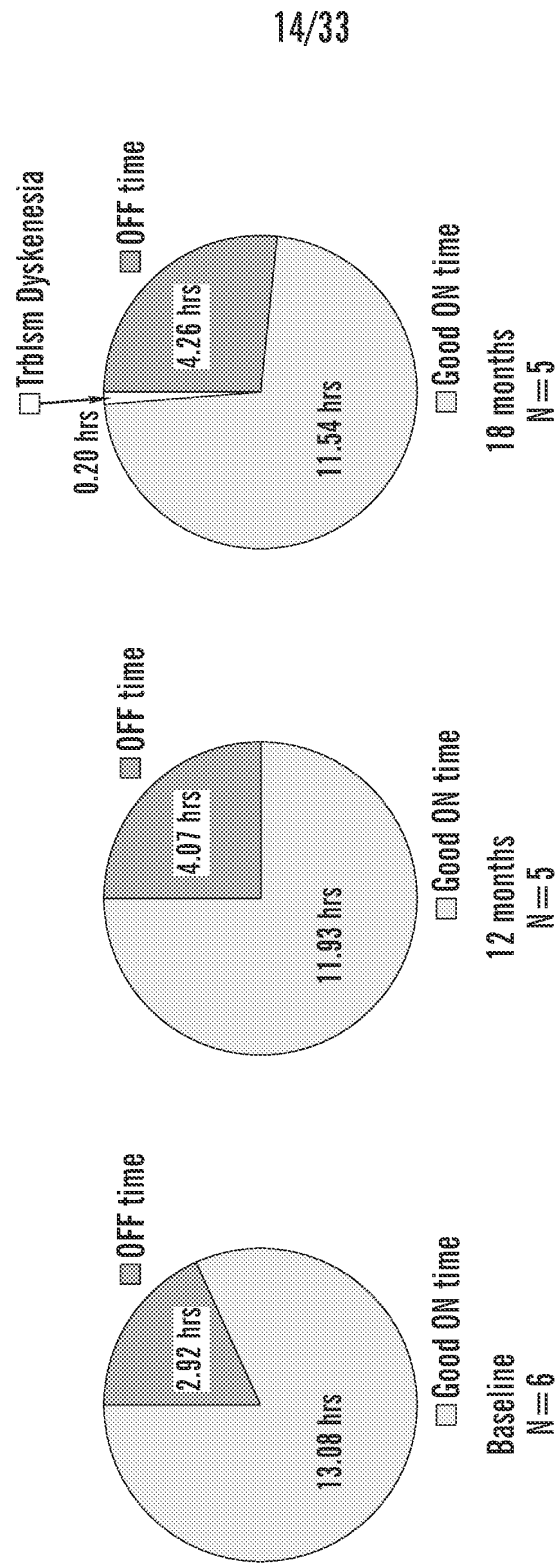


FIG. 9D

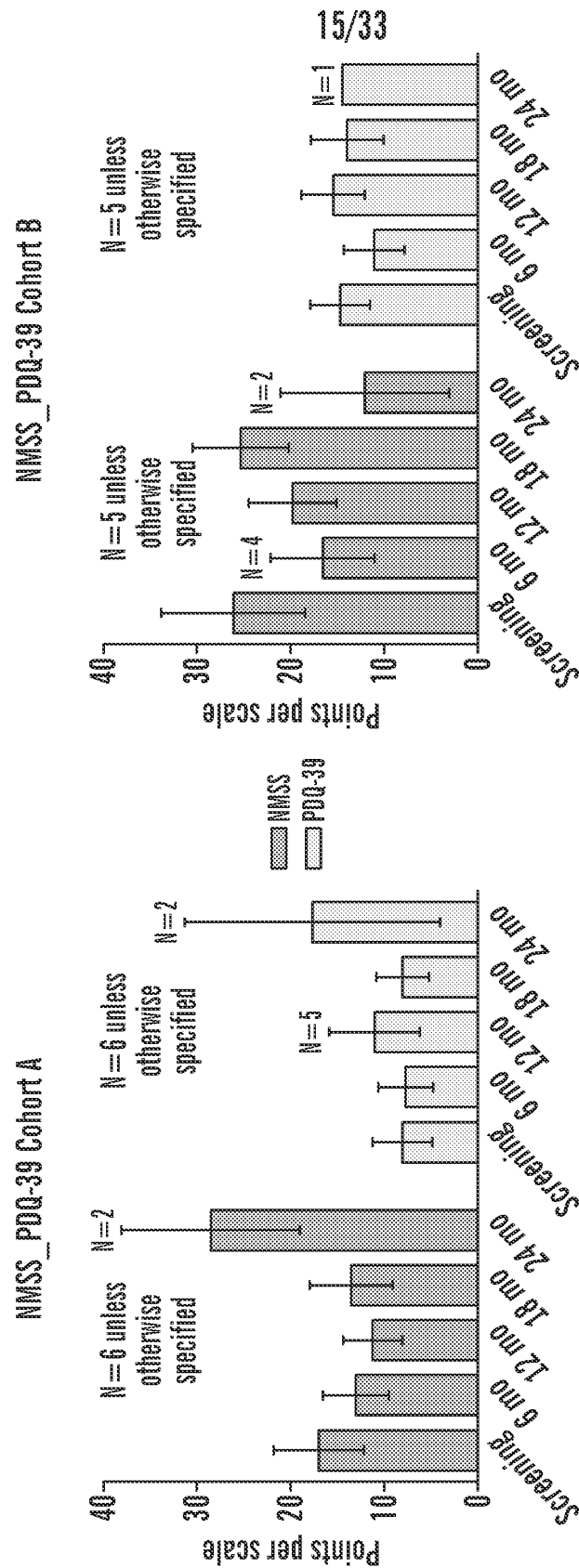


FIG. 10A

FIG. 10B

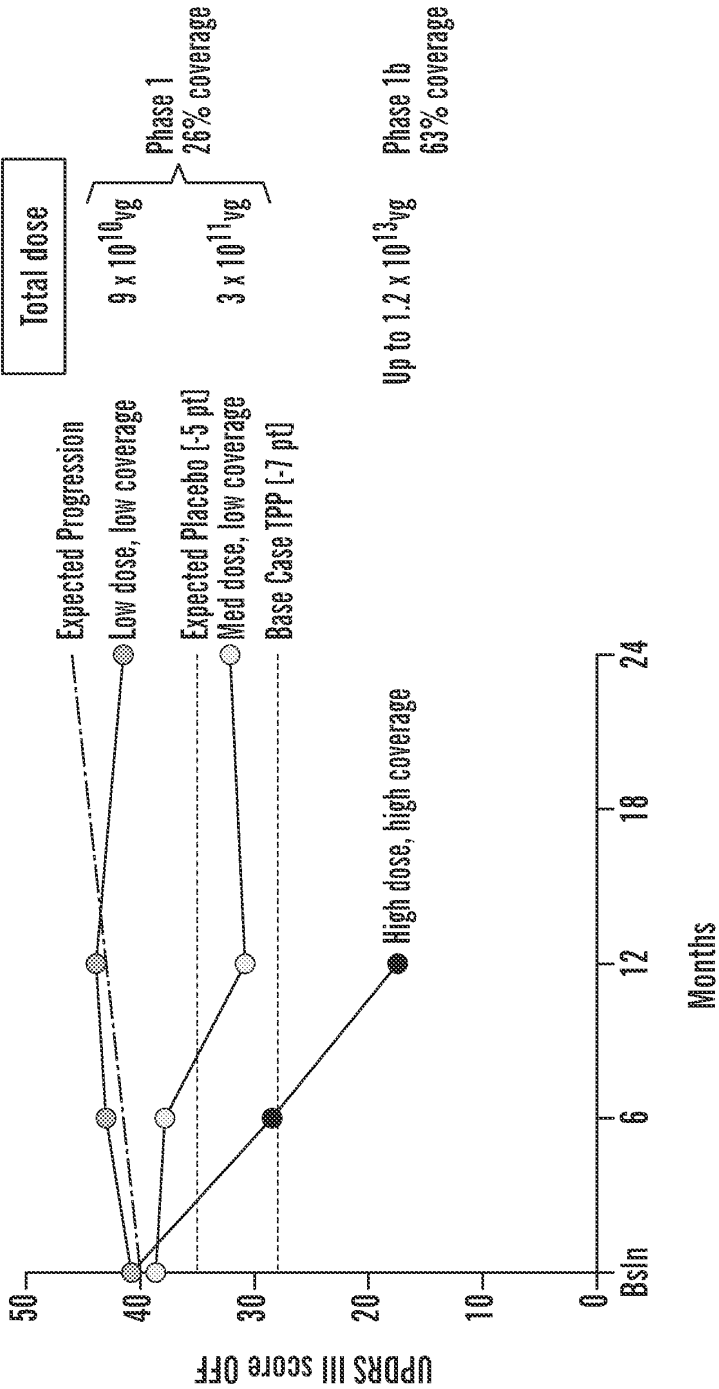


FIG. 11

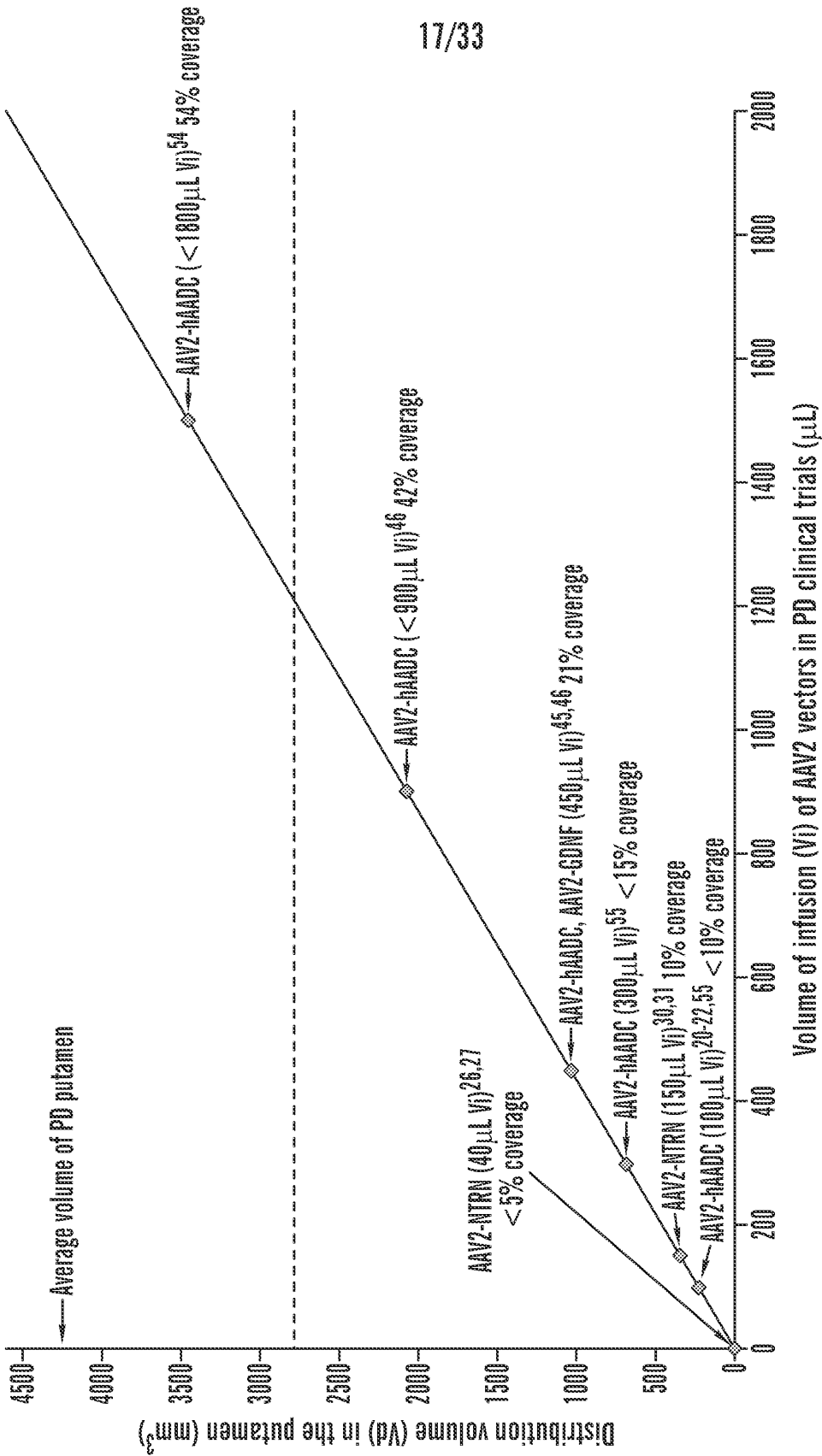


FIG. 12

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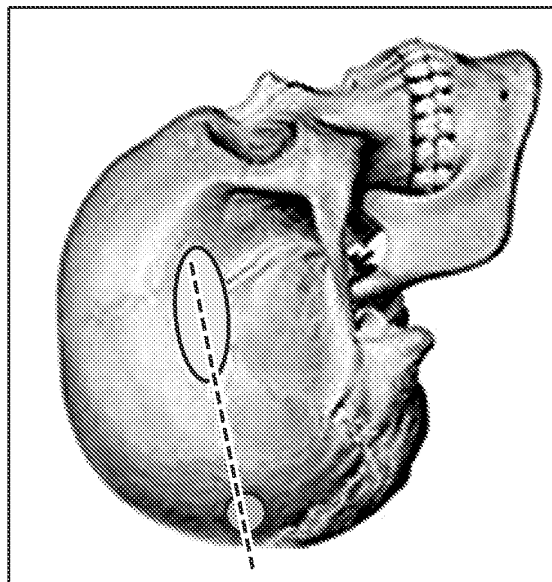


FIG. 13B

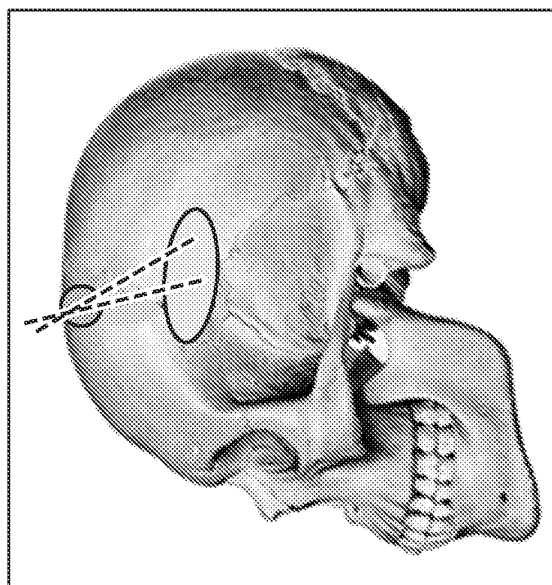


FIG. 13A

	Clinical Sites	No. Participants & Stage of PD	Delivery Approach	Vector Dose (vg/ml)	Infusion volume (µL/putamen)
Phase 1 Open Label, Dose Escalation Safety Trial 	NIH Clinical Center	All Advanced stage Cohort 1 - n=6 Cohort 2 - n=6 Cohort 3 - n=1 [^] Cohort 4 - n=0 [^] [^] recruitment was stopped prior to completing these cohorts due to low putamen coverage	• Bifrontal with 2 trajectories per putamen; • Convection-enhanced delivery (CED); • Intraoperative MRI (iMRI) monitoring; • Gadoteridol co-infusion	Cohort 1 - 9E10 Cohort 2 - 3E11 Cohort 3 - 9E11 Cohort 4 - 3E12	Total - 450 Precommissural - 300 Postcommissural - 150 Mean Volumetric Putamenal Coverage (26 putamenal/52 infusion trajectories) 26%
Phase 1b Open Label, Single Dose Safety Trial 	OSU UCSF UCI# #neurology site only	Early stage - n=6 Moderate stage - n=6 [^] [^] 5/6 treated by end of Mar '22	• Bi-occipital with single trajectory per putamen; • Otherwise, same as above	Both Cohorts - 3E12	Total ≤1800 Mean - 1500 Mean Volumetric Putamenal Coverage (20 putamenal/ 20 infusion trajectories) 62.5%

FIG. 14A

Putaminal Coverage Achieved in Phase 1 Study by Cohort

	Low Dose Cohort n=6	Medium Dose Cohort n=6	High Dose Cohort n=1
Mean (range) putamen volume, mm ³	4453 (3310-5247)	4261 (3570-5486)	3463 (3320-3606)
Mean (range) infusion volume, μ L	900	900	900
Mean (range) putamen coverage, %	28 (18-43)	22 (9-48)	38 (37-39)

Putaminal Coverage Achieved in Phase 1b Study by Cohort

	Mild Cohort N=6	Moderate Cohort (N=5)
Mean (range) putamen volume, mm ³	3670 (3019-4159)	3701 (3242-4461)
Mean (range) infusion volume, μ L	1464 (1140-1800)	1529 (955-1800)
Mean (range) putamen coverage, %	62 (53-70)	64 (40-81)

FIG. 14B

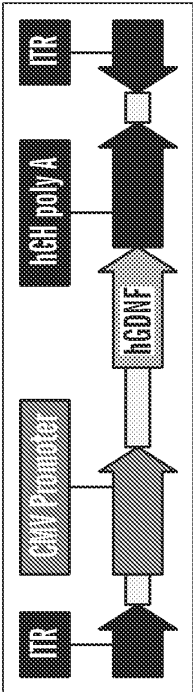


FIG. 15

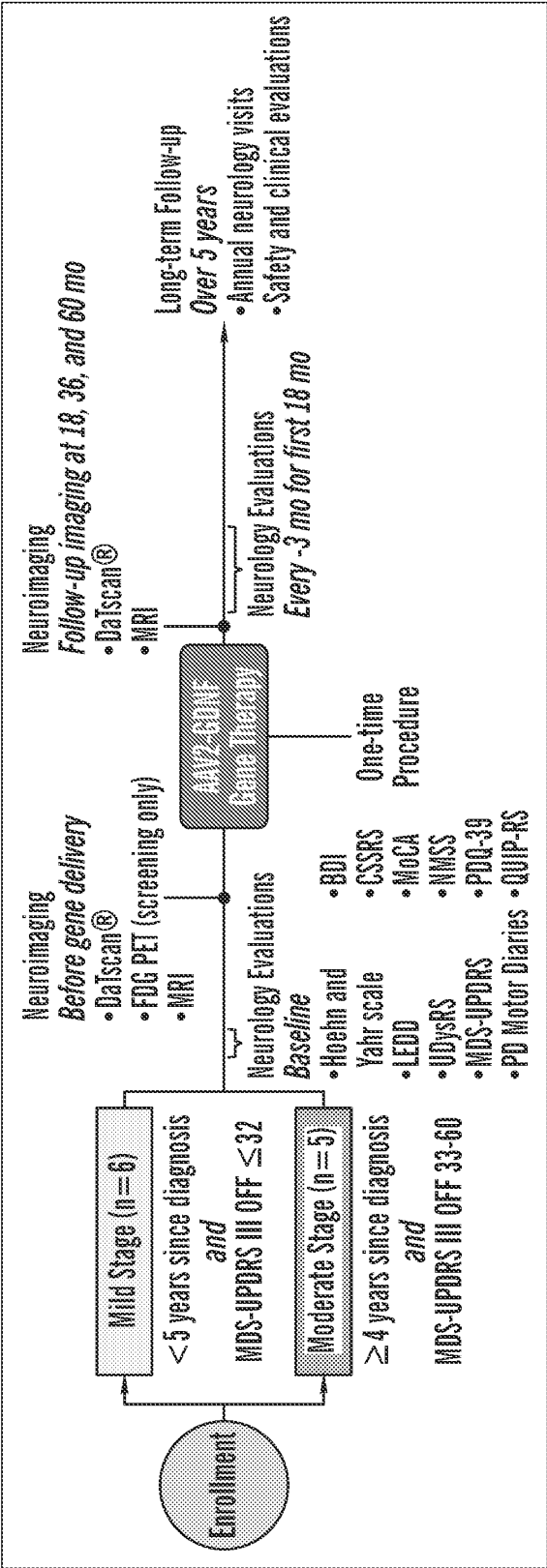


FIG. 16

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System Organ Class Preferred Term	Perioperative N=11 n (%)	Post-treatment N=11 n (%)
Subjects with at least 1 TEAE	11 (100)	11 (100)
Nervous system disorders	8 (73)	3 (27)
Headache	4 (36)	
Tremor	2 (18)	
Hypoaesthesia	1 (9)	
Hypoaesthesia oral	1 (9)	
Orthostatic hypotension	1 (9)	
Parkinsonism	1 (9)	
Balance disorder		1 (9)
Cerebral ischemia		1 (9)
Diplopia		1 (9)
Dyskinesia		1 (9)
Dystonia		1 (9)
Freezing phenomenon		1 (9)
Musculoskeletal and connective tissue disorders	5 (45)	3 (27)
Arthralgia	2 (18)	
Musculoskeletal chest pain	2 (18)	
Back pain	1 (9)	
Pain in extremity	1 (9)	
Spinal fracture	1 (9)	1 (9)
Muscle spasms		1 (9)
Muscle stiffness		1 (9)
General disorders and administration site conditions	3 (27)	2 (18)
Fatigue	3 (27)	
Injection site bruising	1 (9)	
Swelling face	1 (9)	
Asthenia		1 (9)
Influenza-like illness		1 (9)
Infections and infestations	0 (0)	5 (45)
COVID-19		2 (18)
Bacterial infection		1 (9)
Cellulitis		1 (9)
Nasopharyngitis		1 (9)
Viral infection		1 (9)

FIG. 17

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Gastrointestinal disorders	2 (18)	1 (9)
Nausea	1 (9)	
Vomiting	1 (9)	
Abdominal pain		1 (9)
Psychiatric disorders	1 (9)	2 (18)
Anxiety	1 (9)	
Hallucination		1 (9)
Impulsive behavior		1 (9)
Investigations	0 (0)	2 (18)
Magnetic resonance imaging abnormal		2 (18)
Blood and lymphatic system disorders	0 (0)	1 (9)
Thrombocytosis		1 (9)
Injury, poisoning and procedural complications	1 (9)	0 (0)
Incision site pain	1 (9)	
System Organ Class Preferred Term	Perioperative N = 11 n (%)	Post-Treatment N = 11 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	1 (9)
Tonsil cancer		1 (9)
Reproductive system and breast disorders	0 (0)	1 (9)
Vulvovaginal discomfort		1 (9)
Respiratory, thoracic and mediastinal disorders	1 (9)	0 (0)
Throat irritation	1 (9)	
Skin and subcutaneous tissue disorders	1 (9)	0 (0)
Face oedema	1 (9)	
Vascular disorders	1 (9)	0 (0)
Raynaud's phenomenon	1 (9)	
Subjects with at least 1 SAE	1 (9)	3 (27)
Infections and infestations	0 (0)	1 (9)
Cellulitis		1 (9)
Musculoskeletal and connective tissue disorders	1 (9)	0 (0)
Spinal fracture	1 (9)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	1 (9)
Tonsil cancer		1 (9)
Nervous system disorders	0 (0)	1 (9)
Cerebral ischemia		1 (9)

FIG. 17 (cont.)

	Participant	Timepoint	H&Y	MDS-UPDRS				UPDRS	Motor Diary			LEDD	Non-Motor/Neuropsychiatric					
				Part II	Part III OFF	Part III ON	Part IV		Tribl Dys	OFF	Good ON		PDQ-36	NMSS	QUIP-RS	BDI	MoCA	CSSRS
Mild Cohort	1	6 mo																
		12 mo																
	2	6 mo																
		12 mo																
	3	6 mo																
		12 mo																
	4	6 mo																
		12 mo																
	5	6 mo																
		12 mo																
	6	6 mo																
		12 mo																

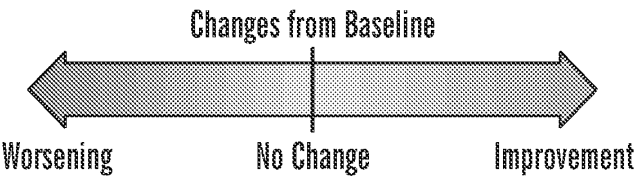


FIG. 18A

			Participant	Timepoint	H&Y	MDS-UPDRS				UPDysRS	Motor Diary			LEDD	Non-Motor/Neuropsychiatric					
						Part II	Part III OFF	Part III ON	Part IV		Trbl Dys	OFF	Good ON		PDQ-36	NMSS	QUIP-RS	BDI	MoCA	CSSRS
Moderate Cohort	1	6 mo																		
		12 mo																		
	2	6 mo																		
		12 mo																		
	3	6 mo																		
		12 mo																		
	4	6 mo																		
		12 mo																		

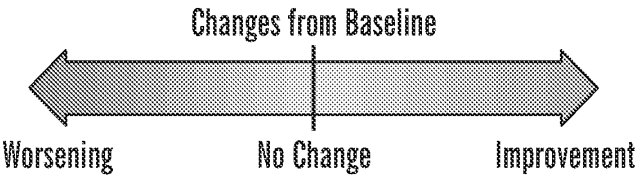


FIG. 18B

FIG. 19A

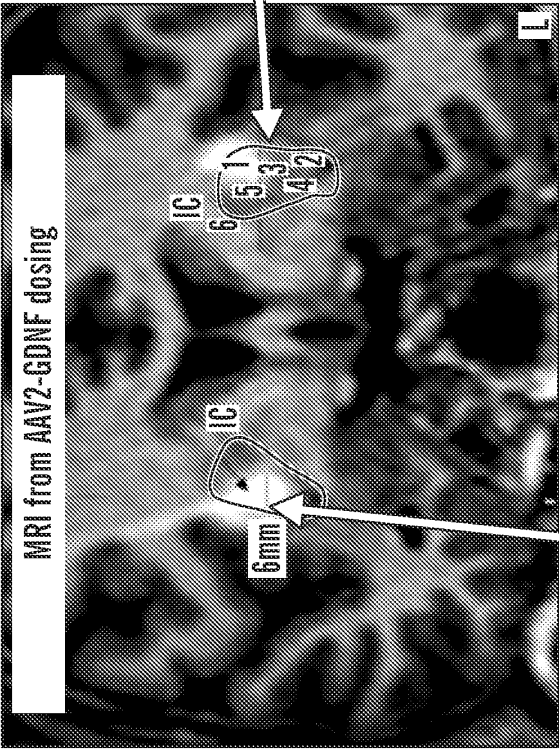


FIG. 19E

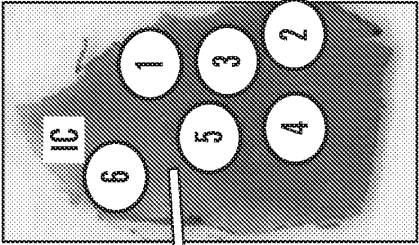


FIG. 19F

punch #	pg GDNF/mg protein
1	1932.5
2	213.8
3	60.9
4	413.0
5	1124.1
6	0.0

Dopaminergic neurons (tyrosine hydroxylase staining)

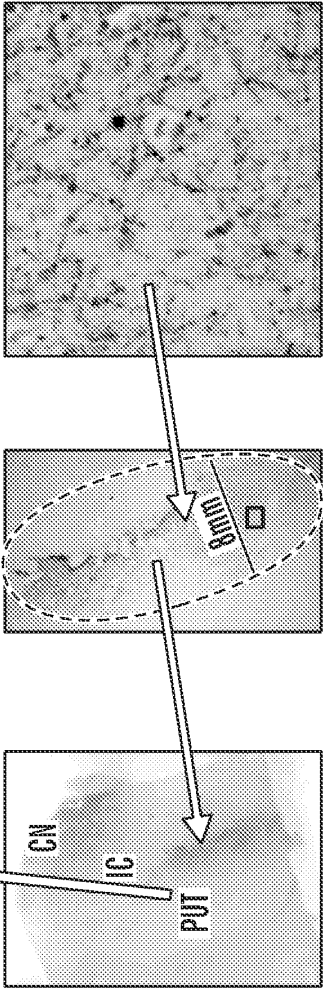


FIG. 19B FIG. 19C FIG. 19D

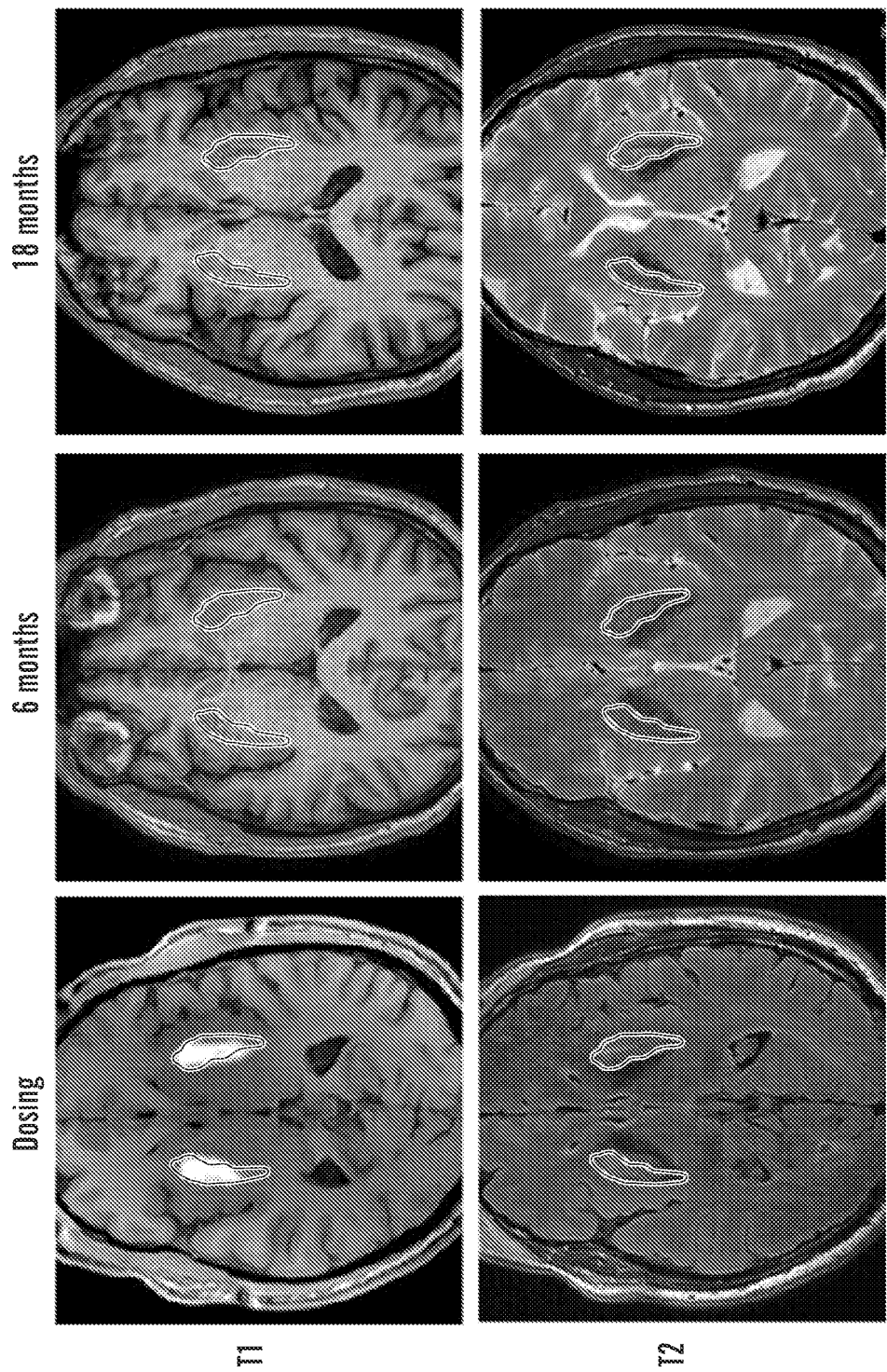


FIG. 20

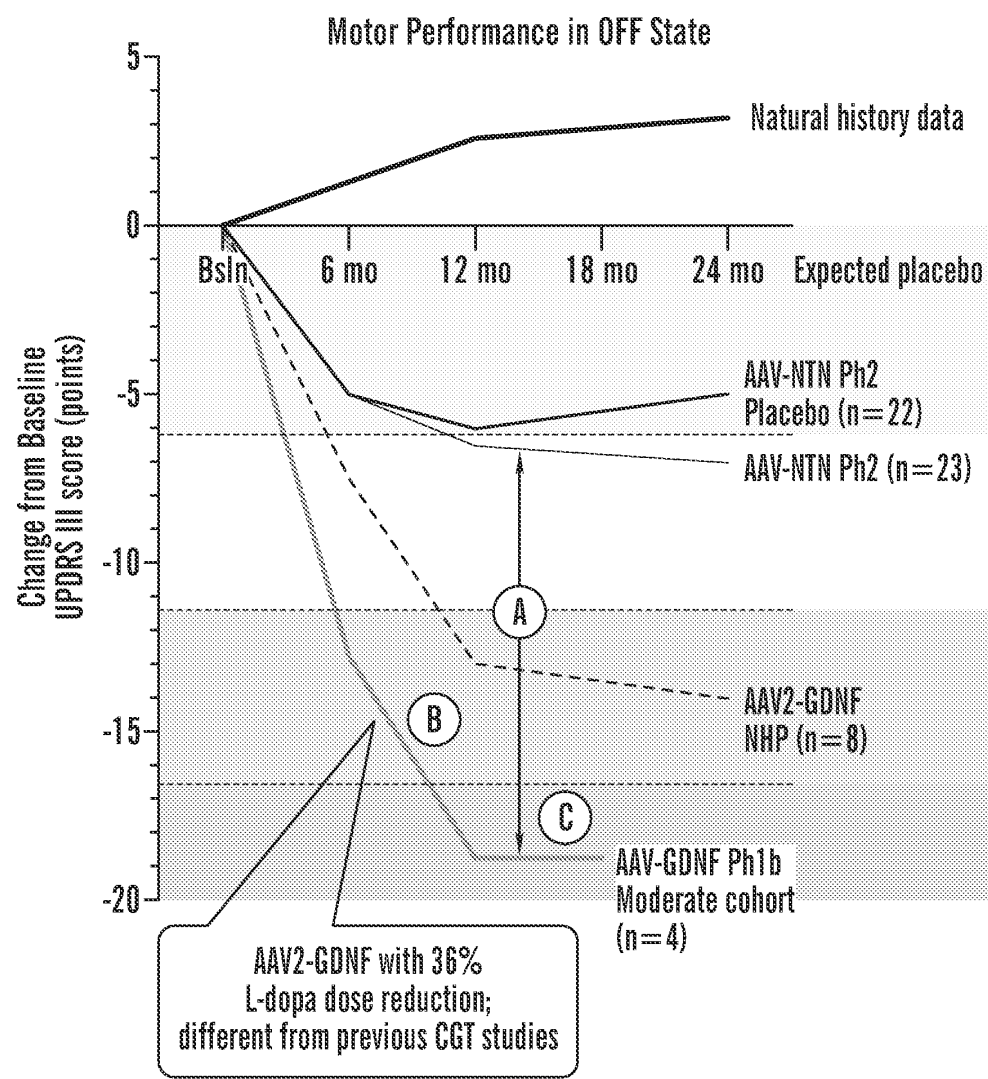


FIG. 21

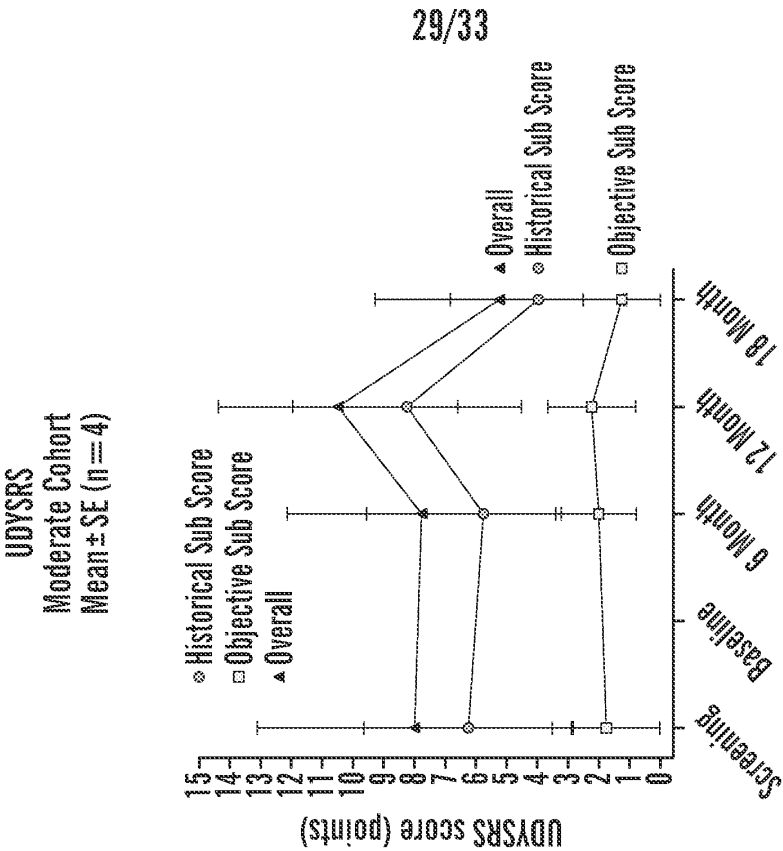


FIG. 22B

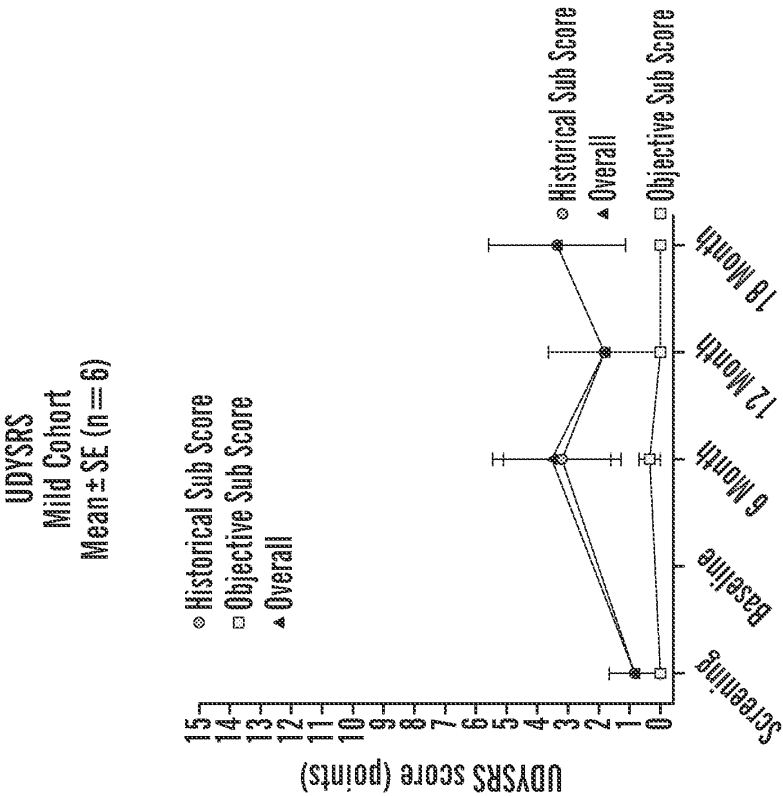


FIG. 22A

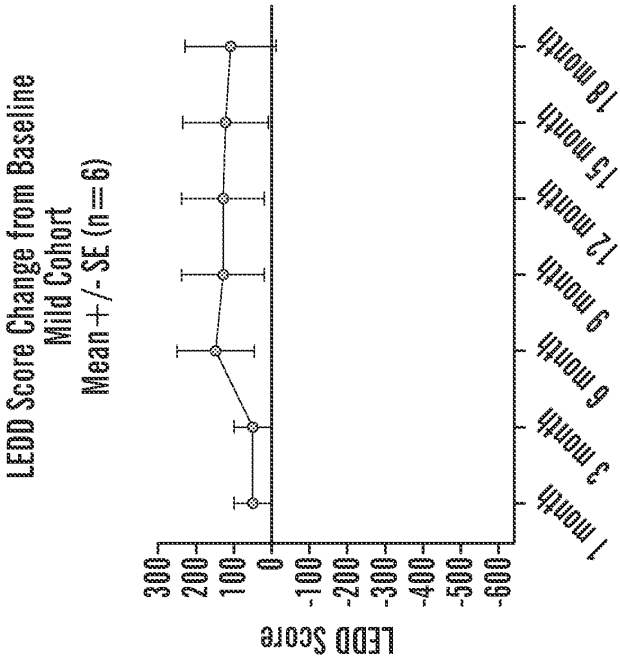


FIG. 23A

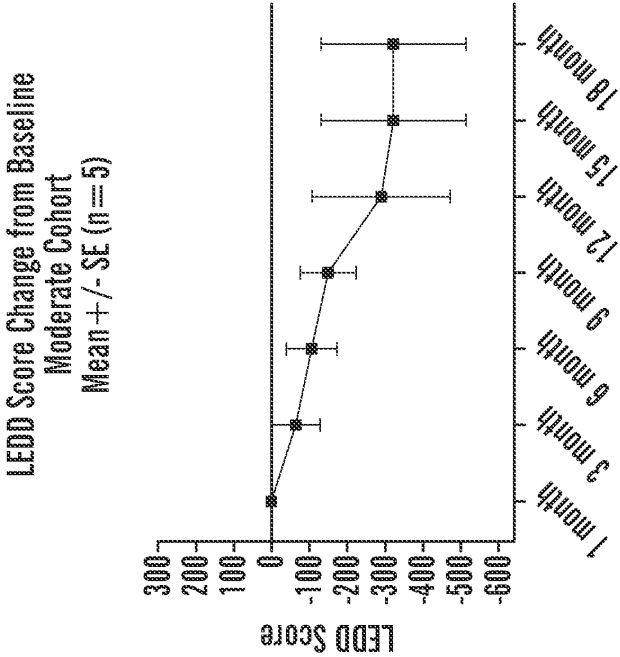


FIG. 23B

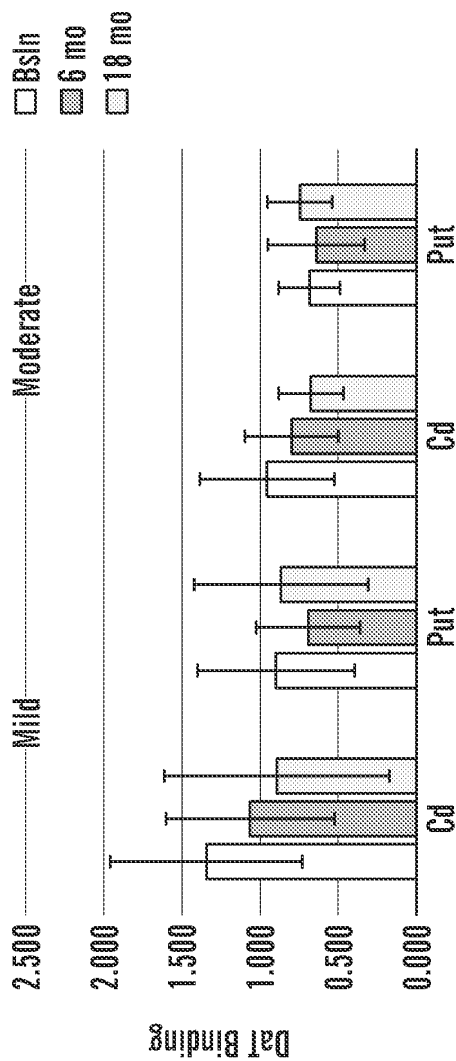


FIG. 24A

Mild	Bsln	6mo	18mo
Caudate nucleus	1.341 ± 0.518	1.066 ± 0.512	0.891 ± 0.545
Putamen	0.899 ± 0.407	0.693 ± 0.266	0.864 ± 0.438

FIG. 24B

Moderate	Bsln	6mo	18mo
Caudate nucleus	0.954 ± 0.401	0.802 ± 0.389	0.677 ± 0.257
Putamen	0.677 ± 0.258	0.643 ± 0.169	0.746 ± 0.198

FIG. 24C

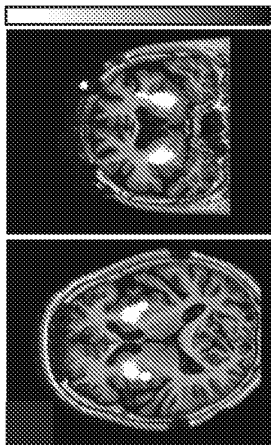


FIG. 25A

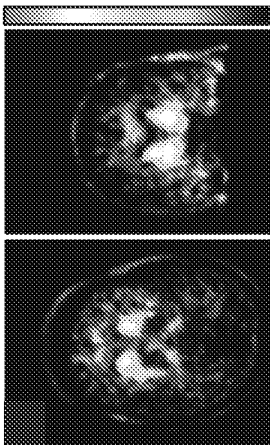


FIG. 25B

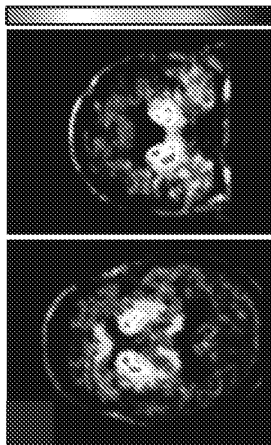


FIG. 25C

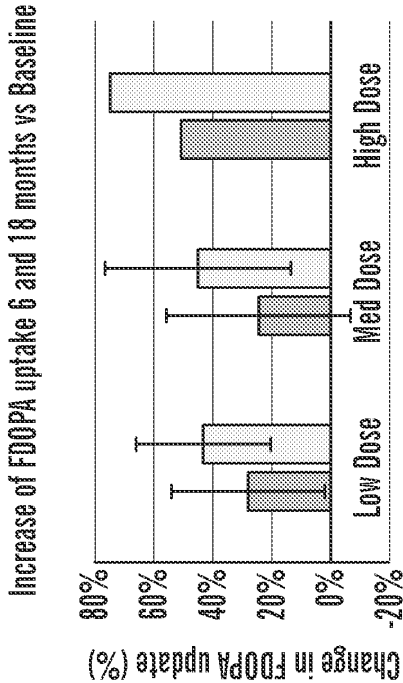
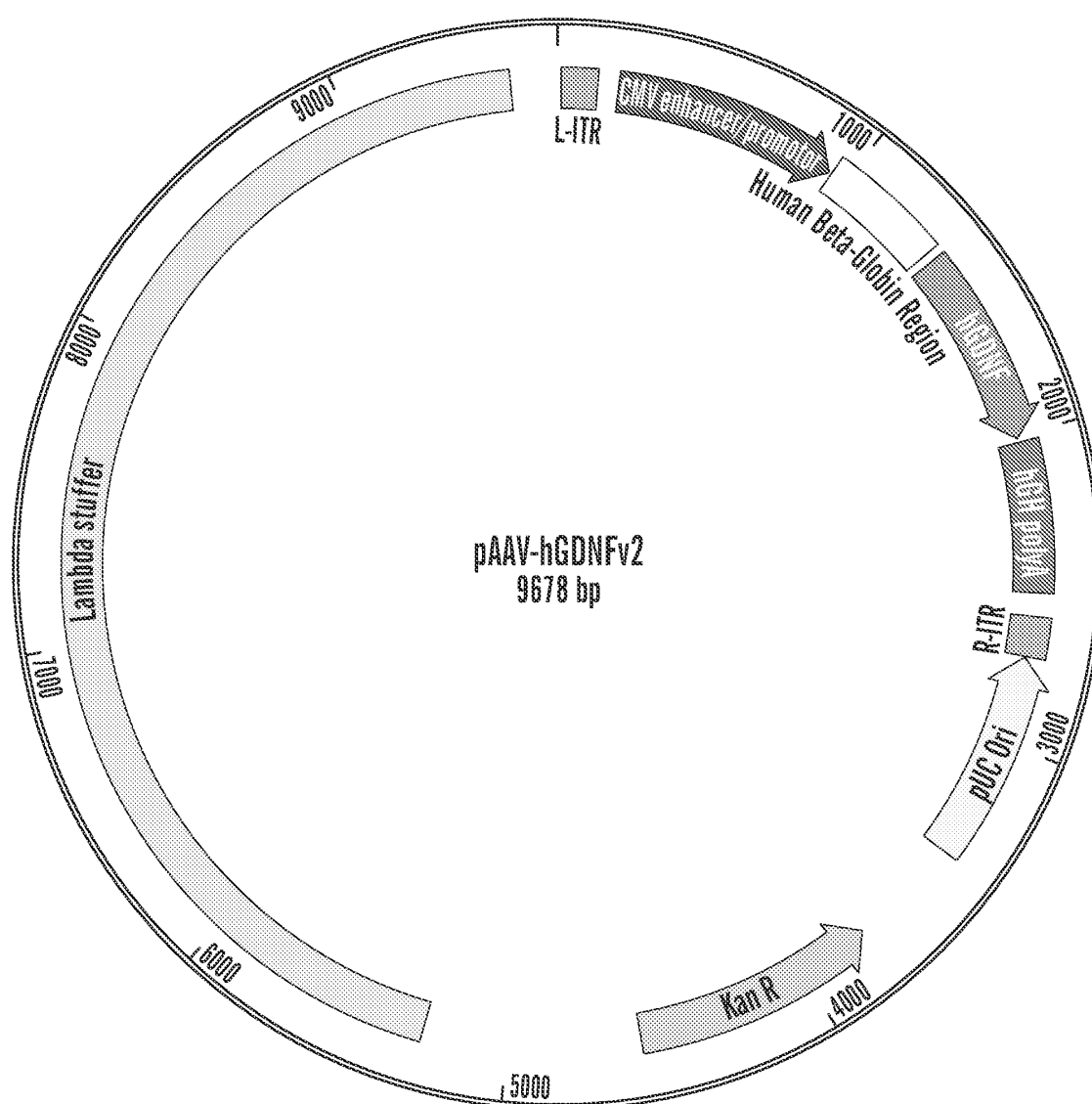


FIG. 25D

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**FIG. 26**