Multicenter Post-Approval Study of the RNS System in Focal Epilepsy

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American Academy of Neurology™

Disclosures

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Responsive Neuromodulation – The RNS® System

Monitors brain activity continuously

Recognizes & Responds to patient-specific seizure patterns

Records ongoing iEEG data for physicians to review

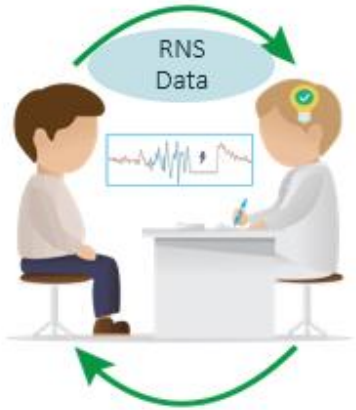
Implantable Device

Physician Programmer

Patient Remote Monitor

Patient Data Management System

Detection and stimulation adjusted using RNS System brain data



Optimal Management

Candidates for Treatment with the RNS System

- ≥18 years of age
- Are refractory to two or more medications
- Focal onset seizures with 1-2 seizure foci
- Are not good candidates for epilepsy resection or ablation
- Do not want an irreversible/destructive procedure

RNS System Clinical Trials in Focal Epilepsy

- Class I evidence of safety and effectiveness from RCT[1,2]
- Total nine-year follow-up; >1,900 years of patient data[3]
- 580 patients treated in prospective trials

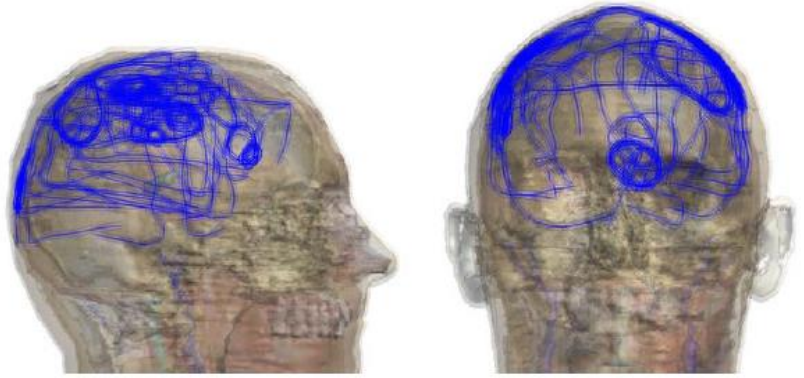
Feasibility Trial
Open Label Safety, 2yr follow-up
65 implanted patients

Pivotal Trial
Double blind RCT, 2yr follow-up
191 implanted patients

Open Label Long-term Treatment Trial
7 year follow on study
230 enrolled patients

Post-approval Study[4]
324 patients; 32 centers
Followed for 5 years

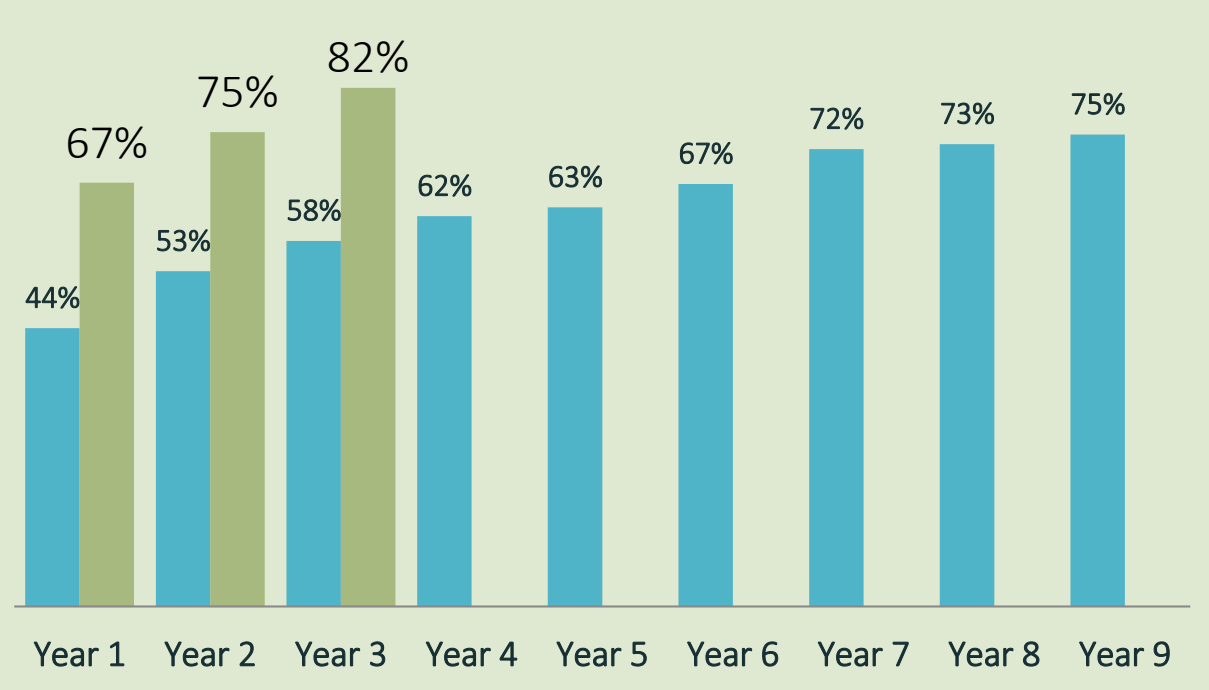
Lead locations in clinical trials



[1] Morrell et al, Neurology 2011
[2] Heck et al, Epilepsia 2014
[3] Nair et al, Neurology 2020
[4] www.clinicaltrials.gov (NCT02403843)

Effectiveness in multicenter real-world study exceeded results of earlier randomized controlled trial

Median % Reduction in Seizures



Original RCT Study[1]

- Efficacy improved over time
- 75% median seizure reduction at 9 years
- Statistically greater seizure reduction than sham stimulation at 5 months

Real World Retrospective Study[2]

- 15 centers, 150 patients
- 67% median seizure reduction at 1 year
- 82% median seizure reduction at ≥ 3 years
- 1 in 3 patients with ≥ 90% seizure reduction
- 18% of patients' seizure free at most recent follow up[3]

[1] Heck et al., Epilepsia 2014 and Nair et al., Neurology 2020
[2] Razavi and Rao, et al., Epilepsia 2020

RNS System Post-Approval Study

Five-year post-approval study required as a condition of FDA approval in 2013

- Study designed in consultation with FDA
- Primary effectiveness endpoint at 3 years; primary safety at 5 years
- First enrollment June 2015
- 324 patients implanted at 32 centers; 271 patients completed 3 years for effectiveness endpoint
  - Represents 1381 patient implant years and 1301 years of brain-responsive neurostimulation
  - Data and analyses reviewed by FDA

Post-Approval Study: Patient Characteristics Similar to Long-term Treatment (LTT) Trial

PAS patients

- Mean duration of epilepsy 17.8 years
- Median baseline seizure frequency 6.0/month

Seizure onsets in PAS similar to LTT trial

- 67% had two seizure foci
- Lead locations
  - Mesial temporal only = 178
  - Neocortical only = 110
  - Mesial temporal plus neocortical = 36

Not all patients required intracranial monitoring

- 33% of PAS patients did not have intracranial monitoring
  - 35% in LTT trial[1]

PAS patients more likely to receive RNS before other therapies

- 19.4% had prior epilepsy surgery
  - 34% in LTT trial[1]
- 7.7 % had prior treatment with VNS
  - 32% in LTT trial[1]

[1]Nair et al., Neurology 2020

Primary Efficacy Endpoint by Time from Implant[1]

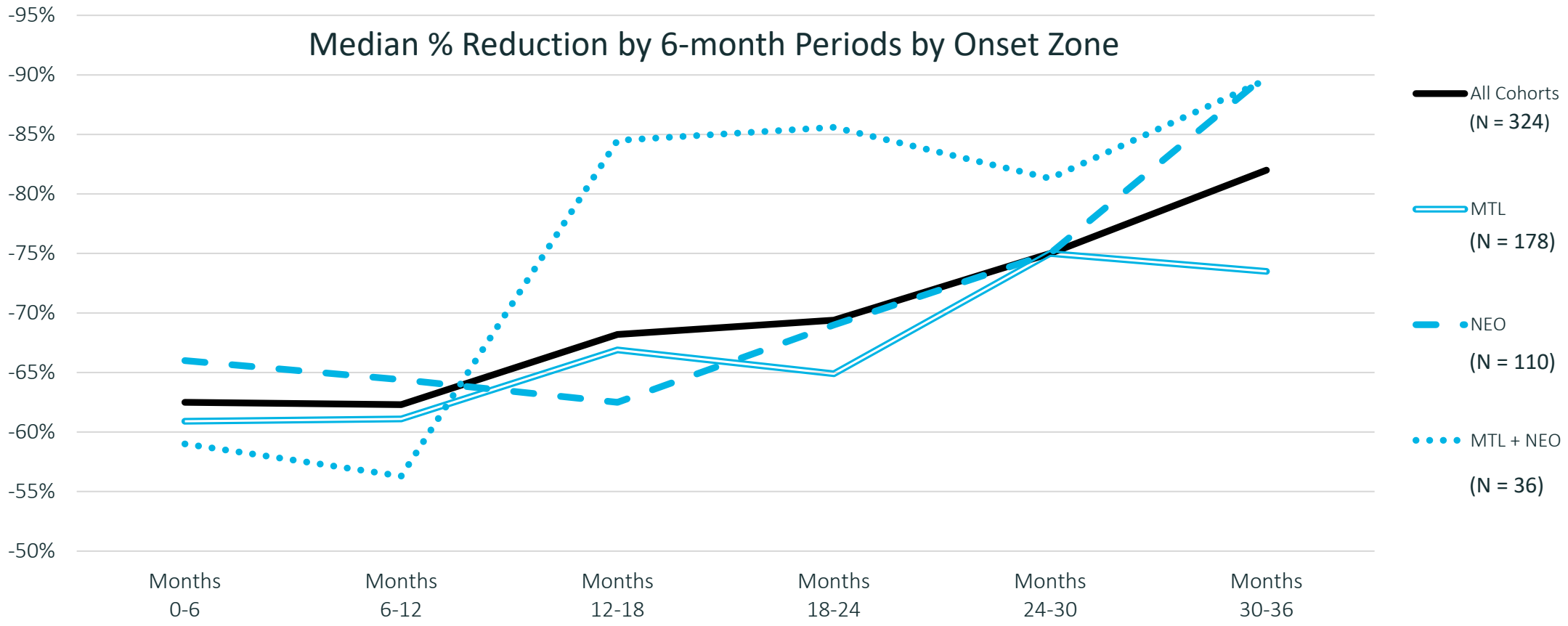
Time after Implant	N	Median % Change in Seizure Frequency Compared to Baseline[1] (1st quartile, 3rd quartile)
Months 0-6	314	-62.5% (-91.6%, -11.8%)
Months 6-12	292	-62.3% (-93.3%, -14.6%)
Months 12-18	282	-68.2% (-97.4%, -15.5%)
Months 18-24	273	-69.4% (-98.4%, -19.4%)
Months 24-30	260	-75.0% (-99.2%, -25.8%)
Months 30-36	255	-82.0% (-100.0%, -29.2 %)

- 42.5% of patients were seizure free for at least 6 months during follow-up
- 22% of patients were seizure free for at least 1 year during follow-up

[1]Intent-to-treat population (ITT)

Seizure Reductions Similar for All Seizure Onset Zones

Improvement in seizure frequency for patients with mesial temporal, neocortical, and mesial temporal + neocortical onset seizures



Clinical Predictors of Effectiveness

Median percent reduction in seizures did not differ according to:

- Age or duration of epilepsy
- Abnormality by MRI
- One or two seizure onsets
- Intracranial EEG monitoring before treatment
- Prior treatment with epilepsy surgery or VNS
- Change in antiseizure medications during treatment

Interim Safety Results Consistent Long-term Treatment Trial[1]

No SAEs reported to be related to the chronic use of the RNS System

Surgical procedure related SAEs in 22/324 patients (6.8%; 22 events)

All anticipated and resolved

SAE rate similar in each of the onset zone subpopulations

Safety outcomes similar across Neurosurgeons (p = <.0001) and Centers (p = <.0001)

SAEs in > 1 Patient	Surgical Procedure Related
Implant site infection	7
Hemorrhage	6
Implant site erosion	2
CSF leakage	2

Two SUDEP events

- SUDEP rate (data from all RNS System focal epilepsy trials[2]) = 2.3/1000 patient years

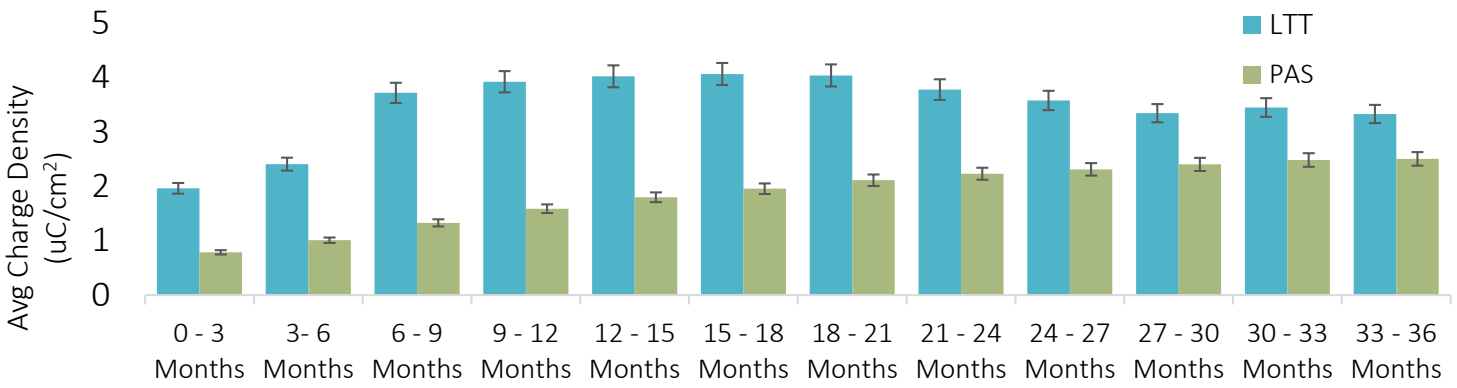
[1] Nair et al., Neurology 2020

[2] SUDEP rate calculated from 645 patients/3000 patient years

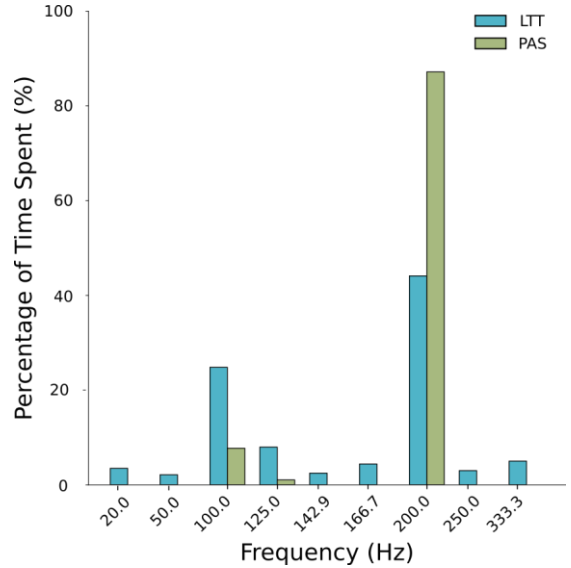
Stimulation Parameters in PAS: Consistent with Suggested Therapy Protocol Developed from Experience in LTT Trial

Stimulation Parameter	Long-Term Treatment Trial[1]	Post-Approval Study
Pulse width	160 µsec	160 µsec
Burst duration	100 msec	100 msec
Mean # of detections/day	1028 detections/day	1077 detections/day
Median total daily duration of stimulation	3.4 minutes/day	3.6 minutes/day

Charge density started lower and increased slower



93% started with ≥200 Hz stimulation



[1]Nair et al., Neurology 2020

ITT – All patients

RNS Post-Approval Study: Effectiveness Conclusions Based on 3-Year Results

RNS System therapy is observed to be effective for all types of focal epilepsy

- Efficacy improves over time
- Seizure reduction in upper quartile[1]
  - Exceeds 90% within 6 months of implant
  - 100% at 3 years

Results may have improved compared to prior studies because we learn from the data: target of future research

- Patterns that should be detected
- Lead locations and stimulation targets
- Initial stimulation strategies
- Fine-tuning therapy based on clinical response and intracranial EEG

[1] ITT

FDA Indication for Use

The RNS® System is an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures.

℞ Only

See important prescribing and safety information in the RNS® System labeling. This is intended as supplementary information and should be used in conjunction with the labeling. Refer to the labeling for a description of the RNS® System and its components, indications for use, contraindications, warnings, cautions, adverse events and instructions for use. The manuals are available at www.NeuroPace.com.

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