# Preliminary Safety and Effectiveness of RNS® System Responsive Thalamic Stimulation for Treatment of IGE with GTCs: 18-Month Data

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## Introduction

Approximately 30% of persons with idiopathic generalized epilepsy (IGE) are resistant to antiseizure medications (ASMs). There are no options for a surgical or ablative procedure to reduce seizure frequency, nor is there an FDA approved neuromodulation therapy.

FDA granted NeuroPace a Breakthrough Device Designation to study the RNS® System as a treatment for ASM-resistant IGE with bilateral responsive stimulation of the CM nucleus of the thalamus. NAUTILUS is a randomized sham stimulation controlled Pivotal trial (NCT05147571) to evaluate whether the RNS System is a safe and effective long-term treatment for persons with ASM-resistant IGE and GTCs.

Preliminary safety and effectiveness results to 18 months of CM responsive stimulation therapy for IGE are provided here.

## Methods

*Eligibility (key)*

- ASM resistant IGE with GTCs (+/- absence or myoclonic seizures)
- ≥ 12 years of age
- Confident diagnosis of IGE by history and EEG

*Design*

- Three-month baseline with ≥ 2 GTCs to be eligible for implant
- Depth leads placed in the right and left CM nuclei of the thalamus
- Post-op month 1: randomized 1:1 active or sham stimulation
- Post-op month 4: entered Effectiveness Evaluation Period.
- Once 2nd GTC occurred, sham patients able to receive active therapy - randomization not revealed

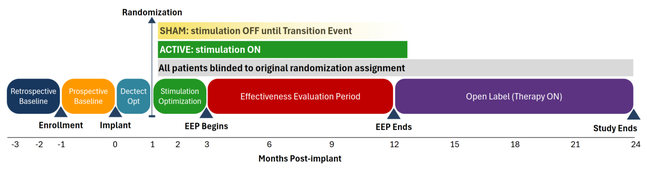



**Figure 1: Nautilus Trial Design**

*Safety Endpoints*

- Primary: SADEs over 84 days post-op period
- Secondary: Safety over 12 months and SAEs of Special Relevance

*Effectiveness Endpoints*

- Primary: Time to 2nd GTC
- Secondary: Change in # of GTCs or days on which a GTC or any type of generalized seizure occurred compared to baseline over time of stimulation
- Other secondary and additional endpoints included days quality of life, and global impression of change.

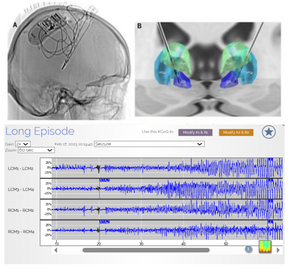



**Figure 2: Neurostimulator and CM depth leads.** Four channels of iEEG recorded from the CM and displayed on the RNS System Patient Data Management System (PDMS)



## Results

### Patient Disposition through 18 Month Follow-up.

- 100 participants enrolled; 87 implanted across 23 centers (ITT)
- 84 completed 1 year; 80 have completed 18 months
- The per-protocol population excludes 5 patients who did not meet eligibility criteria

**Table 1: Clinical Characteristics (ITT, N=87)**

| Clinical Characteristics | Median (Min, Max) |
|---|---|
| Age at diagnosis | 13 years (0 - 38 years) |
| Age at RNS System implant | 28 years (14 - 66 years) |
| Duration of epilepsy | 17.7 years (1 - 54) |
| Number of ASMs | 3 (1 - 8) |
| **Baseline Seizure Frequency** | |
| GTCs/month | 1.7 (0.5 - 24.1) |
| Days with GTCs/month | 1.6 (0.5 - 24.1) |
| Days with any type of generalized seizure/month | 6.5 (0.6 - 26.4) |

**Table 2. Primary Effectiveness Endpoint-Time to 2nd GTC[1]**

| K-M Estimate Median Time to 2nd GTC | | Cox Model Estimate Odds Ratio | 95% CI for Odds Ratio | Cox Model p-value for Ho: OR=1 |
|---|---|---|---|---|
| Active | Sham | | | |
| 76.0 (39.0, 127.0) | 67.0 (40.0, 84.0) | 0.894 | (0.532, 1.504) | 0.6745 |

[1] Cox proportional hazards regression model, with an effect for treatment, stratifying for pre-implant baseline GTC seizure frequency (≤ 2 vs > 2/month in Baseline Period), and prior VNS treatment (yes or no). Kaplan Meier Estimate (ITT)

The Cox proportional hazards statistical model assumptions for the Time to 2nd Seizure endpoint were violated because of the wide range in baseline seizure frequency, over dispersion of seizure counts and time-varying implant and emerging stimulation effects.

A post-hoc statistical analysis method, more appropriate to the characteristics of the data, applies a mixed-effects model (negative binomial variance structure, fixed effects for time and treatment group, and random effects for site and subject) to monthly seizure count data. All data is considered according to randomization groups over the EEP.

*Modified statistical analysis method observes a 62% reduction in seizure frequency with respect to baseline in patients randomized to active stimulation; 27% greater reduction than in sham (95% CI 7%-43%, p=0.0111[1,2])*

*[1] p value not adjusted; [2] per-protocol population*

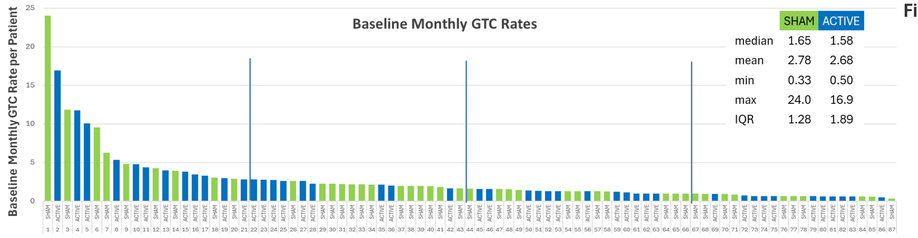



**Figure 3: Distribution of baseline frequency of GTCs.** Each bar represents one patient. Randomized to Sham are green and Active are blue. Vertical lines represent median, 1st, and 3rd quartile of patients grouped by GTC baseline frequency

**Table 3. Serious device related AEs (SADEs) to 84 days post-implant and annualized SADE rate (ITT)**

| n/N | % | 95% C.I. | p-value for $H_0$:p>=25% |
|---|---|---|---|
| 6/87 | 6.90% | (2.92%, 14.52%) | <0.0001 |

| # SADEs | Patient Days | Annualized SADE Rate |
|---|---|---|
| 10 | 39289 | 0.0855 |

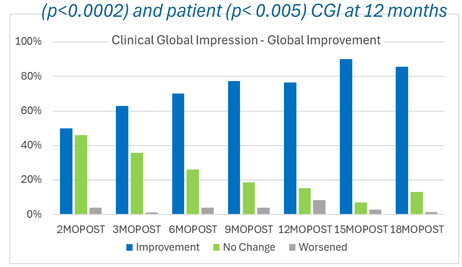
**Table 4. Additional Safety Endpoint: Device and non-device related SAEs of Special Relevance (# of events) (ITT)**

| | |
|---|---|
| Implant site infection[1] | 2 |
| Intracranial hemorrhage (due to seizure) | 1 |
| Intracranial hemorrhage | 1 |
| Encephalopathy[2] | 1 |
| Suicidal ideation[3] | 1 |

[1] Both explanted, one re-implanted; [2] Patient excluded from per-protocol due to nonepileptic seizures; [3] Prior history of suicidality; current history of depression and anxiety at enrollment

**Figures 6,7. Physician & Patient Global Impression of Change**

*A reduction in GTCs was highly correlated with physician (p<0.0002) and patient (p< 0.005) CGI at 12 months*



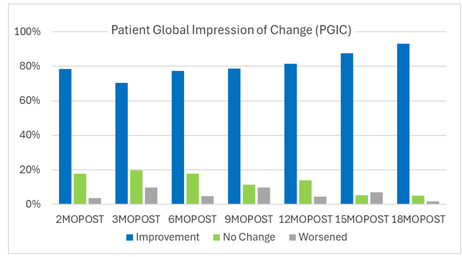
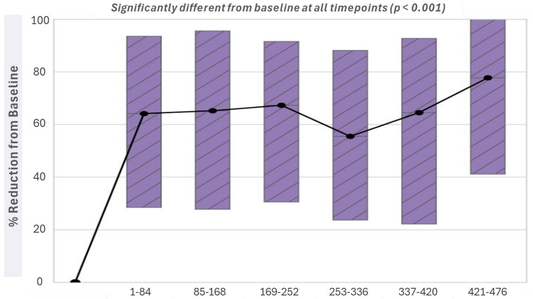
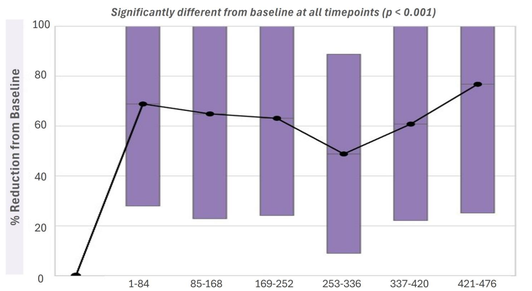




**Figure 4. Median % reduction in days with any generalized seizure by months of stimulation***




| | 1-84 | 85-168 | 169-252 | 253-336 | 337-420 | 421-476 |
|---|---|---|---|---|---|---|
| N | 82 | 82 | 74 | 64 | 52 | 40 |
| Median | 64.2 | 65.2 | 67.3 | 55.5 | 64.5 | 77.8 |
| Min, Max | -304.8, 100 | -540.9, 100 | -203.6, 100 | -102.4, 100 | -107.9, 100 | -214.8, 100 |

**Figure 5. Median % reduction in GTCs by months of stimulation***




| | 1-84 | 85-168 | 169-252 | 253-336 | 337-420 | 421-476 |
|---|---|---|---|---|---|---|
| N | 82 | 82 | 74 | 64 | 52 | 40 |
| Median | 68.9 | 64.9 | 63.1 | 48.8 | 60.8 | 76.8 |
| Min, Max | -331.5, 100 | -262.5, 100 | -136.1, 100 | -111.9, 100 | -160.6, 100 | -304.8, 100 |

* Per-protocol population. Excludes patients with < 28 days of data in timeframe. Differences from baseline assessed using the Wilcoxon signed-rank test with Bonferroni correction for multiple comparisons. p < 0.001 for all timepoints. Full range values are provided in the table.

## Discussion

A time to 2nd GTC endpoint was employed to permit an efficient, patient acceptable and ethical study design in a patient population with very frequent ASM resistant GTCs. The primary specified Cox analysis method was unable to address 1) extreme variance in baseline seizure frequency, 2) over-dispersion of seizure counts and 3) time varying effect of the implant and stimulation treatment. A clinically and statistically justifiable mixed-effects model addresses these characteristics, considers all data for the randomization groups, and demonstrates a significant effect of treatment.

All secondary endpoints demonstrate a highly significant effect of treatment compared to baseline at all timepoints during which stimulation therapy is provided and reach a 76.8% reduction in GTCs by 18 months of stimulation. Benefits are supported by patient and physician perception of sustained benefit with treatment.

**•Nautilus Trial PIs:** U Uysal, P Landazuri, KUMC; D Burdette, Corewell; A Crudele, VUMC; J Gavvala, UTHealth; J Neimat, ULouisville; S Sheth, Baylor; D Barnett, UNM; L Kaye, UColorado; S Rahimpour, UUtah; A Urban, UPMC; J Van Gompel, MayoMN; M Richardson, MGH; V Salanova, Indiana; D Spencer, OHSU; U Amin, TGH-USF; B Jobst, Dartmouth; C Skidmore, TJU; J Roland, WashU; M Fajardo, Nicklaus; P Dugan, NYU; C Drees, MayoAZ; J Szaflarski, UAB; T Ganguly, UPenn

## Conclusions

The NAUTILUS Trial is the first RCT of a neuromodulation therapy for the treatment of ASM-resistant IGE with GTCs. Responsive stimulation delivered to the CM was safe. Statistically significant, rapid, and sustained reductions in days with any type of generalized seizure and in GTC frequency are demonstrated. A submission to FDA seeking an expansion of the indication for use of the RNS System to include patients with ASM-resistant IGE with GTCs is forthcoming.