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rAAV-GAD for Parkinson's Disease

Update and Discussion on Protocol # 0710-877

Phase 2 Safety and Efficacy Study Evaluating Glutamic Acid Decarboxylase Gene Transfer to the Subthalamic Nuclei in Subjects with Advanced Parkinson's Disease

RAC Meeting Date: June 8, 2011

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Overview: Clinical Development of rAAV-GAD

- Specific clinical outcome is measurable
  - Pre-clinical studies have indicated potential safety and efficacy
  - Clinical testing has demonstrated treatment effects in both the UPDRS Part 3 and certain secondary measures
    - Phase 1 Study–12 treated subjects
    - Phase 2 Study–22 treated subjects, 23 sham subjects (crossover to Open-label)
    - Both studies demonstrated excellent safety profile
      - No SAEs related to the surgical procedure or product
      - Anticipated AEs were minimal
- Long Term Follow-Up Study was initiated this year
- Open-label Arm will commence this month

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rAAV-GAD Mechanism of Action

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rAAV-GAD Mechanism of Action

- Subthalamic nucleus (STN)
  - Central role in regulating movement
  - Hyperactive in PD and downstream effects contribute to PD motor symptoms
- rAAV-GAD administration into the STN
  - Reduces glutamate concentrations
  - Quiets hyperactivity through local GABA production
  - GABA release from STN to other downstream hyperactive targets
- rAAV-GAD focuses on GABA and is not considered another dopaminergic approach

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Preclinical Studies Overview

- Study Endpoints - Safety and Efficacy of AAV-GAD administration into STN
- Over 100 normal and Parkinsonian rodents and non-human primates received rAAV-GAD
- Summary of rAAV-GAD Results
  - Vectors revealed superior safety profile
  - GAD expression restricted to STN region - GABA produced by GAD had downstream effects
  - Improved motor symptoms in treated animals
  - AAV vector has been shown in other studies to have long-lasting or permanent treatment effects

Preclinical animals	Treatment sustainability	Approximate lifespan
Mouse[1]	>8 months	2.5 years
Dog[2]	>17 months	11.5 years
Monkey[3]	>6 years	25 years

  - Behavioral therapeutic effects - GAD changes cell electrophysiology during 5 months after GAD injection in rat brain[4]
  - Efficacy of GAD for Parkinson's in monkeys - therapeutic effect remained stable during the 55-week period post-surgery[5]

1 Snyder RO, et al. Correction of hemophilia B in canine and murine models using recombinant adeno-associated viral vectors. Nat Med. 1999 Jan;5(1):64-70.
2 Mount JD, et al. Sustained phenotypic correction of hemophilia B dogs with a factor IX null mutation by liver-directed gene therapy. Blood. 2002 Apr 15;99(8):2670-6.
3 Bankiewicz KS, et al. Long-Term Clinical Improvement in MPTP-Lesioned Primates after Gene Therapy with AAV-hAADC. Mol Ther. 2006 Oct;14(4):564-70. Epub 2006 Jul 7.
4 Luo J, et al. Subthalamic GAD Gene Therapy in a Parkinson's Disease Rat Model. Science Mag. 2002 Oct; 298: 425-429.
5 Emborg ME, et al. Subthalamic Glutamic Acid Decarboxylase Gene Therapy Changes in Motor Function and Cortical Metabolism. Cerebral Blood Flow & Metabolism. 2007; 27: 501-509.

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Phase 1 Study Design

- Key inclusion criteria
  - 25 -70 years of age
  - Disease duration of at least 5 years
  - Hoehn and Yahr stage 3 or higher
  - UPDRS motor "off" score ≥30
  - Motor complications of therapy with levodopa
  - Stable anti-parkinsonian medication for 1 month before baseline
- Key exclusion criteria
  - Substantial cognitive dysfunction revealed by neuropsychological testing
  - Medical contraindication to surgery
  - Secondary or atypical parkinsonism
  - Substantial psychiatric illness

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Phase 1 Study Outcomes and Conclusions*

- Unilateral STN AAV-GAD was well tolerated with a good safety profile
- Significant improvement in both "off" and "on" UPDRS largely limited to contralateral side of treated hemisphere and demonstrated network changes that correlated with improved clinical disability ratings as measured by PET
- Effects seen starting at 3 months (trend at 1 month) and stable to one year with persistent activity of motor-related network decline as measured by PET
- Strong trend toward improved ADLs and dyskinesia scores
- No decline in neuropsych scores or other non-motor parameters (isolated neuropsych measures improved; not published) which coincided with PET measurements of no change on the cognition-related network
- No evidence of inducing an anti-AAV immune response or effect on outcome dependent on pre-existing antibody levels
- Provided biological basis for observed response in PD subjects following rAAV-GAD therapy

Adapted from Kaplitt MG, et al. Lancet. 2007;369:2097-2105 and Feigin A, et al. PNAS. 2007; 104(49) 19559-19564.

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Phase 2 Study
Design & Demographics

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Transition from Phase 1 to Phase 2 Study

Similarities

- Phase 1 highest dose = Phase 2 dose: 3.5×10^{10} vector genomes
- FDG-PET imaging
- Cognition and neuropsychological testing
- Surgery under local anesthesia

Differences

- Open-label vs. Randomized blinded trial
- Unilateral vs. bilateral
- Infusion method vs. Medtronic brain infusion system
- Dose escalation vs. fixed dose
- Infusion volume: 50 µL vs. 35 µL
- Single clinical site vs. multiple sites (7)
- Manufacturing – Product comparability studies performed and filed with FDA.

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Phase 2: Double Blind Randomized Controlled Study

- Primary Endpoint
  - To evaluate the clinical anti-parkinsonian efficacy (UPDRS Part 3 “off”) of rAAV-GAD administered bilaterally into the STN of subjects with advanced PD for comparison to sham-operated PD controls subjects at 6 months after the procedure

- Secondary Endpoints
  - To evaluate the safety of rAAV-GAD administered into the STN through 12 months after the procedure
  - To assess the outcomes of rAAV-GAD administration on PD disability, activities of daily living, motor fluctuations, dyskinesias, and quality of life assessments through 12 months after the procedure
  - To evaluate metabolic activity related to PD measured by FDG-PET through 12 months after the procedure

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Key Inclusion Criteria

- Age 30 to 75 years
- Diagnosis of idiopathic PD with features for at least 5 years
- Levodopa responsiveness demonstrated for at least 12 months
- UPDRS motor "off" score ≥25
- Stable antiparkinsonian drug regimen for ≥4 weeks prior to enrollment
- FDG-PET

Key Exclusion Criteria

- Receipt of any experimental therapy within 3 months of enrollment
- Prior history of brain surgery for PD
- Mental retardation or impaired cognitive ability
- Focal neurological deficits
- Neurological features of Parkinson-plus syndrome or normal pressure hydrocephalus
- Significant medical or psychiatric disorder

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Phase 2 Clinical Study Sites

Site	Principal Investigator	Neurosurgeon
Henry Ford	Peter Lewitt, MD	Jason Schwalb, MD
Massachusetts General Hospital	Alice Flaherty, MD	Emad Eskandar, MD
The Ohio State University	Sandra Kostyk, MD, PhD	Atom Sarkar, MD, PhD Ali Rezai, MD
Stanford University	Kathleen Poston, MD, PhD	Jaimie Henderson, MD
University of Colorado	Maureen Leehey, MD	Steven Ojemann, MD
University of Rochester	Roger Kurlan, MD/ Irene Hegeman Richard, MD	Jason Schwalb, MD
Wake Forest University	Mustafa Siddiqui, MD	Stephen Tatter, MD, PhD
The Feinstein Institute (Centralized PET imaging)	Andrew Feigin, MD, PhD	-------

Each surgeon completed a minimum of 4 surgeries

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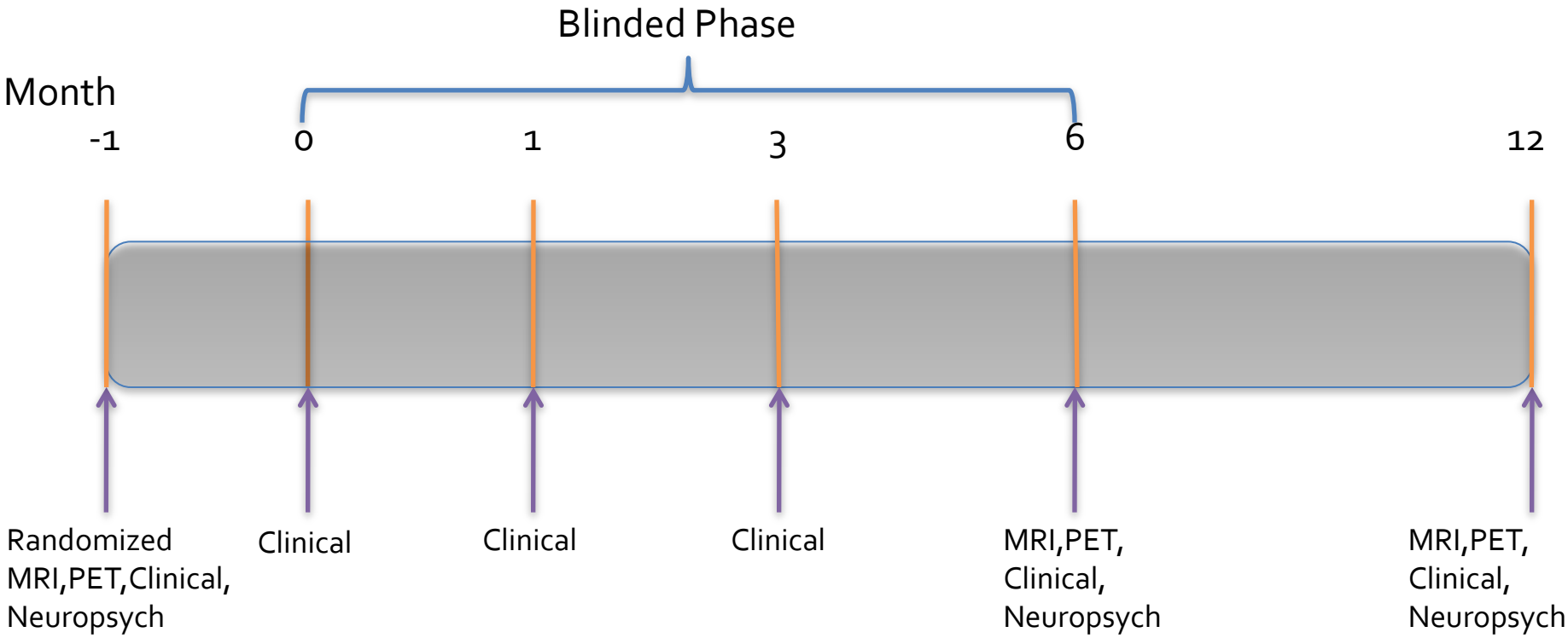
Study Design Overview

CRO: Randomization scheme, study monitoring, database maintenance, quality control, and statistical analysis



All subjects and raters remained blinded until final subject reached 6 months post-surgery

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Subject Demographics

Variable	Sham Surgery (N=23)	rAAV-GAD (N=22)	Total (N=45)
Age (years)			
Mean	60.3	61.2	60.8
Range	47-75	43-71	43-75
Gender			
Male	17	17	34
Female	6	5	11
Ethnicity			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	22	22	44
Race			
White	23	22	45
Black or African American	0	0	0
Asian	0	0	0
American Indian or Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0

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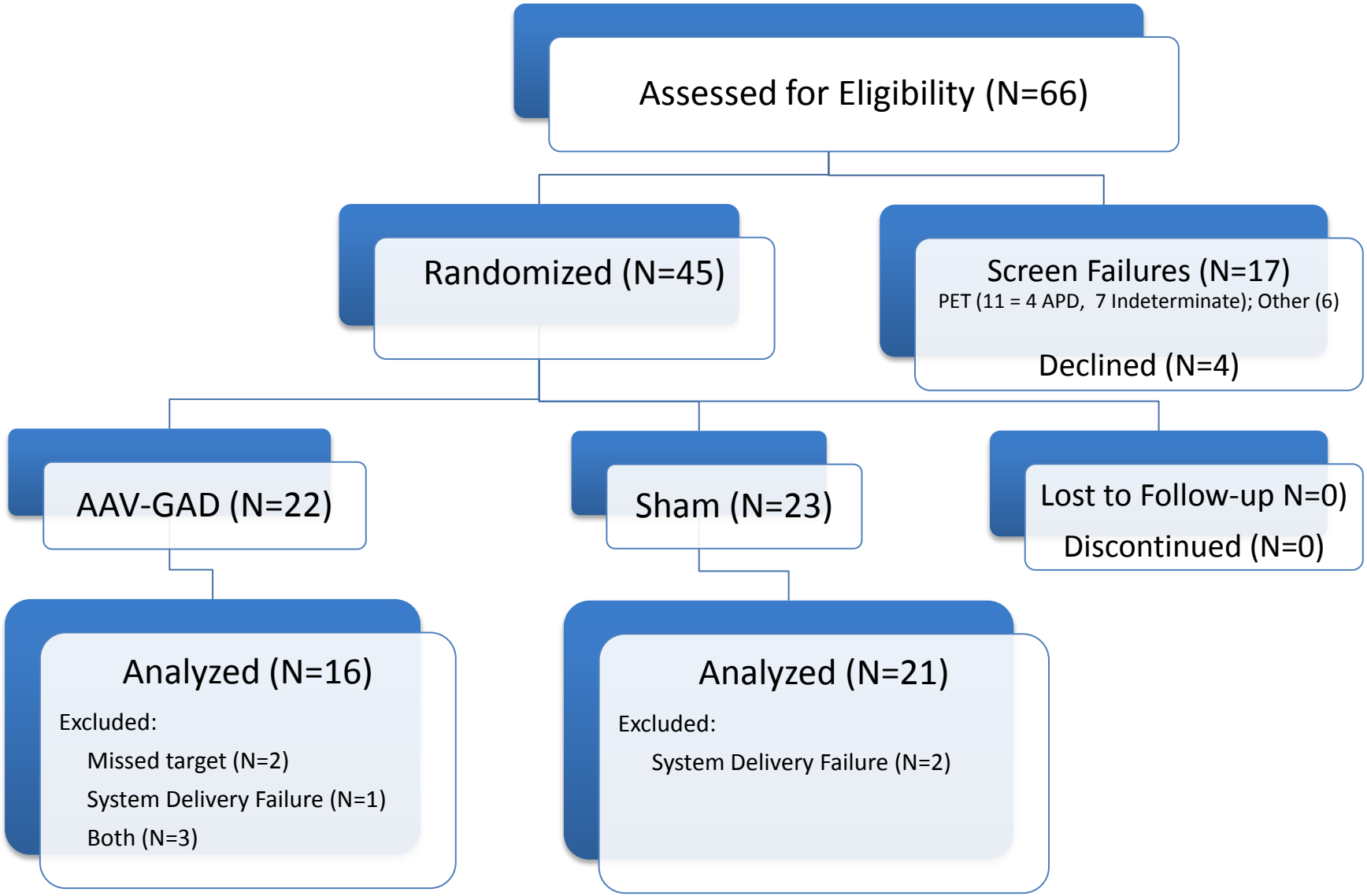
Assessed for Eligibility (N=66)
Randomized (N=45)
Screen Failures (N=17)
PET (11 = 4 APD, 7 Indeterminate); Other (6)
Declined (N=4)
AAV-GAD (N=22)
Sham (N=23)
Lost to Follow-up N=0)
Discontinued (N=0)
Analyzed (N=16)
Excluded:
Missed target (N=2)
System Delivery Failure (N=1)
Both (N=3)
Analyzed (N=21)
Excluded:
System Delivery Failure (N=2)

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Reason for Exclusion from Efficacy Analysis Set	Number of Subjects (n=7)	Hemisphere		% Removed (From 88 Hemispheres)
		Right (n=3)	Left (n=4)	
STN mistargeting only	2	---	2 (Treated)	2.3%
Device related issues only:				3.4%
Pump malfunction	2	---	2 (1 Sham & 1 Treated)	
Catheter explantation	1	1 (Sham)	---	
Combination*:				2.3%
STN mistargeting & pump malfunction	1	1 (Treated)	---	
STN mistargeting & catheter explantation	1	1 (Treated)	---	

*STN mistargeting and device issue occurred in the same hemisphere

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Phase 2 Study Results
Primary Outcome Measure

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Six Month Efficacy & Safety Data Analysis

- Efficacy Analysis set
  - Subject population was defined in SAP
  - Excluded subjects who did not receive full infusion and/or catheter was not positioned within the target region of the STN
  - Repeated measures analysis on UPDRS Part 3 in the OFF state
  - Paired t-test comparing treatment and sham groups at Months 1, 3, 6, and 12
  - Ratio of scores at months 1, 3, and 6 were natural logarithm-transformed and analyzed with repeated measures ANOVA
- Safety Analysis set
  - Included all subjects who had either sham or rAAV-GAD surgery
  - Analyzed AE's, SAE's, shift tables of lab tests and summaries of markedly abnormal vital signs and ECG's
- Results published in The Lancet Neurology (LeWitt et al, 2011)

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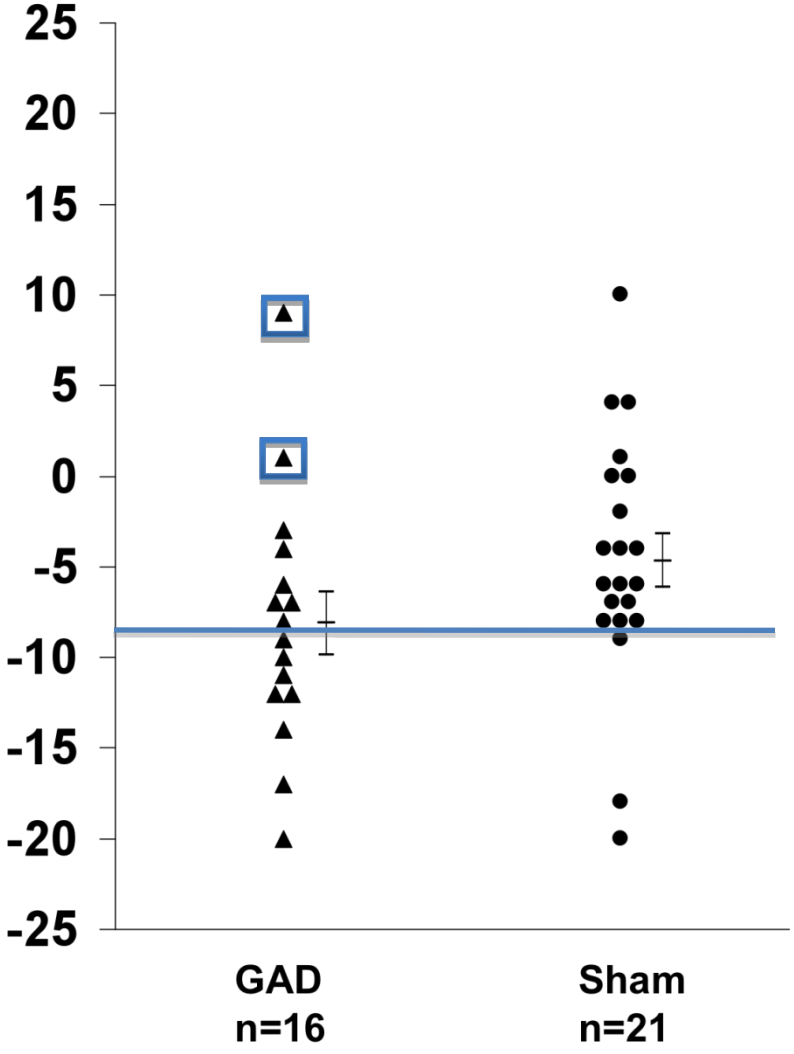
Change in 6 Month UPDRS Part 3 From Baseline



(**p<0.03**; Fisher's exact test is for the number of responders; i.e. number of below the line)

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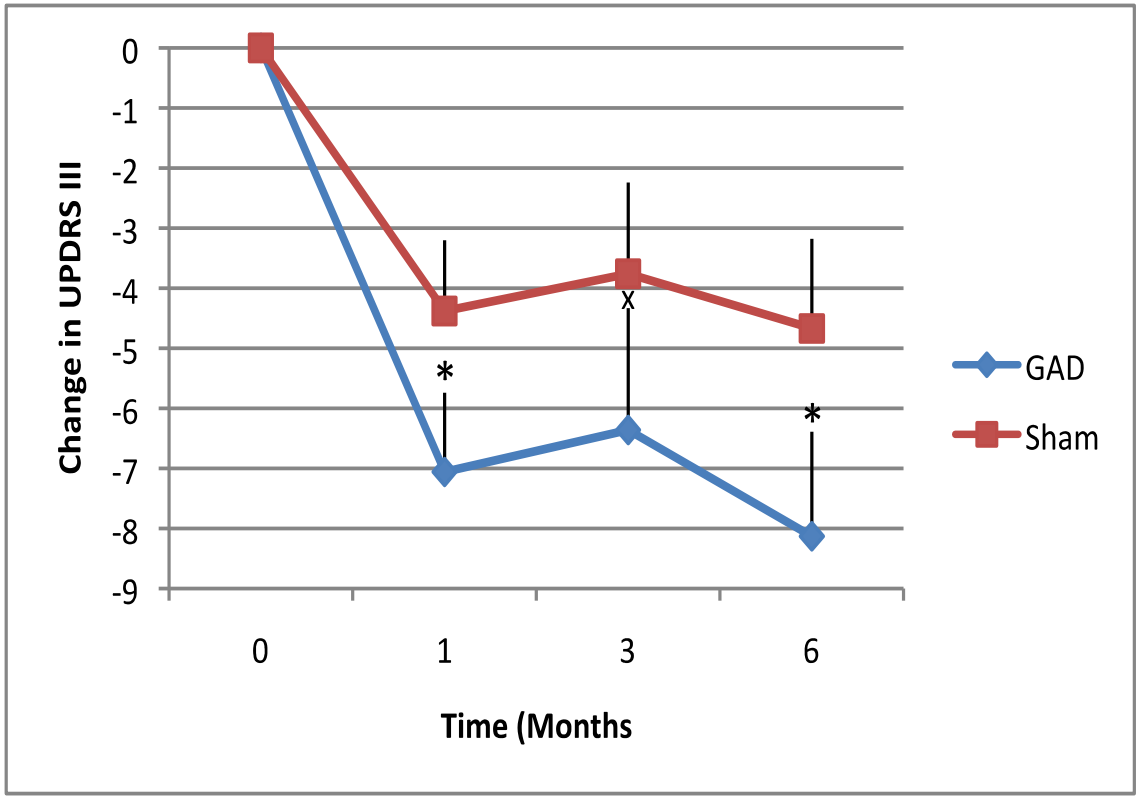
Change in UPDRS Part 3 Over Time



Overall P=0.04 (rmANOVA)

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Phase 2 Surgical Procedure

- AAV-GAD
  - Frame; Standard awake MER mapping
  - Bilateral STN infusion of 3.5×10^{10} vg/STN in 35 µl of 1 × PBS/1mM $MgCl_2$
- Sham
  - Frame; Partial-thickness burr hole; Sham awake MER mapping
  - Bilateral infusion of 35 µl sterile saline into burr hole
- All received CT before and after catheter removal
  - Each site used measures to blind scans (alias, marked as study and not read/on PACS)
  - CTs reviewed by Dr. Ali Rezai for location of catheter tip in X,Y,Z relative to MCP while study was blinded
- All received catheter patency check following removal and evaluation of syringe for infusion volume

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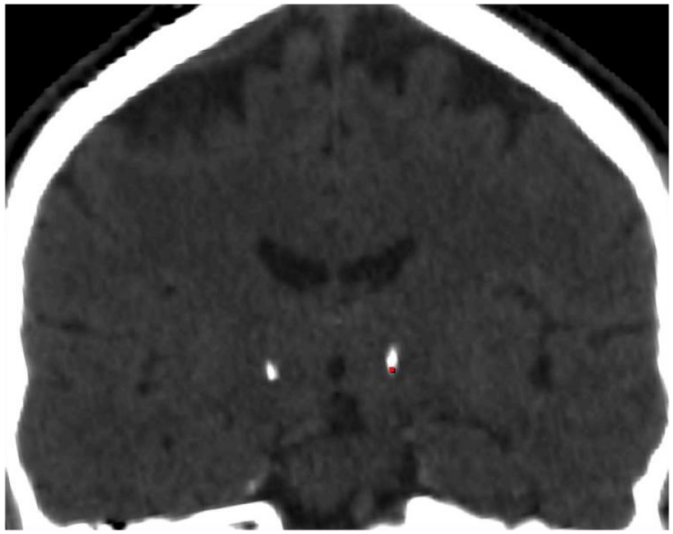
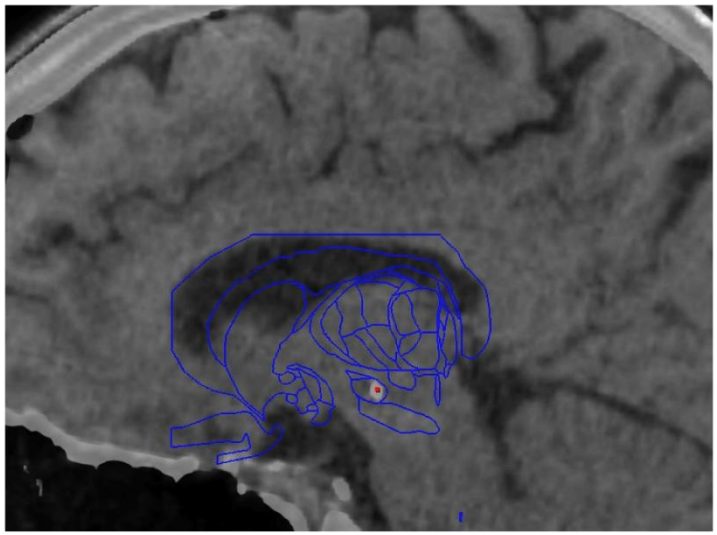
Blinded Catheter Tip Localization





Target Area Relative to Mid-Commissural Point:
X=9-14mm lateral
Y=2mm anterior-5mm posterior
Z=1mm dorsal-7mm ventral

(Standard DBS tip coordinates in postero-ventral STN:
X=12mm lateral, Y=3.5mm posterior, Z=4mm ventral)

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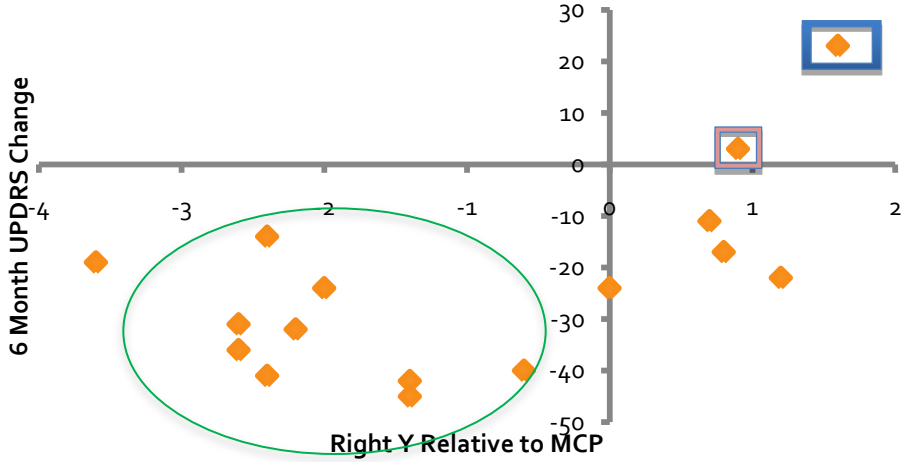
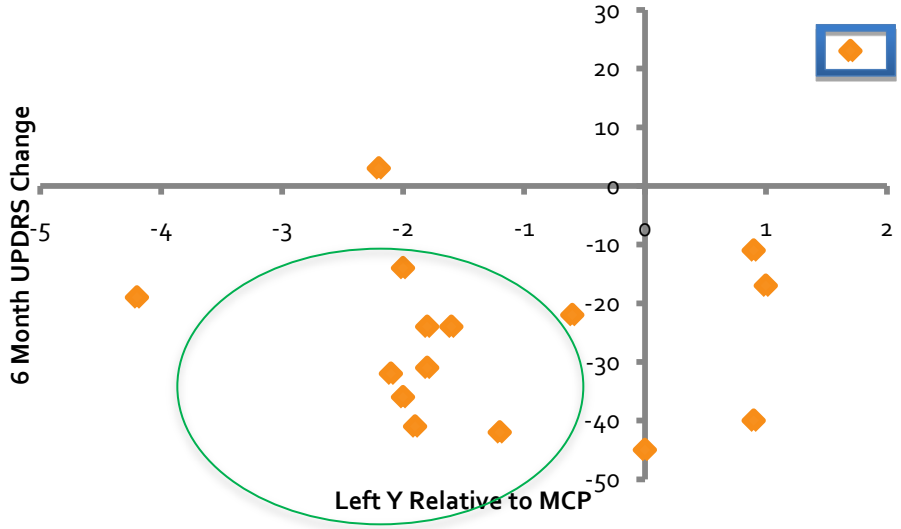
6 Month Outcome vs. Anterior Posterior Location



R=0.58



R=0.24

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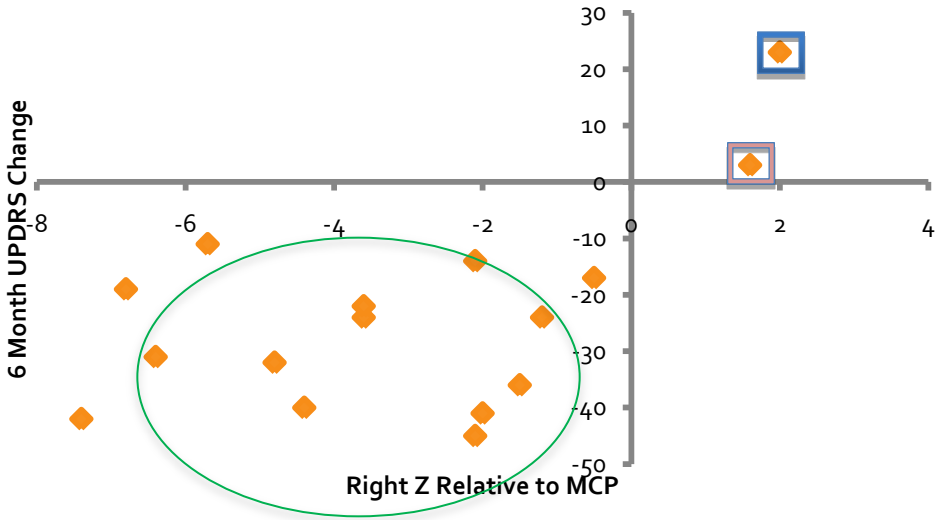
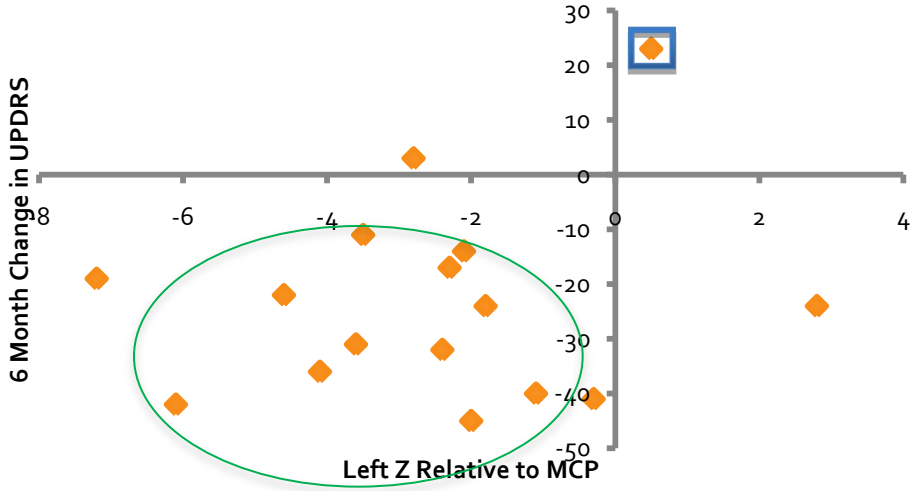
6 Month Outcome vs. Depth



R=0.55



R=0.18

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Survey Assessment of the Blind

Subject Opinion: Post-Surgery Day 3

Actual Group		Treated	Sham	Unknown
	Sham	9	5 (2 improved UPDRS and 3 changed opinion at 6 mo)	7
	AAV-GAD	10	0	6

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Phase 2 Study Results
Secondary Outcome Measures

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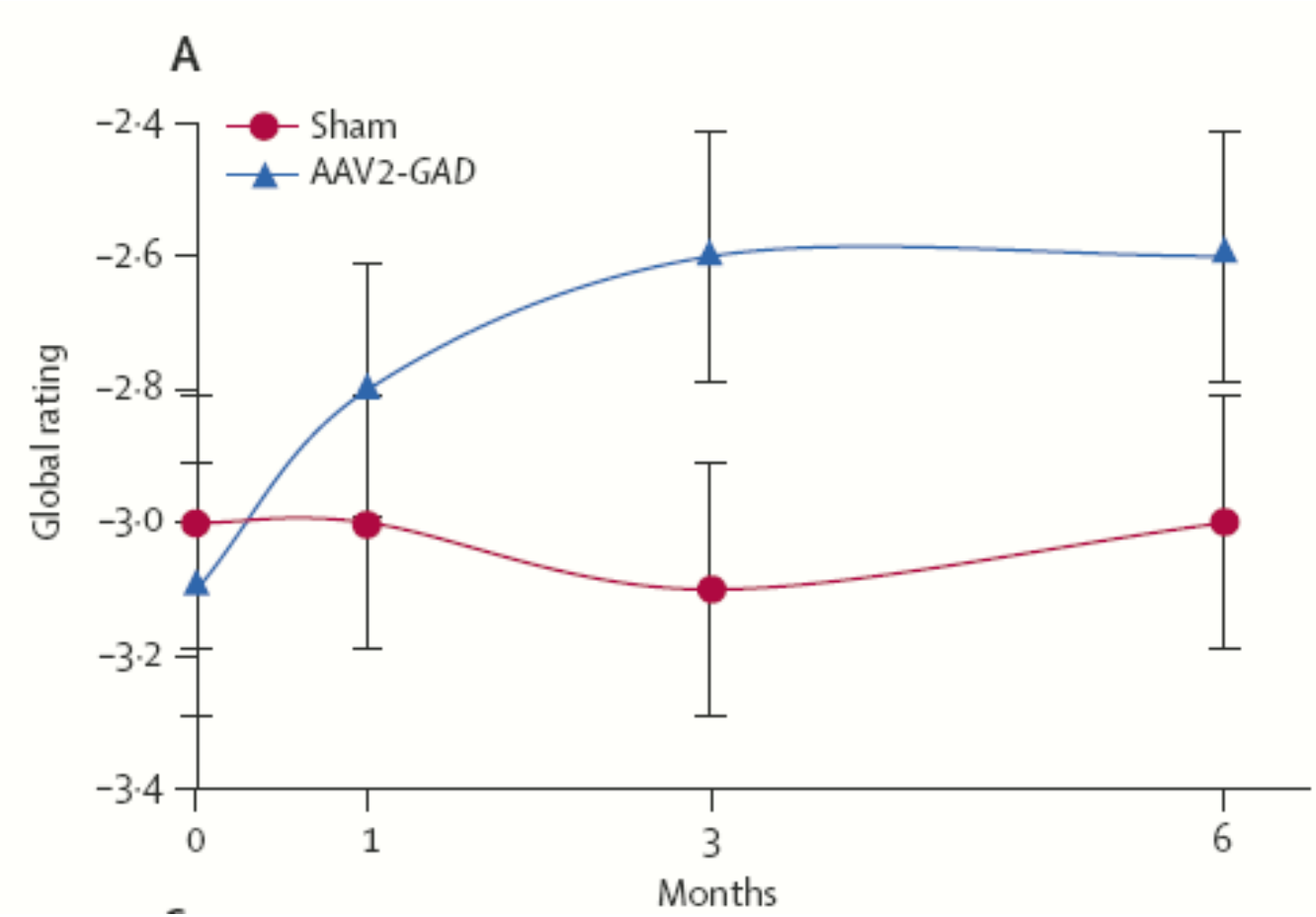
Change in Off-Medication Global Rating of PD



Overall P=0.02 (rmANOVA)

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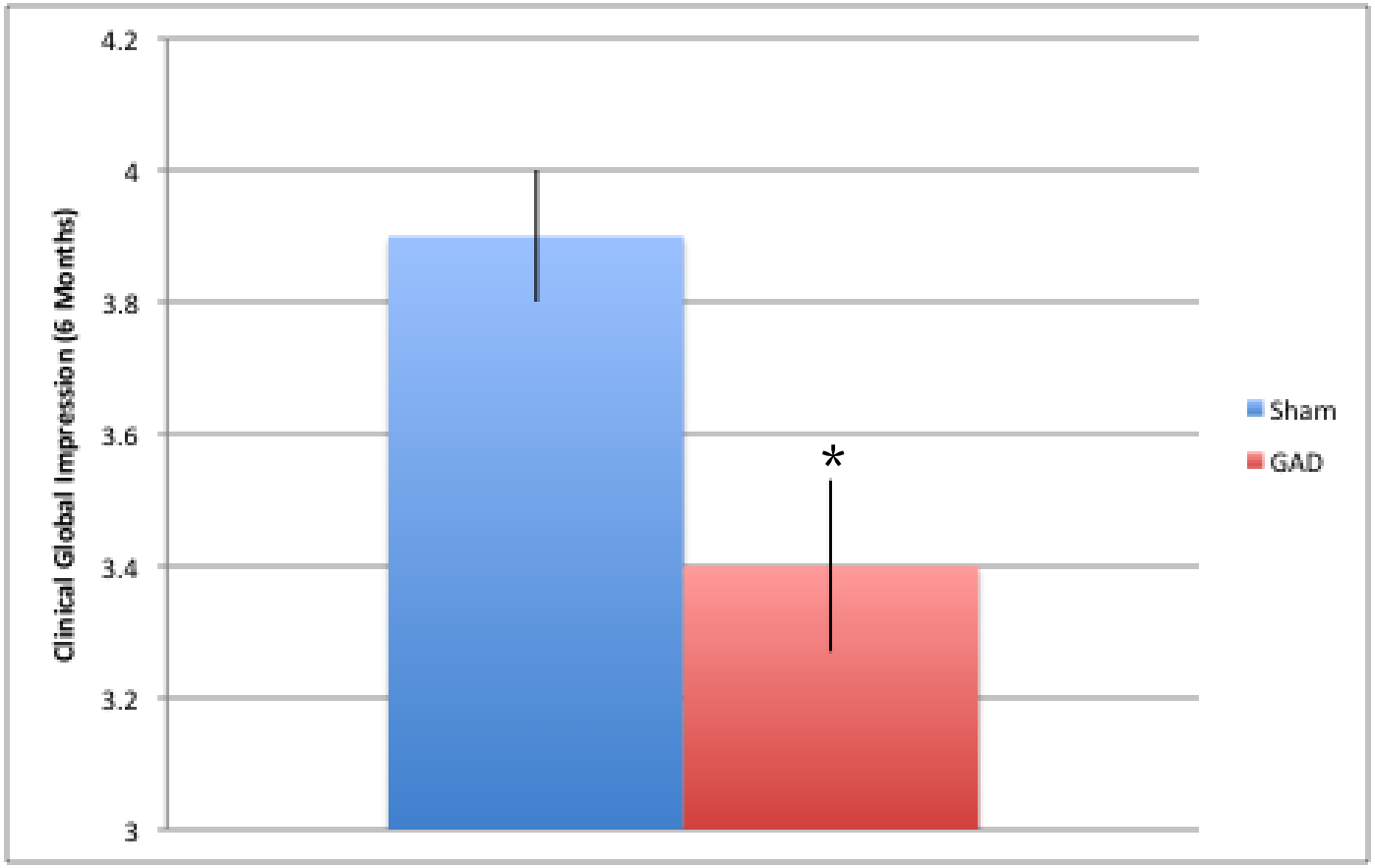
Increase in 6 Month Clinical Global Impression Score



*p=0.02; two-tailed t-test

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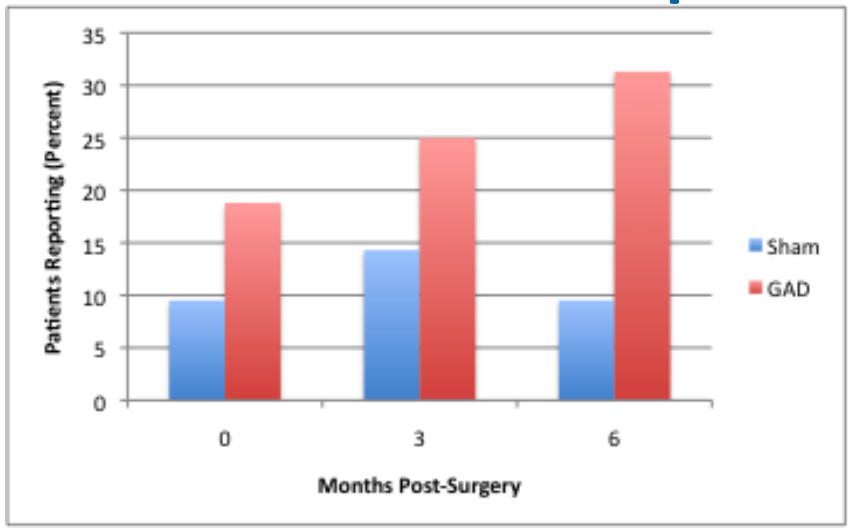
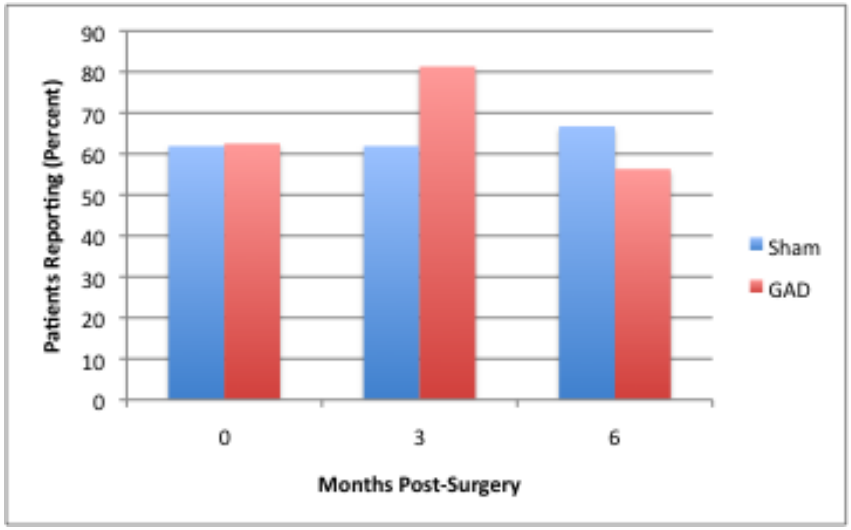
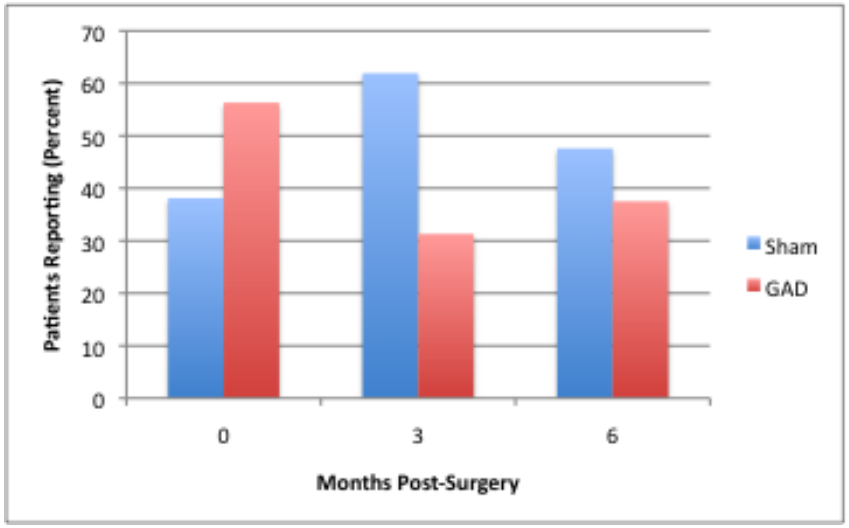
Motor Fluctuation Impact



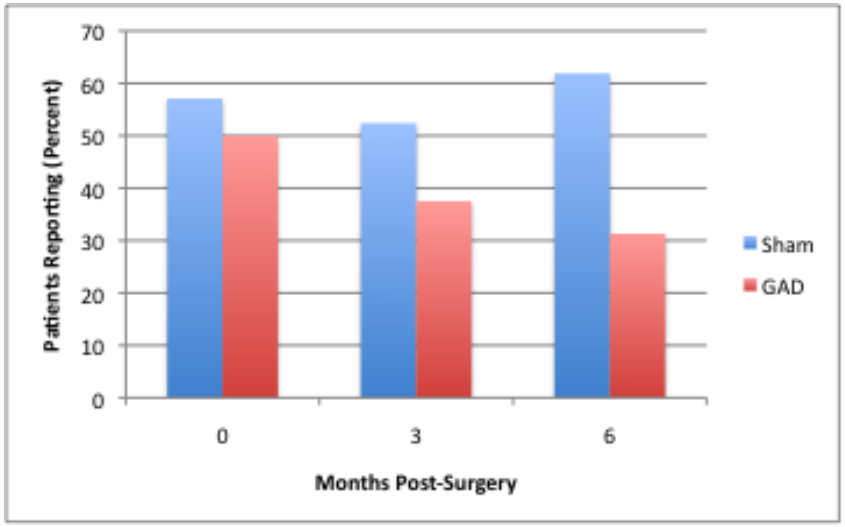
Consistent Medication Effect



Wearing Off



On-Off Fluctuations



Freezing

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Phase 2 Study
Initial 12 Month Data

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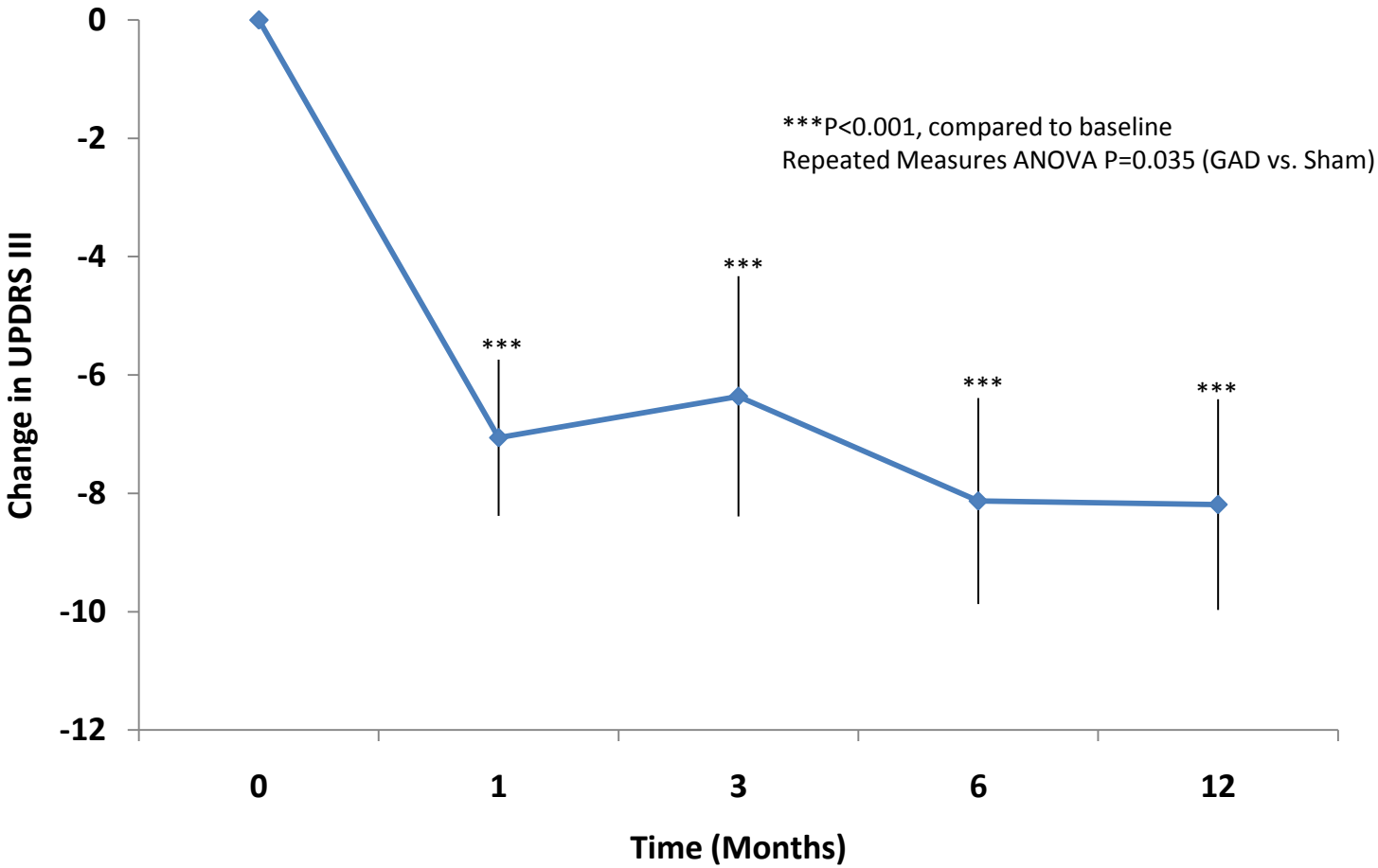
AAV-GAD Average Change in UPDRS Over 12 months



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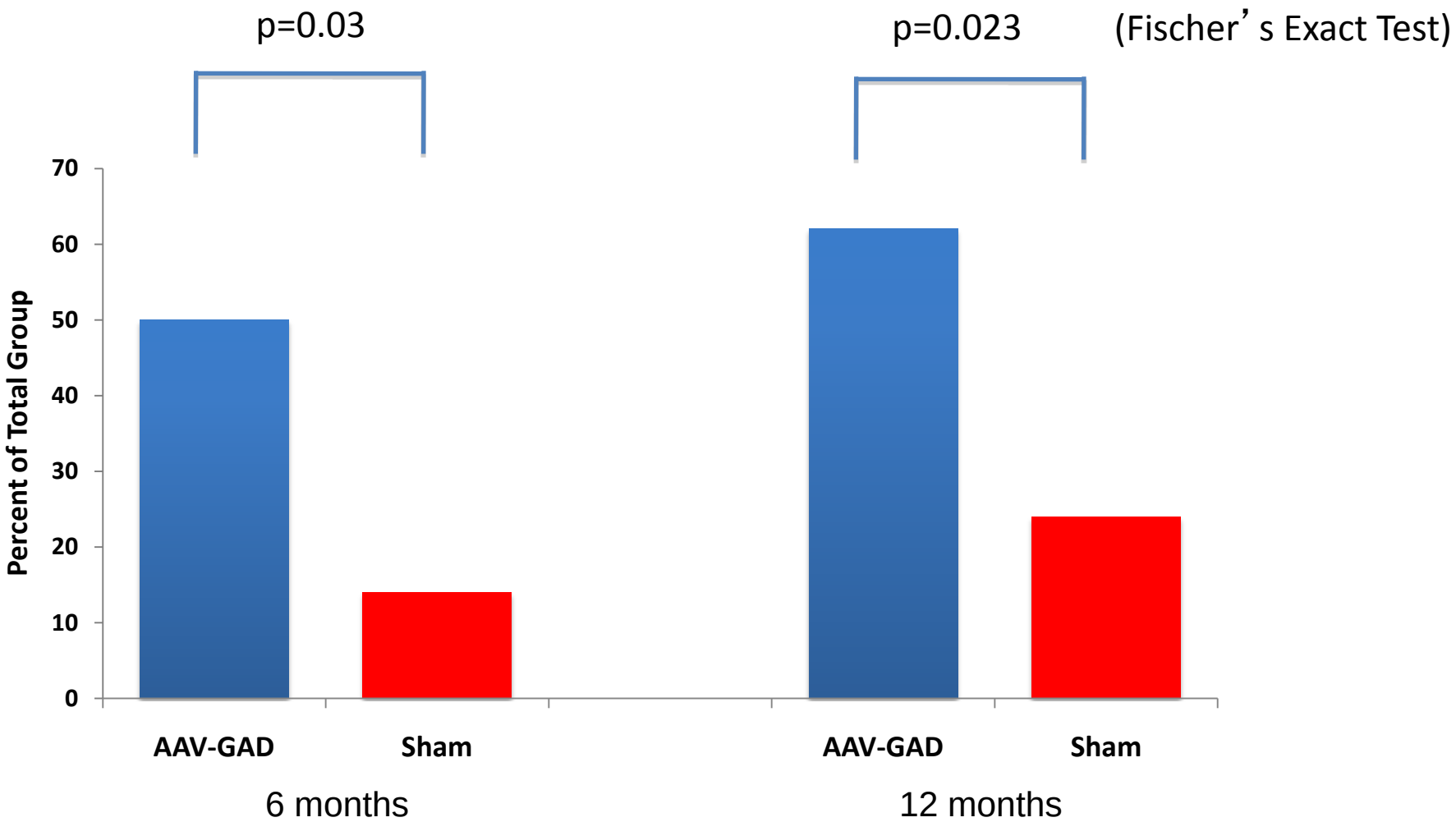
Responder Analysis: 6 months vs. 12 months



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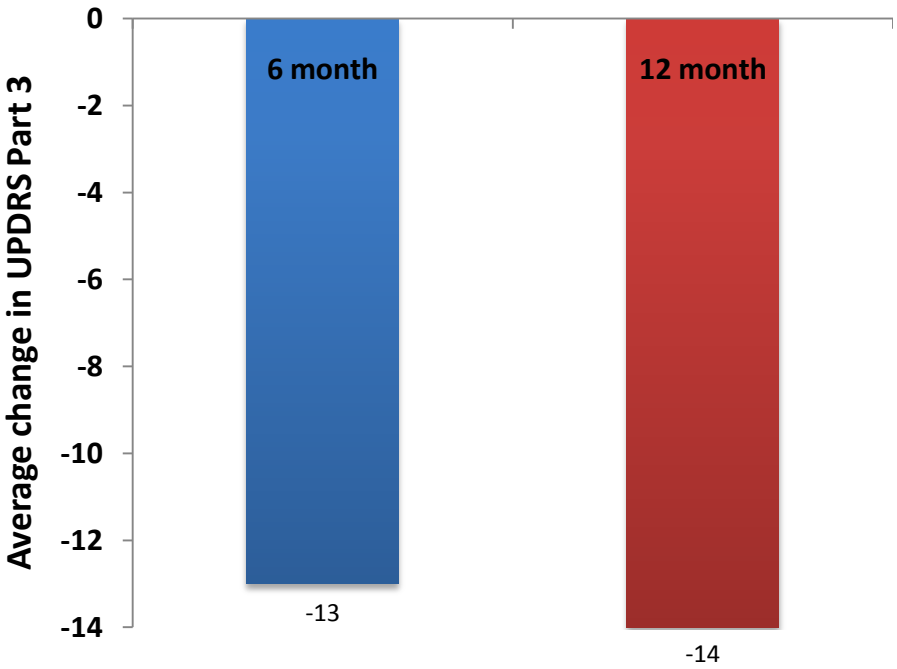
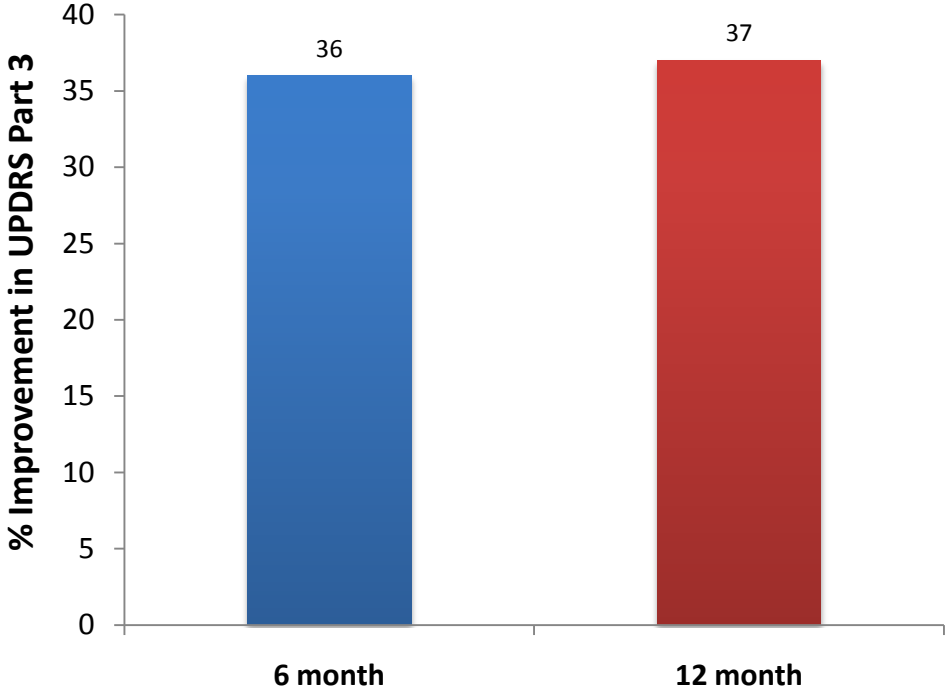
Change in Responder Group UPDRS Part 3 Scores





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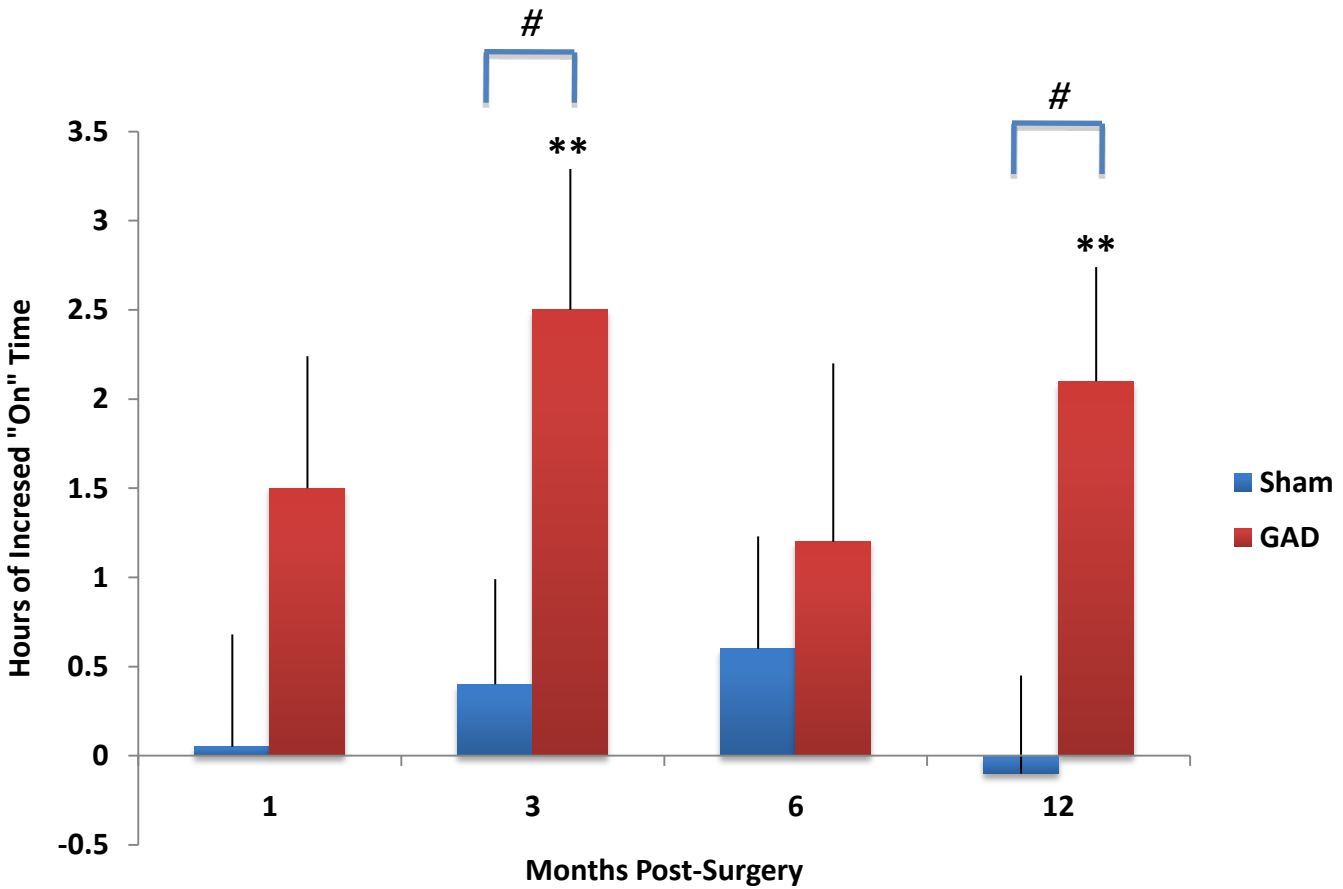
Increase in "ON" Time Following AAV-GAD



#p<0.05 vs. Sham (t-test)

**p<0.01 vs. baseline (t-test)

Overall change in "ON" time GAD vs. sham p=0.044 (ANOVA)

(p=0.06 GAD 1 month vs. baseline)

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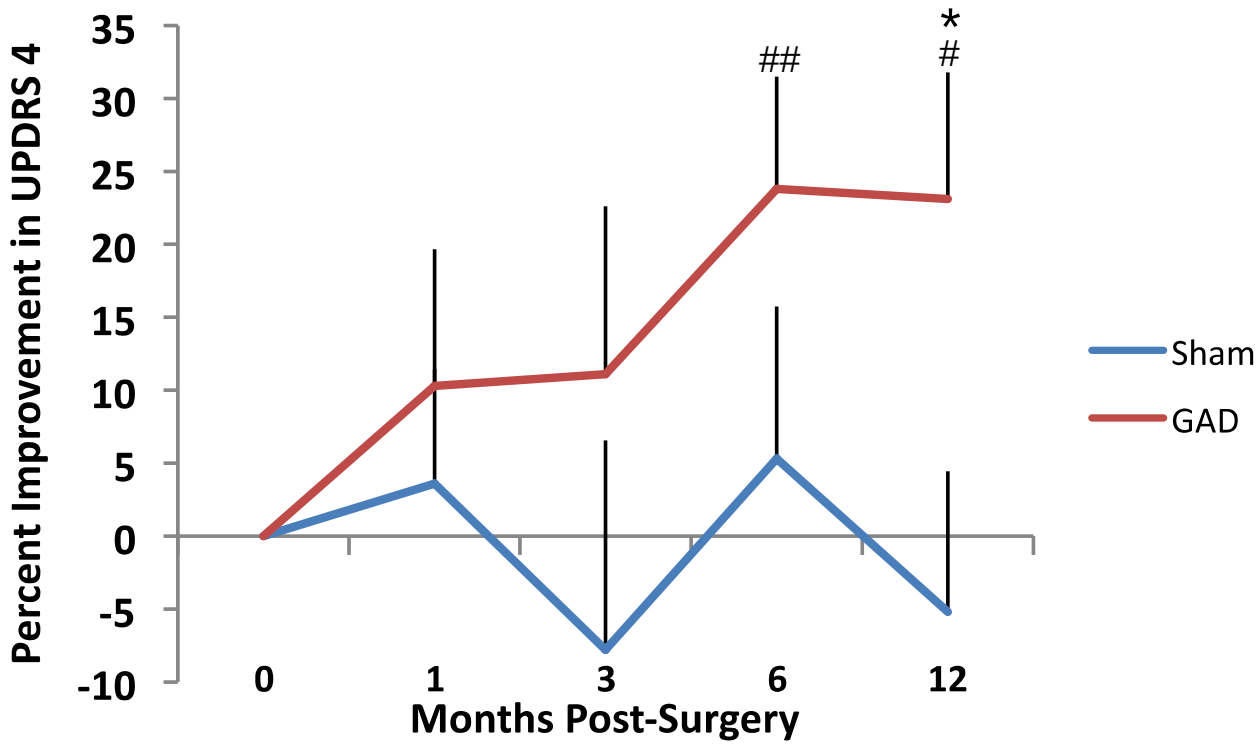
Improvement in Medication Complications (UPDRS Part 4) Following rAAV-GAD



(UPDRS Part 4 is a composite score of dyskinesias, on/off fluctuations, dystonia, insomnia and other complications)

*p<0.05 vs. sham (t-test)
#p<0.05 vs. baseline (t-test)
##p<0.01 vs. baseline (t-test)

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Phase 2 Study Conclusions

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Phase 2 Study Outcomes and Conclusions

- Study met primary outcome measure
- Statistically significant improvements from baseline UPDRS Part 3 "off" score seen in rAAV-GAD compared to sham over six month blinded phase ($p<0.04$ rmANOVA)
  - Sham methodology effective, small sham effect, both treatment and sham effect stable over time
- Significantly greater moderate to large clinically-meaningful responder rate ($\geq$9 points).
  - 6 months: 50% AAV-GAD subjects compared to 14% sham subjects ($p=0.03$; Fisher's exact test) .
  - 12 months: Increased to 63% AAV-GAD subjects compared to 24% sham subjects ($p=0.023$ Fisher's exact test).
  - Shulman, et. al. (2010) Arch Neurol 67:64-70.
- Correlation between AP and DV catheter tip location and outcome
  - True biological effect of rAAV-GAD is highly dependent upon the catheter tip location

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Phase 2 Study Outcomes and Conclusions

- UPDRS outcomes comparable to DBS studies
  - Percent change and clinically-meaningful responder rates of GAD
- Several additional secondary clinical outcomes with significant improvement over sham
  - Average daily increase of 2.5 hours of "ON" time at 3 months ($p<0.01$ relative to baseline; t-test) and was sustained at 2.1 hours of greater "ON" time at 12 months ($p<0.01$ relative to baseline; t-test). No significant increase in "ON" time in sham patients at any time point.
  - UPDRS Part 4 demonstrated significant reduction in complications of medication in AAV-GAD group at 6 and 12 months following treatment ($p<0.01$ and $p<0.05$, respectively; t-test). No reduction in the sham group at any time point.
- Neuropsychological and depression ratings without significant decline or difference between groups throughout study period.
- GAD therapy was well-tolerated with a good safety profile

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Phase 2 Study Results
Safety

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Phase 2 Clinical Study – Excellent Safety Profile to Date

- No SAEs reported related to rAAV-GAD, surgical procedure and/or Medtronic brain infusion system
- All SAEs have resolved
- No deaths, no drug-related SAEs/AEs that lead to withdrawal
- Data Monitoring Committee (DMC)
  - Charter role in the Phase 2 Study – Review safety
  - Conducted five meetings to date
    - Recommended trial to continue unmodified until next scheduled meeting
  - Will continue their role in the Open-label Arm
- GeMCRIS Database is complete for safety data

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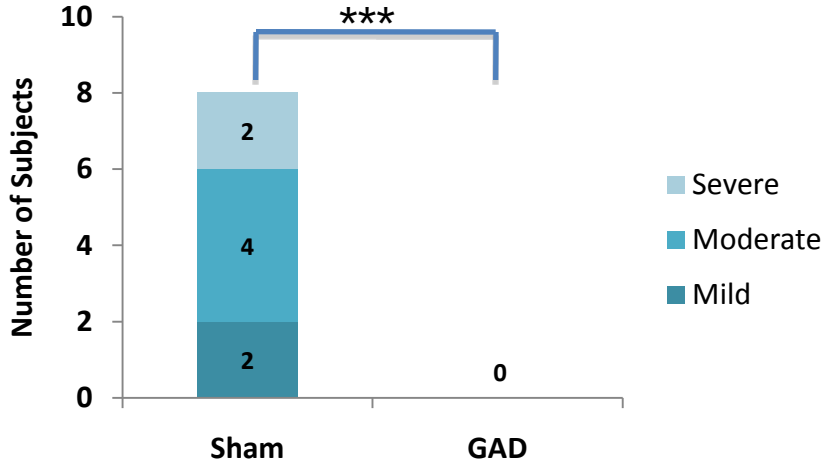
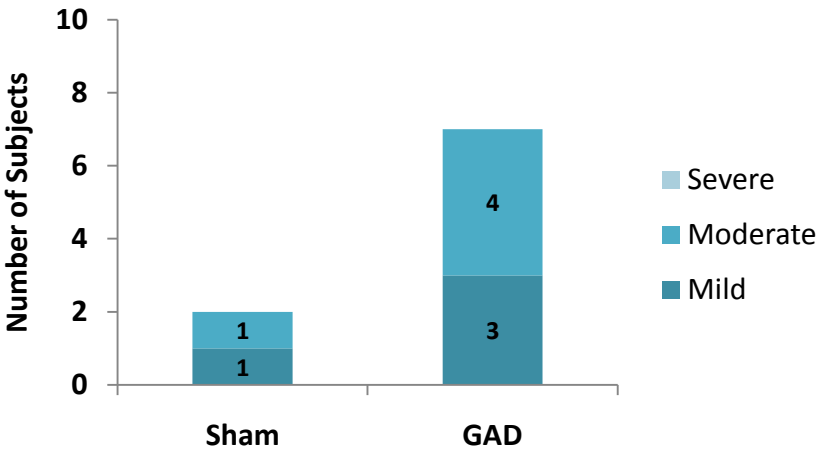
Adverse Events Over 12 Months (20% or Greater Frequency)

Parkinson's Disease



***p<0.005; Fisher Exact Test

Headache

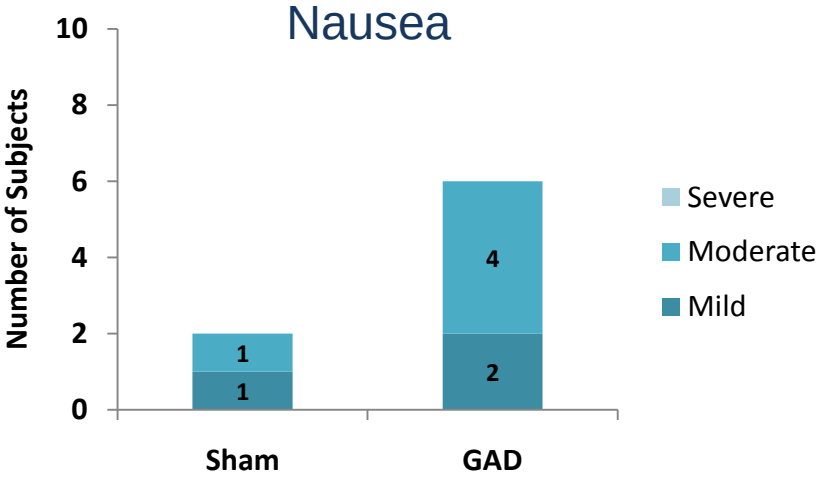


Serious Adverse Events* (Number of Subjects)

	Sham	GAD
Intestinal Obstruction		1
Accidental drug overdose		1
Prostatitis		1
Delusion Hallucination Parkinson's Disease	1	

*All SAEs occurred 4-12 months post-surgery

Nausea



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rAAV-GAD Clinical Development Plan

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rAAV-GAD Current and Future Plans

- Phase 2 Open-label study is commencing this month
  - Enhance the safety database and support efficacy claim
  - rAAV-GAD manufacturing and release equivalent to Phase 2 product
- Long-Term follow-up study initiated this year
  - Provide longitudinal data to confirm sustainability of therapeutic effect
- Phase 3 Protocol Development
  - Plan to file under Special Protocol Assessment in 2011