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

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Abstract

Objective

To 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 in 2-year feasibility or randomized controlled trials were enrolled in 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 with the Quality of Life in Epilepsy (QOLIE-89) inventory.

Results

Of 256 patients treated in the initial trials, 230 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. We found that 18.4% (47 of 256) experienced ≥1 year of seizure freedom, with 62% (29 of 47) seizure-free at the last follow-up and an average seizure-free period of 3.2 years (range 1.04–9.6 years). Overall QOL and 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, 1-tailed χ²).

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Glossary

AE = adverse event; CI = confidence interval; DBS = deep brain stimulation; ECoG = electrocorticographic; FDA = Food and Drug Administration; GEE = generalized estimating equation; IQR = interquartile range; LOCF = last observation carried forward; LTT = long-term treatment; QOL = quality of life; QOLIE-89 = Quality of Life in Epilepsy; SAE = serious AE; SUDEP = sudden unexplained death in epilepsy; VNS = vagus nerve stimulation.

Conclusions

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

ClinicalTrials.gov identifier

NCT00572195.

Classification of evidence

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

About 30% to 40% of patients with epilepsy 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 neurologic risk or insufficient likelihood of benefit. Neuromodulation approaches, including vagus nerve stimulation4,5 (VNS), deep brain stimulation6,7 (DBS), and brain-responsive neurostimulation8–10 (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 US Food and Drug Administration (FDA) as an adjunctive treatment for adults with medically refractory focal onset seizures arising from 1 or 2 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 analysis8 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 (ECoG) 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 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 ECoG activity through the electrodes and is programmed by the physician to detect specific ECoG patterns and to deliver stimulus pulses in response to detections. The physician adjusts detection and stimulation parameters for each patient as needed for seizure reduction.8

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 up for an additional 7 years. Adverse event (AE) and daily seizure diary data were collected every 6 months at a minimum. Quality of life (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 also 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% reduction in seizure frequency) for each 6-month
period compared to the prospective preimplantation baseline for patients with a minimum diary requirement of 91 recorded days per 182-day period (≥91 days diary requirement). The significance of the reduction in seizure frequency at each time point was assessed with the Wilcoxon signed rank test (α < 0.05). The robustness of the efficacy outcome was tested with several different analysis approaches, including a constant cohort (data at each time point from all patients who completed the trial) analysis and a last observation carried forward (LOCF) analysis. If improvements in seizure frequency over time were driven primarily by patient dropout, then the median percent reduction for the constant cohort, 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 with 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 participant, only periods with at least 91 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 participant 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 (α < 0.05). Additional GEE models were performed on subgroups to assess whether clinical covariates such as age at enrollment (by median split), age at 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 (1/2), 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% increase in dose, the addition of a medication not taken at baseline, or both. A decrease was defined as a ≥25% reduction in dose, the discontinuation of an antiseizure medication, or both. Patients in the mixed category had both a qualifying increase in ≥1 medications and a qualifying decrease in ≥1 medications. Patients in the no change category were on the same medications and doses (±<25%) at the 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 4 groups (increase, decrease, mixed, or no change) with the Wilcoxon rank sum tests (α < 0.05).

Average changes in the QOLIE-89 overall T score and 4 subdomains of QOL were compared to the preimplantation baseline with 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 FDA and the institutional review boards of the participating investigation sites. All participants gave written informed consent. The LTT study is registered on 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 QOL in adults with medically refractory focal onset seizures over a mean follow-up of 7.5 years (range 5 weeks–11.2 years; median follow-up 8.97 years). One hundred seventy-three of the participants 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 fifty-six participants 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 1,895 patient-implantation years and 1,788 years over which brain-responsive neurostimulation was enabled. The mean follow-up period was 7.5 years (SD 2.9 years, range 5 weeks–11.2 years), and the median follow-up was 8.97 years. Subject accountability is provided in figure 2.

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

Efficacy
Device settings
Over the 9 years of follow-up, patients received an average of 1,028 detections per day (range 5–3,091). The most common stimulation therapy settings were 2 bursts of stimulation at 100 to 200 Hz, 160-microsecond pulse width, and 100-millisecond 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 receiving on average 3.4 minutes of stimulation per day.

Seizure reduction
Seizure reductions in 6 months 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 (3–9 years after implantation). The reduction in seizures is displayed for the population who met the 91-day minimum diary requirement, a constant cohort, and an 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 with the other analysis approaches, suggesting that the improvement over time was not due to enrichment in the patient population (figure 3A). In 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 participants with at least 91 days of seizure diary data; the responder rate was 73%; 35% had a ≥90% reduction in their seizures; and 21% were seizure-free in the last 6 months of follow-up.

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 participants with and without prior epilepsy surgery (p = 0.33), VNS (p = 0.70), or intracranial monitoring (p = 0.39). In addition, the reduction in seizure frequency over time was not influenced by the participant’s age at enrollment (p = 0.26), age at 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).

Figure 2 RNS System studies, participant accountability

| Feasibility study | Pivotal study |
|-------------------|--------------|
| Implanted (N = 65<sup>a</sup>) | Implanted (N = 191<sup>b</sup>) |
| LTT study | Enrolled (n = 230) |
| Discontinued (n = 68) | Lost to follow-up (n = 5): |
| Completed (n = 162) | • Withdrawn (30<sup>c</sup>) |
|                   | • Emergent explant (4) |
|                   | • Deceased (9) |

<sup>a</sup>Feasibility study: 6 participants discontinued before completing the study; 2 participants completed the study but elected not to enroll in the long-term treatment (LTT) study. Thus, 57 participants in the feasibility study enrolled in the LTT study.<sup>b</sup>Pivotal study: 16 participants discontinued before completing the study; 4 participants completed the study but elected not to enroll in the LTT study. Two participants who discontinued early were granted waivers and were allowed to enroll, resulting in 173 pivotal participants enrolling into LTT. A total of 230 participants chose to enroll in the LTT study, and 162 participants completed the study. <sup>c</sup>Reasons for early withdrawal from the LTT study included the following: chose not to replace neurostimulator (n = 20); to pursue other treatment options (n = 10); insufficient efficacy (n = 8); study noncompliance (n = 7); and to receive medical care at a nonstudy center (n = 5).
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, and those who had no change ($p > 0.05$).

Seizure reductions and lobe of seizure onset

In addition, median percent seizure reductions at 9 years were similar for participants with seizure onsets in the mesial temporal lobe, unilateral or bilateral (73%; interquartile range [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.

Seizure freedom

Over the 9 years of follow-up, many patients experienced prolonged seizure-free periods (figure 3C); 28.1% (72 of 256) had at least 1 seizure-free period of ≥6 months, while 18.4% (47 of 256) had at least 1 seizure-free period of ≥1 year. 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 of 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 AEs

Over the entire follow-up, the only device-related serious AEs (SAEs) that were reported in ≥5% of patients cumulatively were implantation site infection and elective explantation of the neurostimulator, leads, or both. The risk of infection per procedure (initial implantation, replacement, or revision) was 4.1%. Over the cumulative 1,895 patient-implantation years, serious device-related implantation site infection was reported in 12.1% of participants. The events were typically reported shortly after a surgical procedure (median 36 days; range 0–1,261 days), and 16 of the 35 infections led to a device explantation. All but 1 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 implantation procedure and had no neurologic sequelae. Status epilepticus occurred in 8.2% of participants during the study; 52% (15 of 29) of the events were nonconvulsive status epilepticus. The majority of these events were not device related (26 of 29) and were considered serious (27 of 29) due to hospitalization.

Depression and suicidality

At enrollment in the RNS System studies, 60% of all participants reported a medical history of depression, suicidality, or both. Cumulatively, 1.6% (4 of 256) of participants reported an SAE related to depression, and 23.4% (60 of 256) reported a mild AE; the majority of these participants (71%) had a 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 participants over the 9 years; 68% of the events were considered serious, and the majority of these participants (86%) had a history of depression. In addition, 2 patients completed suicide, 1 of whom was being treated with brain-responsive neurostimulation at the time. Both had a history of depression, and 1 also had a history of suicidality.

Memory

Only 1 participant reported an SAE related to memory. Cumulatively, 12.5% of patients had a non–device-related AE (typically mild) related to memory impairment over the 9 years. AEs related to memory impairment occurred most often in patients who reported memory impairment before enrollment (69%).

SUDEP findings

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; 4 due to definite SUDEP; 2 due to probable SUDEP; and 3 due to possible SUDEP. Two of the patients who had 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 1,000 patient-stimulation years (95% confidence interval [CI] 1.2–6.7) and 3.2 per 1,000 patient-implantation years (95% CI 1.4–7.0). This is lower than the prespecified comparator of 9.3 per 1,000 patient-years for patients who are epilepsy surgery
candidates and statistically significantly lower than the comparator of 6.9 per 1,000 patient-years for patients with medically intractable epilepsy in the placebo arm of randomized controlled medication trials \((p < 0.05, 1\text{-tailed } \chi^2)\).15

**Neurostimulator battery longevity**

The Kaplan-Meier survival analysis of the RNS-300M neurostimulator model found the median time to replacement to be \(\approx 1,284\) days or 3.5 years. For the RNS-300M neurostimulator, there were no device malfunctions related to the battery.

**Discussion**

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 \(\geq 90\%\) 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 with the previously published interim analysis8 that found improvement in seizure frequency through the first 2 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 modalities7 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 1 period of \(\geq 6\) months, and 18% had at least 1 period of \(\geq 12\) months 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 we consider that these patients had a nearly 20-year history of epilepsy, had \(>10\) 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 1 or 2 foci; and for those with and without a lesion on brain MRI.

| Region of seizure onset | Median reduction (IQR), % | Responder rate, % |
|-------------------------|---------------------------|------------------|
| All MTL (n = 66)        | 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               |

Abbreviations: IQR = interquartile range; MTL = mesial temporal lobe.

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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 who 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 affected in persons with intractable seizures.17,18

Responsive neurostimulation was well tolerated and safe over time. AEs 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 with resective epilepsy surgery,19,22,23 or with DBS devices for treatment of movement disorders24 or for epilepsy.6,7

Deaths, including deaths by SUIDP, were not more frequent than is expected in patients with medically intractable focal onset seizures,25,26 and the SUIDP rate was significantly lower than the prespecified comparator estimate of 9.3 per 1,000 patient years. An analysis of SUIDP events in a larger population of patients treated with the RNS System (n = 707) provides a more confident estimate of the SUIDP risk, with a rate of probable and definite SUIDP of 2.0 per 1,000 patient-stimulation years (95% CI 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 use a pectorally implanted pulse generator such as VNS28 and DBS for Parkinson disease24 or for epilepsy.6,7

Depression comorbidity in patients with medically intractable focal onset seizures reaches 66%.29 Validated inventories of depression (Beck Depression Inventory, Center for Epidemiologic Studies Depression) showed that there was no deterioration in mood in patients treated with the RNS System during the randomized controlled trial,10 and there were modest group improvements.30 Patients in the RNS System trials who had a history of depression, suicidality, or both were more likely to experience AEs related to depression or suicidality.

AEs 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.31 These results contrast sharply with memory outcomes after temporal lobectomy or selective amygdalo-hippocampectomy, after which significant declines in verbal memory may occur, particularly following dominant hemisphere procedures.32,33 Small but statistically significant cognitive declines in verbal and narrative memory have also been reported after laser interstitial thermal therapy for mesial temporal lobe epilepsy, particularly in the dominant hemisphere.34

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.35 This is shorter than observed for the Kineta and Activa-PC DBS neurostimulators on the basis of experience in Parkinson disease for which the median survival was 6.5 and 4.6 years, respectively.36 However, the newest neurostimulator model (RNS-320) is anticipated to increase battery longevity to 8 years at moderate stimulation use.

While the RNS System provides a considerable amount of ambulatory ECoG data that necessitate interpretation by the physician, these ECoG data may provide insights relevant to the clinical care of persons with epilepsy. For example, RNS System long-term ECoG data have been used to refine localization of the seizure onset and to inform decisions about resective or ablative surgery.37–39 ECoG data may provide an early indication of the clinical response to antiseizure medications40 and to changes in lifestyle.41 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.42,43 In addition, it may be possible to use an individual patient’s ECoG data to identify periods of heightened seizure risk.44,45 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.

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. In addition, 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.

The long-term efficacy and safety of brain-responsive neurostimulation for the treatment of medically intractable focal seizures are established on the basis of results in 256 patients who were followed up 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 QOL, as well as SUDEP rates that were lower than anticipated for similar patient populations. The safety of the surgical procedure and the implanted device compared favorably to other brain stimulation devices used for the treatment of movement disorders and epilepsy.

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

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D. Nair has received travel or speaker honorarium from Medtronic, has consulted for NeuroPace, has been on the speakers’ bureau for NeuroPace, has received research effort from the NIH and NeuroPace, and has received research support from Brain Sentinel and NeuroPace. K. Laxer reports no disclosures relevant to the manuscript. P. Weber has consulted for NeuroPace. A. Murro and Y. Park report no disclosures relevant to the manuscript. G. Barkley has been on the speakers’ bureau for NeuroPace and has received research support from the NIH and NeuroPace. B. Smith has received travel and honorarium for being on the scientific advisory board for NeuroPace SK Life Science and UCB, has received research effort from NeuroPace,
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### Appendix

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**Appendix (continued)**

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