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Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy

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Abstract

Objective. Prospectively evaluate safety and efficacy of brain-responsive neurostimulation in adults with medically intractable focal onset seizures (FOS) over 9 years.

Methods. Adults treated with brain-responsive neurostimulation within 2 year feasibility or randomized controlled trials enrolled into a long-term prospective open label trial (LTT) to assess safety, efficacy, and quality of life (QOL) over an additional 7 years. Safety was assessed as adverse events (AEs), efficacy as median percent change in seizure frequency and responder rate, and QOL using the quality of life in epilepsy (QOLIE-89) inventory.

Results. 230 of 256 patients treated in the initial trials participated in the LTT. At 9 years, the median percent reduction in seizure frequency was 75% ($p<0.0001$; Wilcoxon Signed Rank), responder rate was 73%, and 35% had a ≥90% reduction in seizure frequency. 18.4% (47/256) experienced ≥1 year of seizure freedom with 62% (29/47) seizure free at last follow-up and an average seizure-free period of 3.2 years (range: 1.04 – 9.6 years). Overall QOL, epilepsy-targeted and cognitive domains of QOLIE-89 remained significantly improved ($p<0.05$). There were no serious AEs related to stimulation and the sudden unexplained death in epilepsy (SUDEP) rate was significantly lower than predefined comparators ($p<0.05$; one-tailed Chi Square).

Conclusions. Adjunctive brain-responsive neurostimulation provides significant and sustained reductions in the frequency of FOS with improved QOL. Stimulation was well tolerated, implant related AEs were typical of other neurostimulation devices, and SUDEP rates were low.

Classification of Evidence. This study provides Class IV evidence that brain-responsive neurostimulation significantly reduces focal seizures with acceptable safety over 9 years.

Introduction

About 30-40% of epilepsy patients are refractory to medications. While resective or ablative procedures provide the best likelihood of seizure freedom[1-3], these approaches are not an option for many patients due to the potential for neurological risk or insufficient likelihood of benefit. Neuromodulation approaches including vagus nerve stimulation[4, 5] (VNS), deep brain stimulation[6, 7] (DBS) and brain-responsive neurostimulation[8-10] (RNS® System, NeuroPace, Inc.) have been demonstrated to be safe and effective treatments to reduce seizure frequency for these patients. In contrast to DBS, brain-responsive neurostimulation delivers stimulation only in response to changes in ongoing neural activity at the seizure focus.[8-10] While this approach requires the identification of the seizure focus, it limits the amount of stimulation delivered per day.[8-10]

The RNS System is approved by the United States Food & Drug Administration (FDA) as an adjunctive treatment for adults with medically refractory focal onset seizures (FOS) arising from one or two seizure foci.[8-10] An initial 2 year feasibility study (n=65) demonstrated safety and provided preliminary evidence of effectiveness, and a 2 year double-blinded randomized controlled trial (n=191) demonstrated safety and effectiveness. Final results are provided from an FDA requested and approved prospective open-label long-term treatment (LTT) clinical study intended to collect an additional 7 years of prospective data on the safety and effectiveness of the RNS System. This report of 9 years of patient follow-up supplements and extends the experience and observations presented in an interim analysis[8] and represents the largest multicenter prospective trial in the field of neuromodulation to date.

Methods

The RNS® System (NeuroPace, Inc., Mountain View, CA) provides brain-responsive (closed-loop) neurostimulation when abnormal electrocorticographic activity is detected, typically epileptiform activity that is observed at the onset of electrographic seizures. As described in a prior publication[11], a cranially-implanted programmable neurostimulator is connected to depth and/or subdural cortical strip leads that are placed according to the patient's previously identified seizure focus or foci. Each lead contains 4 electrode contacts (Figure 1). Two leads can be connected to the neurostimulator at a time and as many as 4 leads could be implanted in the clinical trials (no more than 2 depth leads). The neurostimulator continually senses electrocorticographic (ECoG) activity through the electrodes and is programmed by the physician to detect specific ECoG patterns and deliver stimulus pulses in response to detections. The physician adjusts detection and stimulation parameters for each patient as needed for seizure reduction.[8]

Figure 1

The LTT study was open to patients who participated in the 2 year feasibility or pivotal studies beginning in 2004 and completed in 2018. Patients were followed for an additional 7 years. Adverse event (AE) and daily seizure diary data were collected every 6 months at a minimum. QOL was assessed yearly by the Quality of Life in Epilepsy (QOLIE-89).[12] Safety was assessed as spontaneously reported AEs, which were categorized by the investigator as mild or serious, and as device related, of uncertain device relation or not device related. An independent data monitoring committee reviewed all AEs. All deaths were additionally evaluated by a Sudden

Unexplained Death in Epilepsy (SUDEP) analysis committee that adjudicated whether the death was possibly, probably or definitely related to SUDEP, or not SUDEP.

Efficacy was assessed as median percent change in seizure frequency and as responder rate (the percentage of patients with a 50% or greater reduction in seizure frequency) for each 6 month period compared to the prospective pre-implant baseline for patients with a minimum diary requirement of 91 recorded days per 182 day period (≥91 day diary requirement). The significance of the reduction in seizure frequency at each timepoint was assessed using the Wilcoxon Signed Rank Test ($\alpha < 0.05$). The robustness of the efficacy outcome was tested using several different analysis approaches, including a constant cohort (data at each time point from all patients that completed the trial) analysis, and a last observation carried forward (LOCF) analysis. If improvements in seizure frequency over time were driven primarily by patient drop-out, then the median percent reduction for either the constant cohort or LOCF populations or both would be expected to remain similar at all time points.

To test whether there was continued improvement in seizure frequency over time, the percent change in seizure frequency for each 6 month period was modeled using a generalized estimating equation (GEE) model with time (defined as 0,1, 2, 3…for each consecutive 6 month period beginning with months 6-12 as the first period). For each subject, only periods with at least 91 out of 182 days of seizure diary data were included; the remaining periods were considered missing data. The GEE model used a compound symmetry correlation structure to account for repeated measurements per subject over the course of the study. In this model, the estimated value of the intercept was interpreted as the estimated percent change in the first 6 month period (months 6-12). The estimated value of the slope was then interpreted as the estimated linear

change in the percent change in seizure frequency over the remaining periods ($\alpha < 0.05$). Additional GEE models were performed on subgroups to assess whether clinical covariates such as age at enrollment (by median split), age of onset (by median split), prior surgery for epilepsy (yes/no), prior intracranial monitoring (yes/no), prior VNS (yes/no), abnormality on brain MRI (yes/no), number of seizure onset zones (one/two), and seizure onset location (mesial temporal lobe/ neocortical / both) were predictive of outcome.

Antiseizure medications could be adjusted as medically necessary. The impact of changing antiseizure medications on the clinical outcomes at the last follow-up was compared to baseline. An increase in antiseizure medications was defined as a 25% or greater increase in dose, the addition of a medication not taken at baseline, or both. A decrease was defined as a 25% or greater reduction in dose, the discontinuation of an antiseizure medication, or both. Patients in the mixed category had both a qualifying increase in one or more medications and a qualifying decrease in one or more medications. Patients in the no change category were on the same medications and doses (+/- less than 25%) at last follow-up as at baseline. The reduction in clinical seizure frequency during the last 6 months of follow-up using the LOCF population was then compared between the patients in the four groups (increase, decrease, mixed, or no change) using Wilcoxon rank sum tests ($\alpha < 0.05$).

Average changes in the QOLIE-89 overall T-score and 4 subdomains of QOL were compared to the pre-implant baseline using a paired t-test.

Neurostimulator battery longevity

A Kaplan-Meier survival analysis was used to estimate the median survival of the RNS-300M (the neurostimulator model primarily used in the LTT study). The analysis included all RNS-300M devices implanted through April 2019 and excluded devices explanted for reasons other than battery depletion (e.g. infection or lead revision).

Standard Protocol Approvals, Registrations, and Patient Consents

All study protocols were approved by the Food and Drug Administration (FDA) and the institutional review boards of participating investigation sites. All subjects gave written informed consent. The LTT study is registered on www.clinicaltrials.gov (NCT00572195).

Classification of evidence

This prospective open-label study provides Class IV evidence that brain-responsive neurostimulation is acceptably safe, reduces seizure frequency and improves quality of life in adults with medically refractory focal onset seizures, over a mean follow-up of 7.5 years (range 5 weeks to 11.2 years; median follow-up 8.97 years). One hundred and seventy three of the subjects were part of the original randomized double blinded trial that provided Class I evidence for safety and effectiveness.

Data Availability

No data are available.

Results

Two hundred and fifty six subjects were initially implanted with the RNS Neurostimulator and NeuroPace Leads within the feasibility and pivotal studies combined; 230 enrolled in the LTT

study, and 162 completed all 9 years of follow-up. This provides an accumulated experience of 1895 patient implant years and 1788 years over which brain-responsive neurostimulation was enabled. The mean follow-up period was 7.5 years (SD 2.9 years, range 5 weeks to 11.2 years) and the median follow-up was 8.97 years. Subject accountability is provided in Figure 2.

Figure 2

Subject demographics and clinical characteristics for all implanted subjects are provided in Table 1. The subjects had experienced frequent seizures (mean seizure frequency per month ± SD: 50.7 ± 177.4) for many years (mean duration of epilepsy ± SD: 19.7 ± 11.4 years). One third had been treated with VNS and one third with epilepsy surgery.

Table 1

Efficacy

Device Settings

Over the 9 years of follow-up, patients received an average 1028 detections per day (range: 5 to 3091). The most common stimulation therapy settings were two bursts of stimulation at 100-200 Hz, 160 μs pulse width, and 100 ms burst duration with the majority of detections resulting in the delivery of a single therapy. Thus, for this cohort the maximum amount of stimulation delivered per day was 10.3 minutes with patients on average receiving 3.4 minutes of stimulation per day.

Seizure Reduction

Seizure reductions in 6 month intervals were statistically significant over the entire 9 years of follow-up compared to baseline. Figure 3A shows the median seizure frequency change from baseline during the LTT study (3 to 9 years post-implant). The reduction in seizures is displayed for the population who met the 91 day minimum diary requirement, a constant cohort, and a last observation carried forward (LOCF) population. The reduction in seizures improved over the additional 7 years of follow-up. Based on the 91 day minimum diary requirement population, the median percent reduction at the end of year 3 was 58%. This improved steadily, reaching 75% by the end of 9 years of treatment ($p < 0.0001$; Wilcoxon Signed Rank). Similar results were observed using the other analysis approaches, suggesting that the improvement over time was not due to enrichment in the patient population (Figure 3A). Using the 91 day seizure diary requirement population, the GEE estimated a statistically significant continued reduction in seizures of 1.2% per 6 month period over time ($p < 0.001$). Figure 3B shows the distribution of individual responses to treatment at 9 years for subjects with at least 91 days of seizure diary data; the responder rate was 73%, 35% had a 90% or greater reduction in their seizures, and 21% were seizure-free in the last 6 months of follow-up.

Figure 3

Seizure Reductions and Clinical Covariates

The slope of the median percent reduction in seizure frequency over time was not influenced by any of the clinical covariates. The improvement in the median percent reduction in seizure frequency was similar for subjects with and without prior epilepsy surgery (p=0.33), VNS

(p=0.70), or intracranial monitoring (p=0.39). Also, the reduction in seizure frequency over time was not influenced by the subject's age at enrollment (p=0.26), age of seizure onset (p=0.24), the presence or absence of any brain abnormality on imaging (p=0.51), the seizure onset location (p=0.34) or the number of seizure foci (p=0.20).

Seizure Reductions and Antiseizure Medications

Antiseizure medications were adjusted in many patients over the open-label follow-up, as was allowed in the protocol (Table 2). There were no statistically significant differences in the efficacy endpoints at last follow-up between patients who had an addition or increase in antiseizure medications, patients who had a decrease, or those who had no change ($p > 0.05$).

Table 2

Seizure Reductions and Lobe of Seizure Onset

In addition, median percent seizure reductions at 9 years were similar for subjects with seizure onsets in the mesial temporal lobe, unilateral or bilateral, (73%; IQR: 58-96%; n=66), or in the neocortex (81%; IQR: 34-100%; n=70), including frontal lobe (93%; IQR: 31-100%; n=21), and other regions of the neocortex (79%; IQR: 52-93%; n=30). Seizure reductions for each onset region are provided in Table 3.

Table 3

Seizure Freedom

Over the 9 years of follow-up, many patients experienced prolonged seizure free periods (see Figure 3C); 28.1% (72/256) had at least one seizure-free period of 6 months or longer, while 18.4% (47/256) had at least one seizure-free period of 1 year or longer. For patients with at least 1 year of seizure freedom, the average duration of their longest consecutive period of seizure free days was 3.2 years (range: 1.04 – 9.6 years). At the completion of the study, 62% (29/47) of patients with ≥1 year of seizure freedom were also seizure free during the last year of follow-up.

Quality of life

Overall QOLIE-89 scores improved at 1 year (N=212, mean. = +3.2, SD=8.6, $p < 0.0001$) and improvements were maintained through Year 9 of treatment (N=145, mean = +1.9, SD=11.1, $p < 0.05$), as were statistically significant improvements in epilepsy targeted (N=145, mean = +4.5, SD=10.4, $p < 0.001$) and cognitive (N=145, mean = +2.5, SD=10.5, $p =0.005$) domains.

Safety

Device-related serious adverse events

Over the entire follow-up, the only device-related serious adverse events (SAEs) that were reported in 5% or more of patients cumulatively were implant site infection and elective explant of the neurostimulator, leads, or both. The risk of infection per procedure (initial implant, replacement, or revision) was 4.1%. Over the cumulative 1895 patient-implant years, serious device-related implant site infection was reported in 12.1% of subjects. The events were typically reported shortly after a surgical procedure (median 36 days; range: 0-1261 days), and 16 of the 35 infections led to a device explant. All but one of the infections involved only soft

tissue, and cultures most often indicated skin flora; there were no instances of meningitis or brain parenchymal infection.[13, 14]

Other device-related SAEs included non-seizure related hemorrhage in 7 patients (2.7%), 4 of which occurred within a few days of an implant procedure and had no neurological sequelae. Status epilepticus occurred in 8.2% of subjects during the study; 52% (15/29) of the events were nonconvulsive status epilepticus. The majority of these events were not device related (26/29) and were considered serious (27/29) due to hospitalization.

Depression and Suicidality

At enrollment in the RNS System studies, 60% of all subjects reported a prior medical history of depression, suicidality, or both. Cumulatively, 1.6% (4/256) of subjects reported an SAE related to depression and 23.4% (60/256) reported a mild adverse event; the majority of these subjects (71%) had a prior medical history of depression. The majority of AEs associated with depression (82%) were not considered to be device-related.

AEs related to suicidality (suicidal depression, suicidal ideation, suicidal behavior, and suicide attempts) were reported in 9.8% of subjects over the 9 years; 68% of the events were considered serious and the majority of these subjects (86%) had a prior history of depression. In addition, 2 subjects completed suicide, one of whom was being treated with brain-responsive neurostimulation at the time. Both subjects had a prior history of depression and one also had a history of suicidality.

Memory

Only one subject reported a SAE related to memory. Cumulatively, 12.5% of patients had a non-device related adverse event (typically mild) related to memory impairment over the 9 years. AEs related to memory impairment occurred most often in patients who reported memory impairment prior to enrollment (69%).

SUDEP

There were 16 deaths in the 256 patients over the 9 years of follow-up: 2 due to suicide; 1 each due to status epilepticus, herpes encephalitis, sepsis, lung/colon cancer, and lymphoma; and 4 due to definite SUDEP; 2 due to probable SUDEP; and 3 due to possible SUDEP. Two of the patients who suffered SUDEP were not being treated with brain-responsive neurostimulation at the time of death. The rate of probable or definite SUDEP combined was 2.8 per 1000 patient stimulation years (95% CI: 1.2-6.7) and 3.2 per 1000 patient implant years (95% CI: 1.4-7.0). This is lower than the pre-specified comparator of 9.3 per 1000 patient years for patients who are epilepsy surgery candidates and statistically significantly lower than the comparator of 6.9 per 1000 patient years for patients with medically intractable epilepsy in the placebo arm of randomized controlled medication trials ($p < 0.05$; one-tailed Chi Square).[15]

Neurostimulator battery longevity

The Kaplan-Meier survival analysis of the RNS-300M neurostimulator model found the median time to replacement to be approximately 1284 days or 3.5 years. For the RNS-300M neurostimulator, there were no device malfunctions related to the battery.

Discussion

Long-term efficacy

Treatment with the RNS System significantly and progressively improved seizures over 9 years of prospective follow-up. At the completion of 9 years of treatment, the median percent seizure reduction was 75%, the responder rate was 73%, and more than one third of patients had a 90% or greater reduction in seizures. Unlike antiepileptic medications[16], the clinical response to brain-responsive neurostimulation improved over time. The analysis of the completed study showed a progressive improvement in seizure frequency through the end of 9 years of treatment. This contrasts the previously published interim analysis[8], that found improvement in seizure frequency through the first two years followed by a plateau in response. The discrepancy is likely due to the smaller sample size at later time points in the interim analysis while the study was ongoing. The progressive improvement through 9 years of follow-up is consistent with other neuromodulation modalities[7] and suggests that there could be longer-term neuromodulatory effects of neurostimulation that result in continued improvement in outcomes.

Many patients had long seizure free periods. At the completion of the study, 21% of patients were seizure free. Over the course of the study, 28% of patients were seizure free for at least one period of 6 months or more and 18% had at least one period of 12 months or longer without seizures. In addition, patients with at least 1 year of seizure freedom experienced an average period of 3.2 years without a seizure. These results are especially meaningful when considering that these patients had a nearly 20 year history of epilepsy, more than 10 disabling seizures a month at baseline and had failed multiple epilepsy therapies.

Significant seizure reductions were similarly likely in patients with and without prior brain resective surgery, VNS, or intracranial monitoring, in patients with seizures arising from the mesial temporal lobe or neocortex, for those with one or two foci, and for those with and without a lesion on brain MRI. The reduction in seizures with RNS System treatment was not significantly associated with changes in antiseizure medications. While there were no apparent differences in seizure frequency reductions for these different subgroups in the clinical study, it should be noted that the study was not powered for subgroup comparisons. As a result, larger sample sizes may be needed to identify the characteristics of patients that are most likely to benefit from brain-responsive neurostimulation.

The response to treatment with the RNS System is supported by significant and sustained improvements in overall QOL and in individual domains of QOL that indicate less vulnerability to seizures and a more positive perception of cognitive function. These are areas of function that are often profoundly impacted in persons with intractable seizures.[17, 18]

Long-term safety

Responsive neurostimulation was well-tolerated and safe over time. Adverse events related to the implanted device, including infection, were anticipated and the rates were not higher than reported with implantation of intracranial electrodes to localize the seizure focus[19-21] and with resective epilepsy surgery,[19, 22, 23] or with DBS devices for treatment of movement disorders[24] or for epilepsy.[6, 7]

Deaths, including deaths by SUDEP, were not more frequent than is expected in patients with medically intractable focal onset seizures[25, 26], and the SUDEP rate was significantly lower than

the pre-specified comparator estimate of 9.3/1000 patient years. An analysis of SUDEP events in a larger population of patients treated with the RNS System (N=707) provides a more confident estimate of the SUDEP risk, with a rate of probable and definite SUDEP of 2.0/1000 patient stimulation years (95% C.I. 0.9-5.4).[27]

The risk for infection is 4.1% with each RNS Neurostimulator procedure and was previously shown not to increase with subsequent routine neurostimulator replacements[13]. This compares favorably to other neurostimulation therapies that utilize a pectorally implanted pulse generator such as VNS[28] and DBS for Parkinson's disease[29] or epilepsy.[6, 7]

Depression

Depression comorbidity in patients with medically intractable focal onset seizures reaches 66%.[30] Validated inventories of depression (Beck Depression Inventory [BDI-II], Center for Epidemiologic Studies Depression [CES-D]) showed that there was no deterioration in mood in patients treated within the RNS System during the randomized controlled trial[10], and there were modest group improvements.[31] Patients in the RNS System trials who had a history of depression, suicidality, or both, were more likely to experience adverse events related to depression or suicidality.

Memory

Adverse events related to memory impairment were infrequent in patients treated with brain-responsive neurostimulation, were almost all mild, and were predominantly from patients with a history of memory impairment.

In the RNS System randomized controlled trial, there was no deterioration in any of 14 cognitive domains over 2 years. Verbal fluency improved significantly in patients with seizure onsets in neocortical regions. In addition, there were small but statistically significant improvements in verbal memory that were specific to patients with seizures arising from the mesial temporal lobe.[32] These results contrast sharply with memory outcomes following temporal lobectomy or selective amygdalohippocampectomy (SAH), after which significant declines in verbal memory may occur, particularly following dominant hemisphere procedures.[33, 34] Small but statistically significant cognitive declines in verbal and narrative memory have also been reported following laser interstitial thermal therapy for mesial temporal lobe epilepsy, particularly in the dominant hemisphere.[35]

Neurostimulator battery longevity

The neurostimulator battery longevity for the RNS-300M model observed in the clinical trial was consistent with that anticipated by the battery longevity estimates provided in the user manual, which indicates a time to end-of-service of 2.6 to 4.2 years depending on the device settings[36]. This is shorter than observed for the Kinetra® and Activa-PC DBS neurostimulators based on experience in Parkinson's disease where the median survival was 6.5 and 4.6 years respectively[37]. However, the newest neurostimulator model (RNS-320) is anticipated to increase battery longevity to 8 years at moderate stimulation usage.

Chronic ambulatory electrocorticography

While the RNS System provides a considerable amount of ambulatory electrocorticographic data that necessitates interpretation by the physician, these ECoG data may provide insights relevant to clinical care of the person with epilepsy. For example, RNS System chronic ECoG data have

been used to refine localization of the seizure onset and inform decisions about resective or ablative surgery.[38-40] ECoG data may provide an early indication of the clinical response to antiseizure medications[41] and to changes in lifestyle.[42] In addition, recent studies have shown that features in the ECoG data may provide objective biomarkers that can be used to assess the clinical response to stimulation.[43, 44] Also, it may be possible to use an individual patient's ECoG data to identify periods of heightened seizure risk.[45, 46] In the future these data may be used to supplement the patient's clinical report. However, these potential biomarkers require further research and validation before they can be widely used in the RNS System patient population.

Limitations and possible bias in the study results

The results are provided from an open-label long-term study and may be influenced by selection bias, expectation bias, a prolonged placebo response or regression to the mean. However, a significant improvement was evident in treated patients compared to sham stimulated patients in the blinded portion of a randomized controlled trial, and an improvement in the sham stimulated patients was evident when stimulation was first provided, despite maintenance of the randomization blind. Also, these patients had a 20 year history of intractable epilepsy on average, so it is unlikely that sustained and significant 9 year reductions would be observed. Finally, such long-term experience could not be feasibly obtained in a blinded and randomized trial.

Conclusions

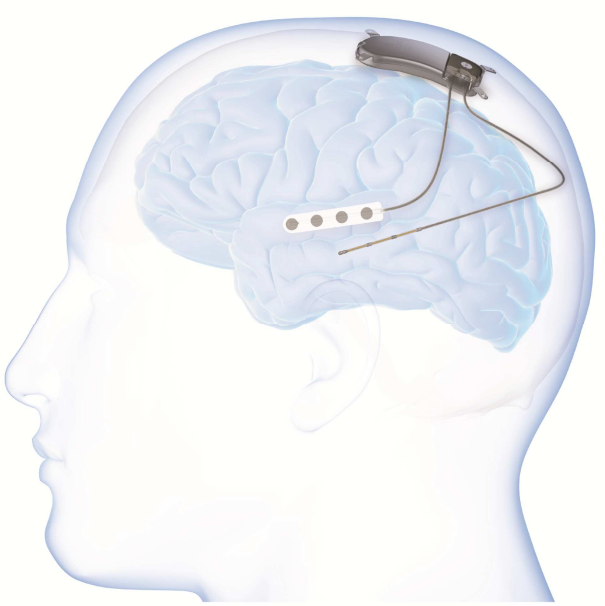
The long-term efficacy and safety of brain-responsive neurostimulation for the treatment of medically intractable focal seizures is established based on results in 256 patients who were followed prospectively for a median of 9 years. As with all other epilepsy therapies, there was a

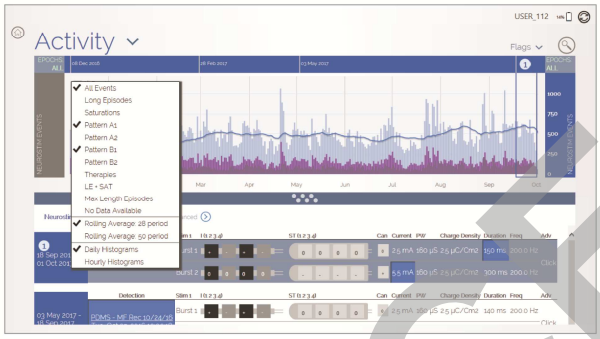
range of patient responses. However, this study provides substantial evidence that adjunctive treatment with brain-responsive neurostimulation is safe, and provides persons with medically intractable focal epilepsy an opportunity for significant and sustained reductions in disabling seizures with enduring improvements in quality of life, and SUDEP rates that were lower than anticipated for similar patient populations. The safety of the surgical procedure and the implanted device compares favorably to other brain stimulation devices used for treatment of movement disorders[29] and epilepsy.[7]

Future research will explore methods by which brain-responsive neurostimulation can be optimized for individual patients with medically intractable epilepsy. Using machine and deep learning techniques, clinical and electrocorticographic data features may be identified that can direct personalized neurostimulator detection and stimulation programming. Additional work to define the acute and chronic mechanism(s) of action may help to determine the optimal application of these devices.

Figures

Figure 1: **RNS® System**. Left: RNS® Neurostimulator and NeuroPace® Cortical Strip and Depth Leads. Upper right: record of the number of electrographic events detected by the neurostimulator over time for an individual patient. Lower right: snapshots of electrographic activity recorded by the RNS® System for an individual patient. © 2020 NeuroPace, Inc.





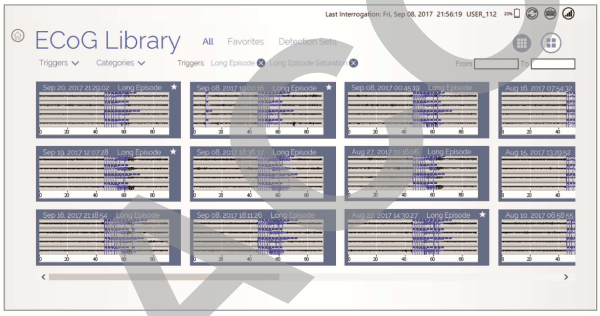


Figure 2: **RNS® System Studies, Subject Accountability**. [a]Feasibility study: Six participants discontinued before completing the study; 2 participants completed the study, but elected not to enroll in the LTT study. Thus, 57 participants in the Feasiblity study enrolled in the LTT study. [b]Pivotal study: Sixteen participants discontinued prior to completing the study; 4 participants completed the study, but elected not to enroll in the LTT study. Two subjects who discontinued early were granted waivers and were allowed to enroll, resulting in 173 pivotal subjects enrolling into LTT. A total of 230 subjects chose to enroll in the LTT study and 162 subjects completed the study. [c]Reasons for early withdrawal from the LTT study included: chose not to replace neurostimulator (n=20); to pursue other treatment options (n=10); insufficient efficacy (n=8); study noncompliance (n=7); to receive medical care at a non-study center (n=5). © 2020 NeuroPace, Inc.

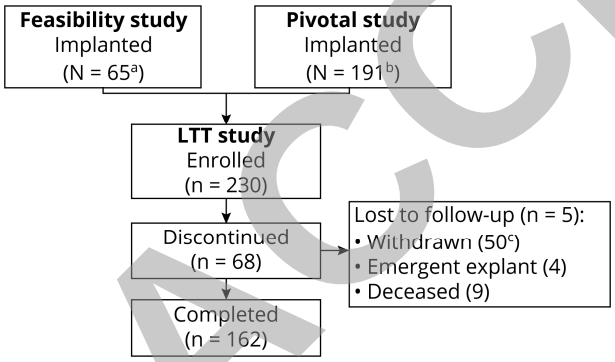
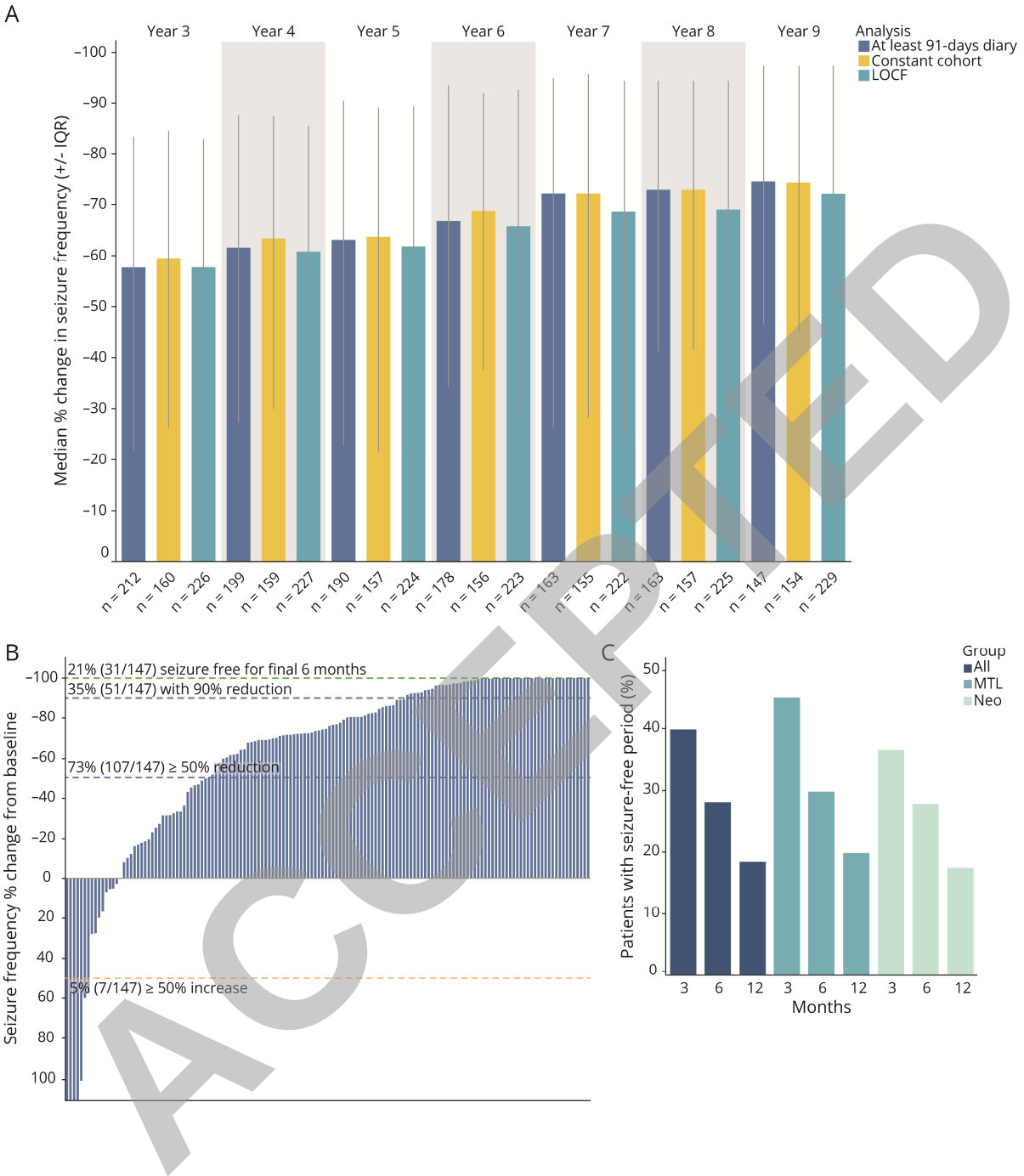


Figure 3: **A. Median percent reduction ± IQR over time**. Plot showing the median percent reduction ± IQR in seizure frequency for the last 6 months of each year in the LTT study (years 3 through 9 of treatment) compared to baseline for the 91 day minimum diary requirement population, the constant cohort population, and the last observation carried forward population. **B. Individual changes in clinical seizure frequency**. Changes in clinical seizure frequency during the last 6 months of follow-up before the year 9 visit for each subject who had at least 91 days of seizure diary data. Negative values indicate a seizure frequency reduction compared with baseline. **C.** Bar graph showing the percent of all subjects (All) and subjects with onsets in the mesial temporal lobe (MTL) or neocortex (Neo) with at least 1 period of seizure freedom lasting at least 3, 6, and 12 months. © 2020 NeuroPace, Inc.



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Data Safety Monitoring Board.. Roger Porter, MD (Chair), Gary Mathern, MD, Joan Conry, MD, John "Jack" Pellock, MD (in memoriam), Lorene Nelson, PhD, and Dan Bloch, PhD

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Tables

Table 1: Demographics and Characteristics of All Implanted Subjects (n=256)

Female	49% (125/256)
Age in years[1] (mean, SD, range)	34.0 ± 11.3 (18 - 66)
Duration of epilepsy in years[1] (mean, SD, range)	19.7 ± 11.4 (2 - 58)
Number of AEDs[1] (mean, SD, range)	2.9 ± 1.1 (0 - 8)
Pre-implant disabling seizures per month (mean, SD)	50.7 ± 177.4 median = 10.2
Prior intracranial monitoring	65% (166/256)
Prior epilepsy surgery	34% (86/256)
Prior vagus nerve stimulator	32% (82/256)
Two seizure foci (vs. one)	48% (124/256)
Mesial temporal lobe only onsets (vs. other)	43% (111/256)
[1]at enrollment in initial study (feasibility or pivotal) © 2020 NeuroPace, Inc.	

Table 2: LOCF Seizure Frequency Reduction and Responder Rates Based on Antiseizure Medication Changes

Changes in antiseizure medications	**N**	**Median % Change* (+/- IQR)**	**Responder Rate* (n/N)**
No Change	22	-71% (-35 to -92%)	64% (14/22)
Increase	52	-68% (-12 to -82%)	63% (33/52)
Mixed (Increase and Decrease)	139	-73% (-32 to -97%)	68% (94/139)
Decrease	16	-96% (-61 to -100)	75% (12/16)
*LOCF most recent 6 months of follow-up © 2020 NeuroPace, Inc.			

Table 3: Seizure Frequency Reduction and Responder Rates at 9 Years According to Region of Seizure Onset

Region of seizure onset	Median % Reduction (IQR)	Responder Rate
All MTL (n=66)[1]	73% (58-96%)	77%
MTL Bilateral (n = 48)	71.9% (56-90%)	77%
MTL Unilateral (n = 18)	94% (64-100%)	78%
All Temporal (n=95) (MTL, lateral, MTL+ lateral)	73% (47-93%)	72%
All Neocortical (n=70)	81% (34-100%)	70%
Lateral Temporal (n=19)	81% (33-99%)	58%
Frontal (n=21)	93% (31-100%)	71%
Other (n=30)	79% (52-93%)	77%

[1]MTL= mesial temporal lobe

Contributions:

Appendix 1: Authors

Name	Location	Contribution
Dileep R Nair, MD	Cleveland Clinic Foundation, Cleveland, OH	Major role in the acquisition of data; analysis or interpretation of the data; drafting/ revising manuscript for intellectual content
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Peter B Weber, MD	California Pacific Medical Center, San Francisco, CA	Major role in the acquisition of data
Anthony M Murro, MD	Augusta University, Augusta, GA	Major role in the acquisition of data
Yong D Park, MD	Augusta University, Augusta, GA	Major role in the acquisition of data
Gregory L Barkley, MD	Henry Ford Hospital, Detroit, MI	Major role in the acquisition of data
Brien J Smith, MD	Ohio Health Neuroscience, Columbus, OH	Major role in the acquisition of data
Ryder P Gwinn, MD	Swedish Neuroscience Institute, Seattle, WA	Major role in the acquisition of data
Michael J Doherty, MD	Swedish Neuroscience Institute, Seattle, WA	Major role in the acquisition of data
Katherine H Noe, MD, PhD	Mayo Clinic Arizona, Scottsdale, AZ	Major role in the acquisition of data
Richard S Zimmerman, MD	Mayo Clinic Arizona, Scottsdale, AZ	Major role in the acquisition of data; drafting/revising manuscript for intellectual content
Gregory K Bergey, MD	Johns Hopkins Medicine, Baltimore, MD	Major role in the acquisition of data; drafting/revising manuscript for intellectual content

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Robert B Duckrow, MD	Yale University School of Medicine, New Haven, CT	Major role in the acquisition of data
Lawrence J Hirsch, MD	Yale University School of Medicine, New Haven, CT	Major role in the acquisition of data; drafting/revising manuscript for intellectual content
Robert E Wharen, Jr., MD	Mayo Clinic Florida, Jacksonville, FL	Major role in the acquisition of data
William Tatum, DO	Mayo Clinic Florida, Jacksonville, FL	Major role in the acquisition of data
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Guy M McKhann, MD	Columbia University Medical Center, New York, NY	Major role in the acquisition of data
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Appendix 1: Authors

Name	Location	Contribution
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Andrew J Cole, MD	Massachusetts General Hospital, Boston, MA	Major role in the acquisition of data
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Name	Location	Contribution
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Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy

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