RNS® SYSTEM FOR EPILEPSY
NEUROPACE, INC.

SPONSOR EXECUTIVE SUMMARY

PREPARED FOR THE FEBRUARY 22, 2013 MEETING OF THE NEUROLOGICAL DEVICES ADVISORY PANEL

List of Tables

List of Figures

Abbreviation	Full Word or Phrase
AE	Adverse Event
AED	Antiepileptic Drug (or antiseizure medication)
BDI-II	Beck Depression Inventory (version 2) survey
BEP	Blinded Evaluation Period (Pivotal study)
CES-D	Center for Epidemological Studies Depression survey
CI	Confidence Interval
CRF	Case Report Form
CSF	Cerebrospinal Fluid
DBS	Deep Brain Stimulation
D-KEFS	Delis-Kaplan Executive Function System
dts	due to seizure
ECoG	Electrocorticogram
EEG	Electroencephalogram
FDA	United States Food and Drug Administration
Feasibility study	RNS System Feasibility Clinical Investigation in Epilepsy
GEE	Generalized Estimating Equations
Hz	Hertz
ICTAL	Scaled LSSS score
IRB	Institutional Review Board
ITT	Intent-to-Treat
LSSS	Liverpool Seizure Severity Scale (version 2) inventory
LTT study	RNS System Long-term Treatment Clinical Investigation in Epilepsy
mA	Milliamp
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
Min	Minimum
MRI	Magnetic Resonance Imaging
ms	Millisecond
N/A or n/a or n.a.	Not Applicable
n.s.	not (statistically) significant
PDMS	NeuroPace® Patient Data Management System
Pivotal study	RNS System Pivotal Clinical Investigation in Epilepsy
POMS	Profile Of Mood States survey
Post-Op	Post-Operative Stabilization Period (Pivotal study)
PT	MedDRA Preferred Term
QOLIE	Quality Of Life in Epilepsy inventory
QOLIE-89	Quality Of Life in Epilepsy inventory, 89 question
RAVLT	Rey Auditory Verbal Learning Test
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	MedDRA System Organ Classification
SUDEP	Sudden Unexplained Death in Epilepsy
VNS	Vagus Nerve Stimulator
WAIS	Wechsler Adult Intelligence Scale

1 OVERALL EXECUTIVE SUMMARY

1.1 Device Description and Intended Clinical Benefit

NeuroPace, Inc. is applying for premarket approval of the NeuroPace® RNS® System. The RNS System consists of a cranially implanted programmable Neurostimulator that senses and records brain activity through electrode-containing leads that are placed at the patient's seizure focus. The system is intended to reduce the frequency of seizures in patients with epilepsy. It is indicated for use as an adjunctive therapy in individuals 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more antiepileptic medications.

Patients with medically intractable partial onset seizures who are not adequately served by available therapies need new treatments.[1] These patients know the risks of seizures and the wide-ranging impact of epilepsy on their family and themselves. They have already accepted the sometimes considerable risks of multiple different treatments in the hope of improved seizure control and quality of life. Unfortunately, available therapies are not of sufficient help to all. The RNS System provides the potential for reduced seizure frequency and improvement in quality of life without risks to neuropsychological function. The RNS System provides another treatment option for persons with medically intractable partial onset seizures who have failed, are not candidates, or do not choose to pursue other treatments, such as additional antiepileptic medications (AEDs), the Vagus Nerve Stimulator (VNS), or epilepsy surgery.

1.2 Background

Epilepsy is a brain disorder characterized by recurrent, unprovoked seizures. At least 1% of the population has epilepsy, making it one of the most common serious neurological disorders.[1] Seizures occur when brain function is disrupted by abnormal electrical activity. In partial (or focal-onset) epilepsy, the most common type of epilepsy in adults, seizures begin in a specific region or regions of the brain and often spread to involve other regions or even all of the brain. Symptoms of the seizure depend on where the seizure starts and how far the seizure spreads. A partial onset seizure can cause temporary loss of motor function or sensation, abnormal movements, confusion, loss of consciousness, and convulsions (generalized tonic clonic or grand mal seizures). These seizures are not only disruptive, distressing and embarrassing, but often result in injuries such as tongue bites, broken teeth, abrasions, lacerations, burns, drowning, and falls. In addition, many patients have after-seizure (post-ictal) symptoms such as fatigue, headache, memory loss, confusion, and depression that persist for minutes, hours, or even days.

The goal of epilepsy treatment is to control seizures, avoid antiepileptic medication side effects, and to help people with epilepsy and their families achieve the highest possible quality of life. A number of antiepileptic medications are available; however, 30 to 40% of patients continue to have seizures, life-impacting antiepileptic medication side effects, or both. These individuals have intractable epilepsy, defined by the International League Against Epilepsy as

> "a failure to control seizures after 2 seizure medications that have been appropriately chosen and used."[2]

In addition to the acute consequences of seizures, patients with medically intractable epilepsy must deal with the chronic consequences of seizures. Among these are cognitive deterioration, including problems

with memory, attention and concentration, depression and anxiety, and death. The mortality rate for patients with epilepsy is 1.6 to 3 times higher than for those without epilepsy.[3]

Some patients with medically intractable partial onset seizures may be candidates for the Vagus Nerve Stimulator (VNS) or for surgical removal of the seizure focus. However, these treatments are not appropriate or helpful for all patients. Therefore, there is an urgent and unmet clinical need for additional therapies for partial onset seizures. According to the Institute of Medicine (2012),

> "New treatment options are needed for those whose epilepsy does not respond to available treatments or who have unacceptable treatment side effects." [1]

The RNS® System addresses this unmet clinical need by providing a novel treatment option for the more than 500,000 patients in the U.S. with medically intractable partial epilepsy.

1.3 Device Description

The RNS System is the first closed loop responsive brain stimulator designed to treat partial onset seizures. A cranially implanted programmable Neurostimulator senses and records brain activity through electrode-containing leads that are placed at that patient's seizure focus. The Neurostimulator detects electrographic patterns previously identified by the neurologist or neurosurgeon as abnormal, and then provides brief pulses of electrical stimulation through the leads to interrupt those patterns. The typical patient is treated with a cumulative total of 5 minutes of stimulation a day.

1.4 Intended Patient Population

The RNS System is intended for patients 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more antiepileptic medications.

1.5 Study Design

The **Pivotal study** of the RNS System was an FDA approved multi-center, double-blinded, randomized, sham-stimulation controlled study to support the safety and effectiveness of the RNS System. Subjects were followed for a minimum of 3 months pre-implant during which seizure frequency, quality of life, neuropsychological function, and mood data were obtained. Upon meeting implant eligibility, subjects were implanted with the RNS Neurostimulator and Leads. During the first month post-implant, the Neurostimulator was programmed in all subjects to detect abnormal electrographic patterns but not to provide responsive stimulation. At the end of the first month post-implant, subjects were randomized 1:1 to the Treatment group (stimulation on) or the Sham group (stimulation off). During the blinded periods in the study (months 2-5 post-implant), subjects in the Treatment group received responsive stimulation while the Sham group did not. The primary effectiveness endpoint compared seizure frequency during the Blinded Evaluation Period (3rd, 4th, and 5th months post-implant) to the seizure frequency during the Pre-Implant Period (3 month baseline). At the end of the Blinded Evaluation Period, all subjects entered an Open Label period that continued through 2-years post-implant; both Treatment and Sham group subjects received stimulation during this period.

A multi-center, controlled, **Feasibility study** was conducted prior to the Pivotal study. Patients were followed for 2 years after implant to demonstrate safety and provide sufficient evidence for effectiveness to support commencement of a Pivotal study. The Feasibility study also demonstrated that a blinded study could be performed. An open-label **Long-term Treatment study** continues to follow subjects who completed either the Feasibility or Pivotal study so that an additional 7 years of safety and

effectiveness data can be collected. Safety data from the Pivotal, Feasibility and Long-term Treatment studies are combined for open-label safety analyses.

1.6 Methods

The effectiveness endpoints used seizure data collected in daily seizure diaries as is standard practice in trials of epilepsy treatments and in clinical practice. The subject and/or family members recorded the numbers and types of seizures in the diaries. The safety endpoints used adverse event data collected by the investigators at every appointment. Quality of life, mood, and neuropsychological function were assessed at baseline, the end of the Blinded Evaluation Period, and at 1 and 2 years after implant using standardized, validated tools.

The primary effectiveness objective of the Pivotal study was to demonstrate a significantly greater reduction in seizures in the Treatment group compared to the Sham group during the 3-month Blinded Evaluation Period relative to the Pre-Implant Period. The primary effectiveness endpoint was assessed using Generalized Estimating Equations (GEE), which was the analysis method requested by FDA in order to properly account for over-dispersed and highly variable longitudinal seizure count data. The pre-specified GEE model used daily seizure count data. It assumed an overdispersed Poisson variance function to control for the expectedly highly variable seizure count data. Although there was a statistically significant favorable effect of treatment using this GEE model ($p < 0.0001$), it was evident that this GEE model did not adequately account for the large variance in the daily seizure count data within and across subjects. Therefore, seizure data were also analyzed with modifications to the initial GEE model that FDA agreed are appropriate for analyzing seizure count data. This GEE modified model uses seizure data grouped by month, assumes a negative binomial variance function, and includes the clinical characteristics used in randomization.

The primary safety objective of the Pivotal study was to establish that the proportion of RNS System subjects having a serious adverse event (SAE) is no worse than historical comparator rates. For the primary safety endpoint, the SAE rates were calculated for two time periods, the Acute Period (first month post-implant) and the Short-Term Chronic Period (first 3 months post-implant). The comparator rate for the Acute Period is 15%, which is based on the combined SAE risk associated with acute implantation of intracranial electrodes for seizure localization and with epilepsy resective surgery.[4-8] The comparator rate for the Short-Term Chronic Period is 36%, which is the 3 to 4 months SAE rate for deep brain stimulation for treatment of movement disorders. [8-14]

1.7 Subjects

In the Pivotal study, 191 subjects were implanted with the RNS Neurostimulator and Leads. The average subject was 35 years old with more than 20 years of epilepsy, had 34.2 disabling seizures per month (range 3 to 338) and was taking 2.8 antiepileptic medications at enrollment. Nearly 60% had been implanted with intracranial electrodes as part of an evaluation for epilepsy surgery. Half had been previously treated with VNS, an epilepsy surgery with cortical resection, or both.

All 191 implanted subjects were randomized and included in ITT analyses: 189 subjects entered the Blinded Evaluation Period, and 187 subjects completed it. 175 subjects completed the 2-year Pivotal study. In the Feasibility and Pivotal studies combined, 256 subjects were implanted with the RNS Neurostimulator and Leads (Feasibility study n=65; Pivotal study n=191).

1.8 Study Conduct

The Pivotal study established the benefits and risks of treatment with the RNS System through a rigorous multicenter, double-blinded, prospective, randomized and sham-stimulation controlled clinical investigation.

- All subjects receiving implants were randomized and the blinding was successfully maintained.
- 98% of the data were captured for the primary effectiveness endpoint.
- 92% of implanted subjects completed the entire Pivotal study, which included 2 years of post-implant follow-up.
- No subject was lost to follow-up in the Pivotal study.

1.9 Results

1.9.1 Effectiveness: Reduction in Seizures

Treatment with the RNS System resulted in both a statistically and clinically significant reduction in seizure frequency in a significant portion of the target population. The primary effectiveness endpoint of the Pivotal study was met: during the Blinded Evaluation Period, there was a statistically significantly greater reduction in seizures in the Treatment group compared to the Sham group (p = 0.012, GEE, **Table 1**). Averaged over the entire Blinded Evaluation Period, there was a 37.9% reduction in seizures in the subjects receiving responsive stimulation (Treatment group, N=97) compared to a 17.3% reduction in the group receiving sham stimulation (Sham group, N=94). The treatment effect maintains statistical significance with pre-specified GEE sensitivity analyses, pre-specified analyses with exclusion of the few subjects with significant protocol deviations, pre-specified analyses with imputation for missing data, and analyses with exclusion of extreme data. Bootstrap analyses further demonstrate the reliability and reproducibility of the results.

The effect of treatment was also evaluated by month over the Blinded Evaluation Period. Both the Treatment and Sham groups experienced an initial reduction in seizures after the implant procedure (the implant effect). A reduction in seizure frequency with neurosurgical procedures has been described in the literature.[15,16] As is evident in **Table 1** and **Figure 1,** the Treatment group continued to improve over each month of the Blinded Evaluation Period, whereas the Sham group approached their baseline seizure frequency as the implant effect waned. By the third month of the Blinded Evaluation Period, seizure frequency was reduced by 41.5% in the Treatment group compared to 9.4% in the Sham group (p=0.008, GEE, **Table 1**), further distinguishing the favorable effect of responsive stimulation from an implant effect.

Table 1: Pivotal Study – Seizure frequency percent change: Blinded Evaluation Period

	% change in seizure frequency[1]		
	Treatment (N=97)	**Sham (N=94)**	**P-value[2]**
Entire Blinded Evaluation Period (BEP)	**-37.9%**	**-17.3%**	**0.012**
BEP 1 (Post-op Month 3)	-34.2%	-25.2%	0.279
BEP 2 (Post-op Month 4)	-38.1%	-17.2%	0.016
BEP 3 (Post-op Month 5)	-41.5%	-9.4%	0.008

[1] Using GEE: percent change calculated as $(e^{\beta} - 1)$ 100% where β for the Sham group is the parameter estimate of the Time covariate and β for the Treatment group is the parameter estimate of the Time covariate + the parameter estimate of the Group-by-Time covariate.

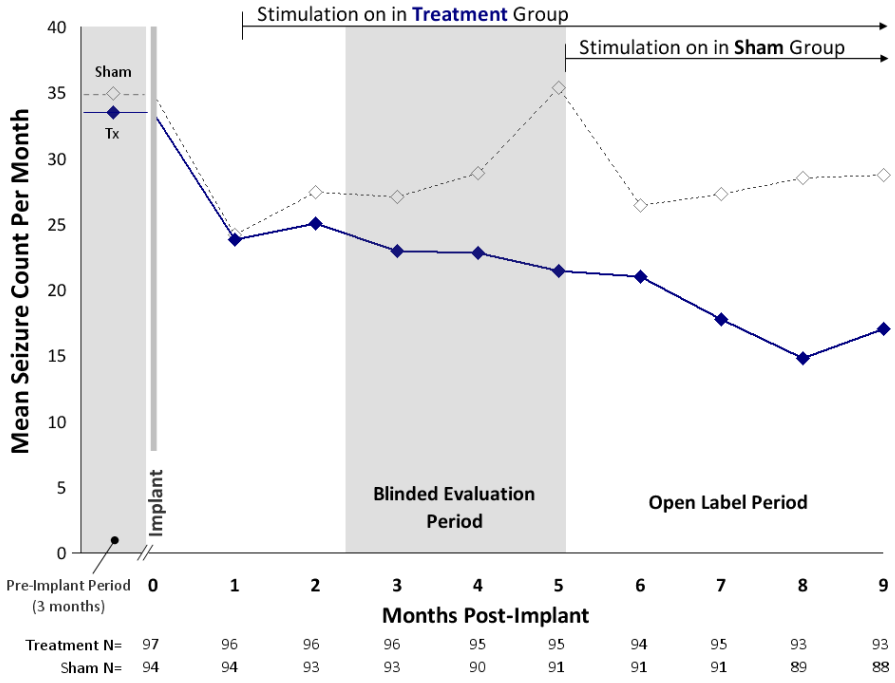
[2] P-value of treatment effect (Group-by-Time interaction).

Data as of 5/12/2011

Secondary effectiveness endpoints support the treatment effect. A statistically significant difference between the Treatment and Sham groups was not demonstrated over the entire Blinded Evaluation Period due to the early implant effect. However, a within-group analysis (not pre-specified in the protocol), showed that there was a statistically significant improvement in the Treatment group in all of the secondary measures of seizure frequency (percentage of subjects with a 50% or greater reduction in seizures, change in mean seizure frequency, and change in days with seizures) relative to baseline. Moreover, the Treatment group's response improved over time in the Blinded Evaluation Period. In contrast, the Sham group's overall seizure frequency response was lower than the Treatment group and did not improve over time.

The favorable effect of stimulation is further evidenced by the immediate and sustained reduction in seizures in the Sham group when responsive stimulation was first delivered in the Open Label Period (**Figure 1**). This reduction was statistically significant (p = 0.04 compared to baseline). Neither Treatment nor Sham subjects were ever told to which group they had been randomized during the Blinded Evaluation Period, so this effect in the Open Label Period is unlikely due to a "placebo" response. Rather, this demonstrates the favorable effects of stimulation independent of the effect of the implant procedure.

Figure 1: Pivotal Study – Mean seizure count per month: Pre-Implant Period through 9 months



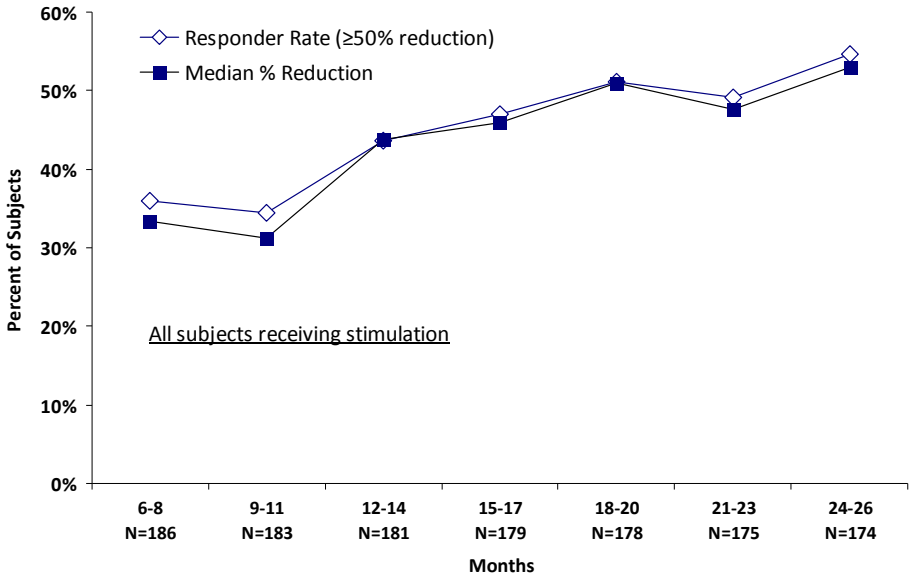
N = number of subjects in Sham group for whom any seizure data are available during that interval.

Data as of 5/12/2011

The effectiveness of responsive stimulation was sustained over years of follow-up. Seizure frequency continued to improve over the Open Label Period of the Pivotal study (**Figure 2**) and was sustained over the Long-term Treatment study (**Figure 3)**. In the Pivotal study, the percentage of subjects with a 50% or greater reduction in seizures (responder rate) was 44% at 1 year and 55% at 2 years. The median

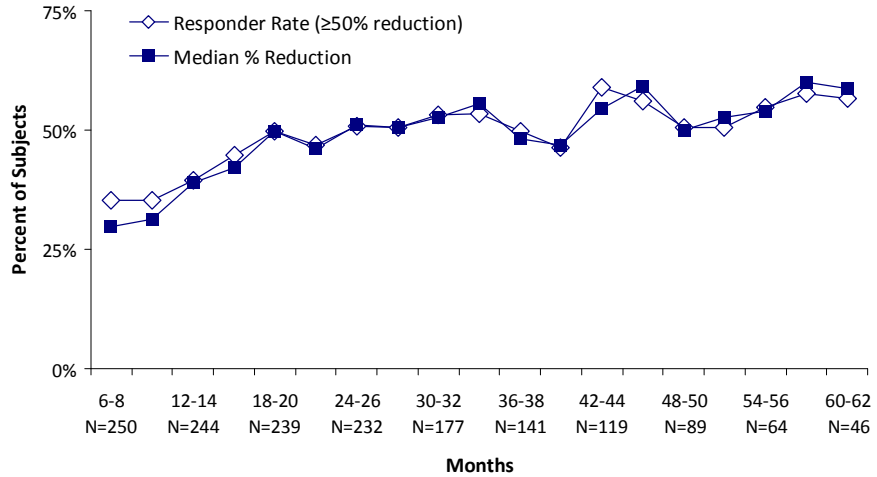
percentage seizure reduction at 1 year was 44% and at 2 years was 53%. Estimates of the slope of improvement through 2 years in the Pivotal study for both of these effectiveness measures are statistically significant ($p < 0.001$, GEE (**Figure 2**). At 3 and 4 years after implant (the Long-term Treatment study), the median percent reduction in seizures was maintained at about 50% (**Figure 3**) and was sustained in those subjects who had longer follow-up as of May 12, 2011. In addition, 27% of subjects participating in any RNS System study experienced at least one 3-month period of seizure freedom and 14.5% had at least one 6-month seizure free period.

Figure 2: Pivotal Study – Responder rate and median percent reduction in seizure frequency: Open Label Period



Includes all subjects for whom any data are available for each 3 month period.
Data as of 5/12/2011

Figure 3: Combined Studies – Responder rate and median percent reduction in seizures: all subjects through LTT



Data combined from Feasibility, Pivotal and Long-term Treatments studies.
Includes all subjects for whom any data are available for each 3 month period.
Data as of 5/12/2011

1.9.2 Effectiveness: Quality of Life

A number of aspects of quality of life were improved in the subjects treated with the RNS System as measured by a validated and widely used inventory of quality of life in epilepsy (the QOLIE-89). In the Pivotal study, there were statistically significant over-all group improvements at 1 and 2 years after implant in the overall QOLIE-89 score, as well as in 9 of 17 QOLIE-89 scales including memory, language, attention/concentration and medication effects (**Table 2**). There was no significant decline in any scale.

Table 2: Pivotal Study – Significant changes in QOLIE-89 primary scale scores at 1 or 2 years

Overall/Primary Scale (T-scores)	1 Year Post-Implant Change from Baseline			2 Years Post-Implant Change from Baseline		
	N	mean ± SD	P-value[1]	N	mean ± SD	P-value[1]
QOLIE-89 Overall Score	166	3.57 ± 8.89	<0.001	154	3.99 ± 10.37	<0.001
Seizure Worry	167	4.54 ± 9.81	<0.001	155	5.22 ± 9.96	<0.001
Health Discouragement	165	4.76 ± 10.92	<0.001	153	4.97 ± 11.03	<0.001
Memory	165	3.09 ± 8.73	<0.001	153	3.06 ± 9.50	<0.001
Language	164	3.53 ± 11.40	<0.001	152	3.66 ± 12.04	<0.001
Attention/Concentration	167	4.36 ± 9.10	<0.001	155	4.22 ± 9.99	<0.001
Work/Driving/Social Function	167	3.31 ± 9.33	<0.001	155	4.07 ± 9.85	<0.001
Energy/Fatigue	167	2.49 ± 9.62	0.001	155	2.08 ± 9.85	0.009
Overall Quality of Life	167	2.16 ± 9.86	0.005	155	1.68 ± 10.35	0.046
Role Limitation - Physical	165	2.46 ± 11.23	0.006	153	3.37 ± 13.06	0.002
Health Perceptions	165	1.52 ± 8.51	0.023	153	0.69 ± 7.36	0.245
Medication Effects	167	1.46 ± 10.00	0.061	155	2.04 ± 10.31	0.015

[1] Paired t-test.

Analysis includes subjects (N) with assessments available at Open Label and Baseline time points.

Data as of 5/12/2011

In addition to group improvements in QOL, more than one-third of the individual subjects had clinically significant improvements in the overall QOLIE-89 score at 1 and 2 years as well as in a number of the subscales of quality of life that are most severely impacted in persons with intractable partial onset seizures (**Table 40 of Appendix 15.7**). A clinically significant improvement is defined as an increase in the T-score of ≥ 5 points, which is equivalent to an improvement of ≥ 0.5 SD from baseline.[17-19]

1.9.3 Safety

The safety profile of the RNS System is acceptable and the risks can be defined and quantified based on adverse event data collected in 256 subjects in the Feasibility, Pivotal, and Long-term Treatment studies (over 903 patient implant years and 819 patient stimulation years of data). Treatment with the RNS System is well tolerated and acceptably safe, especially considering the risks of alternative treatments and the risks of doing nothing.

The primary safety endpoints in the Feasibility and Pivotal studies were met: the rate and type of serious adverse events (SAEs) during the first month (Acute Period) after implantation and during the first 3 months (Short Term Chronic Period) after implantation of the RNS Neurostimulator and Leads were comparable to pre-specified historical comparators. In the Feasibility study, the comparator was the expected rate of SAEs with deep brain stimulation (DBS) for treatment of movement disorders. For the Pivotal study, the comparators were the expected rates of SAEs with implantation of intracranial electrodes and epilepsy surgery and of DBS for treatment of movement disorders.

Safety and tolerability of stimulation were demonstrated during the blinded periods of the Pivotal study (Stimulation Optimization and Blinded Evaluation Period), during which there was no difference between the Treatment and Sham groups in the overall percentage of subjects experiencing an adverse event. The only specific type of adverse event that was different between the groups was toxicity related to antiepileptic medications (therapeutic agent toxicity) which was more frequent in subjects in the Sham group (6 mild events in 6 subjects in the Sham group, 0 in the Treatment group).

The RNS System is acceptably safe over the longer-term. No unanticipated device-related SAEs occurred in any of the studies. Adverse events were consistent with the risks associated with epilepsy, and the risks of alternative treatments and procedures. Adverse events did not increase in frequency or type over time, with an average patient follow-up of 3.3 years (**Table 3**).

Table 3: Combined Studies – SAEs in ≥ 2.5% of subjects through 5 years[1]

	Year 1 N=256	Year 2 N=246	Year 3 N=235	Year 4 N=148	Year 5 N=85
Related to implanted device					
Implant site infection	2.3%	0.4%	2.6%	1.4%	--
Medical device removal[2]	0.4%	1.6%	0.9%	1.4%	1.2%
Premature battery depletion[3]	1.6%	2.4%	0.4%	--	--
Lead damage	2.0%	0.8%	0.9%	--	--
Lead revision	1.6%	1.2%	--	--	--
Related to seizures					
Increase in complex partial seizures	4.7%	1.2%	0.4%	0.7%	1.2%
Increase in tonic clonic seizures	2.0%	2.0%	1.7%	1.4%	--
Exacerbated tonic clonic seizures	2.0%	1.2%	0.9%	--	1.2%
Other Serious Adverse Events					
EEG monitoring	2.3%	3.7%	3.0%	1.4%	4.7%
Antiepileptic drug toxicity	1.6%	1.2%	--	--	1.2%
Death	1.6%	1.2%	0.4%	0.7%	--

[1] Includes device-related and not device-related events.
[2] Other than for routine neurostimulator replacement procedures.
[3] Occurred with battery from manufacturer that is no longer used.
Data as of 5/12/2011

1.9.3.1 *Hemorrhage*

Adverse events related to intracranial hemorrhage with the RNS System across the combined studies were not different or more frequent than those reported in the published literature for implantation of intracranial electrodes for epilepsy surgery evaluation (1.5-2.0%),[20] epilepsy surgery (5%),[21,22] or with DBS for treatment of movement disorders (3-10%).[23-28] The rate of subjects experiencing SAEs related to hemorrhage in the acute post-operative period, whether device-related or not, was 1.6% and the rate over all the study periods was 4.7% (12/256 subjects) over 903 implant years (event rate = 0.013 per implant year). The SAEs related to hemorrhage in 5 of the 12 subjects were attributed to seizure related head trauma. Six of the 12 subjects required no surgical intervention, 5 had a hematoma evacuated, and 1 subject had the Neurostimulator and Leads explanted. Nine of the subjects experienced no neurological sequelae, 1 subject had mild hand weakness, 1 had exacerbation of a preexisting memory deficit, and 1 subject had an ongoing headache.

1.9.3.2 *Infection*

The rate of SAEs related to implant site infection across the combined studies was comparable to rates reported in the literature for implantation of intracranial electrodes for an epilepsy surgery evaluation (1.1 to 3.5%),[4,6,8,29] epilepsy surgery (5%),[21] or DBS for treatment of movement disorders the first year after implant (10%).[28] SAEs related to infection occurred in 2.0% of the 256 patients in the acute post-operative period and 7.0% over the 903 patient implant years (event rate = 0.022 per implant year). 4.3% of subjects had the Neurostimulator and Leads explanted because of infection. No case of sepsis, meningitis or parenchymal infections occurred, and there were no reported adverse neurological consequences related to infection.

1.9.3.3 *Mood and neuropsychological function*

Mood and neuropsychological function were secondary safety endpoints. There was no adverse effect of treatment with the RNS System on neuropsychological function or mood. There was no difference between the Treatment and Sham groups in any of the neuropsychological inventories or in the inventories of mood at the end of the Blinded Evaluation Period. There was no deterioration in any measure compared to baseline at the end of the Blinded Evaluation Period or at 1 and 2 years after implant.

1.9.3.4 *Deaths*

Deaths were adjudicated by the Sudden Unexplained Death in Epilepsy (SUDEP) Analysis Committee and reviewed by the Data Monitoring Committee. 11 occurred deaths in the 256 subjects in the combined studies over 1103 patient years of stimulation and 1195 patient years of implant experience (as of October 24, 2012). Causes of death were suicide (n=2; 1 was not receiving stimulation), status epilepticus (n=1), lymphoma (n=1), and definite, probable, or possible SUDEP (n=7; 2 were not receiving stimulation). The risk for SUDEP in subjects treated with the RNS System cannot be confidently estimated until 1500 patient years of data are accumulated. However, based on the current experience, the risk is not increased above the comparator rate of 9.3 SUDEP events/1000 patient years in a population of persons with similarly severe partial epilepsy.[30] The current rate of SUDEP for subjects receiving responsive stimulation (pre-specified analysis) is 4.5/1000 [95% CI: 1.9 – 10.9] patient years. The rate for all subjects implanted with the RNS System (treated and not treated with responsive stimulation) is 5.9/1000 [95% CI: 2.8 – 12.3] patient years.

1.9.4 Retention rate

The high retention and low withdrawal rates in the studies suggest that subjects perceived that treatment was of benefit. 92% of implanted subjects in the Pivotal study completed the entire two year study. 97% of subjects eligible to enroll in the Long-term Treatment study after completion of the Pivotal or Feasibility studies did so, and 93% of subjects chose to have their Neurostimulator replaced at end of battery service.

1.10 Conclusions

The RNS System is a first-of-a-kind approach for treating partial onset seizures in patients with medically intractable epilepsy who have seizures that originate from one or two locations in the brain. The RNS System's novel closed-loop technology provides targeted responsive stimulation to the region of the brain from which seizures arise when abnormal electrographic activity (as defined by the physician) occurs. Total stimulation time is typically 5 minutes a day. Treatment with the RNS System is non-destructive and reversible.

The effectiveness of the RNS System in treating medically intractable partial onset seizures was demonstrated in a well-designed and rigorously conducted double-blinded, randomized, sham stimulation controlled Pivotal study. The primary effectiveness endpoint was met, establishing that patients receiving responsive stimulation experienced a significantly greater reduction in seizure frequency than those who received sham stimulation. Seizure frequency dropped by 37.9% in the Treatment group compared to 17.3% in the Sham group averaged over the Blinded Evaluation Period ($p = 0.012$). In the final month of the Blinded Evaluation Period, when the implant effect had largely waned, the seizure reduction was 41.5% in the Treatment group and 9.4% in the Sham group. One and two year reductions in seizures of about 50% in the RNS System Pivotal study and over 50% in the Long-term Treatment study establish that the treatment response is long-lasting and clinically meaningful.

These studies establish that the safety profile of the RNS System is acceptable, with sufficient safety experience to identify and quantify the risks of treatment. There was no difference in the overall adverse event rate between Treatment and Sham subjects during blinded periods. There were no negative effects on neuropsychological function or mood. Safety data combined from all RNS System studies and a review of the related published literature demonstrate that serious adverse events, including infection and hemorrhage, were anticipated and were not higher than with comparable procedures.

The benefits of treatment with the RNS System for patients with medically intractable partial onset seizures are the potential for reduced seizure frequency and improvement in quality of life, with acceptable safety and without risks to neuropsychological function and mood. The RNS System provides another treatment option for a population of patients for whom there is a compelling unmet need.[1]

2 DEVICE DESCRIPTION

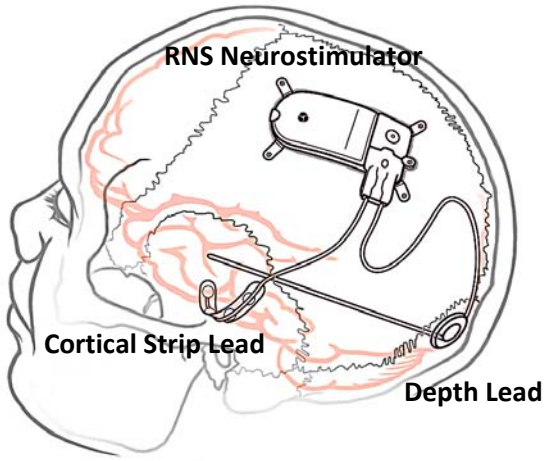
2.1 Indication for Use

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 from no more than two foci that are refractory to two or more antiepileptic medications.

2.2 The RNS System

The RNS System is the first device to provide closed loop responsive brain stimulation. A cranially implanted programmable Neurostimulator is connected to one or two Depth and/or subdural Cortical Strip Leads that are surgically placed in the brain at one or two seizure foci (**Figure 4**). The location of the leads is determined by standard diagnostic testing to identify the seizure focus. Non-implanted components of the RNS System are the Programmer; a patient Remote Monitor; and an Internet based interactive database (the Patient Data Management System, PDMS) (**Figure 9**).

Figure 4: Implanted RNS Neurostimulator and Leads



2.2.1 The RNS Neurostimulator

The RNS Neurostimulator contains electronic circuitry and a battery that are hermetically sealed within a flat curved titanium enclosure (**Figure 5**). The Neurostimulator is implanted within a craniectomy, is contained within the skull, and is covered by the scalp.

Figure 5: Neurostimulator and Leads

As illustrated in **Figure 6,** a Ferrule (a titanium tray, which is secured to the skull) mechanically supports and secures the Neurostimulator in the skull so that there is no direct contact of the Ferrule or Neurostimulator with the brain. The Ferrule is placed in a full-thickness craniectomy that corresponds to the size and shape of the Neurostimulator. The Ferrule is secured in the skull (bone) just above the dura mater (connective tissue below the bone).

The proximal portion of the Leads is placed within the Neurostimulator's connector assembly, and the Neurostimulator is secured within the Ferrule (**Figure 7**).

The procedure to place the Neurostimulator and Leads takes about 4 hours. When a replacement is required, the Neurostimulator is lifted from the Ferrule, the Leads are connected to the new Neurostimulator, and the new Neurostimulator is placed within the existing ferrule. The replacement can be accomplished typically within one hour.

Figure 6: Placement of Ferrule in the craniectomy

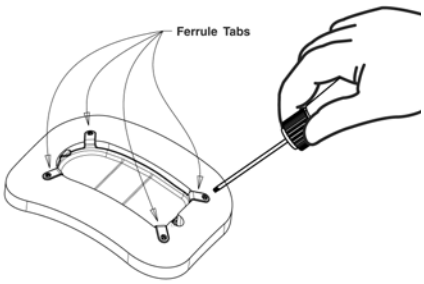
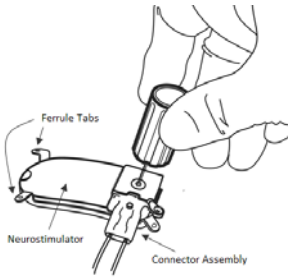


Figure 7: Placement of Neurostimulator within Ferrule



The Neurostimulator continuously senses electrocorticographic (ECoG) activity through the Leads. In response to the detection of patterns previously identified by the physician as abnormal (such as epileptiform activity), the Neurostimulator delivers short trains of constant current, charge balanced pulses (responsive stimulation) to one or two epileptic foci. Detection and stimulation parameter programming is non-invasively adjusted by the physician to optimize control of clinical seizures for each patient.

In addition to continuous ECoG sensing, detection and stimulation, the Neurostimulator stores information on the time and date of detections and stimulation. The physician can also program the Neurostimulator to store records of the electrographic activity immediately before and after pre-specified events such as a detection of abnormal electrical activity, responsive stimulation, a Magnet swipe (used by the patient to indicate a clinical event), or according to time of day. The physician can review this information at any time using the Patient Data Management System (PDMS), which is described below.

2.2.2 The RNS Leads

There are 2 types of RNS Leads. Depth Leads are implanted into the brain and Cortical Strip Leads are placed on the surface of the brain to provide an interface through which electrical activity of the brain can be sensed and recorded by the Neurostimulator and through which responsive electrical stimulation can be delivered (**Figure 8**). The Leads have a flexible, silicone lead body that encloses four insulated wires, and have four platinum/iridium electrodes at their distal end. The proximal end for both the Depth and Cortical Strip Leads has four contacts that connect to the Neurostimulator. The Cortical Strip

Leads are typically placed through a small craniectomy and the Depth Leads are placed through a burr hole using standard stereotactic techniques.

Figure 8: Electrodes on the distal end of the Cortical Strip Lead and Depth Lead

2.2.3 Programmer

The RNS Programmer communicates with the Neurostimulator using a Wand with a short-range wireless radiofrequency link. The physician uses the Programmer to program detection and stimulation in the Neurostimulator and to view the electrocorticogram in real-time. In addition, the Programmer tests the integrity of the Neurostimulator and Leads and uploads data from the Neurostimulator such as the time of detections and stimulations. The Programmer can also use a secure Internet connection to transmit these data to the PDMS for storage and later physician review.

2.2.4 Remote Monitor

The Remote Monitor is a home-use monitoring device that utilizes a Wand to communicate with an implanted RNS Neurostimulator using a short-range wireless radiofrequency link. A patient or caregiver uses the Remote Monitor to collect data from the Neurostimulator, and then transmits these data using a telephone line or the Internet by way of a secure connection to the Patient Data Management System (the PDMS). The uploaded data are accessible for review on the Internet by physicians through the PDMS web site using a secure web browser. This allows the patient to share information with the physician between clinic visits. The Remote Monitor cannot be used by the patient to reprogram the Neurostimulator.

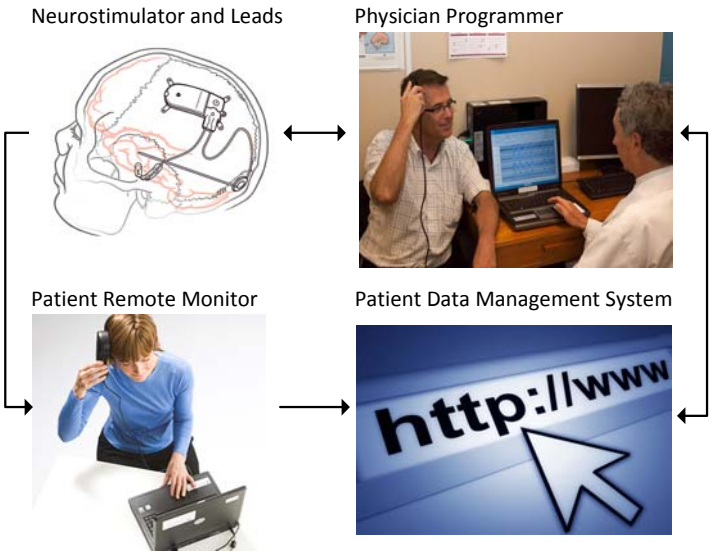
2.2.5 Patient Data Management System (PDMS)

The PDMS stores Neurostimulator and patient data for review by a physician or other authorized user. Data obtained by the RNS Programmer or the patient Remote Monitor are sent to the PDMS and stored. These data include information regarding detections and stimulations, stored electrocorticogram recordings, programming history and Neurostimulator self-diagnostic information such as battery voltage and lead impedances. Data transferred using the PDMS are encrypted to ensure security and integrity of the data.

2.2.6 Magnet

A Magnet is provided to the patient that can be swiped over the Neurostimulator to trigger the storage of a record of the date and time of the Magnet swipe. If desired by the physician, the electrocorticogram recording will also be stored. This allows the patient to store Neurostimulator information when clinical seizures occur. Holding the magnet over the Neurostimulator stops stimulation therapy.

Figure 9: The RNS System



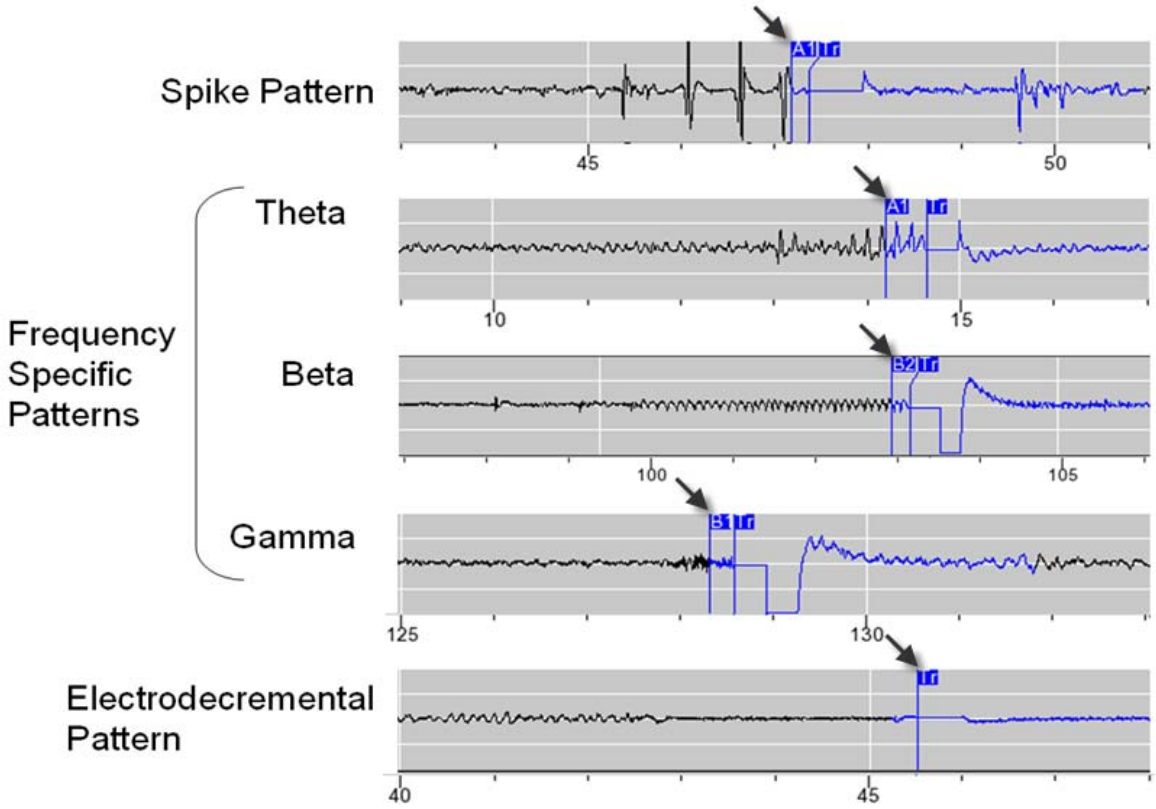
2.3 Clinical Use of the RNS System

The physician programs the Neurostimulator to detect and to stimulate. Detection is programmed after the physician decides which electrocorticographic (ECoG) patterns should be detected. Neurologists trained in EEG already possess the skills to identify the abnormal electrographic patterns to detect. Stimulation is programmed initially to standard settings and then adjusted as necessary, similar to standard practice with the VNS and with DBS for treatment of movement disorders.

Once the Neurostimulator is programmed, the physician can review Neurostimulator information on the Programmer or on the PDMS. Information stored on the Neurostimulator is transmitted to the PDMS from the Programmer (by the physician) or from the Remote Monitor (by the patient). The physician can see the date and time of detections and stimulations, prior detection and stimulation programmings, and can review stored ECoGs to see the actual detections and the effects of stimulation. Patient Magnet swipes (usually indicating that a seizure has occurred) can also be reviewed. Depending on the patient's clinical response, the physician decides whether to adjust detection and stimulation programmed settings.

The physician usually programs the Neurostimulator to detect epileptiform activity. Epileptiform ECoG activity is typically characterized by spikes or by changes in background frequency or amplitude. Examples of electrographic patterns as detected using the RNS System are shown in **Figure 10**. The arrow indicates detection of epileptiform activity. "Tr" indicates delivery of responsive stimulation.

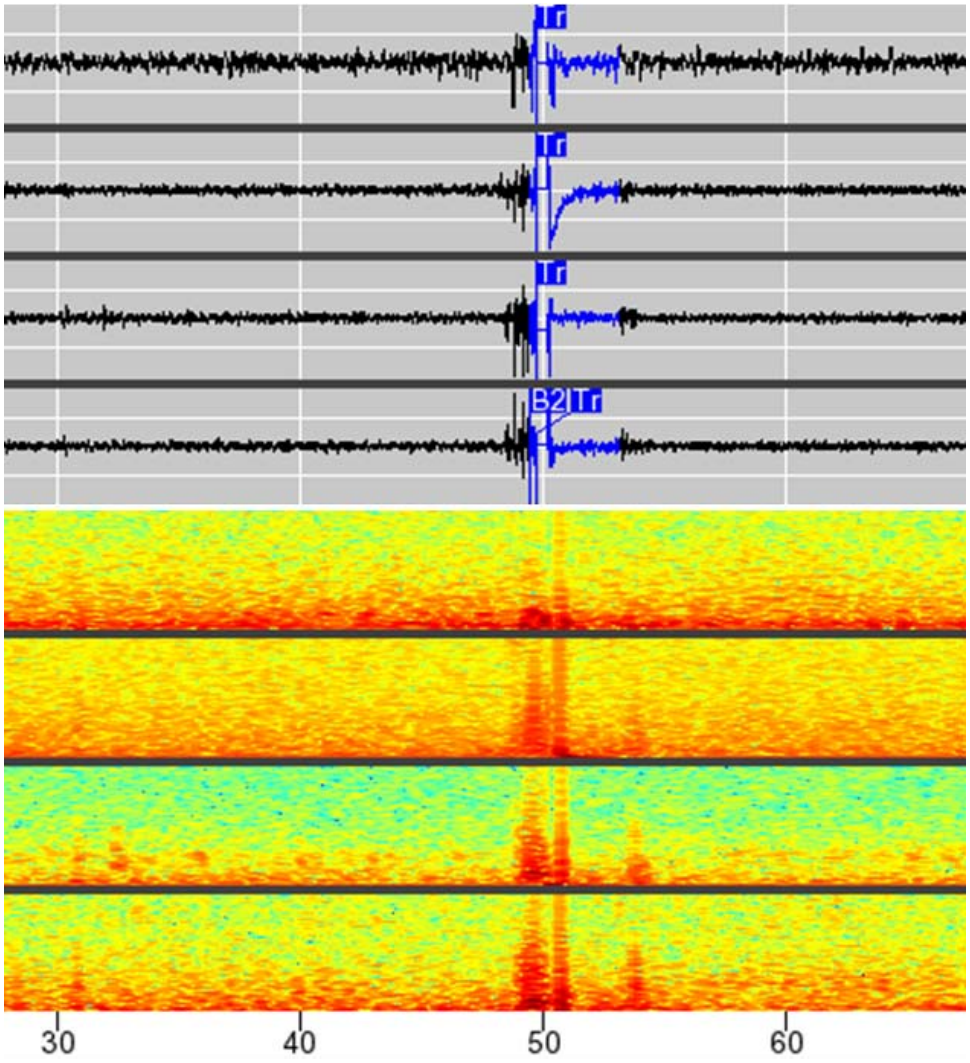
Figure 10: Typical electrographic patterns detected by the Neurostimulator



Examples of different types of electrographic patterns as detected in real-time using the implanted RNS Neurostimulator as displayed on the PDMS. There is an artifact in the ECoG recording when responsive stimulation is delivered and immediately after.

Another typical epileptiform discharge stored by the Neurostimulator and displayed on the Programmer and on the PDMS is shown in **Figure 11**. In addition to the ECoG, PDMS provides frequency spectograms (fast Fourier transform) as another way of visualizing ECoG activity. In this example, the Neurostimulator has been programmed by the physician to detect a sudden burst of high amplitude sharply contoured activity considered typical of this patient's interictal epileptiform activity. The vertical lines identify the time of detection; stimulation is delivered immediately following detection.

Figure 11: Detected electrographic seizure with frequency spectogram



This event was stored using the Neurostimulator with detection and stimulation enabled. The upper panel displays the ECoG for the four sensing channels. The lower panel shows the frequency spectrograms (fast Fourier transform) for the same four channels. The display is from the PDMS.

The Neurostimulator delivers current-controlled, charge-balanced biphasic pulses. Stimulation parameters that can be adjusted include frequency (1 to 333 Hz), current amplitude (0.5 to 12 mA), pulse width per phase (40 to 1000 µs), and burst duration (10 to 5000 ms). The initial recommended programming settings are 200 Hz, 160 µs, 100 ms burst duration, and a current amplitude to achieve a charge density between 0.5 and 2.0 µC/cm^2. The RNS System does not permit the Neurostimulator to be programmed so that the charge density exceeds 25 µC/cm^2, ensuring that the charge density remains within the safe range.[31]

3 SUMMARY OF PRE-CLINICAL STUDIES

Laboratory and animal testing of the RNS System were performed to assure conformance to design specifications. Verification and validation were conducted to provide sufficient data to support the intended use of the RNS System. All verification tests and validation activities were performed successfully and met their acceptance criteria. Study results, including biocompatibility and animal studies, are presented in the Summary of Safety and Effectiveness Data (SSED) provided in **Appendix 15.8**.

4 REGULATORY HISTORY

International

There are no international clinical study data for the RNS® System and no application for marketing outside of the United States has been submitted or approved.

United States

Beginning in December 2000 NeuroPace initiated a series of discussions with FDA, introducing them to responsive neurostimulation technology. In pre-IDE meetings in September 2002 and March 2003, NeuroPace met with FDA to reach agreement on the design of the feasibility study and the overall regulatory strategy for the RNS System.

NeuroPace began the series of RNS System clinical investigations by conducting a nonsignificant risk study titled “Prospective Seizure Frequency (PSF) Clinical Investigation” that provided the recruitment pool and the baseline seizure data for the Feasibility study.

Three clinical investigations of the RNS System conducted under Investigational Device Exemption (IDE G030126) support the safety and effectiveness of the RNS® System in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more antiepileptic medications. The original IDE was submitted in May 2003 and full FDA approval was granted September 2003 for the Feasibility study. An IDE supplement was submitted in May 2005, followed by discussions with FDA, and full approval in November 2005 to commence both the Pivotal and Long-term Treatment studies.

In a Pre-PMA Meeting on March 15, 2010 NeuroPace requested input from FDA regarding the appropriate data and statistical analyses to be included in the PMA submission. NeuroPace submitted the PMA application with the requested data and analyses on July 2, 2010. FDA accepted the PMA for filing on November 9, 2010 and a Day-100 meeting took place between FDA and the company on February 22, 2011. FDA issued a major deficiency letter on June 14, 2011 and NeuroPace responded on April 20, 2012 providing clarification on clinical and statistical issues. NeuroPace continued communications with FDA with the objective of having the PMA considered by an expert advisory panel. On October 5, 2012 FDA notified NeuroPace that the PMA for the RNS® System was being referred to the Neurological Device Panel for its review and recommendation.

5 CLINICAL LITERATURE REVIEW

5.1 Disease Background

Epileptic seizures occur when abnormal electrical activity suddenly disrupts brain function. Although there are a number of causes of epilepsy and several different types of seizures, most adults have partial onset seizures that arise from one or two foci in the brain. Although these seizures are called partial onset, their impact on the patient is profound. These seizures can cause loss of motor, sensory or language function, confusion, loss of awareness and even generalized tonic clonic seizures (grand mal or convulsive seizures). Many people are fatigued and confused for hours or even days after a seizure. Uncontrolled seizures bring social disability, loss of driving privileges, and limit education and employment opportunities. In addition, these patients live with the constant fear that a seizure might occur.

Although there are a number of treatments for epilepsy, approximately 30% of the more than 2.2 million persons in the United States with epilepsy do not have their seizures controlled despite treatment with antiepileptic medications. A similar percentage experience medication related side effects that impact quality of life, such as impaired cognition, fatigue, problems with coordination, nausea or other gastrointestinal symptoms. These patients may consider the VNS or epilepsy surgery. Although these treatments, like antiepileptic medications, carry some risk, the risk and disability imposed by frequent seizures are generally higher. However, not all patients are candidates for these treatments and these treatments do not always work. This leaves at least 500,000 adults with partial onset seizures in the U.S. who have no other treatment options.

5.2 Risks and Benefits of Alternative Treatments

5.2.1 Antiepileptic Medications (AEDs)

AEDs are the first-line of treatment for persons with epilepsy but 30 to 40% of persons with partial onset seizures do not achieve seizure control. According to the International League Against Epilepsy, patients who fail treatment with 2 different AEDs are considered to be medically intractable[2,32,33] and the chance of complete seizure control with subsequent trials of AEDs is less than 5%.[34,35]

Approximately 50% of persons have side effects from AEDs; side effects are the most common reason for discontinuation (**Appendix 14.2**). These include problems with cognition, coordination and mood.[36-38] The frequency and severity of these types of side effects is higher for patients who require higher dosages and those who are treated with multiple AEDs concurrently. There are also general health risks of AEDS that include allergic reactions,[39-41] bone loss,[42] changes in body weight and metabolism[43] and adverse fetal effects.[44,45]

Despite introduction of more than a dozen new AEDs for treatment of partial onset seizures since 1993, efficacy rates are not substantially improved.[40,41] Median percent reductions in seizures range from 25 to 40% in the blinded periods of randomized controlled trials of AEDs approved as adjunctive treatment of adults with partial onset seizures (**Appendix 14.2**). Therefore, there is still a pressing need for additional treatment options.[1]

5.2.2 The Vagus Nerve Stimulator (VNS)

The VNS (Cyberonics, Inc.), the only device approved in the U.S. for the treatment of epilepsy, is indicated for use as an adjunctive therapy in reducing seizure frequency in adults and adolescents over 12 years of age with partial onset seizures that are refractory to AEDs. The VNS provides scheduled (nonresponsive) stimulation to the left vagus nerve using a pulse generator in the left pectoral region connected to a lead tunneled subdermally from the chest to the left vagus nerve in the neck.

Two randomized, blinded, active control (high stimulation/low stimulation) trials evaluated the median percent reduction in seizures over a 12-week efficacy period. The median percent reduction in daily seizures was 23 to 24% in the high stimulation group and 6 to 21% in the low stimulation group. The reduction in seizures in an open label extension was 31% at one year and 41% at 2 years.[46]

The most common types of adverse events in the randomized and extension phases of the trials were voice alteration (50% of subjects), increased cough (41%), paresthesia (28%), pharyngitis (27%), nausea (19%) and dyspnea (18%). In a U.S. based randomized double-blind controlled study[47] infection occurred in 11.6% and infection leading to explantation occurred in 1.8%.

Based on post-approval medical device reports (MDR) for the VNS epilepsy indication submitted to FDA from July 1, 1997 through October 8, 2004, serious injuries were reported in 0.9% of patients.[48] The most common serious injuries were related to infection and increased seizure activity. Less common serious injuries were due to vagus nerve injury, respiratory injuries including sleep apnea, dyspnea and aspiration, cardiac events including changes in heart rhythm, changes in blood pressure and asystole, chest and neck pain, gastrointestinal events including dysphagia and weight loss, and depression. Forty-two percent of these serious events were associated with device explantation.

5.2.3 Epilepsy Surgery

Traditional epilepsy surgery to remove the seizure focus is an important therapeutic option for some persons with medically intractable partial onset epilepsy.[21,49] The best candidates for resective surgery are those with a seizure focus that can be precisely localized to a well-defined area of the brain that can be removed without incurring unacceptable neurological deficits. Anterior temporal lobectomy (removal of the hippocampus and a portion of the anterior temporal lobe) is the most common and successful epilepsy surgery procedure and is suitable for patients with seizures localized to the mesial temporal lobe. In carefully selected candidates, 1-year seizure-freedom is achieved in 65% to 77% [21,50] although this rate may drop with time.[51] Other types of epilepsy surgery are less successful. Surgery to resect a well-defined lesion in the brain (such as a tumor or vascular malformation) achieves 1-year seizure remission in only 56% of patients. Non-lesional resections outside of the temporal lobe have a lower chance for meaningful improvement.[21]

Not all persons with medically intractable epilepsy are candidates for resective surgery. For example, some persons with mesial temporal lobe epilepsy, particularly those with dominant hemisphere or bilateral mesial temporal lobe onsets, are not candidates because of the risk for significant memory impairment with removal of the mesial temporal lobe(s).[21] Others have seizure onsets that cannot be resected without risk to vital functional areas, such as those controlling motor, sensory, visual or cognitive function. Risks of traditional epilepsy surgery are discussed below.

5.3 Risks of Comparable Procedures

Patients with medically intractable epilepsy may undergo intracranial surgical procedures such as intracranial monitoring and resective surgery. Therefore, these procedures provide comparative data regarding the risks of intracranial procedures in patients with epilepsy. As there currently are no approved brain stimulation devices for treatment of epilepsy, the experience of deep brain stimulation for the treatment of movement disorders provides a relevant comparator for risks associated with long-term implantation and brain stimulation.

5.3.1 Intracranial Electrodes Implanted for Localization of the Epileptogenic Focus

Depth and subdural strip leads are implanted in some patients with medically intractable epilepsy in order to determine whether these individuals are candidates for epilepsy surgery.[21,52] Electrodes are surgically placed for as long as several weeks to identify the region(s) of seizure onset and/or map areas of brain function.

Retrospective series of patients implanted with intracranial electrodes for diagnostic purposes generally report an overall complication rate in the range of 4% to 7% [8,53,54] but complication rates as high as 25.4% have also been reported.[20] One of the anticipated acute risks of implantation of intracranial electrodes for this diagnostic purpose is hemorrhage, with a risk of 3% to 16%.[6-8,20,55,56] The types of hemorrhages with intracranial leads include acute extradural hematomas in about 2%,[6,7,20,55,56] subdural hemorrhages in 1 to 16%,[6,8,20,55] and intraventricular and intracerebral hemorrhages in 3 to 7%.[28,57-59] Asymptomatic hemorrhages are evident by neuroimaging in 11.8% of patients.[29] Other risks are edema in 0.5% to 2% [6,7,20,55] and acute infection in about 1.1 to 3.5%.[4,6,8,29,60] Adverse neurological events occur in between 1% and 11% of persons implanted with intracranial electrodes for epilepsy surgery evaluations.[6,7,20] Most are transient and include aphasia and dysphasia, cranial nerve abnormalities, hemiparesis, hemianesthesia and visual field deficits. [7,20]

5.3.2 Epilepsy Resective Surgery

The risks of an epilepsy resective procedure include general complications associated with neurosurgical procedures as well as complications specific to the area of the resection. Anticipated complications after neurosurgical procedures in general include postoperative headache and discomfort, swelling local to the incision, neck stiffness, fatigue and sleepiness, deep venous thrombosis, pulmonary embolism and aseptic meningitis.

About 5% of patients undergoing epilepsy surgery have a serious complication.[21,22] Specific anticipated adverse events with epilepsy surgery include hemorrhage, infection, hydrocephalus and neurological complications. In one series,[8] 8.4% of patients had complications, including meningitis (11.4%), deep wound infections that required removal of the bone flap (3.5%), and post-operative hydrocephalus (0.7%). Reoperations because of hemorrhage were required in 3% of patients undergoing a temporal lobe resection in one series.[61] The overall rate of infection is about 5%.[21,22] The overall rate of hemorrhage is 1% to 3%.[21]

Neurological complications, an accepted risk of epilepsy surgery, occur in 3 to 6% of cortical resections for epilepsy,[21,52] including hemiparesis (1.6% to 2.3%)[4,8]. Other risks are visual field deficits,[50] deficits in language due to damage of language cortex, motor or sensory deficits because of disruption of primary or supplementary motor or sensory cortex, and cranial nerve palsies caused by damage to the brain stem.[4,8]

The risk for acute neurological complications after a cortical resection for epilepsy depends on the site and size of the resection.[8] Neurological complications may be higher in patients undergoing extratemporal resections (5.6%) than in temporal resections (1.2%) because extratemporal resections are more likely to include critical functional cortex.[62] For example, 30% of persons undergoing a resection in the parietal lobe had neurological complications including hemisensory loss, hemiparesis, visual field deficits and right-left disorientation.[63] In 7.5%, these neurological complications were permanent. Visual field deficits are anticipated in 55% of persons undergoing a temporal lobectomy.[50]

5.3.3 Deep Brain Stimulation Systems (DBS)

DBS systems are approved in the U.S. for treatment of Parkinson's disease, essential tremor and other movement disorders. The overall rate for adverse events is 15 to 26%.[9,13,58] Implantation related complications range from relatively minor effects such as headache (16.5%),[28] transient confusion (10.7%),[28] or drowsiness, to more serious effects, such as stroke or intracranial hemorrhage leading to permanent neurological sequelae (< 5%).[24-27,64] Three to 10% of patients with DBS for treatment of movement disorders[25,28] have a hemorrhage. Persistent post-operative neurological adverse effects with implantation of DBS Systems for movement disorders are relatively infrequent. However, hemiparesis and/or aphasia because of implant related hemorrhages is described in about 2 to 3% of patients.[25,27] The most common long-term significant complication of DBS is infection; the rate varies across studies from 1.2% to 15.2% of patients.[23-27] The infection rate in 121 patients followed prospectively for one year after implantation of a DBS for Parkinson's disease was 9.9%.[28]

5.4 Specific Risks for Persons with Epilepsy

In addition to the risks that accompany treatments for epilepsy, there are significant risks from intractable seizures. These include psychiatric disorders, impairment of cognitive function, and sudden unexplained death in epilepsy (SUDEP).

5.4.1 Adverse Changes in Seizures

Subjects with partial onset seizures experience seizure fluctuations, even when receiving an effective treatment. In short term (12-16 weeks) randomized double-blind controlled trials of AEDs approved for adjunctive treatment of partial onset seizures, including levetiracetam,[65] lacosamide[66] and gabapentin,[67] 10 - 20% of persons receiving the active treatment reported adverse events related to an increase in seizure frequency.

5.4.2 Status Epilepticus

Persons with epilepsy are at risk for status epilepticus, which is defined as a seizure that lasts more than 30 minutes, or 2 or more seizures without full recovery of consciousness.[68] More than 15% of adults with epilepsy will have at least one episode of status epilepticus [69] and 13% of persons with one episode of status epilepticus will have subsequent episodes.[68]

5.4.3 Depression and Suicidality

Depression and suicidality are prevalent in epilepsy. The risks for these conditions are highest in those with more severe and more frequent seizures.[70-72] The prevalence of depression in persons with medically intractable seizures treated at epilepsy centers is as high as 55%.[70,73-77] Suicidal thoughts were present in 19% of persons with medically intractable epilepsy admitted to an in-patient video-EEG monitoring unit.[78] In addition to suicidal thoughts, there is an increased risk for attempted and

completed suicide.[79,80] The rate of completed suicide in persons with epilepsy is three times higher than in those without epilepsy (SMR 3.5, CI 2.6-4.6).[81]

Suicidality is especially prevalent in persons with epilepsy who are depressed.[79,81] A case-controlled study of persons with epilepsy found that a history of psychiatric disease, especially depression, was associated with a nine-fold increase in risk of suicide.[79]

5.4.4 Cognitive Dysfunction

Symptoms of cognitive dysfunction, especially disturbances in memory, are common in persons with epilepsy. More than half of the adults in a recent survey conducted by the International Bureau for Epilepsy (IBE) reported that cognitive impairment significantly affected their ability to engage in work, education, and leisure activities, and had a negative impact on family and relationships.[82] Memory deficits were documented by neuropsychological testing in more than 50% of persons with partial epilepsy being treated at one epilepsy center.[83] Cognitive dysfunction can be progressive and the severity is related to a longer history of epilepsy, more frequent seizures and higher dosages and/or multiple AEDs.[36,84-86]

5.4.5 Sudden Unexplained Death in Epilepsy (SUDEP)

Mortality is increased as much as three-fold in persons with epilepsy compared to the general population.[87,88] Seizure-related deaths are due to status epilepticus, accidents caused by seizures[89,90] and SUDEP.[91,92] SUDEP is believed to be a consequence of autonomic events triggered by ictal and/or interictal activity leading to cardiorespiratory disturbances. The reported incidence of SUDEP ranges from 6.3 deaths per 1000 person-years in a cohort with refractory epilepsy [93] to 9.3/1000 person-years rate in patients followed in an epilepsy surgery program.[30] Mortality rates for all causes are highest in those with more frequent seizures and those with generalized tonic clonic seizures;[91] therefore, a reduction in seizure frequency, especially generalized tonic clonic seizures, may reduce mortality.

5.5 Summary of Literature Review

The patient with intractable epilepsy who is considering whether to pursue a new treatment weighs the chance for fewer seizures and an improvement in quality of life against the risks of the therapy and the risks of doing nothing. All treatments for partial onset seizures carry risk, whether that is adding or changing the dose of an AED, or treatment with a VNS or with epilepsy surgery. Each seizure also carries a risk. Patients with more frequent seizures have poorer cognitive function, significant increases in anxiety, depression and suicidality, poorer employment status, a lower quality of life and worse overall health than patients with fewer seizures.[72,94,95] Patients do not need to achieve complete seizure freedom in order to experience positive life changes.[96] A reduction in seizure frequency, even without seizure freedom, can improve mood, employment, perceived health and quality of life. [84,97,98]

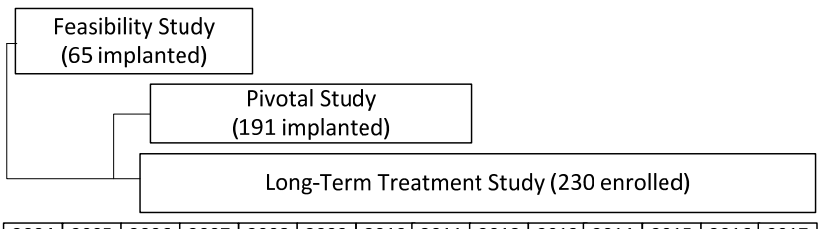
6 SUMMARY OF CLINICAL INVESTIGATIONS

Three clinical investigations of the RNS System support the safety and effectiveness of the RNS® System in reducing the frequency of seizures in individuals with refractory partial onset seizures:

- RNS System Feasibility Clinical Investigation (Feasibility study)
- RNS System Pivotal Clinical Investigation (Pivotal study)
- RNS System Long-term Treatment Clinical Investigation (LTT study)

Figure 12 provides information on the timeline of the studies, the numbers of subjects who were implanted in the Feasibility and Pivotal studies, and the numbers of subjects who have continued into the Long-term Treatment study.

Figure 12: Study Timelines



6.1 Feasibility Study

The **Feasibility study** was designed to demonstrate adequate safety and provide sufficient evidence of effectiveness for the RNS System to support the commencement of a Pivotal study. This prospective, primarily open label study implanted 65 subjects at 12 Comprehensive Epilepsy Centers in the United States. Subjects were followed for 2 years post-implant. The primary safety endpoint was met: the serious adverse event (SAE) rates during the first 3 months post implant were not worse than the pre-specified historical controls (SAE rates with implantation and treatment with DBS for movement disorders). There were no unanticipated device-related SAEs. The effectiveness endpoint was met: the percentage of subjects receiving stimulation who had a ≥ 50% reduction in seizures (responder rate) was greater than the prospectively defined rate to show preliminary evidence for effectiveness. In addition, the study demonstrated that subjects could be randomized to active or sham stimulation while adequately maintaining the treatment blind. Data from the Feasibility study are presented within combined open label effectiveness analyses (**Section 10.2**) and combined safety analyses (**Section 11.2**), which include all study periods. The Feasibility study design, subject demographics, accountability, and results are provided in **Appendix 15.3**.

6.2 Pivotal Study

The multi-center prospective **Pivotal study** was designed to demonstrate reasonable assurance of the safety and effectiveness of the RNS System. This randomized, double-blinded, sham-stimulation controlled study was conducted at 32 Comprehensive Epilepsy Centers in the United States. Subjects were followed for 2 years post-implant. 191 subjects were implanted during this study. The primary effectiveness endpoint was met, demonstrating that the reduction in seizure frequency in subjects randomized to receive responsive stimulation during the Blinded Evaluation Period was significantly greater than that experienced by subjects randomized to receive sham stimulation. The primary safety endpoint was met, demonstrating that the rate of subjects experiencing one or more SAEs did not

exceed the SAE rates for comparator procedures over the first 4 and 12 weeks after implant. The Pivotal study protocol is presented in **Section 7** and Pivotal study results are presented in **Section 10.1** (effectiveness) and **Section 11.1** (safety).

6.3 Long-term Treatment (LTT) Study

The **LTT study** is an ongoing multi-center prospective open label study to assess the long-term safety and effectiveness of the RNS System. Subjects already implanted during the Feasibility or Pivotal study enrolled in the LTT study in order to continue follow-up for up to 7 years. Safety and effectiveness data are collected at 6-month intervals, and data regarding quality of life are collected at yearly intervals. 230 of the 256 implanted subjects enrolled in the LTT study. Data from the LTT study are presented within the combined open label effectiveness analyses (**Section 10.2**) and the combined safety analyses (**Section 11.2**), which include all study periods. The LTT study design, subject accountability and demographics are provided in **Appendix 15.4**.

6.4 Effectiveness and Safety Datasets

Data used to support safety and effectiveness analyses from each of these three studies are described in **Table 4**.

Complete data as of June 4, 2010 were provided to FDA in the PMA submission submitted November 8, 2010. NeuroPace provided updated safety and effectiveness data as of May 12, 2011 in a subsequent submission (dated April 20, 2012). Safety data provided were a summary of all adverse events and SAEs during the first 28 days after implant and by year from initial implant (combined studies, percentages and rates). Additional safety data provided were neuropsychological data, adverse events of particular relevance (death, intracranial hemorrhage, infection, status epilepticus, psychiatric events, including depression and suicidality, perception of stimulation, and changes in seizures), and Neurostimulator explant and replacement procedures. The final Pivotal study effectiveness analyses for responder rate, median percent change and quality of life data through the end of the Pivotal study were also provided, as were the updated responder rate and median percent change data for the Long-term Treatment study.

Table 4: Safety and effectiveness data

Effectiveness Data

• **Primary**
  ▸ **Pivotal Study**: Seizure data from the Blinded Evaluation Period
• **Supportive**
  ▸ **Pivotal Study**: Seizure and quality of life data from all study periods
  ▸ **Combined Studies**: Seizure data from the open label periods of the Feasibility, Pivotal and LTT studies combined*

Safety Data

• **Primary**
  ▸ **Pivotal Study**: AE data from the first 12 weeks post-implant
• **Supportive**
  ▸ **Pivotal Study**: AE data and affective and neuropsychological assessment data from all study periods
  ▸ **Combined Studies**: AE data from all periods of the Feasibility, Pivotal and LTT studies combined*
• **SUDEP**: Deaths from all three studies are also used for the analysis to estimate the risk for sudden unexplained death in epilepsy (SUDEP)

* Subject demographics, epilepsy characteristics, study design and treatment were sufficiently similar to justify combining data from the three clinical investigations for supportive analyses.

7 PIVOTAL STUDY PROTOCOL SUMMARY

7.1 Pivotal Study Objective

The primary objective of the RNS System Pivotal Clinical Investigation was to assess safety and to demonstrate that the RNS System is effective as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures from no more than two foci that are refractory to two or more AEDs.

7.2 Pivotal Study Design

The RNS System Pivotal Clinical Investigation was a multi-center prospective, randomized, double-blinded, concurrent sham-stimulation controlled clinical investigation of individuals (18 – 70 years of age) with medically intractable epilepsy with partial onset seizures. The first subject was implanted in May 2006 and the last subject completed the open label follow-up in May 2011. The study time periods are described below and illustrated in **Figure 13**.

7.2.1 Study Periods

Baseline and Pre-Implant Periods

Subjects meeting the enrollment criteria entered the baseline period and recorded daily seizure data. AEDs were to remain stable from enrollment to the end of the Blinded Evaluation Period. To qualify for implantation with the RNS Neurostimulator and Leads, subjects were required to have an average of 3 or more disabling seizures (simple partial motor seizures, complex partial seizures and/or secondarily generalized seizures) per month (1 month = 28 days) over 3 consecutive months, with no month with less than 2 seizures, while maintaining a stable AED regimen. The Pre-Implant Period was the 3 consecutive months prior to the subject's qualification for RNS System implant.

Implantation

The RNS Neurostimulator and Leads were to be implanted within 1 month of the date that the subject met the implant criteria.

Post-Operative Stabilization Period (1 month)

During the Post-Operative Stabilization Period (1st month post-implant) the Neurostimulator was programmed in all subjects to enable detection but not provide stimulation. At the week 4 post-implant appointment, subjects were randomized 1:1 to the Treatment group (responsive stimulation programmed on) or Sham group (responsive stimulation programmed off).

Stimulation Optimization Period (1 month)

During the Stimulation Optimization Period (2nd month post-implant) subjects who were randomized to the Treatment group had responsive stimulation settings optimized. In order to maintain the blind, subjects in the Sham group had sham programming at each visit and face-to-face time with the clinician investigators was the same as for subjects in the Treatment group.

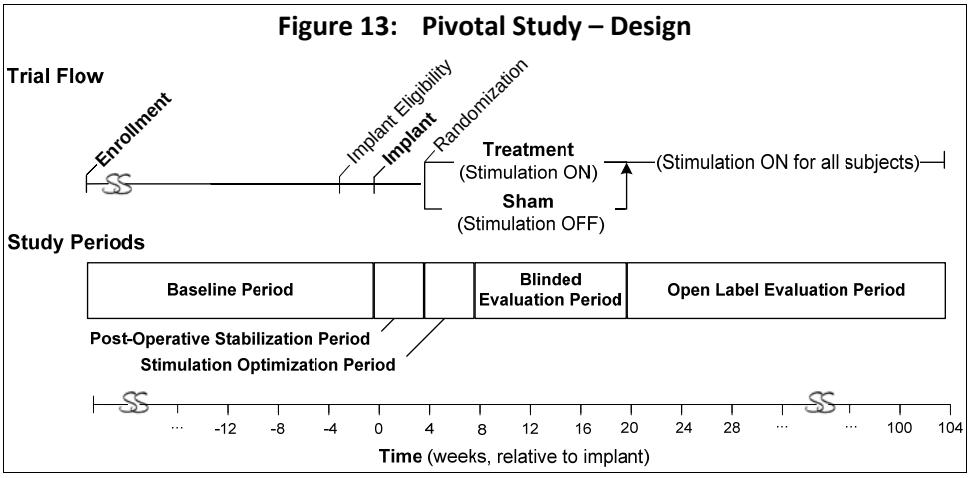
Blinded Evaluation Period (3 months)

Over the 12 week Blinded Evaluation Period (3rd, 4th and 5th months post-implant) subjects in the Treatment group continued to receive responsive stimulation. Subjects in the Sham group did not receive responsive stimulation but continued to receive sham programming. Face-to-face time with the clinician investigators was the same for Sham and Treatment subjects.

Open Label Period (21 months)

At the end of the Blinded Evaluation Period, subjects transitioned into the Open Label Period (months 6 to 26 post-implant) and all subjects (from both the Treatment and Sham groups) received responsive stimulation. AEDs could be adjusted as needed.

Figure 13: Pivotal Study – Design



7.2.2 Inclusion and Exclusion Criteria

Inclusion criteria for enrollment

1. Subject has disabling motor simple partial seizures, complex partial seizures, and/or secondarily generalized seizures. Disabling refers to seizures that are severe enough to cause injuries, or significantly impair functional ability in domains including employment, psychosocial education and mobility.
2. Subject has seizures that are distinct, stereotypical events that can be reliably counted, in the opinion of the investigator, by the subject or caregiver.
3. Subject failed treatment with a minimum of two anti-seizure medications (used in appropriate doses) with adequate monitoring of compliance and the effects of treatment, as determined by the physician investigator.
4. Subject has remained on the same antiepileptic medication(s) over the three most recent consecutive 28-day periods (other than acute, intermittent use of benzodiazepines). Subjects on the ketogenic diet are permitted if the diet has been stable for the preceding 12 weeks (three 28-day periods).
5. Subject reports having an average of 3 or more disabling motor simple partial seizures, complex partial seizures and/or secondarily generalized seizures per 28 days over the three most recent consecutive 28-day periods, with no 28-day period with less than 2 seizures.
6. Subject is between the ages of 18 and 70 years.
7. Subject has undergone diagnostic testing as part of his/her standard care that has identified no more than 2 epileptogenic regions.
8. Subject is male or a female of childbearing potential using a reliable method of contraception (hormonal, barrier method, surgical or abstention), or is at least two years post-menopause.
9. Subject or legal guardian is able to provide appropriate consent to participate.
10. Subject can be reasonably expected to maintain a seizure diary alone or with the assistance of a competent individual.

11. Subject is able to complete regular office and telephone appointments per the protocol requirements (including behavioral (mood) surveys and neuropsychological testing).
12. Subject is willing to be implanted with the RNS System as a treatment for his/her seizures.
13. Subject is able to tolerate a neurosurgical procedure.
14. Subject is considered a good candidate to be implanted with the RNS System.

Note: A subject was still eligible to participate if AEDs were temporarily discontinued for the purposes of diagnostic or medical procedures during the preceding 12 weeks.

Exclusion criteria for enrollment

1. Subject has been diagnosed with psychogenic or non-epileptic seizures in the preceding year.
2. Subject has been diagnosed with primarily generalized seizures.
3. Subject has experienced unprovoked status epilepticus in the preceding year.
4. In the opinion of the investigator, the subject has a clinically significant or unstable medical condition (including alcohol and/or drug abuse) or a progressive central nervous system disease.
5. Subject is taking chronic anticoagulants.
6. Subject has been diagnosed with active psychosis, major depression or suicidal ideation in the preceding year. Subjects with post-ictal psychiatric symptoms need not be excluded.
7. Subject is pregnant or planning on becoming pregnant in the next two years.
8. Subject is enrolled in a therapeutic investigational drug or device trial.
9. Subject has an implanted VNS or is unwilling to have the VNS explanted (excluding leads) prior to or at the time of the RNS System implant. (Subjects with VNS devices must have had VNS therapy discontinued for at least three months prior to enrollment.)
10. Subject has had therapeutic surgery to treat epilepsy in the preceding 6 months. Subjects who have had epilepsy surgery (such as cortical resection, subpial transection or corpus callosotomy) more than 6 months ago are eligible.
11. Subject has had a cranial neurosurgical procedure (including endovascular procedures) other than an epilepsy surgery involving the skull or brain in the previous 1 month.
12. Subject is implanted with an electronic medical device that delivers electrical energy to the head.
13. Subject is an unsuitable candidate for neurosurgery in the opinion of the investigator.
14. Subject requires repeat MRIs in which the head is exposed to the radio frequency field.
15. Subject's epileptogenic region(s) is/are located caudal to the level of the thalamus.
16. In the opinion of the investigator, implantation of the RNS Neurostimulator and Lead(s) would present unacceptable risk.

Inclusion criteria for implant

A subject was required to meet the following criteria during the Baseline Period of the study in order to be implanted with the RNS System:

1. Subject had an average of 3 or more disabling partial onset seizures per month (28 days) over the 3 most recent consecutive months in the Baseline Period, with no month with less than 2 seizures.
2. Subject remained on the same antiepileptic medication(s) over the 3 most recent consecutive months (other than acute, intermittent use of benzodiazepines).

7.2.3 Randomization and Blinding

Randomization occurred at the week 4 post-implant appointment. Subjects were randomized 1:1 to the Treatment group (responsive stimulation programmed on) or Sham group (responsive stimulation programmed off) using a stratified adaptive randomization algorithm with investigational site as the randomization variable of highest priority, followed by three clinical characteristics which may influence the outcome variable: seizure localization (mesial temporal origin versus other region), number of seizure foci (one versus two), and prior therapeutic epilepsy surgery.

In order to maintain the investigator blind, the study had 2 protocols (Assessment and Treatment) performed by separate clinicians. Clinicians conducting the Assessment Protocol were blinded to the subject's randomization; these clinicians collected all study data related to the effectiveness endpoints (including daily seizure diary data, the QOLIE-89 and the Liverpool Seizure Severity Survey) from the time the subject was enrolled until the subject completed the end of the Blinded Evaluation Period. Clinicians conducting the Treatment Protocol were aware of the subject's randomization and managed the RNS System. Both Assessment and Treatment teams collected information on adverse events. The subject's randomization group was not revealed to the subject or Assessment clinicians at any time in the study.

In order to maintain the subject blind, every subject received test stimulations at each study visit during the blinded portions of the study (Stimulation Optimization and Blinded Evaluation Periods). Stimulation settings for Treatment group subjects were selected so that there was no perception of stimulation. In addition, visit activities and face-to-face time with the Assessment and Treatment Investigators were the same for Treatment and Sham subjects.

7.2.4 Study Data Collected

Seizure Data

Subjects or their caregivers recorded seizure frequency and severity on a daily seizure diary. Disabling seizures were defined as simple partial motor seizures, complex partial seizures and/or secondarily generalized seizures. The seizure diary was reviewed and documented by the Assessment clinician at monthly study appointments for the first year post-implant, then every 3 months for the second year post-implant. Safety data were monitored continuously by both Assessment and Treatment investigators throughout the study.

Adverse Event Data

Adverse events for the Pivotal study were collected on case report forms (CRFs) at every study visit and were classified by the reporting investigator according to the definitions presented in **Table 5**. The method for collecting adverse events in the Feasibility and LTT studies was identical. Each adverse event was categorized using the Medical Dictionary for Regulatory Activities (MedDRA) terminology, consistent with the MedDRA Term Selection: Points to Consider document.

An independent Data Monitoring Committee (DMC) was chartered to review all adverse events (including deaths) for all studies in order to confirm the MedDRA categorization and the investigator's assessment of severity and device relation. An additional responsibility of the DMC was to determine whether the study should be stopped early because of safety concerns. A second committee (the SUDEP adjudication committee) reviewed all deaths independently and determined whether the death was possibly, probably or definitely related to SUDEP.

The Pivotal study collected extensive data on all adverse events, regardless of relatedness to the device. This increases the overall rate of adverse events but provides the most comprehensive portrayal of the safety experience. Because many of the adverse events are anticipated in persons with seizures and persons taking AEDs, adverse events are presented by device relation, as well as by summed total.

Table 5: Adverse event classification definitions

Term	Definition
Adverse Event (AE)	A negative change in the subject's physical or mental health as experienced by the subject or observed by the clinician during any part of the clinical investigation.
Mild Adverse Event	Non-serious; minor in nature or behavior; acute and self-limited or transient; no need for invasive medical or procedural intervention to alleviate the adverse event or any adverse event that is not serious
Serious Adverse Event (SAE)	Significant risks or consequences to the subject's acute or long-term health; serious injury or death; hospital admission or invasive medical intervention required to alleviate the adverse event.
Device-Related	The event is definitively or potentially related to the RNS System.
Not Device-Related	The event is not related to the RNS System.
Anticipated Adverse Event	A device-related adverse event noted in the Investigational Plan as potentially caused or contributed to by the investigational device. (Note: Only device-related events were required to be classified as anticipated/unanticipated.)
Unanticipated Adverse Event	A device-related adverse event not noted in the Investigational Plan as potentially caused or contributed to by the investigational device.

All determinations of severity, device-relation, anticipation, and resolution were made by the investigator and confirmed by the DMC.

Additional Data Collected

- Quality of Life in Epilepsy inventory (QOLIE-89) during the pre-implant Baseline Period, at the end of the Blinded Evaluation Period and at 1 and 2 years post-implant.
- Surveys of affective status during the pre-implant Baseline Period, at the end of the Blinded Evaluation Period, and at 1 and 2 years post-implant. These were the Beck Depression Inventory (BDI-II), Profile of Mood States (POMS), and Center for Epidemiological Studies Depression Scale (CES-D).
- Standardized inventories of neuropsychological functioning administered by neuropsychologists during the pre-implant Baseline Period, at the end of the Blinded Evaluation Period and at 1 and 2 years post-implant.
- The Liverpool Seizure Severity Scale (LSSS) at the end of each 28-day period.

The schedule of appointments and data collected at each appointment is provided in **Table 53** in **Appendix 15.7**.

7.3 Pivotal Study Pre-specified Endpoints and Statistical Methods

7.3.1 Primary Effectiveness Endpoint

The primary effectiveness objective was to demonstrate a significantly greater reduction in the frequency of disabling seizures in the Treatment group compared to the Sham group during the Blinded Evaluation Period relative to the Pre-Implant Period. Data used for the endpoint were seizure count data recorded by the subject or caregiver in seizure diaries during the Pre-Implant and Blinded Evaluation Periods.

The pre-specified analysis method modeled seizure count data using generalized estimating equations (GEE), which accounts for within-subject correlations and variability across subject populations. The objective is met with a statistically significant treatment-by-time interaction. Data were analyzed using both the pre-specified GEE model as well as a modified GEE model that appropriately accounts for the variability in the seizure count data.

The pre-specified GEE model used daily seizure count data, assumed an overdispersed Poisson variance function (in which the variance is assumed to have a linear relationship to the mean) and included a scale parameter to account for overdispersion of the variance. Additionally, the investigational plan pre-specified that models may also include covariates that potentially influence the endpoint and are found not to be balanced between treatment groups. The GEE provides two estimates of standard errors (SEs): model-based and empirical. Model-based SEs use the scale parameter, whereas empirical SEs do not. Model-based SEs are preferred when the number of patients (191) is small relative to the number of repeated measures (31,434 observations of daily seizure count data). In this setting, empirical SEs can be highly variable and inefficient (giving p-values that are too large).[99]

When the study was completed, it was evident that the pre-specified GEE model did not adequately account for the large variability in the daily seizure count data; objective diagnostic metrics such as the large discrepancies between the model-based and empirical SEs, and an indicator that the extent of dispersion of the seizure count data was higher than the model assumptions (the overdispersion parameter) confirmed that the pre-specified model was not appropriate for the data.[100,101] NeuroPace brought this to the attention of the FDA in a pre-PMA meeting on March 15, 2010. Through discussion, it was mutually agreed that a modified GEE model was necessary to account for the large variability in the seizure data and to interpret the study result. Therefore, seizure data were also analyzed using a modified GEE model that FDA agreed is appropriate and an efficient method for analyzing these seizure frequency data. The modified GEE model accounts for the within- and across- subject variance by grouping the seizure count data by month, by assuming a negative binomial distribution for the seizure count data (which permits the variance to exceed the mean), and by including the clinical covariates that were used in subject randomization to Treatment or Sham. Details regarding the modifications to the GEE model are provided in **Section 10.1.2** and in greater detail in a statistical appendix (**Appendix 15.1)**.

7.3.2 Secondary Effectiveness Endpoints

The objective of the secondary effectiveness endpoints was to provide support for the superiority of the clinical response in the Treatment group relative to the Sham group during the Blinded Evaluation Period. Seizure frequency related analyses used data obtained from the seizure diaries.

7.3.2.1 *Percent of responders*

A responder is defined as a subject having a 50% or greater reduction in seizure frequency. The analysis method compared responder rates during the Blinded Evaluation Period between the Treatment and Sham groups using the z-statistic.

7.3.2.2 *Change in mean frequency of seizures*

The analysis method compared the change in mean seizure frequency during the Blinded Evaluation Period compared to the Pre-Implant Period between the Treatment and Sham groups using 2-sample t-tests.

7.3.2.3 *Proportion of seizure-free days*

The analysis method used the GEE model to evaluate the significance of group (Treatment versus Sham) on the change in the proportion of seizure-free days during the Blinded Evaluation Period compared to the Pre-Implant Period.

7.3.2.4 *Change in seizure severity*

Data collected for this endpoint were the Liverpool Seizure Severity Scale (LSSS) 2.0 scaled summary score.[102] The analysis method compared the change in the LSSS during the Blinded Evaluation Period compared to the Pre-Implant Period between the Treatment and Sham groups using 2-sample t-tests.

7.3.3 Additional Effectiveness Endpoints

The objective of the additional effectiveness endpoints was to demonstrate that treatment with the RNS System improved quality of life at 1 and 2 years after implantation and to demonstrate that the RNS System was effective as a treatment of medically intractable partial onset seizures in patients with different clinical characteristics.

7.3.3.1 *Quality of Life*

Quality of life was measured with the QOLIE-89 assessment inventory. The QOLIE-89 was administered during the Baseline Period, at the end of the Blinded Evaluation Period and at 1 and 2 years after implantation. Comparisons to baseline were performed using the paired t-test and comparisons between Treatment and Sham groups were performed using the 2-sample t-test. One year is generally considered the earliest that improvements in quality of life can be accurately assessed in response to a seizure treatment.[103] An improvement of 0.5 SD is considered a clinically meaningful difference.[17-19,104]

7.3.3.2 *Subset Analyses*

Although the study was not powered to statistically assess the effectiveness of treatment across patient subsets, pre-specified subset analyses were performed to evaluate whether clinical characteristics used as randomization variables could affect the clinical outcome to treatment with the RNS System. These were the seizure onset zone (mesial temporal onset versus other regions), number of seizure foci (one or two), and previous resection for treatment of epilepsy (yes or no). In addition, a subset analysis was performed for subjects who had changes in AEDs during the blinded periods of the study (this was not allowed in the protocol unless considered medically necessary). The possible impact of each of these factors on the clinical response was assessed quantitatively using GEE analyses with interaction terms.

7.3.4 Open Label Effectiveness Endpoints

The objective of the pre-specified long-term effectiveness analyses was to demonstrate a persistent reduction in disabling seizures during the Open Label Evaluation Period and to evaluate the change in seizure frequency in the Sham group once responsive stimulation was enabled in the Open Label Period. Summary statistics of the following effectiveness measures are provided for the Open Label Period.

7.3.4.1 *Responder Rates*

Responder rates for each 3-month period of the Open Label Period (relative to the Pre-Implant Period) were calculated.

7.3.4.2 *Daily seizure frequency counts*

Daily seizure frequency counts for each 3-month period of the Open Label Period (relative to the Pre-Implant Period) were calculated.

7.3.4.3 *Change in seizure frequency*

Change in seizure frequency in the Sham group with start of stimulation in the Open Label Period were calculated. Average seizure frequency in the Sham group during 3 months of the Open Label Period (beginning 1 month after stimulation was enabled) was compared to the average (mean) seizure frequency for those same subjects during the 3-month Blinded Evaluation Period.

7.3.5 Primary Safety Endpoints

The pre-specified primary safety objective was to establish that the RNS System serious adverse event (SAE) rate during the surgical procedure and the following 28 days (Acute Period) was no worse than the combined risks associated with implantation of intracranial electrodes for localization procedures and epilepsy resective surgery, and that the SAE rate during the surgical procedure and the following 84 days (Short-Term Chronic Period) was no worse than the historical SAE rate for deep brain stimulation (DBS) for movement disorders.

The primary safety endpoint variable was the SAE rate in all implanted subjects calculated for the two timeframes, the Acute Period (surgical procedure and the following 28 days) and the Short-Term Chronic Period (surgical procedure and the following 84 days). The SAE rate is defined as the proportion of subjects having a serious adverse event.

7.3.5.1 *Acute safety*

For the surgical procedure and the following month, the RNS System SAE rate was not expected to exceed 15%, which is the combined SAE rate associated with implantation of intracranial electrodes for localization procedures and epilepsy resective surgery.[4,6-8,20] Should the RNS System SAE rate equal 15%, based on a sample of 180 subjects the upper one-sided 95% confidence limit for the SAE rate would equal 20%.

7.3.5.2 *Short-term chronic safety*

For the surgical procedure and the following 3 months, the RNS System SAE rate was not expected to exceed 36%, which is the 3 to 4 months DBS rate.[8-14] Should the RNS System SAE rate be 36%, based on a sample of 180 subjects the upper one-sided 95% confidence limit for the SAE rate would equal 42%.

The analysis method calculated the SAE rate (defined as the proportion of subjects who experienced at least 1 SAE during the specified period, whether reported as device-related or not) and the 95% confidence interval.

7.3.6 Secondary Safety Endpoints

The objective of the pre-specified secondary safety endpoints was to evaluate the occurrence of adverse events and to describe changes in affective status and neuropsychological functioning for both the Treatment and Sham-stimulation groups from the Baseline Period through the post-implant periods, and to describe the long-term safety of responsive stimulation in all subjects through the Open Label Period.

7.3.6.1 *Rate of adverse events*

The objective was to assess the safety of responsive stimulation by comparing the rate of SAEs for the Treatment and Sham groups during the blinded periods of the study and to compare rates of adverse events in all subjects during all study periods. Data were collected as adverse events reported on adverse event case report forms. Subject and event rates were calculated for all adverse events by event type, severity, device-relation, and study period.

7.3.6.2 *Change in neuropsychological function*

The objective was to assess the safety of responsive stimulation by comparing neuropsychological function in subjects in the Treatment and Sham groups during the Blinded Periods of the study relative to the Baseline, and to compare neuropsychological function in all subjects at one and two years after implant relative to the baseline. Data collected were summary scores from validated neuropsychological inventories. The analysis method used descriptive statistics calculated for each summary score.

7.3.6.3 *Change in affective status*

The objective was to assess the safety of responsive stimulation by comparing affective status in subjects in the Treatment and Sham groups during the Blinded Periods of the study relative to the Baseline, and to compare affective status in all subjects at one and two years after implant relative to the baseline. Data collected were summary scores from the Beck Depression Inventory, the Profile of Moods State, and the CES-D surveys. The analysis method used descriptive statistics calculated for each summary score.

7.3.7 Additional Safety Endpoints

7.3.7.1 *The rate of Sudden Unexplained Death in Epilepsy (SUDEP)*

The objective was to begin to collect on-going data from all RNS System studies sufficient to demonstrate that the SUDEP rate is not elevated in persons treated with the RNS System. The endpoint is the upper limit of the 95% confidence interval for deaths identified as SUDEP that occurred in subjects having a Neurostimulator programmed to provide stimulation. Data collected were the number of deaths during the Feasibility, Pivotal and Long-term Treatment studies that were classified as possible, probable or definite SUDEP by an independent SUDEP adjudication committee. The intent is to ultimately collect approximately 1500 patient years of data.

The analysis method calculated the number of SUDEP events in subjects having a Neurostimulator programmed to provide stimulation at the time of the event divided by the total number of patient stimulation years. The upper limit of the 95% confidence interval for SUDEP deaths in subjects in the RNS System group was not to exceed the upper limit of the 95% confidence interval for the expected rate of SUDEP deaths in a similar population of persons with epilepsy, which is 9.3 per 1000 patient years.[30]

In addition, another analysis calculated the number of SUDEP events in subjects implanted with the RNS Neurostimulator and Leads, whether the Neurostimulator was programmed to deliver stimulation or not. The number of SUDEP events in subjects implanted with the Neurostimulator and Leads at the time of the event was divided by the total number of implant years and the upper limit of the 95% confidence interval was calculated.

7.4 Sample Size

The sample size for the Pivotal study was calculated based on an expected responder rate in the Treatment group of 40% vs. a 20% responder rate in the Sham group. Using an overall 2-sided Type 1 error of 0.05, 180 subjects were required for the Blinded Evaluation Period. Assuming a 20% drop-out rate in the Baseline Period, and a 10% drop-out rate in the post-implant Period, a minimum of 240 subjects would need to be enrolled.

8 SUBJECT ACCOUNTABILITY AND DEMOGRAPHICS

8.1 Pivotal Study

8.1.1 Enrollment by Site

Two hundred and forty subjects enrolled in the RNS System Pivotal Clinical Investigation at 32 Comprehensive Epilepsy Centers in the US; enrollment per clinical site is presented in **Table 6**. 191 subjects were implanted with the RNS Neurostimulator and Leads; all implanted subjects were randomized. The majority of sites implanted 5 or more subjects. The first subject was implanted in May 2006 and the last subject completed the open label follow-up in May 2011.

Table 6: Pivotal Study – Enrollment by clinical site

Site Name & Location	Principal Investigator	Enrolled & Screened	Implanted & Randomized
Baylor College of Medicine, Houston, TX	Eli Mizrahi, MD	6	4
California Pacific Medical Center, San Francisco, CA	David King-Stephens, MD	23	19
Cleveland Clinic Foundation, Cleveland, OH	Dileep Nair, MD	10	7
Columbia Presbyterian Medical Center, New York, NY	Carl Bazil, MD, PhD	4	4
Dartmouth-Hitchcock Medical Center, Lebanon, NH	Barbara Jobst, MD	9	7
Emory University, Atlanta, GA	Robert Gross, MD, PhD	3	3
George Washington University, Washington, DC	James Leiphart, MD, PhD	5	4
Henry Ford Hospital, Detroit, MI	Gregory Barkley, MD	9	8
Indiana University, Indianapolis, IN	Vicenta Salanova, MD	9	7
Johns Hopkins University School of Medicine, Baltimore, MD	Gregory Bergey, MD	8	6
Massachusetts General Hospital, Boston, MA	Andrew Cole, MD	9	8
Mayo Clinic – Arizona, Scottsdale, AZ	Richard Zimmerman, MD	7	6
Mayo Clinic – Jacksonville, Jacksonville, FL	Robert Wharen, MD	5	5
Mayo Clinic – Rochester, Rochester, MN	W. Richard Marsh, MD	4	2
Medical College of Georgia, Augusta, GA	Yong Park, MD	8	7
Medical University of South Carolina, Charleston, SC	Jonathan Edwards, MD	6	6
Miami Children's Hospital, Miami, FL	Michael Duchowny, MD	8	5
Oregon Health & Science University, Portland, OR	David Spencer, MD	7	6
Rush University Medical Center, Chicago, IL	Michael Smith, MD	9	8
Saint Barnabas Medical Center, Livingston, NJ	Eric Geller, MD	8	5
Swedish Medical Center, Seattle, WA	Ryder Gwinn, MD	9	8
Thomas Jefferson University, Philadelphia, PA	Christopher Skidmore, MD	9	8
University of Alabama at Birmingham, Birmingham, AL	A. LeBron Paige, MD	1	0
University of Florida at Gainesville, Gainesville, FL	Stephan Eisenschenk, MD	3	2
University of Rochester, Rochester, NY	Michel Berg, MD / A. James Fessler, MD	5	4
University of Southern California, Los Angeles, CA	Christianne Heck, MD	12	10
University of Texas Southwestern Medical Center, Dallas, TX	Paul Van Ness, MD	9	9
University of Virginia, Charlottesville, VA	Nathan Fountain, MD	5	4
University of Wisconsin Hospital and Clinics, Madison, WI	Paul Rutecki, MD, PhD	8	5

Table 6: Pivotal Study – Enrollment by clinical site

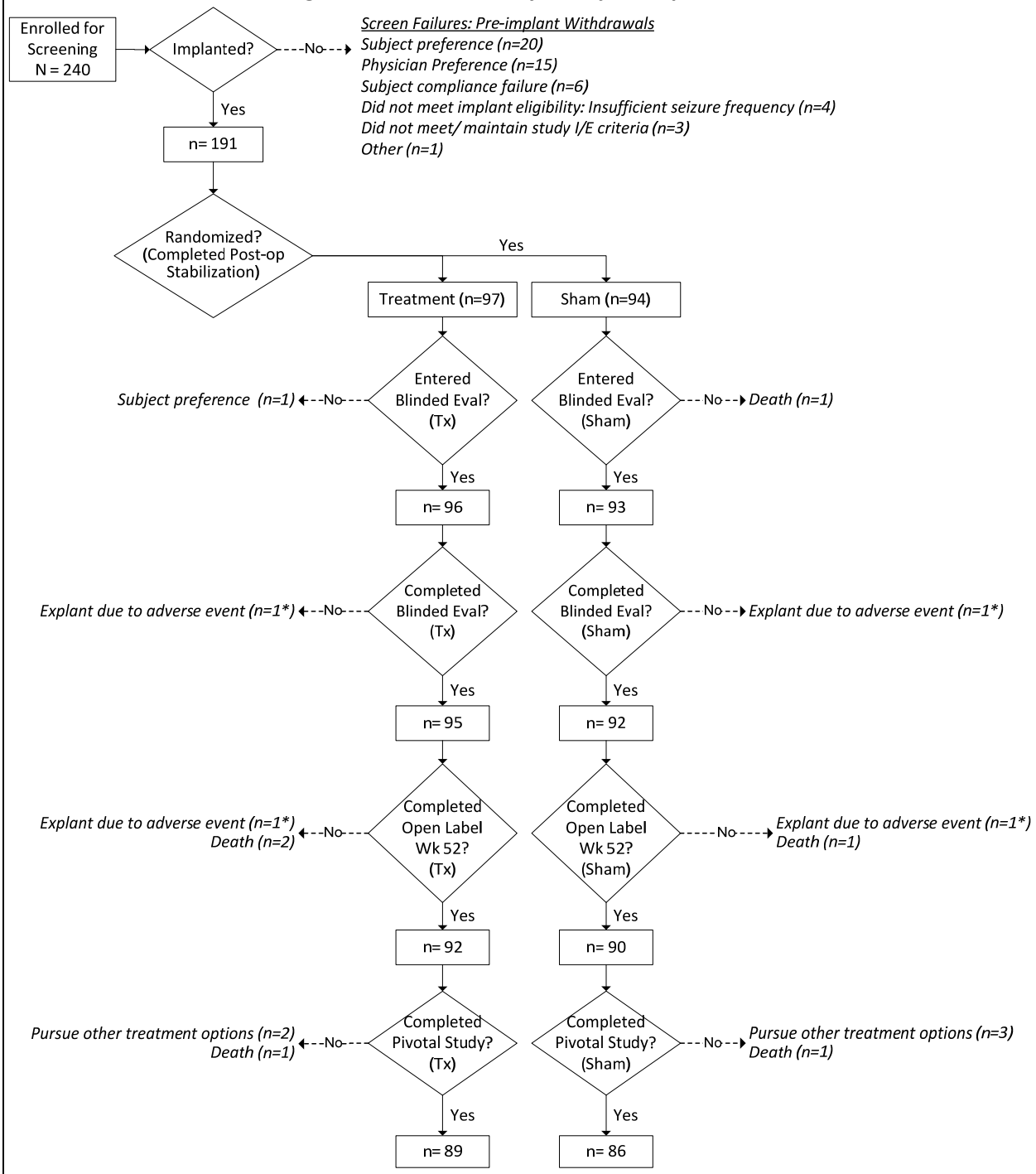
Site Name & Location	Principal Investigator	Enrolled & Screened	Implanted & Randomized
Via Christi Comprehensive Epilepsy Center, Wichita, KS	Andrew Massey, MD	18	11
Wake Forest University Health Sciences, Winston-Salem, NC	Cormac O'Donovan, MD	1	1
Yale University School of Medicine, New Haven, CT	Robert Duckrow, MD	3	2
	Total	**240**	**191**

8.1.2 Subject Accountability

Subject accountability for the Pivotal study is summarized in **Figure 14**. 240 subjects enrolled in the baseline period during which they were screened for eligibility for implant. Forty-nine subjects did not meet eligibility for implant. Reasons are presented in **Table 7**. 191 subjects were implanted with the RNS Neurostimulator and Leads. All were randomized at one month post-implant. 98% (187) of the subjects completed the Blinded Evaluation Period, and 92% (175) completed the entire investigation (2 years post-implant). Sixteen subjects discontinued the study post-implant. Reasons for post-implant discontinuation are provided in **Table 8**. No subject was lost to follow-up.

The average length of post-implant participation was 2.0 years (range 5 weeks to 151 weeks). Within the Pivotal study, there were 379 years of implant experience and over 328 patient years of experience with responsive stimulation enabled.

Figure 14: Pivotal Study – Subject disposition



* All explants due to infection.

Data as of 5/12/2011

Table 7: Pivotal Study – Reasons for pre-implant withdrawal

Reason	# subjects/240
Subject preference	**20**
Anxiety about the surgical procedure and implantation	7
Stress related to participating in the study	3
Uncertainty about the potential benefits	3
Improved seizure frequency / personal reasons	1
Non-compliance	1
Consideration of other therapeutic options	2
Family reasons	2
Withdrew consent (reason unknown)	1
Physician preference	**15**
Concern that the subject was no longer a suitable candidate for the study	8
Further characterization of the subject's seizure onset zone	6
Consideration of other therapeutic options	1
Subject unable or unwilling to complete study requirements	**6**
Insufficient number of seizures during the Baseline Period	**4**
Did not meet inclusion/exclusion criteria	**3**
Did not meet seizure frequency requirements prior to enrollment	1
More than two epileptogenic regions	1
Clinically significant medical condition (alcohol abuse)	1
Investigational site closed due to low enrollment	**1**

Table 8: Pivotal Study – Reasons for post-implant withdrawal

Reason	# subjects/191
Subject preference	**6**
Cortical resection surgery	5
No longer wished to participate	1
Explant due to infection	**4**
Death	**6**
Possible/Probable/Definite SUDEP	4
Suicide	1
Lymphoma	1

8.1.3 Demographics

Demographics and baseline characteristics of the implanted subjects are summarized in **Table 9**. Subjects participating in this study had severe epilepsy. The average subject had been challenged by epilepsy for more than 20 of their 35 years. Despite taking more than 2 different AEDs a day, these subjects had a median frequency of more than 9 disabling seizures a month with a range of 3 to 338 seizures per month.

Many of the subjects had undergone surgical procedures to treat their epilepsy. About one third had been treated with a VNS, and one third had been treated with an epilepsy resective surgery. More than half of these subjects had undergone invasive diagnostic testing with acute implantation of intracranial electrodes to be evaluated for epilepsy surgery.

Three patient characteristics were identified *a priori* that were anticipated to be of clinical importance because they could account for the potential variance of the seizure count data and could potentially

influence treatment outcome: seizure onset location (mesial temporal vs. other), number of seizure foci (one vs. two), and prior therapeutic surgery for epilepsy (yes or no). These clinical characteristics were used as randomization strata and were also pre-specified as subpopulations of interest in the analyses of the effectiveness endpoints.

In general, clinical characteristics were well balanced across Treatment and Sham groups. However, two patient characteristics (number of seizure foci and prior EEG monitoring with intracranial electrodes) were moderately out of balance ($p \leq 0.1$). Pre-specified sensitivity analyses were performed to evaluate the effect of these out-of-balance characteristics. Results of these analyses are discussed in **Section 10.1.3.4**.

Table 9: Pivotal Study – Demographic and baseline characteristics

Characteristic	**All Implanted** (N = 191)	**Treatment** (N = 97)	**Sham** (N = 94)	**P-value**
	Mean ± SD (min-max) or % (n)			
Age (years)	34.9 ± 11.6 (18 - 66)	34.0 ± 11.5 (18 - 60)	35.9 ± 11.6 (18 - 66)	0.24[1]
Female	48% (91)	48% (47)	47% (44)	0.82[2]
Duration of epilepsy (years)	20.5 ± 11.6 (2 - 57)	20.0 ± 11.2 (2 - 57)	21.0 ± 12.2 (2 - 54)	0.55[1]
Number of AEDs at enrollment	2.8 ± 1.2 (0 - 8)	2.8 ± 1.3 (1 - 8)	2.9 ± 1.1 (0 - 6)	0.88[1]
Mean seizure frequency during Pre-Implant Period (seizures/month)	34.2 ± 61.9 (3 - 338) median = 9.7	33.5 ± 56.8 (3 - 295) median = 8.7	34.9 ± 67.1 (3 - 338) median = 11.6	0.88[1]
Seizure onset location: Mesial temporal lobe only (vs. other)[3]	50% (95)	49% (48)	50% (47)	0.94[2]
Number of seizure foci -Two (vs. one)[3]	55% (106)	49% (48)	62% (58)	0.09[2]
Prior therapeutic surgery for epilepsy[3]	32% (62)	35% (34)	30% (28)	0.44[2]
Prior EEG monitoring with intracranial electrodes	59% (113)	65% (63)	53% (50)	0.10[2]
Prior VNS	34% (64)	31% (30)	36% (34)	0.44[2]

[1] P-value per two-sample t-test.
[2] P-value per chi-square test.
[3] Characteristics used as strata in randomization algorithm.
Data as of 5/12/2011

As expected, the baseline seizure frequency varied considerably across different subsets (**Table 10**); subjects with seizures arising outside the mesial temporal lobe had more than 3 times as many seizures than the subjects with mesial temporal onset seizures. Subjects with 1 onset had more frequent baseline seizures on average than those with 2 onsets (most of whom had onsets in each mesial temporal lobe), and those with prior surgery had a higher seizure frequency than those with no prior surgery (most of whom had onsets in the mesial temporal lobe).

Table 10: Pivotal Study – Pre-Implant mean seizure frequency by subset populations

	% (n) N = 191	Pre-Implant Seizure Frequency (Mean ± SD, seizures/month)
Onset Location		
Mesial Temporal Lobe	50% (95)	15.8 ± 26.8
Other	50% (96)	52.4 ± 79.2
Number of Seizure Onset Locations		
One	45% (85)	53.8 ± 84.7
Two	55% (106)	18.5 ± 25.3
Prior Therapeutic Surgery for Epilepsy		
Yes	32% (62)	56.4 ± 85.3
No	68% (129)	23.5 ± 43.2

Data as of 5/12/2011

Half of the subjects had mesial temporal lobe epilepsy and 73% of these subjects had seizures arising independently in both the left and right mesial temporal lobes (**Table 11**). The subjects with bilateral mesial temporal lobe epilepsy were not candidates for epilepsy surgery because the potential for benefit did not outweigh the risk of significant memory deficits after a temporal lobe removal. Many of the subjects with unilateral mesial temporal lobe epilepsy had already had a prior temporal lobe resection, and an additional resective surgery would carry too much risk for neurological deficits. Others had epilepsy in the dominant hemisphere (usually the left) and were at risk for significant memory deficits with removal of the dominant temporal lobe. A few did not want to consider a destructive surgical procedure.

Table 11: Pivotal Study – Onset exclusively in mesial temporal lobe (MTL)

Onset		% (#) of subjects (N=95)
Bilateral MTL		73% (69)
Left MTL	(no prior resection)	15% (14)
	(prior resection)	3% (3)
Right MTL	(no prior resection)	4% (4)
	(prior resection)	5% (5)

Data as of 5/12/2011

8.1.4 Study Conduct

8.1.4.1 *Data Quality*

The primary effectiveness endpoint analysis was performed using all available seizure count data collected for the Pre-Implant and Blinded Evaluation Periods; this included partial data for subjects who failed to record their seizure information during some portion of the study and for subjects who discontinued the study prior to completion. Out of the total possible number of daily seizure observations, 98% (31,434/32,088) were captured for the primary effectiveness endpoint.

8.1.4.2 *Maintenance of the Blind*

The blind was successfully maintained. At the end of the Blinded Evaluation Period (5 months post-implant), subjects were asked whether they thought they had been receiving stimulation therapy, were not receiving stimulation therapy, or whether they did not know. The results for the 187 subjects who completed the Blinded Evaluation Period are summarized in **Table 12**. The blind was assessed quantitatively using a blinding index that ranges from 0 to 1, where a value of 0

corresponds to all subjects providing correct guesses (complete lack of blinding), a value of 1 corresponds to all subjects responding "don't know," and a value of 0.5 corresponds to random guessing (receiving/not receiving stimulation.[105] The blinding index for the Pivotal study was 0.572 (95% confidence interval: 0.502, 0.643), indicating an excellent level of blinding.

Table 12: Pivotal Study – Blinding assessment

	Subject Guess		
Randomization Group	**Receiving stimulation**	**Not receiving stimulation**	**"Don't Know"**
Treatment group (total assessed 96)	42[1]	31[2]	23[3]
Sham group (total assessed 91)	31[2]	38[1]	22[3]
	Blinding index[4] = 0.57 (95% CI: 0.50, 0.64)		

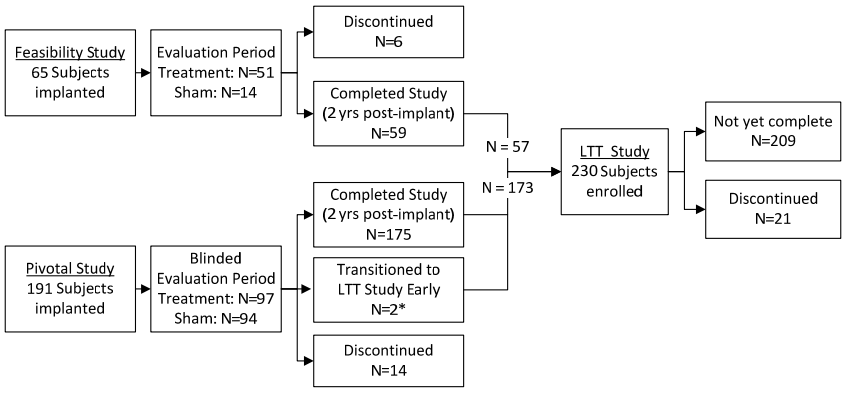
[1] Correct guess: 80/187 (43%).
[2] Incorrect guess: 62/187 (33%).
[3] Declined to guess: 45/187 (24%).
[4] Blinding index and 95% confidence interval calculated per James et al. (1996).
Data as of 5/12/2011

8.2 Combined Studies

8.2.1 Subject Accountability

In the Feasibility and Pivotal studies combined, 256 subjects were implanted with the RNS Neurostimulator and Leads (**Figure 15**). During the Feasibility study, 65 subjects were implanted, 59 subjects completed the study (through 2 years post-implant), and 57 enrolled in the LTT study. During the Pivotal study, 191 subjects were implanted, 175 subjects completed the study (through 2 years post-implant), and 171 subjects enrolled in the LTT study. Additionally, 2 subjects transitioned early from the Pivotal study to the LTT study for a total of 230 subjects who enrolled in the LTT study. The LTT study is ongoing. As of May 12, 2011, 209 subjects were +
The median follow-up time for the 256 subjects was 3.3 years (ranging from 5 weeks to 7 years) with an accumulated experience of 903 patient implant years and 819 patient stimulation years.

Figure 15: Combined Studies – Subject disposition



* Two subjects discontinued early from the Pivotal study to undergo resective epilepsy surgery. Waivers were granted to allow enrollment into the LTT study so that the subjects could continue to receive responsive stimulation to treat seizures arising from the non-resected seizure focus.
Data as of 5/12/2011

Table 13: Combined Studies – Subject discontinuations (N=256)

All discontinuations	**16.8% (43)**
Reasons for discontinuation	
Elective	**8.2% (21)**
To purse other treatment options, including surgery	5.5% (14)
Did not want Neurostimulator replaced	1.2% (3)
Insufficient seizure reduction	1.6% (4)
Physician preference	0.4% (1)
Death[1]	**3.5% (9)**
Non-elective explant (infection/hemorrhage)	**3.1% (8)**
Lost to follow-up	**1.2% (3)**
Not specified	**0.4% (1)**

[1] Two additional deaths occurred after the May 12, 2011 (details in **Table 49**).

8.2.2 Demographics

Subjects participating in the Feasibility and Pivotal studies were similar in demographics and in their experience with epilepsy (**Table 14**). Subjects in both studies had epilepsy for about 20 years on average, were taking nearly 3 AEDs each day, and had a median seizure frequency of approximately 10 per month. Overall, more than two-thirds of these subjects had been implanted with intracranial electrodes for localization of the seizure focus to determine whether they were candidates for a cortical resection. Approximately one-third of the subjects had been treated previously with a VNS and one-third with therapeutic surgery for epilepsy.

Table 14: Combined Studies – Subject demographics

		By Study	
	All (N = 256)	**Feasibility (N = 65)**	**Pivotal (N = 191)**
Characteristic	Mean ± SD (min-max) or % (n/N)		
Age (years) [1]	34.0 ± 11.4 (18 - 66)	30.9 ± 10.3 (18 - 56)	34.9 ± 11.6 (18 - 66)
Gender (Female)	49% (125/256)	52% (34/65)	48% (91/191)
Duration of epilepsy (years) [1]	19.6 ± 11.4 (2 - 57)	17.0 ± 10.1 (2 - 42)	20.5 ± 11.6 (2 - 57)
Number of AEDs at enrollment	2.9 ± 1.1 (0 - 8)	2.9 ± 1.0 (1 - 6)	2.8 ± 1.2 (0 - 8)
Disabling seizures per month [2]	50.7 ± 177.4 (0 – 2320) median = 10.2	99.2 ± 332.8 (0 – 2320) median = 11.3	34.2 ± 61.9 (3 – 338) median = 9.7
Prior VNS	32% (82/256)	28% (18/65)	34% (64/191)
Prior therapeutic surgery for epilepsy	34% (86/256)	37% (24/65)	32% (62/191)
Prior EEG monitoring with intracranial electrodes	65% (166/256)	82% (53/65)	59% (113/191)

[1] Due to hospital confidentiality requirements some institutions did not provide the date of birth for subjects.
[2] Disabling seizures include simple partial motor, complex partial, and secondarily generalized tonic clonic seizures; during the Feasibility study, one subject had only simple partial sensory seizures at baseline.
Data as of 5/12/2011

9 DATA SETS ANALYZED

9.1 Pivotal Study

9.1.1 Intent-to-Treat population

The pre-specified primary safety analysis includes all Pivotal subjects implanted with the Neurostimulator and Leads. The primary effectiveness analysis includes all subjects randomized. Because all subjects implanted were also randomized, the intent-to-treat populations for safety and effectiveness endpoints were the same (N=191).

Treatment Group
Subjects randomized to receive responsive stimulation during the Blinded Evaluation Period (n = 97).

Sham-Stimulation (Sham) Group
Subjects randomized not to receive responsive stimulation during the Blinded Evaluation Period (n = 94).

9.1.2 Per-Protocol population

The primary effectiveness analysis was repeated excluding subjects with protocol deviations that could potentially affect the integrity of the data (N=182).

9.2 Combined Studies

An additional pooled analysis population includes the intent-to-treat population from the RNS System Feasibility and Pivotal Studies, including those who continued into the Long-term Treatment (LTT) study. This includes all 256 subjects implanted with the RNS Neurostimulator and Leads and provides 903 patient implant years and 819 patient stimulation years of experience.

All results presented use data collected up through the last subject visit for the open label period of the Pivotal study (May 12, 2011) with the exception of results for deaths and SUDEP, which are inclusive of October 24, 2012.

10 EFFECTIVENESS RESULTS

10.1 Pivotal Study: Effectiveness Results

Effectiveness of the RNS System was established by the primary effectiveness analysis in the Pivotal study. This demonstrated that the Treatment group experienced a significantly greater reduction in seizures compared to the Sham group during the Blinded Evaluation Period compared to the Pre-Implant Period. Further support for effectiveness is provided by the Open Label Period of the Pivotal study. There was a significant reduction in seizures in subjects randomized to the Sham group when responsive stimulation was first enabled in the Open Label Period. Moreover, seizure rates decreased in both groups over the duration of the Open Label Period. Overall quality of life, another measure of effectiveness, was significantly improved at 1 and 2 years compared to the baseline, as were a number of domains of quality of life concerned with social function, cognition, health discouragement and seizure worry.

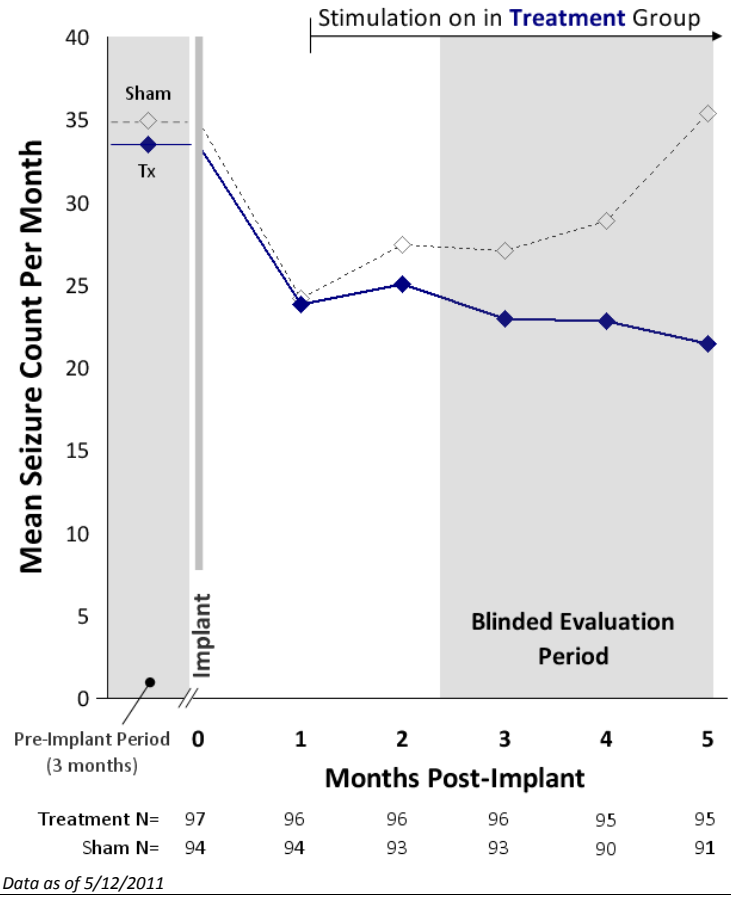
All analyses are for the Intent-to-Treat population (all randomized subjects, N = 191) unless otherwise indicated. Analyses include all subjects for whom data were available for each specified time period.

10.1.1 Primary Endpoint

The primary effectiveness endpoint of the Pivotal study was met, demonstrating that the reduction in seizure frequency in subjects randomized to receive responsive stimulation during the Blinded Evaluation Period was significantly greater than that experienced by subjects randomized to receive sham stimulation.

To provide context for the results of the primary effectiveness analyses, the average (mean) of the observed seizure count data for each interval (Pre-Implant and the first five months post-implant) are presented in **Figure 16**. As expected, there was an initial reduction in seizures after the implant procedure (implant effect). This reduction in seizures began to wane in the subjects not treated with responsive stimulation (Sham group) 3 months after implantation whereas the treated subjects (Treatment group) continued to improve. The effect of implantation on seizure frequency has been described in the literature.[15,16] Whether the transient reduction in seizures seen in persons with epilepsy undergoing a neurosurgical procedure is an effect of the surgical procedure, anesthesia or an effect of lead implantation is not known.

Figure 16: Pivotal Study – Mean seizure count by month



The primary effectiveness endpoint was statistically significant when evaluated using both the pre-specified and the modified GEE models ($p < 0.0001$, and $p = 0.012$, respectively). Moreover, both the pre-specified and modified analyses yield similar treatment effect sizes (effect sizes = -0.25 and -0.29, respectively **Table 16**). However, the pre-specified GEE model did not adequately account for the variability in the seizure data (a discussion regarding the inadequacy of the pre-specified model is provided in **Section 10.1.2**). Therefore results and discussion provided below are based on the modified GEE model, which FDA agrees is an appropriate and efficient analysis for these seizure count data.

Table 15 shows the results using the modified GEE model. Over the entire Blinded Evaluation Period, the Treatment group experienced a reduction in seizure frequency of 37.9% compared to a 17.3% reduction in the Sham group; this difference is statistically significant ($p = 0.012$).

The change in seizure frequency was also evaluated by month of the Blinded Evaluation Period. Consistent with the expected implant effect, the difference in seizure frequency between the Treatment and Sham groups was not significant during the first month of the Blinded Evaluation Period. However, the difference between the groups was significant over the second and third months of the Blinded Evaluation Period (**Table 15**). By the third month (month 5 post-implant), subjects in the Treatment group had a 41.5% reduction in seizure frequency compared to only a 9.4% reduction in the Sham group ($p = 0.008$), further distinguishing the favorable effect of responsive stimulation from an implant effect. The mean monthly seizure counts (using GEE) for the Treatment and Sham groups are shown during the Pre-Implant Period and during each month of the Blinded Evaluation Period in **Figure 17.**

Table 15: Pivotal Study – Seizure frequency percent change: Blinded Evaluation Period

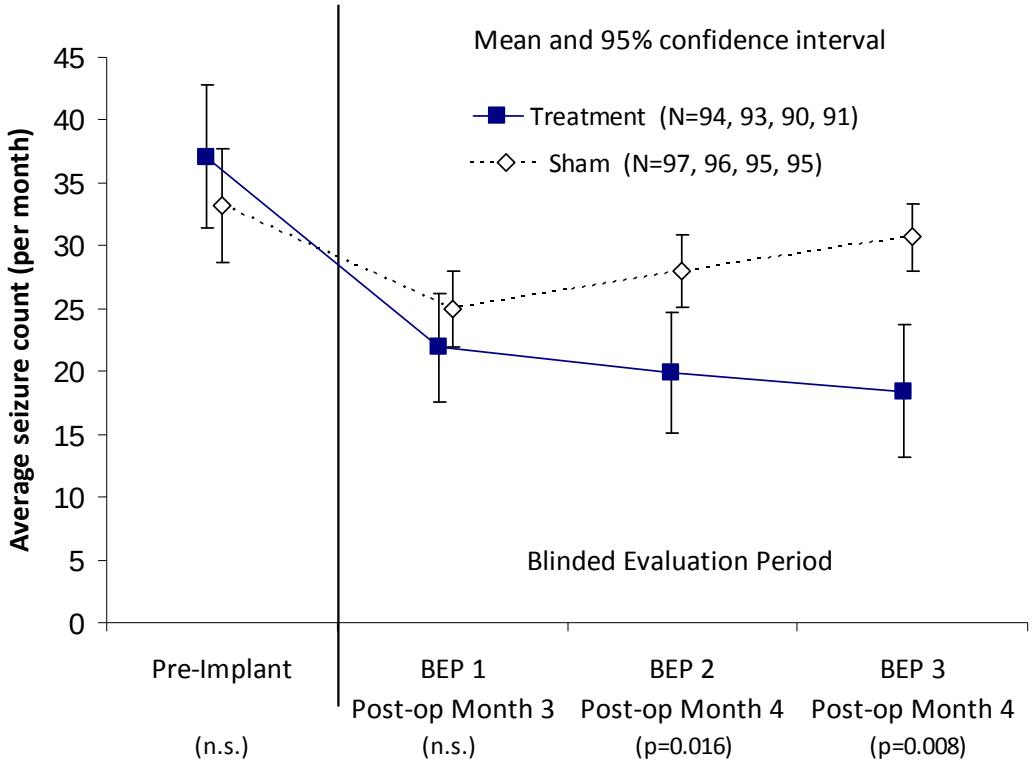
	% Change in Seizure Frequency[1] [95% confidence interval]		
	Treatment (N=97)	**Sham** (N=94)	**P value[2]**
Entire Blinded Evaluation Period (BEP)	**-37.9% [-46.7%, -27.7%]**	**-17.3% [-29.9%, -2.3%]**	**0.012**
	By Month		
BEP 1 (Post-Op Month 3)	-34.2% [-44.1%, -22.6%]	-25.2% [-37.1%, -11.1%]	0.279
BEP 2 (Post-Op Month 4)	-38.1% [-47.3%, -27.3%]	-17.2% [-30.5%, -1.3%]	0.016
BEP 3 (Post-Op Month 5)	-41.5% [-52.0%, -28.7%]	-9.4% [-29.5%, 16.4%]	0.008

[1] Using GEE: percent change calculated as (eβ-1)*100% where for the Sham group is the parameter estimate of the Time covariate and for the Treatment group is the parameter estimate of the Time covariate + the parameter estimate of the Group-by-Time covariate.

[2] P-value of Group-by-Time interaction, GEE.

Data as of 5/12/2011

Figure 17: Pivotal Study – Mean seizure frequency during the Blinded Evaluation Period by month (GEE)



Data as of 5/12/2011

10.1.2 Modifications to the Pre-Specified GEE model

The pre-specified GEE model used daily seizure count data, assumed a Poisson distribution, and did not adjust for covariates. The pre-specified model included estimation of a scale parameter to account for overdispersion of the variance. As such, model-based standard errors were to be used; model-based standard errors include the scale parameter, whereas empirical standard errors do not use the scale parameter. While the pre-specified model yielded a statistically significant result, it was evident that this GEE model did not adequately account for the large variance in daily seizure count data within and across subjects.

Diagnostic metrics generated by standard statistical software indicated that the pre-specified GEE model was not correctly specified (i.e., the data did not fit the model assumptions).

- First, with a properly specified GEE model, the empirical and model-based SE estimates are similar.[100] In the pre-specified model, the empirical SE was 3 times the model-based SE (**Table 16**, row 1), which results in highly discrepant p-values (model-based $p < 0.0001$; empirical $p = 0.15$).
- Second, the overdispersion parameter, a metric provided in standard statistical packages, should be near 1. An overdispersion parameter much greater than 1 (or much smaller than 1) is indicative of an incorrectly specified model or outliers in the data.[101] The overdispersion parameter in the pre-specified model was nearly 9 (**Table 16**, row 1).

Both the discrepancy between the empirical and model-based SEs and the large overdispersion parameter indicate that the pre-specified model was not appropriate for the seizure data. Therefore FDA and NeuroPace agreed that a modified analysis would be necessary to interpret the study results. The modifications decided upon in discussion with FDA were to group seizure data by month, assume a negative binomial distribution, and include clinical covariates used in randomization (rationale for the modifications is provided in **Section 15.1**). In the modified GEE analysis, the model-based and empirical standard errors were similar (having a ratio of 1.1) and the overdispersion parameter was near 1 (ϕ= 1.5, **Table 16**, row 2). These metrics near 1 provide confidence that the modified analysis is appropriate for the seizure count data.

Six additional *post hoc* GEE analyses were considered by FDA (**Table 16**, rows A-F). However, in all cases, either the empirical and model-based standard errors were considerably different (empirical-to-model-based ratio > 1) or the overdispersion parameter was much greater than 1. When either metric deviates from 1, the appropriateness of the analysis is called into question.[100]

Table 16: Pivotal Study – GEE Models: Diagnostic Metrics

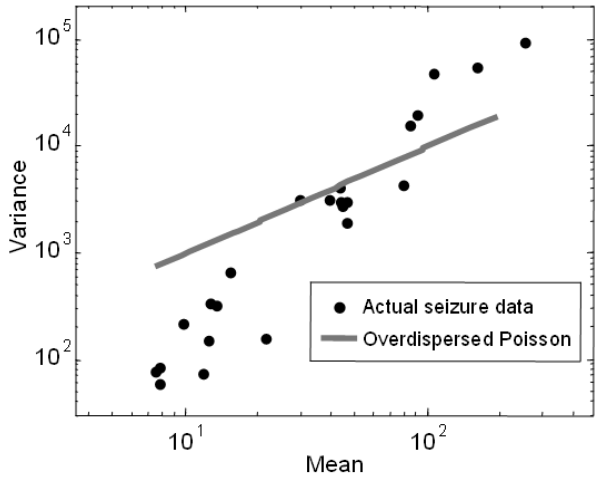
	Analysis description	Parameter estimate of Treatment Effect (log scale)	Standard Error of Treatment Effect			Over-dispersion parameter (ϕ, should be near 1)
			Empirical	Model-based	Empirical-to-model-based ratio (should be near 1)	
1	Pre-specified GEE	-0.251	0.175	0.058	3.0	8.9
2	Modified GEE	-0.287	0.115	0.104	1.1	1.5
	Other GEE Models considered by FDA (i.e. depicted in FDA's "Forest Plot") [1]					
A	NegBin / NoCov / Monthly	-0.266	0.167	0.148	1.1	2.3
B	NegBin / Cov / Daily	-0.259	0.122	0.042	2.9	1.2
C	NegBin / NoCov / Daily	-0.256	0.167	0.052	3.2	1.7
D	Poisson / Cov / Monthly	-0.210	0.217	0.165	1.3	104.8
E	Poisson / NoCov / Monthly	-0.239	0.221	0.214	1.0	181.9
F	Poisson / Cov / Daily	-0.243	0.177	0.046	3.9	5.5

[1] Poisson = overdispersed Poisson variance function; NegBin = negative binomial variance function.
Daily = daily seizure count data; Monthly = monthly seizure count data.
Cov = inclusion of clinical characteristics used in randomization; NoCov = no clinical covariates.

Misspecification of the GEE model (in other words, assuming characteristics of the data that are incorrect) may cause a significant loss of efficiency (disregarding information in the data) and/or provide an uninterpretable result. For example, when the model assumes an overdispersed Poisson variance function, the best fit that can be provided by the model is shown in **Figure 18**, where the actual mean-variance relationship of the seizure data (dots) is shown with the overdispersed Poisson model-fitted mean-variance relationship (line). Due to the requirement that there be a linear mean-variance relationship, the fit to the raw seizure data cannot be improved. When the negative binomial variance function is assumed, the fit to the seizure data is much improved (**Figure 19**). Using an inadequate variance function can significantly reduce the efficiency of an analysis.[106,107] In this case, using the overdispersed Poisson variance function is so inefficient that it is like throwing away over 70% of the patient data relative to using the negative binomial distribution function.

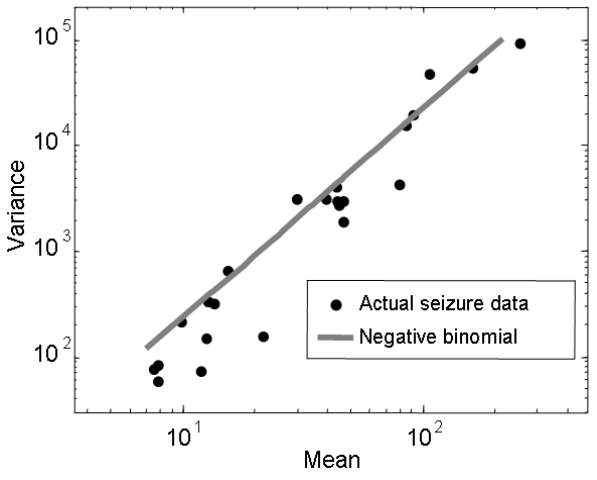
For these reasons, the pre-specified GEE model should not be used to interpret the study results. Instead, study results and discussion are based on the modified GEE model, which appropriately accounts for the variability in the data.

Figure 18: Actual vs. modeled mean-variance relation for the overdispersed Poisson model (var = $\phi\mu$)



Data as of 5/12/2011

Figure 19: Actual vs. modeled mean-variance relation for the negative binomial model (var = $\phi(\mu+k\mu^2)$)



Data as of 5/12/2011

10.1.3 Analyses Supporting Robustness of the Treatment Effect

The effectiveness results show that the magnitude of the seizure reduction in the Treatment compared to Sham groups (the treatment effect) is -0.29, which translates to a 25% reduction of seizures in the Treatment group over the Sham. Sensitivity analyses demonstrate robustness of the treatment effect; the treatment effect size is not altered when the few subjects with potentially significant protocol deviations or extreme data are excluded, and is not sensitive to imputation of missing data. Moreover, the results are consistent across pre-specified GEE sensitivity analyses. Two *post hoc* analyses were performed at FDA's suggestion. These analyses also support robustness of the treatment effect: 1) a bootstrap analysis demonstrates that the results are reproducible, and 2) an analysis excluding influential patients demonstrates that the results are maintained even with the removal of several influential patients.

10.1.3.1 *Pre-specified Per-protocol Analysis*

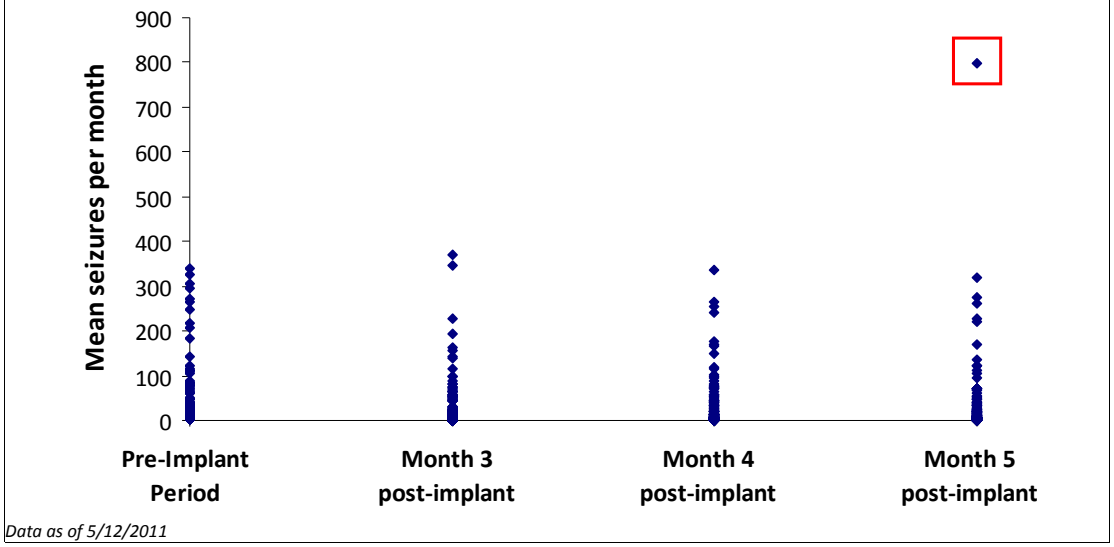
The treatment effect is robust to exclusion of subjects with significant protocol deviations. As pre-specified, the primary effectiveness endpoint analysis was repeated excluding data from subjects with protocol deviations that could seriously affect the integrity of the data collected, e.g. a "per-protocol" analysis. 9 such subjects were identified: 6 had medication changes during the Pre-Implant or Blinded Evaluation Period, 2 had inadequate pre-implant seizure counts, and 1 had intentional partial removal of hippocampal tissue from the temporal lobe during the Neurostimulator and Leads implant procedure. The primary effectiveness endpoint analysis repeated excluding data from these 9 subjects (the Per-Protocol Population) shows that the treatment effect remained significant (p = 0.027), demonstrating that removing these subjects does not materially change the conclusions of the primary endpoint analysis.

10.1.3.2 *Exclusion of Extreme Data*

The treatment effect is robust to exclusion of extreme data. Although there were no subjects identified as outliers based on the clinical assessment, the data were examined with respect to extreme data. One subject had a high seizure frequency during the third month of the Blinded Evaluation Period (**Figure 20**). Although the data point was high, the seizure frequency was not qualitatively different from other seizure frequency data reported for this subject during other periods of the study. Thus, this data point was not considered to be an outlier.

Nevertheless, sensitivity analyses were conducted to assess whether or not this subject and this data point had a large influence on the outcome by (1) removing the single data point and (2) removing all of the subject's data from the analysis. In both cases, with the single data point removed and with the subject removed, the treatment effect (Group-by-Time interaction) remained significant (p = 0.021 and p = 0.037, respectively).

Figure 20: Pivotal Study – Mean seizures per month



Data as of 5/12/2011

10.1.3.3 *Pre-Specified Missing Data Analyses*

The treatment effect is robust to missing data imputation. Pre-specified analyses assessed the impact of missing data on the primary effectiveness endpoint. Results of the missing data analyses demonstrate that the missing data do not bias the results and that the treatment effect was significant for all methods of data imputation.

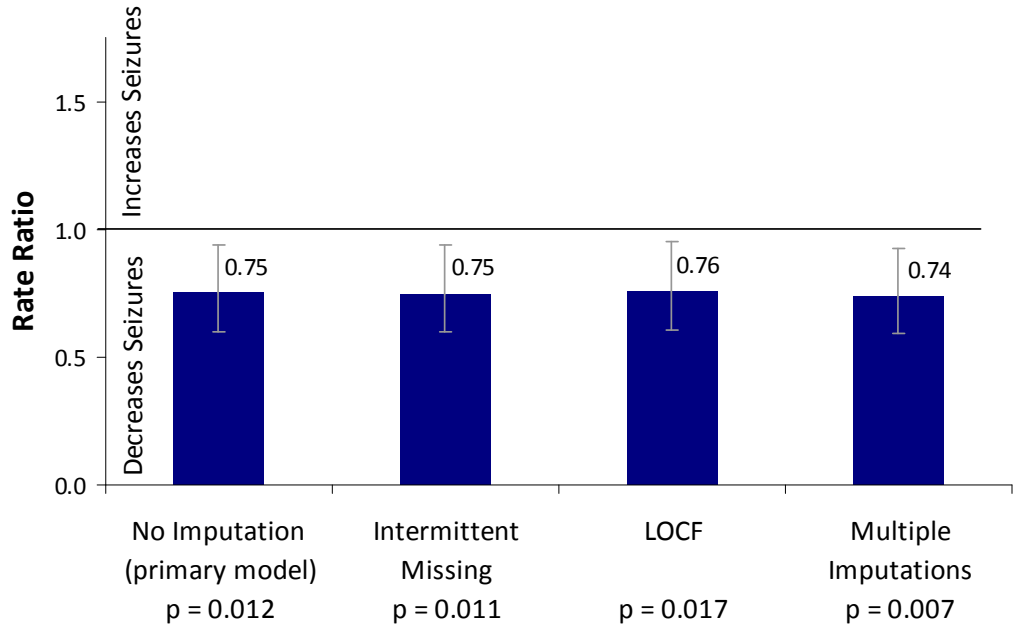
Out of a maximum possible number of observations for the primary effectiveness endpoint analysis of 32,088 [191 subjects * (84 observations in the Pre-Implant Period + 84 observations in the Blinded Evaluation Period)], a total of 31,434 data points were collected. Therefore, only 2% of the observations were missing.

Missing data were imputed using three different methods. For subject data that were 'intermittent' missing, seizure counts for each missed day were imputed by averaging the seizure counts of the latest and earliest non-missed days before and after the missed day (respectively). For subject data that were truncated (e.g., if the subject withdrew from the study before the end of the Blinded Evaluation Period), analyses were performed using two different methods. In the first method,

missing seizure count data were imputed with randomly chosen values from non-missing observations of subjects within the same stratus. In the second method, truncated missing data were imputed using the last observed value "carried forward" (LOCF).

Results demonstrate that the missing data do not bias the results (**Figure 21**). In all cases, imputation of missing data did not change the estimate of the treatment effect by more than 5%, and in all cases the p-value remained statistically significant ($p < 0.02$).

Figure 21: Pivotal Study – Rate ratios from GEE analyses with missing data imputed



Rate ratio = ratio of reduction in seizures in the Treatment group relative to the Sham group. A rate ratio < 1 indicates that the Treatment group had a greater reduction in seizures than the Sham group. LOCF = Last observation carried forward. Error bars = 95% confidence interval.
Data as of 5/12/2011

10.1.3.4 *Pre-specified GEE Sensitivity Analyses*

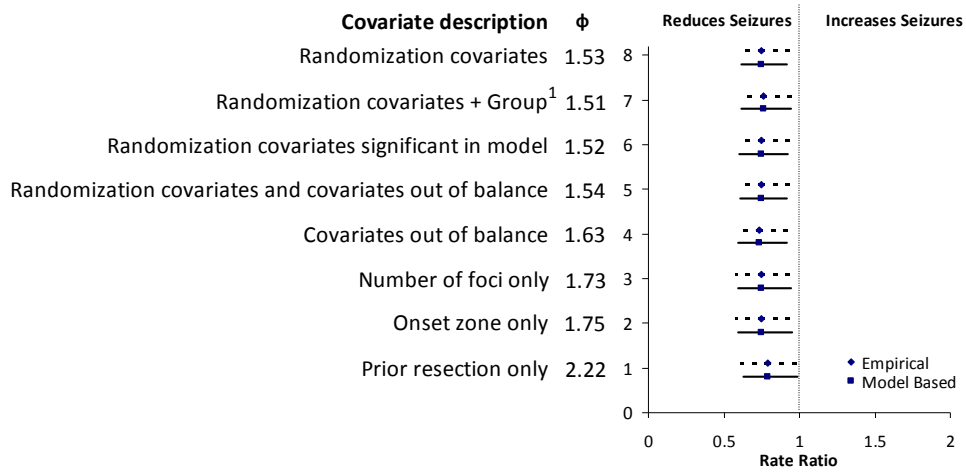
The treatment effect is robust to model modifications. Pre-specified sensitivity analyses included adjusting for clinical characteristics found to be out of balance between the Treatment and Sham groups, and including the main effect of group. Results from these analyses demonstrate that the treatment effect is robust to inclusion of different clinical covariates; across all models, there is a consistent reduction in seizures in the Treatment group of approximately 25% beyond the reduction in the Sham group.

Figure 22 presents the rate ratios and confidence intervals for 8 different models, adjusting for different clinical characteristics as pre-specified. A rate ratio is the ratio of the reduction in seizures in the Treatment group relative to the Sham group; a rate ratio < 1 indicates that the Treatment group had a greater reduction in seizures than the Sham group. The clinical characteristics considered were those used in the adaptive randomization process (onset zone, number of foci, and prior resection), the clinical characteristics found to be out of balance ($p \leq 0.1$) between the Treatment and Sham groups (number of foci, and prior intracranial EEG monitoring), and the main effect of group, which adjusts for differences in baseline seizure frequency between Treatment and Sham groups.

For each model, the 95% confidence intervals are shown for both the empirical and model-based methods for estimating the SE. The model-based method was pre-specified; the empirical method was preferred by FDA. The consistency between the empirical and model-based confidence intervals provides confidence that the model is properly specified. Moreover, the consistency across models demonstrates that the results are robust to inclusion (and exclusion) of different clinical covariates. With the exception of the poorest fitting model (Prior resection only), the treatment effect maintains statistical significance.

Across all of these models, the rate ratio is around 0.75, which corresponds to an additional reduction in seizure frequency in the Treatment group of 25% beyond the reduction in the Sham group, for a total reduction in seizure frequency in the Treatment group of approximately 38%. The consistent results across a number of models support the robustness of the positive effect of treatment with the RNS System.

Figure 22: Pivotal Study – Rate ratios from pre-specified GEE sensitivity analyses with different clinical covariates



[1] "Group" covariate adjusts for differences in baseline seizure frequency between Treatment and Sham groups.

Rate ratio = ratio of reduction in seizures in the Treatment group relative to the Sham group.

ϕ = overdispersion parameter.

The models are ordered from best to worst fit using quasi-likelihood information criterion (QIC), which is the standard quantitative goodness-of-fit metric for assessing how well each GEE model fits the data (smaller, more negative QIC indicates better fit).

Data as of 5/12/2011

10.1.3.5 *Summary of Sensitivity Analyses*

Sensitivity analyses of the primary effectiveness endpoint demonstrate that the treatment effect is robust (**Table 17**). The treatment effect is statistically significant when analyzed for the intent-to-treat population using the pre-specified as well as the agreed-upon modified primary GEE model. The treatment effect remains statistically significant when subjects with significant protocol deviations are excluded (a pre-specified sensitivity analysis). The treatment effect is also statistically significant when extreme data are excluded. Furthermore, the treatment effect is robust to missing data imputation (a pre-specified sensitivity analysis). Additionally, the treatment effect is statistically significant when the model is modified to include the 'Group' covariate and covariates that were out

of balance (both pre-specified sensitivity analyses). Refer to **Appendix 15.1** for details regarding specific analyses.

Table 17: Pivotal Study – Summary of primary and sensitivity analyses

Analysis Description		N	Treatment Effect P-value[1]
Pre-specified primary GEE model		191	< 0.0001
Agreed upon modified GEE model		191	0.0123
Pre-specified Per-Protocol analysis		182	0.0267
Exclusion of extreme data	Removing data point	191	0.0213
	Removing subject	190	0.0372
Pre-specified missing data imputation	Intermittent missing	191	0.0109
	LOCF[2]	191	0.0165
	Multiple imputations	191	0.0074
Pre-specified adjusting for covariates[3]	Inclusion of 'Group' covariate	191	0.0175
	Covariates out of balance	191	0.0115

[1] The p-value for the pre-specified primary GEE model refers to the model-based p-value as pre-specified; all others refer to the empirical p-value as requested by FDA.
[2] LOCF = Last observation carried forward.
[3] **Table 6** in **Appendix 15.1** provides a complete list of the analyses adjusting for different covariates.

10.1.3.6 *Post Hoc Bootstrap Analysis*

The robustness of the treatment effect is further supported by the results of a *post hoc* bootstrap analysis that shows a < 2% probability that under the null hypothesis the results of the Pivotal study could have occurred by chance. Bootstrap analyses are powerful methods to assess the accuracy and reproducibility of statistical results using minimal assumptions. FDA suggested that a *post hoc* bootstrap analysis be conducted to assess the likelihood that the results observed in the Pivotal study could have occurred by chance.

The bootstrap analysis was conducted by creating 2500 simulated datasets. For each simulated dataset, 97 subjects were chosen randomly from the entire population of 191 subjects and assigned to the Treatment group. Another 94 subjects were chosen randomly from the entire population and assigned to the Sham group. In other words, simulated study datasets were generated without respect to the patient's original treatment allocation. To estimate the consistency of this result, the bootstrap analysis was performed 5 times with 2500 simulated datasets each.

The bootstrap analysis shows that there was < 2% probability that under the null hypothesis the results of the Pivotal study could have occurred by chance. The results were consistent across the 5 bootstrap analyses, and support the true effect of treatment. **Appendix 15.1** provides additional detail.

10.1.3.7 *Post Hoc Analysis Excluding Influential Subjects*

FDA performed a *post hoc* sensitivity analysis selectively removing two Sham subjects identified by FDA as influential using a metric called cluster-level Cook's distance. Cook's distance estimates the amount of influence each subject has on the overall result. Importantly, these two subjects were not outliers based on a standard definition of outlier using Cook's distance (a value > 1).[108] These subjects had a Cook's distance of 0.11 and 0.10. Additionally, these subjects were not clinical or

statistical outliers: the subjects were not those with the highest seizure frequency, nor were they the subjects who had the largest percent change in seizure frequency. In fact, there were 20 subjects with a similar percent change in seizure frequency as the two identified in this analysis.

FDA concluded from this analysis that the primary effectiveness endpoint result appears to be sensitive to the inclusion of these two subjects because their removal results in a loss of statistical significance in the empirical but not the model-based p-value. While it is not recommended that subjects be removed from analyses, as a diagnostic exercise, NeuroPace further extended the sensitivity analysis. Extension of this analysis by sequential elimination of other subjects demonstrates that the statistical significance of the treatment effect is not dependent solely on the inclusion of influential subjects.

The properly executed deletion of influential subjects shows no evidence of a lack of robustness. Statistical significance is maintained in both the empirical and model-based p-values with deletion of the top 1, 3, 4, 5, 6, 7, and 8 most influential subjects. Loss of statistical significance in only the empirical p-value only with deletion of two influential subjects but not with deletion of other influential subjects simply reflects the variability inherent in sampling of real data.

Table 18: Pivotal Study – Sequential exclusion of most influential patients

# Patients excluded	Empirical p-value	Model-based p-value
None (original)	0.012*	0.006*
1	0.037*	0.012*
2	0.086	0.029*
3	0.012*	0.004*
4	0.026*	0.006*
5	0.014*	0.003*
6	0.032*	0.011*
7	0.024*	0.006*
8	0.045*	0.016*
9	0.081	0.039*
10	0.141	0.085

* Statistically significant results ($p < 0.05$)

10.1.4 Secondary Endpoints and Additional Analyses

The secondary effectiveness analyses were intended to provide supportive evidence for the superiority of the clinical response in the Treatment group compared to the Sham group during the Blinded Evaluation Period. Pre-specified secondary effectiveness analyses are responder rate, change in mean seizure frequency, proportion of seizure-free days, and self-reported seizure severity according to the Liverpool Seizure Severity Scale (LSSS). In addition, FDA requested a *post hoc* analysis of median percent reduction in seizures.

The secondary endpoints are less sensitive than the primary endpoint because they do not account for the significant variability in seizure data across subjects. However, these analyses support the conclusion of the primary endpoint analysis: the Treatment group experiences a clinically significant reduction in the frequency of disabling seizures that is greater than in the Sham stimulation group. Although the secondary endpoints did not demonstrate a statistically significant difference between the Treatment and Sham groups for the Blinded Evaluation Period, the secondary endpoints consistently support greater improvement in subjects in the Treatment group than in the Sham group.

10.1.4.1 *Change in Mean Seizure Frequency*

The change in mean seizure frequency for subjects in the Treatment and Sham groups over the entire Blinded Evaluation Period compared to the Pre-Implant Period is shown in **Table 19**. Although there is not a statistically significant difference in the mean reduction in seizures between the Treatment and Sham groups, the reduction of seizures in the Treatment group (-11.4) was about twice that of the Sham group (-5.3). As an additional analysis (not pre-specified), the within group reduction in mean seizure frequency during the Blinded Evaluation Period was compared to the Pre-Implant Period; this was significant in the Treatment group ($p < 0.001$), but not in the Sham group ($p = 0.195$).

Table 19: Pivotal Study – Change in mean seizure frequency: Blinded Evaluation Period, Treatment vs. Sham

	Mean Frequency of Seizures (seizures/month)		
Period	**Treatment (N = 96)[1]** (mean ± SD)	**Sham (N = 93)[1]** (mean ± SD)	**Across Group P-value[3]**
Pre-Implant	33.8 +/- 57.0	35.2 +/- 67.4	--
Blinded Evaluation	22.4 +/- 40.0	29.9 +/- 66.5	
Change	-11.4 +/- 32.1	-5.3 +/- 39.1	0.238
Within-Group P-value[2]	< 0.001	0.195	

[1] Includes subjects who have at least 1 day of data in the Pre-Implant and Blinded Evaluation Periods.
[2] Additional analysis (not-pre-specified) by paired t-test.
[3] Pre-specfied secondary analysis by two-sample t-test.
Data as of 5/12/2011

10.1.4.2 *Seizure-Free Days*

Subjects in both the Treatment and Sham groups had an increase in the proportion of seizure-free days during the Blinded Evaluation Period compared to the Pre-Implant Period. While the Treatment group experienced a greater increase in the proportion of seizure-free days than the Sham group (8% vs. 6%), the difference was not statistically significant. Refer to **Table 41** in **Appendix 15.7**

10.1.4.3 *Responder Rate*

The responder rate is the percentage of subjects who experienced a 50% or greater reduction in disabling seizures during the Blinded Evaluation Period compared to the Pre-Implant Period. The responder rate in the Treatment group was 29%, the responder rate in the Sham group was 27%; the difference between the groups was not statistically significant. Refer to **Table 42** in **Appendix 15.7**.

10.1.4.4 *Change in the Liverpool Seizure Severity Scale (LSSS)*

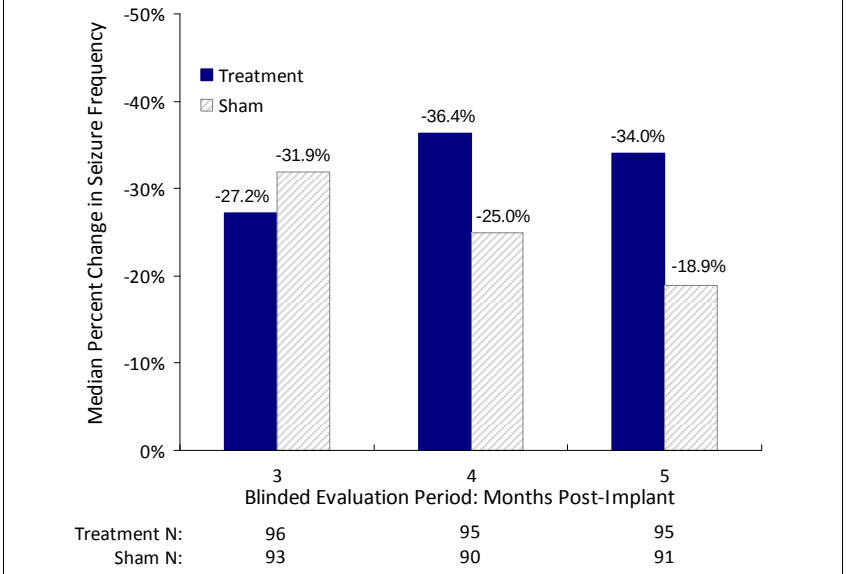
The LSSS 2.0 is a questionnaire in which the subject self-rates the severity of symptoms during and immediately following the most severe seizure experienced in the previous 28 days, such as loss of consciousness, post-ictal confusion, headache and injury. The inventory does not reflect the total number of seizures or post-ictal periods. There was a reduction in the self-reported severity of seizures as measured by the LSSS in both groups during the Blinded Evaluation Period ($p < 0.001$ for both groups per paired t-test), but the difference between groups was not statistically significant ($p = 0.574$). Refer to **Table 43** of **Appendix 15.7**.

10.1.4.5 *Median Percent Reduction*

FDA requested that NeuroPace perform an additional *post hoc* analysis of median percent change. The median percent change in seizure frequency across subjects in the Treatment and Sham groups are presented for each month of the Blinded Evaluation Period in **Figure 23**.

The Treatment and the Sham groups experienced a similar reduction in seizures in the first month of the Blinded Evaluation period (3 months post-implant). Over the fourth and fifth months post-implant (the second and third months of the Blinded Evaluation Period) the response in the Sham group lessens, while the response in the Treatment group continues. By the end of the Blinded Evaluation period, the Treatment group experienced a 34% median reduction in seizure frequency, while the Sham group had less than a 20% reduction in seizures.

Figure 23: Pivotal Study – Median percent change by month during the Blinded Evaluation Period compared to the Pre-Implant Period



10.1.5 Subset Analyses

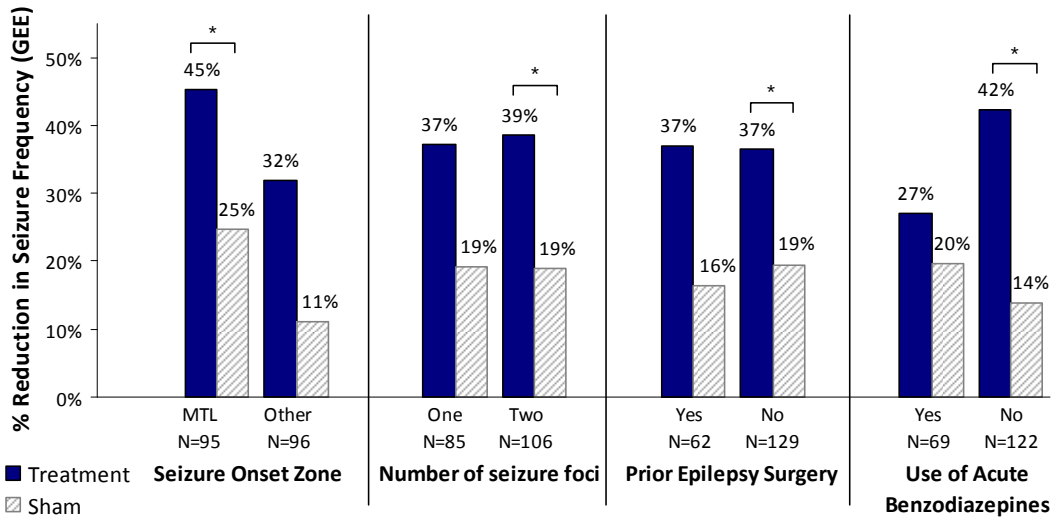
10.1.5.1 *Pre-specified Subset Analyses*

Subset analyses indicate that patients respond to treatment with the RNS System regardless of seizure onset zone, number of seizure foci (1 or 2), and prior surgery for epilepsy. It was recognized that there would not be sufficient numbers of subjects in each subset to demonstrate statistical significance. Nevertheless, these subset analyses were pre-specified to evaluate whether these clinical characteristics used as randomization strata could affect the clinical outcome of treatment with the RNS System. An additional pre-specified subset analysis was also performed for subjects who used acute benzodiazepine medications as a seizure rescue and for subjects who had a change in their AEDs from the Pre-Implant Period through the end of the Blinded Evaluation Period.

In all subsets, the Treatment group experienced a greater reduction than the Sham group (**Figure 24**). While the study was not powered to provide effectiveness conclusions within each subset, there was a statistically significant difference between the Treatment and Sham groups for some of the subsets (those with mesial temporal lobe onsets, those with two seizure foci, those who had not had prior surgery, and those who did not use benzodiazepines as a rescue medication). For each

subset, the possible impact of each of these factors on the clinical response was also assessed quantitatively using GEE analyses with interaction terms. None of the interaction terms were significant, demonstrating that the clinical characteristics do not predict the likelihood that there will be a favorable response to treatment.

Figure 24: Pivotal Study – Seizure frequency percent change by subset



* Statistically significant difference between Treatment and Sham ($p < 0.05$).
Data as of 5/12/2011

The investigational plan also pre-specified subset analyses based on changes in AEDs. Six subjects had changes in their AED treatment regimen during the Pre-Implant Period through the Blinded Evaluation Period: 3 subjects in the Pre-Implant Period and 3 subjects in the Blinded Evaluation Period. This sample size is too small to draw conclusions with respect to a difference between the groups.

Because any significant changes to the AED regimen were protocol deviations, these 6 subjects were excluded from analyses of the Per-Protocol Population. Results of the Per-Protocol analysis indicate that the Treatment Effect remains significant with the subjects who had significant protocol deviations (including AED changes) removed from the analysis ($p = 0.027$).

The results from these subset analyses demonstrate that the likelihood of experiencing a meaningful clinical benefit with treatment by responsive stimulation is not influenced by the area of the brain from which seizures arise, whether the seizures arise from one or two brain locations, whether an epilepsy surgery was previously performed or whether a subject uses rescue benzodiazepines.

10.1.5.2 *Post hoc analysis of baseline seizure frequency*

FDA also evaluated subsets of patient by seizure frequency. The subsets were those with 0-28 seizures per month (N=140), those with 29-56 seizures per month (N=20), those with 57-84 seizures per month (N=12), and those with more than 84 seizures per month (N=19). Note that the N's are small in several of the subsets and the study was not powered to demonstrate statistical significance in any of these subsets. However, in all subsets, the Treatment group improved relative to the Sham group, and in the subset of 19 patients with the highest seizure frequency, the Treatment Effect was significant ($p < 0.019$). The interaction terms between baseline seizure frequency categorization and the treatment effect were not significant, indicating that baseline seizure frequency is not predictive of the response to treatment.

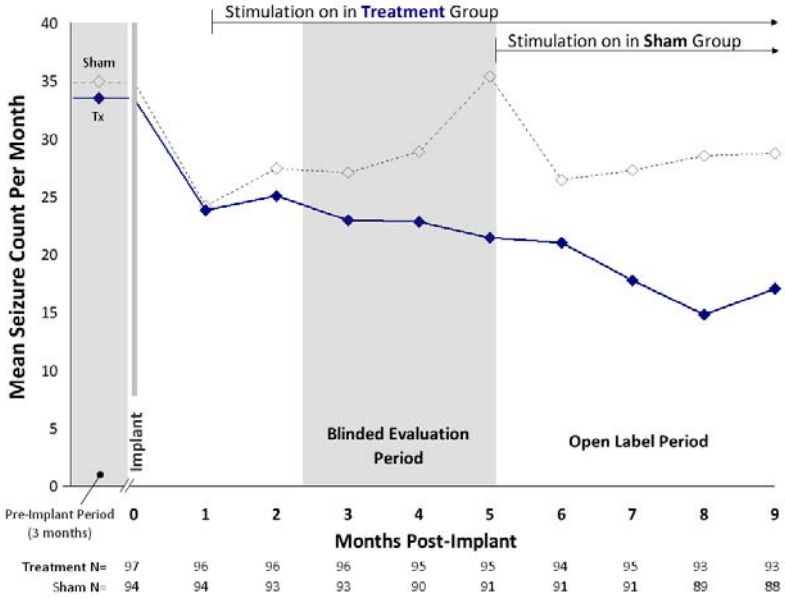
10.1.6 Open Label Period

The Open Label Evaluation Period began at 6 months post-implant and continued to 2 years post-implant. At the 20-week visit, subjects in the Sham group were able to receive responsive stimulation for the first time. Note that the randomization group was not disclosed to subjects or the Assessment investigators at any time during the Pivotal study. In contrast to the Treatment group whose stimulation programming occurred weekly during the Stimulation Optimization Period, stimulation programming for the Sham group during the Open Label period occurred monthly, as specified in the protocol.

10.1.6.1 *Reduction in Seizures in Sham Group with Responsive Stimulation*

The seizure reduction in subjects in the Sham group when responsive stimulation was first enabled demonstrates the effectiveness of responsive stimulation independent of the effect of the implant procedure. When subjects in the Sham group first received responsive stimulation in the Open Label Period, there was an immediate reduction in seizure frequency (**Figure 25**). The reduction in mean seizure frequency in the Sham group over a 3-month period, beginning one month after stimulation had been enabled (months 6-9 post-implant) is significant relative to their Pre-Implant Period ($p = 0.04$, **Table 44** in **Appendix 15.7**) and translates to a reduction of nearly 8 seizures per month. This seizure frequency reduction can be attributed to a favorable effect of stimulation, not an implant or placebo effect. The implant effect was waning in the Sham subjects by the end of the Blinded Evaluation Period, and subjects and the Assessment investigators did not know to which group subjects had been randomized. Also, subjects originally randomized to the Treatment group did not have a similar abrupt change in seizure frequency as they entered the Open Label Period, even though they also did not know whether they had already been receiving responsive stimulation.

Figure 25: Pivotal Study – Mean percent count per month: Pre-Implant Period through 9 months



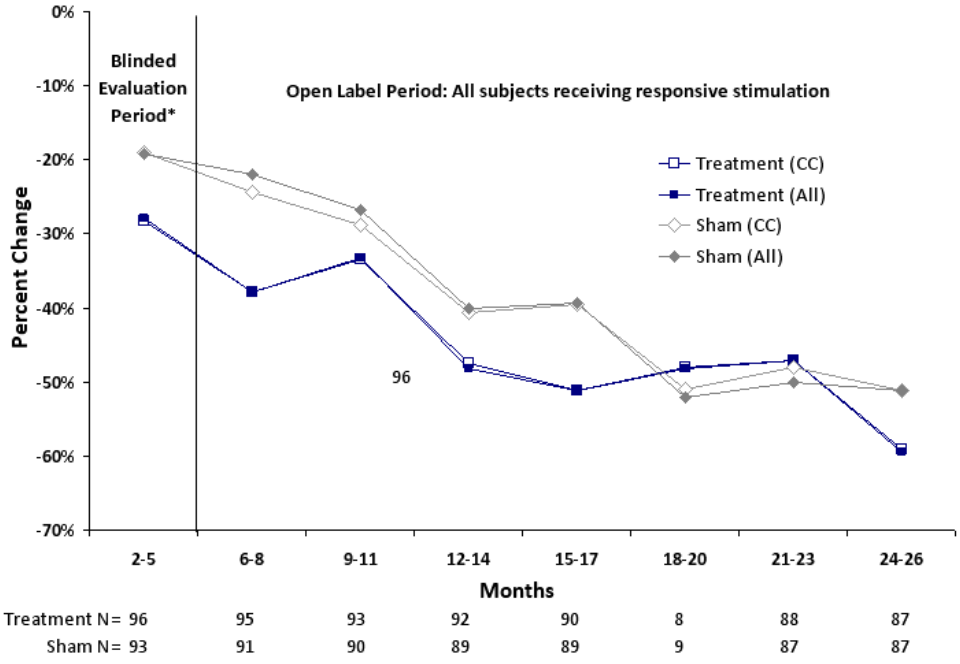
N = number of subjects in Sham group for which any seizure data are available during that interval.
Data as of 5/12/2011

10.1.6.2 *Median Percent Change in Seizures: Open Label Period*

The median percent change during the Open Label Period is presented in **Figure 26** separately for the Treatment and Sham groups. There is a sustained long-term reduction in seizures in both groups during the Open Label Period when both groups are receiving responsive stimulation. The median percent reduction is 44% at 1 year post-implant and is 53% at 2 years. This improvement in the Open Label Period is statistically significant ($p < 0.0001$, GEE).

To illustrate that the improvements are not due to "drop-outs", analyses in **Figure 26** are presented for all subjects for whom any data were available (All) as well as for a constant cohort (CC = subjects for whom data were available for all periods). Because the drop-out rate is low, the constant cohort plots match closely with the "All" subject plots.

Figure 26: Pivotal Study – Median percent reduction in seizure frequency
(All subjects and constant cohort)



N = number of subjects in Sham group for which any seizure data are available during that interval.
* During the Blinded Evaluation Period only the Treatment group had responsive stimulation enabled.
Data as of 5/12/2011

10.1.6.3 *Responder Rates: Open Label Period*

There was a sustained long-term reduction in seizures in subjects treated with responsive stimulation as measured by the responder rate. The responder rates for the subjects randomized to the Treatment and Sham groups during the Blinded Evaluation Period and for all subjects over the Open Label Evaluation Period are presented in **Table 20**. During Months 6-8, subjects in the Treatment group had already been receiving responsive stimulation for 4 months, whereas Sham group subjects had just begun. The responder rate for both groups was 43.6% for all subjects combined at 1 year after implant and reached 54.6% at 2 years. Using the most recent 3 months of data provided in the Open Label Period of the Pivotal study (a last observation carried forward analysis), 9% of subjects were seizure free and 54% of subjects were responders (**Figure 32** of **Appendix 15.7**).

Table 20: Pivotal Study – Responder rates: Open Label Period

Analysis Population	(%, n/N[1])						
	Months 6-8	**Months 9-11**	**Months 12-14**	**Months 15-17**	**Months 18-20**	**Months 21-23**	**Months 24-26**
Combined	36.0% (67/186)	34.4% (63/183)	43.6% (79/181)	46.9% (84/179)	51.1% (91/178)	49.1% (86/175)	54.6% (95/174)
Treatment	41.1% (39/95)	38.7% (36/93)	47.8% (44/92)	51.1% (46/90)	49.4% (44/89)	47.7% (42/88)	58.6% (51/87)
Sham	30.8% (28/91)	30.0% (27/90)	39.3% (35/89)	42.7% (38/89)	52.8% (47/89)	50.6% (44/87)	50.6% (44/87)

[1] All randomized subjects with seizure data during the specified 3-month period.
Data as of 5/12/2011

10.1.6.4 *Quality of Life*

The clinical significance of the seizure reduction with responsive stimulation is demonstrated by significant improvements in quality of life, as measured by a validated and widely used inventory of quality of life in persons with epilepsy (QOLIE-89). At baseline, study subjects had lower overall quality of life than established norms for persons with moderate epilepsy.[109] There were no statistical differences between the Treatment and Sham groups at the end of the Blinded Evaluation Period (**Table 45** of **Appendix 15.7**). At 1 and 2 years after implantation, there were statistically significant group (**Table 21**) and individual (**Table 40** of **Appendix 15.7**) improvements in quality of life overall and in 9 of the 17 primary scale scores, indicating that subjects had a more positive perception of their cognitive function, relationships and social function, overall health and vulnerability to seizures. Improvements in health discouragement and seizure worry are strongly associated with improved quality of life in persons with intractable epilepsy.[109,110] There were no statistically significant declines in any of the quality of life scales at 1 or 2 years post-implant.

Table 21: Pivotal Study – Changes in QOLIE-89 primary scale scores: 1 and 2 years

Overall/Primary Scale (T-scores)	1 Year Post-Implant			2 Years Post-Implant		
	N	Change from Baseline		N	Change from Baseline	
		mean ± SD	P-value[1]		mean ± SD	P-value[1]
QOLIE-89 Overall Score	166	3.57 ± 8.89	<0.001	154	3.99 ± 10.37	<0.001
Seizure Worry	167	4.54 ± 9.81	<0.001	155	5.22 ± 9.96	<0.001
Health Discouragement	165	4.76 ± 10.92	<0.001	153	4.97 ± 11.03	<0.001
Memory	165	3.09 ± 8.73	<0.001	153	3.06 ± 9.50	<0.001
Language	164	3.53 ± 11.40	<0.001	152	3.66 ± 12.04	<0.001
Attention/Concentration	167	4.36 ± 9.10	<0.001	155	4.22 ± 9.99	<0.001

Table 21: Pivotal Study – Changes in QOLIE-89 primary scale scores: 1 and 2 years

Overall/Primary Scale (T-scores)	1 Year Post-Implant			2 Years Post-Implant		
	N	Change from Baseline		N	Change from Baseline	
		mean ± SD	P-value[1]		mean ± SD	P-value[1]
Work/Driving/Social Function	167	3.31 ± 9.33	<0.001	155	4.07 ± 9.85	<0.001
Energy/Fatigue	167	2.49 ± 9.62	0.001	155	2.08 ± 9.85	0.009
Overall Quality of Life	167	2.16 ± 9.86	0.005	155	1.68 ± 10.35	0.046
Role Limitation - Physical	165	2.46 ± 11.23	0.006	153	3.37 ± 13.06	0.002
Health Perceptions	165	1.52 ± 8.51	0.023	153	0.69 ± 7.36	0.245
Medication Effects	167	1.46 ± 10.00	0.061	155	2.04 ± 10.31	0.015
Emotional Well-Being	167	0.69 ± 8.97	0.322	155	1.41 ± 10.36	0.093
Pain	165	-0.78 ± 10.88	0.357	153	-0.18 ± 12.19	0.852
Social Support	165	0.66 ± 9.85	0.393	153	0.38 ± 10.51	0.655
Role Limitations - Emotional	165	0.23 ± 12.00	0.807	153	0.52 ± 13.50	0.634
Physical Function	165	0.22 ± 11.90	0.815	153	-0.14 ± 11.65	0.878
Social Isolation	165	0.12 ± 10.37	0.881	153	0.42 ± 11.60	0.657

[1] Paired t-test.

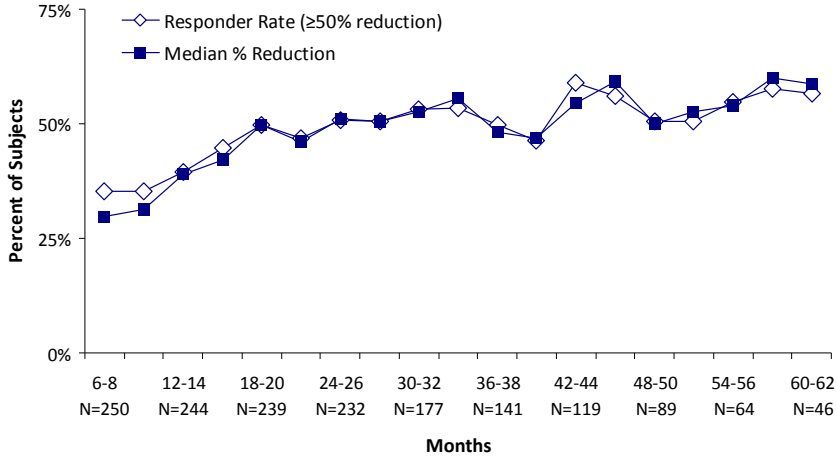
Analysis includes subjects (N) with assessments available at Open Label and Baseline time points.

Data as of 5/12/2011

10.2 Combined Studies: Effectiveness Results

Effectiveness is maintained over years of follow-up. The median follow-up for subjects implanted with the RNS System is 3.3 years. At 1 and 2 years after implant, approximately 70% of subjects experienced a 25% or greater reduction in seizures and approximately 50% experienced a 50% or greater reduction. The magnitude of the reduction in seizure frequency, whether represented as responder rate or median percent reduction in seizures, is maintained in subjects for whom there was longer follow-up as of May 12, 2011 (**Figure 27**).

Figure 27: Combined Studies – Responder rate and median percent reduction in seizures: all subjects through LTT



Data combined from Feasibility, Pivotal and Long-term Treatments studies.

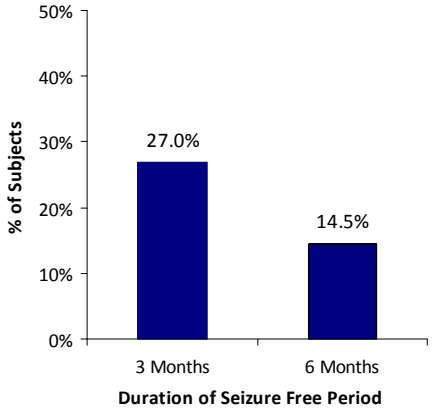
Includes all subjects for whom any data are available for each 3 month period.

Data as of 5/12/2011

Some subjects had periods of seizure freedom (**Figure 28**): 27% had at least one period of 3 months or more with no seizures (69 subjects with 151 periods) and 14.5% had a seizure-free period of 6 months or

more (37 subjects with 55 periods). Seizure-free periods reported in the majority of trials in FDA-approved AEDs for the adjunctive treatment of partial onset seizures is < 15%.[111]

Figure 28: Percent of subjects with seizure-free periods



Data as of 5/12/2011

Patient satisfaction with their response to treatment is evident by the numbers of subjects who choose to continue treatment with the RNS System. 91% of implanted subjects completed the 2-year Feasibility study, and 92% of implanted subjects completed the 2-year Pivotal study. 97% of these subjects elected to enroll in the 7-year Long-term Treatment study. 93% of subjects chose to have their Neurostimulator replaced at expected end of battery service. Note that withdrawing from a study required only that responsive stimulation be programmed off, since the Neurostimulator and Leads are designed to be safely left in place.

10.3 Summary of Overall Effectiveness

Responsive stimulation significantly reduced the frequency of disabling seizures in the Blinded Evaluation Period of the Pivotal Study. The effectiveness of treatment with responsive stimulation is further supported by the extensive open label experience in the Pivotal, Feasibility and Long-term Treatment studies.

- Patients who received responsive stimulation had a reduction in seizures of 37.9%, which was statistically significantly greater than patients who did not receive responsive stimulation (17.3%, p=0.012).
  - These results are robust across a number of statistical analyses, are not altered when extreme data or the few patients with potentially significant protocol deviations are excluded, and are not sensitive to imputation of missing data.
  - Bootstrap analyses establish that there is a < 2% chance that under the null hypothesis these results could have occurred by chance.
- A statistically significant difference in seizure frequency between the Treatment and Sham groups during the Blinded Evaluation period occurred even though there was an effect of the implant procedure that transiently reduced seizure frequency.
- There was a progressive reduction in seizures during the Open Label Period, which was statistically significant.
- Patients receiving responsive stimulation also reported a statistically and clinically significant improvement in quality of life.
- The high subject retention rate indicates that patients were satisfied with treatment.

In conclusion, the effectiveness data demonstrate that responsive stimulation with the RNS System is effective as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years or older with partial onset seizures from no more than 2 foci that are refractory to two or more antiepileptic medications.

11 SAFETY RESULTS

Safety of the RNS System can be confidently assessed by considering the experience of subjects in the Pivotal study and the experience across subjects participating in all studies combined. Treatment with the RNS System was acceptably safe and well tolerated in the 191 subjects implanted in the Pivotal study over a mean follow-up of 2 years, with 379 patient years of implant experience and over 328 patient years experience with responsive stimulation enabled. 256 patients were implanted with the RNS Neurostimulator and Leads across all studies combined with median follow-up period of 3.3 years, over 903 implant years and 819 patient stimulation years. There were no unanticipated device-related SAEs in any RNS System study.

11.1 Pivotal Study: Safety Results

The RNS System Pivotal study met its primary and secondary safety endpoints. The primary safety endpoint demonstrated that the risks associated with the RNS System were no higher than the combined risks associated with implantation of intracranial electrodes for localization procedures and epilepsy resective surgery, and deep brain stimulation (DBS) for movement disorders. There was no difference in the SAE rate in the subjects receiving active stimulation (Treatment) and subjects receiving sham stimulation. Adverse events were consistent with the known risks of implantation of a medical device, seizures and of other therapies for epilepsy. There was no increase in the overall rate of adverse events over time. There were no unanticipated device-related SAEs. The safety data from the Pivotal study are sufficient to demonstrate an acceptable acute and chronic safety profile of the RNS System.

11.1.1 Primary Endpoint

The Pivotal study met the pre-specified primary safety endpoint which required that the rate of subjects experiencing one or more SAEs not exceed the published SAE rates for comparator procedures over the first 4 and 12 weeks after implant (**Table 22**). These data include all SAEs whether reported to be device-related or not.

Table 22: Pivotal Study – Primary safety endpoint

Period	SAE Rate [1]	
	RNS System	Comparator
	% subjects (n/N) [upper 95% CI]	
Acute: Implant – 4 weeks Pre-specified comparator: Intracranial electrodes + surgery	12.0% (23 /191) [16.5%]	15% [20%]
Short-Term Chronic: Implant – 12 weeks Pre-specified comparator: DBS for movement disorders	18.3% (35 /191) [23.4%]	36% [42%]

[1] Upper limit of the one-sided 95% confidence interval, estimated using the Score Interval (also known as the Wilson Interval.[112] Upper limits for literature comparators were pre-specified in the protocol, estimated using the Score Interval based on a sample size of 180.

Data as of 5/12/2011

11.1.2 Secondary Endpoints

Adverse events occurring in the Pivotal study are presented overall and according to the period of the study in which they occurred. During the blinded periods of the study (Stimulation Optimization and Blinded Evaluation Periods), adverse events are presented separately for the Treatment and Sham groups in order to assess the tolerability of responsive stimulation.

11.1.2.1 *Adverse Events: All Post Implant Study Periods*

All adverse events that affected 5% or more of subjects during the Pivotal study are presented in **Table 23**. The most common types of adverse events are those anticipated with the surgical procedure to implant a medical device: implant site pain, procedural headache, and headache. These were typically mild and resolved without intervention. Other common adverse events were nasopharyngitis, upper respiratory tract infection, therapeutic agent toxicity (antiepileptic drug side effects), adverse drug reaction, and injuries due to seizures (contusion and skin laceration).

Table 23: Pivotal Study – Adverse events in ≥ 5% of subjects: all post-implant study periods (N=191)

	Serious		Mild		
	Device-Related[1]	Not Device-Related	Device-Related[1]	Not Device-Related	Total[2]
	%(#) Subjects	%(#) Subjects	%(#) Subjects	%(#) Subjects	%(#) Subjects
Implant site pain	0.5% (1)	--	18.3% (35)	24.1% (46)	37.7% (72)
Procedural headache	0.5% (1)	0.5% (1)	12.0% (23)	16.8% (32)	28.8% (55)
Nasopharyngitis	--	--	--	28.3% (54)	28.3% (54)
Headache	0.5% (1)	--	9.4% (18)	18.8% (36)	25.1% (48)
Therapeutic agent toxicity	--	2.6% (5)	--	21.5% (41)	22.5% (43)
Adverse drug reaction	--	1.0% (2)	--	15.7% (30)	16.8% (32)
Contusion (dts)	--	--	1.0% (2)	16.2% (31)	16.8% (32)
Skin laceration (dts)	1.0% (2)	1.0% (2)	1.0% (2)	14.1% (27)	16.2% (31)
Upper respiratory tract infection	--	--	--	16.2% (31)	16.2% (31)
Complex partial seizures increased	3.1% (6)	2.6% (5)	6.3% (12)	7.3% (14)	15.7% (30)
Influenza	--	1.0% (2)	--	13.6% (26)	14.7% (28)
Depression	--	--	3.1% (6)	11.5% (22)	14.1% (27)
Dizziness	--	--	3.7% (7)	10.5% (20)	13.1% (25)
Complex partial seizures	--	--	7.9% (15)	5.2% (10)	12.6% (24)
Dysesthesia	--	--	7.9% (15)	6.3% (12)	12.6% (24)
Simple partial seizures (sensory)	0.5% (1)	--	6.8% (13)	4.7% (9)	11.0% (21)
Complex partial seizures exacerbated	1.0% (2)	1.0% (2)	4.2% (8)	4.7% (9)	9.9% (19)
Tonic-clonic seizures exacerbated	0.5% (1)	3.1% (6)	5.2% (10)	2.1% (4)	9.9% (19)
Tremor	--	--	1.6% (3)	8.9% (17)	9.9% (19)
Tonic-clonic seizures increased	2.6% (5)	1.0% (2)	5.8% (11)	2.6% (5)	9.4% (18)
Urinary tract infection	--	--	--	9.4% (18)	9.4% (18)
Fatigue	--	--	0.5% (1)	8.4% (16)	8.9% (17)
Head injury (dts)	--	0.5% (1)	--	8.4% (16)	8.9% (17)
Insomnia	--	--	0.5% (1)	7.9% (15)	8.4% (16)
Memory impairment	--	--	5.2% (10)	3.1% (6)	8.4% (16)
Anxiety	--	--	1.0% (2)	7.3% (14)	7.3% (14)
EEG monitoring	0.5% (1)	6.8% (13)	--	--	7.3% (14)
Excoriation (dts)	--	--	--	7.3% (14)	7.3% (14)
Head injury	--	--	0.5% (1)	6.8% (13)	7.3% (14)
Pain in extremity	--	--	0.5% (1)	6.3% (12)	6.8% (13)

Table 23: Pivotal Study – Adverse events in ≥ 5% of subjects: all post-implant study periods (N=191)

	Serious		Mild		
	Device-Related[1]	Not Device-Related	Device-Related[1]	Not Device-Related	Total[2]
	%(#) Subjects	%(#) Subjects	%(#) Subjects	%(#) Subjects	%(#) Subjects
Paresthesia	--	0.5% (1)	2.6% (5)	4.7% (9)	6.8% (13)
Vomiting	--	--	--	6.8% (13)	6.8% (13)
Bronchitis	--	--	--	6.3% (12)	6.3% (12)
Contusion	--	--	--	6.3% (12)	6.3% (12)
Joint injury (dts)	--	--	--	6.3% (12)	6.3% (12)
Muscle twitching	--	--	3.1% (6)	3.7% (7)	6.3% (12)
Photopsia	--	--	5.8% (11)	0.5% (1)	6.3% (12)
Procedural nausea	--	--	1.0% (2)	5.2% (10)	6.3% (12)
Rash	--	--	--	6.3% (12)	6.3% (12)
Simple partial seizures (motor)	--	--	4.2% (8)	3.1% (6)	6.3% (12)
Abdominal pain	--	--	0.5% (1)	5.2% (10)	5.8% (11)
Device interaction	--	--	5.2% (10)	1.0% (2)	5.8% (11)
Implant site swelling	--	--	4.7% (9)	1.0% (2)	5.8% (11)
Seasonal allergy	--	--	--	5.8% (11)	5.8% (11)
Arthralgia	--	0.5% (1)	--	4.7% (9)	5.2% (10)
Back pain	--	--	--	5.2% (10)	5.2% (10)
Implant site infection	3.7% (7)	--	1.0% (2)	0.5% (1)	5.2% (10)
Joint injury	--	0.5% (1)	--	5.2% (10)	5.2% (10)
Nystagmus	--	--	0.5% (1)	4.7% (9)	5.2% (10)

[1] Device-related includes events categorized as device relation uncertain.

[2] Row totals may not add to total as some subjects may have had events in more than one category (mild / serious) or (device-related / not device-related).

dts = due to seizure

Data as of 5/12/2011

11.1.2.2 *Serious Device-Related Adverse Events: All Post Implant Periods*

All SAEs identified by the investigator as device-related or of uncertain relation to the device are provided in **Table 24** by the period of the study in which they occurred. The SAEs are presented by MedDRA Preferred Term in descending order of overall frequency. The most common device-related SAEs were related to infection at the implant site, which was most common in the post-operative period, damage or revisions to the leads, and changes in seizures. Details on these adverse events are provided in **Sections 11.2.2** and **11.2.4**. None of these SAEs caused ongoing medical or neurological consequences.

Table 24: Pivotal Study – All Device-Related[1] Serious Adverse Events by Post-Implant Study Period

	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-12)	Open Label Period		All Study Periods (Post-Implant)
				(Weeks 20 - 52)	(Week 52 - Completion)	
# subjects entering interval / implant years within interval	191 / 14.7	191 / 14.6	189 / 43.2	187 / 113.4	182 / 193.4	191 / 379.2
Preferred Term	% subjects (# subjects)[2] event rate [# events][3]					
Implant site infection	2.6% (5) 0.340 [5]	--	--	1.1% (2) 0.018 [2]	0.5% (1) 0.005 [1]	3.7% (7) 0.021 [8]
Complex partial seizures increased	--	--	1.1% (2) 0.046 [2]	2.1% (4) 0.035 [4]	1.1% (2) 0.010 [2]	3.1% (6) 0.021 [8]
Device lead damage	--	--	--	2.7% (5) 0.044 [5]	0.5% (1) 0.005 [1]	2.6% (5) 0.016 [6]
Tonic-clonic seizures increased	--	--	--	1.1% (2) 0.018 [2]	1.6% (3) 0.016 [3]	2.6% (5) 0.013 [5]
Device lead revision	--	--	--	0.5% (1) 0.009 [1]	1.6% (3) 0.016 [3]	2.1% (4) 0.011 [4]
Complex partial seizures exacerbated	--	--	--	1.1% (2) 0.018 [2]	--	1.0% (2) 0.005 [2]
Depression suicidal	--	--	--	1.1% (2) 0.018 [2]	--	1.0% (2) 0.005 [2]
Extradural hematoma	1.0% (2) 0.136 [2]	--	--	--	--	1.0% (2) 0.005 [2]
Hydrocephalus	1.0% (2) 0.136 [2]	--	--	--	--	1.0% (2) 0.005 [2]
Postictal state	0.5% (1) 0.068 [1]	--	--	0.5% (1) 0.009 [1]	--	1.0% (2) 0.005 [2]
Premature battery depletion	--	--	--	1.1% (2) 0.018 [2]	--	1.0% (2) 0.005 [2]
Skin laceration (dts)	--	--	--	0.5% (1) 0.009 [1]	0.5% (1) 0.005 [1]	1.0% (2) 0.005 [2]
Subdural hematoma (dts)	--	--	--	0.5% (1) 0.009 [1]	0.5% (1) 0.005 [1]	1.0% (2) 0.005 [2]
Acquired epileptic aphasia	--	--	--	0.5% (1) 0.009 [1]	--	0.5% (1) 0.003 [1]
Apraxia	0.5% (1) 0.068 [1]	--	--	--	--	0.5% (1) 0.003 [1]
Cerebral hemorrhage	0.5% (1) 0.068 [1]	--	--	--	--	0.5% (1) 0.003 [1]
Convulsive status epilepticus	--	--	--	--	0.5% (1) 0.005 [1]	0.5% (1) 0.003 [1]
Death	--	--	--	0.5% (1) 0.009 [1]	--	0.5% (1) 0.003 [1]
Dysphemia	0.5% (1) 0.068 [1]	--	--	--	--	0.5% (1) 0.003 [1]
EEG monitoring	--	0.5% (1) 0.068 [1]	--	--	--	0.5% (1) 0.003 [1]

Table 24: Pivotal Study – All Device-Related[1] Serious Adverse Events by Post-Implant Study Period

	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-12)	Open Label Period		All Study Periods (Post-Implant)
				(Weeks 20 - 52)	(Week 52 - Completion)	
Headache	--	--	--	--	0.5% (1) 0.005 [1]	0.5% (1) 0.003 [1]
Implant site discharge	0.5% (1) 0.068 [1]	--	--	--	--	0.5% (1) 0.003 [1]
Implant site erosion	--	--	--	--	0.5% (1) 0.005 [1]	0.5% (1) 0.003 [1]
Implant site pain	--	--	--	--	0.5% (1) 0.005 [1]	0.5% (1) 0.003 [1]
Intracranial hypotension	--	--	--	--	0.5% (1) 0.005 [1]	0.5% (1) 0.003 [1]
Medical device removal	--	--	--	--	0.5% (1) 0.005 [1]	0.5% (1) 0.003 [1]
Nonconvulsive status epilepticus	--	--	--	0.5% (1) 0.009 [1]	--	0.5% (1) 0.003 [1]
Procedural headache	0.5% (1) 0.068 [1]	--	--	--	--	0.5% (1) 0.003 [1]
Simple partial seizures (sensory)	--	--	0.5% (1) 0.023 [1]	--	--	0.5% (1) 0.003 [1]
Simple partial seizures increased (sensory)	--	--	0.5% (1) 0.023 [1]	--	--	0.5% (1) 0.003 [1]
Subdural hematoma	0.5% (1) 0.068 [1]	--	--	--	--	0.5% (1) 0.003 [1]
Suture related complication	--	--	--	--	0.5% (1) 0.005 [1]	0.5% (1) 0.003 [1]
Tonic-clonic seizures exacerbated	--	--	--	--	0.5% (1) 0.005 [1]	0.5% (1) 0.003 [1]

[1] Device-related includes events categorized as device relation uncertain.
[2] % Subjects = # subjects with event / number of subjects entering interval.
[3] Event Rate = # events / implant years within interval.
Data as of 5/12/2011

11.1.2.3 *Serious Adverse Events: Post-Operative Period*

SAEs (no matter the device relation) that occurred at implant or over the first month after implantation (Post-Operative Stabilization Period) are listed in **Table 25**. All were anticipated and resolved. The most frequent SAE during this period was implant site infection, occurring in 2.6% of subjects. There were 5 implant site infections; one of these subjects had the Neurostimulator and Leads explanted. Other events were transient and typical complications after neurosurgical procedures: implant site discharge, procedural headaches, hemorrhages related to the implant procedure (none of which had neurological sequelae), transient neurological complications (apraxia and dysphemia) in one subject related to the procedure to implant the leads in an area with fibrosis from a prior surgery, and post-operative hydrocephalus. One subject was diagnosed with bacterial meningitis from a culture obtained before the Neurostimulator and Leads were implanted. This was attributed to a persistent infection from video-EEG monitoring with intracranial electrodes more than 3 years before. The Neurostimulator and Leads were implanted and the subject was treated

with antibiotics. Additional information on adverse events related to the Neurostimulator and Leads is provided in **Section 11.2.4**.

Table 25: Pivotal Study – SAEs: Post-Operative Stabilization Period[1]

MedDRA Preferred Term	% (#) Subjects (N=191)	# Events [# Device-related[2]]
Implant site infection	2.6% (5)	5 [5]
Extradural hematoma	1.0% (2)	2 [2]
Hydrocephalus	1.0% (2)	2 [2]
Procedural headache	1.0% (2)	2 [1]
Apraxia	0.5% (1)	1 [1]
Biopsy brain	0.5% (1)	1 [0]
Cerebral hemorrhage	0.5% (1)	1 [1]
Complex partial seizures exacerbated	0.5% (1)	1 [0]
Depression suicidal	0.5% (1)	1 [0]
Device lead revision	0.5% (1)	1 [0]
Drug hypersensitivity	0.5% (1)	1 [0]
Dysphemia	0.5% (1)	1 [1]
Implant site discharge	0.5% (1)	1 [1]
Implant site effusion	0.5% (1)	1 [0]
Meningitis bacterial[3]	0.5% (1)	1 [0]
Pneumothorax	0.5% (1)	1 [0]
Postictal state	0.5% (1)	1 [1]
Procedural vomiting	0.5% (1)	1 [0]
Subdural hematoma	0.5% (1)	1 [1]
Therapeutic agent toxicity	0.5% (1)	1 [0]
Summary of All SAEs in this Period	12.0% (23)	27 [16]

[1] All SAEs resolved.
[2] Device-related includes events categorized as device relation uncertain.
[3] Subject was diagnosed with bacterial meningitis before implant.
Data as of 5/12/2011

11.1.2.4 *Adverse Events: Blinded Periods*

In order to assess the tolerability of responsive stimulation, adverse events were considered across the 4 months during which subjects were blinded and randomized to Treatment or Sham (the Stimulation Optimization and Blinded Evaluation Periods). There were no differences between the Treatment and Sham stimulation groups in the overall rate of serious or mild adverse events, including seizure-related or psychiatric-related adverse events (Fisher's exact test).

Every SAE during the blinded periods of the study is listed in **Table 26** for subjects in the Treatment and Sham groups. No type of SAE (by MedDRA Preferred Term) affected more than 1 subject in a group, and there were no significant differences between the Treatment and Sham groups in the rate or type of SAEs.

There were 5 SAEs considered to be device-related (or device relation uncertain); 4 in the Sham group and 1 in the Treatment group. SAEs related to a change in seizures occurred in 1 subject in the Treatment group (an increase in complex partial seizures) and in 1 subject in the Sham group (3 separate events: an increase in complex partial seizures, a new type of simple partial sensory seizure and an increase in simple partial sensory seizures). One subject was admitted for EEG monitoring after a seizure. The investigator identified this as device relation uncertain.

Table 26: Pivotal Study – SAEs: Blinded Periods (Treatment and Sham)

MedDRA Preferred Term	Treatment (N=97)		Sham (N=94)	
	% (#) Subjects	# Events [# Device-related[1]]	% (#) Subjects	# Events [# Device-related[1]]
Complex partial seizures increased	1.0% (1)	1 [1]	1.1% (1)	1 [1]
Device lead revision	1.0% (1)	1 [0]	1.1% (1)	1 [0]
Implant site infection (due to seizure)	1.0% (1)	1* [0]	1.1% (1)	1 [0]
Medical device removal (VNS)[2]	1.0% (1)	1 [0]	1.1% (1)	1 [0]
Adverse drug reaction	1.0% (1)	1 [0]	--	--
Alcohol poisoning	1.0% (1)	1 [0]	--	--
Arthritis	--	--	1.1% (1)	1* [0]
Central venous catheterisation	1.0% (1)	2 [0]	--	--
Death	--	--	1.1% (1)	1 [0]
EEG monitoring	--	--	1.1% (1)	1 [1]
Hernia	--	--	1.1% (1)	1 [0]
Jaw fracture (due to seizure)	--	--	1.1% (1)	1 [0]
Meningioma benign	1.0% (1)	1 [0]	--	--
Myocardial infarction	1.0% (1)	1 [0]	--	--
Nephrolithiasis	--	--	1.1% (1)	1 [0]
Non-cardiac chest pain	--	--	1.1% (1)	1 [0]
Pneumonia	1.0% (1)	1 [0]	--	--
Psychotic disorder	--	--	1.1% (1)	1 [0]
Simple partial seizures (sensory)	--	--	1.1% (1)	1 [1*]
Simple partial seizures increased (sensory)	--	--	1.1% (1)	1 [1]
Skin laceration (due to seizure)	1.0% (1)	1 [0]	--	--
Subdural hematoma (due to seizure)	1.0% (1)	1* [0]	--	--
Syncope	1.0% (1)	1 [0]	--	--
Summary of All SAEs in Period	9.3% (9)	14 [1]	11.7% (11)	14 [4]

Blinded periods include the Stimulation Optimization and Blinded Evaluation Periods.
Differences between Treatment and Sham groups not significant (all p-values > 0.05, Fisher's exact test).
[1] Device-related includes events categorized as device relation uncertain.
[2] Two subjects had a VNS explanted after the RNS System implantation; these are considered SAEs because the subject required a surgical procedure.
* Single SAE in category was ongoing at the time the subject concluded the study; all other events resolved.
Data as of 5/12/2011

All adverse events, serious and mild, that affected ≥ 2.5% of subjects over the blinded periods were assessed to determine whether the types of adverse events were different in the subjects treated and not treated with responsive stimulation (**Table 47** of **Appendix 15.7**). Only one type of adverse event was significantly different between the Treatment and Sham stimulation groups. Therapeutic agent toxicity, which refers to side effects of AEDs, was more common in the Sham group (6 subjects, all mild events) than the Treatment group (none).

11.1.2.5 *Serious Adverse Events: Open Label Period*

All SAEs that occurred during the Open Label Period of the Pivotal study (Week 20 to 2 years) are presented in **Table 27**. The most common SAEs were: an admission to an inpatient epilepsy monitoring unit in order to perform video-EEG monitoring (EEG monitoring), an increase or exacerbation in seizures, death (discussed in detail below), device lead damage and device lead

revision. For all SAEs that affected more than 2 patients, the SAE rate remained stable or decreased from year 1 to year 2 post-implant except for video-EEG monitoring and device lead revision. Video-EEG monitoring is a diagnostic procedure. However it was considered a SAE because the procedure is performed in the hospital. Details regarding device lead revisions are provided in **Section 11.2.4**.

Table 27: Pivotal Study – SAEs: Open Label Period

	Week 20 to Year 1 (N=187)[2]		Year 1 to Completion (N=182)[2]	
MedDRA Preferred Term	**% (#) Subjects**	**# Events** [# Device-related[1]]	**% (#) Subjects**	**# Events** [# Device-related[1]]
EEG monitoring	2.1% (4)	4 [0]	5.5% (10)	13 [0]
Complex partial seizures increased	4.3% (8)	8 [4]*	1.6% (3)	3 [2*]
Tonic-clonic seizures exacerbated	2.1% (4)	4 [0]	1.6% (3)	3 [1]
Tonic-clonic seizures increased	2.1% (4)	5 [2]	1.6% (3)	3 [3]
Death	1.6% (3)	3 [1]	1.1% (2)	2 [0]
Device lead damage	2.7% (5)	5 [5]	0.5% (1)	1 [1]
Device lead revision	0.5% (1)	1 [1]	1.6% (3)	3 [3]
Therapeutic agent toxicity	1.1% (2)	3 [0]	1.1% (2)	2 [0]
Depression suicidal	1.1% (2)	2 [2]	0.5% (1)	1 [0]
Implant site infection	1.1% (2)	2 [2*]	0.5% (1)	1 [1*]
Ovarian cyst	0.5% (1)	1 [0]	1.1% (2)	2* [0]
Skin laceration (due to seizure)	1.1% (2)	2* [1]	0.5% (1)	1 [1]
Tooth extraction	1.1% (2)	2 [0]	0.5% (1)	1 [0]
Acute psychosis	0.5% (1)	3 [0]	0.5% (1)	1 [0]
Angiogram cerebral	--	--	1.1% (2)	2 [0]
Complex partial seizures exacerbated	1.1% (2)	2 [2]	0.5% (1)	1 [0]
Convulsive status epilepticus	0.5% (1)	1 [0]	0.5% (1)	1 [1]
Influenza	--	--	1.1% (2)	2 [0]
Medical device removal	--	--	1.1% (2)	2 [1]
Multiple injuries	--	--	1.1% (2)	2* [0]
Nonconvulsive status epilepticus	1.1% (2)	2 [1]	--	--
Pneumonia	0.5% (1)	1 [0]	0.5% (1)	1 [0]
Premature battery depletion	1.1% (2)	2 [2]	--	--
Subdural hematoma (due to seizure)	0.5% (1)	1 [1]	0.5% (1)	1 [1]
Suicide attempt	0.5% (1)	1 [0]	0.5% (1)	1 [0]
Thermal burn (due to seizure)	0.5% (1)	1 [0]	0.5% (1)	1 [0]
Tubal ligation	--	--	1.1% (2)	2 [0]
Abortion spontaneous	--	--	0.5% (1)	1 [0]
Acquired epileptic aphasia	0.5% (1)	1 [1]	--	--
Adverse drug reaction	--	--	0.5% (1)	
Affect lability	--	--	0.5% (1)	1 [0]
Appendicitis	0.5% (1)	1 [0]	--	--
Arthralgia	0.5% (1)	1 [0]	--	--
Arthritis	0.5% (1)	1* [0]	--	--
Atelectasis	--	--	0.5% (1)	1 [0]
Atonic seizures increased	--	--	0.5% (1)	1[0]
Benign breast neoplasm	--	--	0.5% (1)	1 [0]
Blindness transient	0.5% (1)	1 [0]	--	--
Colon cancer	0.5% (1)	1 [0]	--	--
Contraception	--	--	0.5% (1)	1 [0]
Conversion disorders	--	--	0.5% (1)	1* [0]

Table 27: Pivotal Study – SAEs: Open Label Period

MedDRA Preferred Term	Week 20 to Year 1 (N=187)[2]		Year 1 to Completion (N=182)[2]	
	% (#) Subjects	# Events [# Device-related[1]]	% (#) Subjects	# Events [# Device-related[1]]
Deep vein thrombosis	0.5% (1)	1 [0]	--	--
Epileptic psychosis	--	--	0.5% (1)	1 [0]
Generalized edema	0.5% (1)	1 [0]	--	--
Hallucination, visual	0.5% (1)	1 [0]	--	--
Hand fracture (due to seizure)	0.5% (1)	1 [0]	--	--
Head injury (due to seizure)	--	--	0.5% (1)	1* [0]
Headache	--	--	0.5% (1)	1 [1*]
Hip fracture (due to seizure)	--	--	0.5% (1)	1 [0]
Hypertension	--	--	0.5% (1)	1 [0]
Implant site erosion	--	--	0.5% (1)	1 [1]
Implant site pain	--	--	0.5% (1)	1 [1]
Intervertebral disc protrusion	0.5% (1)	1* [0]	--	--
Intestinal obstruction	--	--	0.5% (1)	1 [0]
Intracranial hypotension	--	--	0.5% (1)	1 [1]
Joint injury	0.5% (1)	1 [0]	--	--
Laceration (due to seizure)	0.5% (1)	1 [0]	--	--
Live birth	--	--	0.5% (1)	1 [0]
Lymphoma	0.5% (1)	1* [0]	--	--
Medical device removal (VNS)	0.5% (1)	1 [0]	--	--
Medical observation	--	--	0.5% (1)	2 [0]
Menstrual disorder	--	--	0.5% (1)	1 [0]
Nephrolithiasis	--	--	0.5% (1)	1 [0]
Edema peripheral	--	--	0.5% (1)	1 [0]
Paresthesia	--	--	0.5% (1)	1 [0]
Peritoneal infection	0.5% (1)	2 [0]	--	--
Pneumonia aspiration	--	--	0.5% (1)	1 [0]
Postictal state	0.5% (1)	1 [1]	--	--
Road traffic accident	--	--	0.5% (1)	1 [0]
Shoulder operation	0.5% (1)	1 [0]	--	--
Simple partial seizures exacerbated (motor)	--	--	0.5% (1)	1 [0]
Simple partial seizures increased (motor)	0.5% (1)	1 [0]	--	--
Skin neoplasm excision	0.5% (1)	1 [0]	--	--
Suture related complication	--	--	0.5% (1)	2 [1]
Tachycardia	--	--	0.5% (1)	1 [0]
Tendon transfer	--	--	0.5% (1)	1 [0]
Tooth infection	--	--	0.5% (1)	1* [0]
Toothache	0.5% (1)	1 [0]	--	--
Toxic encephalopathy	0.5% (1)	1 [0]	--	--
Uterine leiomyoma	--	--	0.5% (1)	1 [0]
Summary of All SAEs in Period	25.7% (48)	79 [26]	29.7% (54)	86 [20]

[1] Device-related includes events categorized as device relation uncertain.

[2] These N represent the number of subjects who entered the specified period as of May 12, 2011 and are used as the denominator in calculating the percentage of subjects with events.

* A single SAE in the category indicated was ongoing at the time of subject conclusion; all other events resolved.

Data as of 5/12/2011

11.1.2.6 *Affective Status*

Treatment with the RNS System had no negative effect on mood as assessed by 3 validated mood inventories: the Beck Depression Inventory (BDI-II), the Profile of Mood States (POMS), and the Center for Epidemiological Studies Depression Scale (CES-D). There was no difference in scores on any inventory between Treatment and Sham subjects at the end of the Blinded Evaluation Period and no deterioration in any score at the end of the Blinded Evaluation Period or across the Open Label Period (**Table 51** and **Table 52** in **Appendix 15.7**).

The numbers of subjects endorsing suicidality did not increase over the study (as assessed on the BDI-II, question 9). Approximately 10% of subjects endorsed suicidality according to the BDI-II during the Baseline Period and this rate remained stable over the course of the study. All but 1 of these subjects had suicidal thoughts but no intent. (Responses to BDI-II question 9 are presented in **Table 28**.) At the end of the blinded evaluation period, 9.6% of subjects in the Treatment group endorsed suicidality (9/94) compared to 16.7% of subjects in the Sham group (15/90); this difference was not statistically significant.

Table 28: Pivotal Study – BDI-II responses[1] regarding suicidality

		Post-Implant				
		20 Weeks [End of Blinded Evaluation Period]				
	Baseline	Treatment	Sham	1 Year	1.5 Years	2 Years
Total # of subject assessments (N)	**187**	**94**	**90**	**174**	**161**	**162**
# subjects reporting {1}	19	8	13	18	20	16
# subjects reporting {2}	0	0	2	1	0	0
# subjects reporting {3}	0	1	0	0	0	0
% (of N) reporting {1, 2, or 3}	**10.2%**	**9.6 %**	**16.7%**	**10.9%**	**12.4%**	**9.9%**

[1] Question #9 on the Beck Depression Inventory (BDI-II).
Response options are: {0} I don't have any thoughts of killing myself; {1} I have thoughts of killing myself, but I would not carry them out; {2} I would like to kill myself; {3} I would kill myself if I had the chance.
Data as of 5/12/2011

11.1.2.7 *Neuropsychological Functioning*

There were no negative effects of treatment with the RNS System on neuropsychological functioning as assessed by validated, standardized inventories of neuropsychological function as administered by neuropsychologists at Baseline, at the end of the Blinded Evaluation Period (20 weeks) and at 1 and 2 years after implantation. The neuropsychological testing assessed 9 domains that include visual and verbal memory, verbal fluency and naming, cognitive flexibility, learning and concentration.

Group comparison of the changes in neuropsychological assessment scores at the end of the Blinded Evaluation Period relative to Baseline showed no negative effects on any of the cognitive variables and no difference between Treatment and Sham group subjects (**Table 50** in **Appendix 15.7**). At 1 and 2 years post-implant, there were no differences across the neuropsychological measures between subjects originally randomized to Treatment and Sham, indicating that there were no delayed or longer-term adverse effects on neuropsychological function.

Additional analyses of neuropsychological functioning during the Open Label Period were performed in which the Sham and Treatment subjects were considered as a single group. Neuropsychological performances at 1 and 2 years were compared to Baseline using single group (within subject) paired t-tests. Mean changes and standard deviations are shown in **Table 29**. There were no assessments with statistically significant worsening.

Table 29: Pivotal Study – Neuropsychological Measures: Change in Summary Scores at 1 and 2 years relative to Baseline

	Change at 1 year			Change at 2 years		
Test	**N**	**Mean ± SD**	**p-value[1]**	**N**	**Mean ± SD**	**p-value[1]**
Visual Motor Speed						
Trailmaking – Part A[2]	157	-1.59 ± 15.29	0.196	154	-1.47 ± 18.75	0.333
Trailmaking – Part B[2]	154	-7.28 ± 43.92	0.041	150	-5.95 ± 46.73	0.121
Motor Speed / Dexterity						
Grooved Pegboard - Dominant[2]	151	-2.47 ± 20.68	0.145	147	-2.00 ± 22.82	0.289
Grooved Pegboard - Nondominant[2]	145	-0.68 ± 28.72	0.776	143	-0.22 ± 30.44	0.932
Auditory Attention						
WAIS-III Digit Span	156	-0.10 ± 2.01	0.526	152	0.04 ± 1.74	0.781
General Verbal Ability						
WAIS-III Information	156	0.19 ± 1.27	0.069	153	0.31 ± 1.32	0.004
General Visuospatial Ability						
WAIS-III Block Design	156	0.44 ± 1.88	0.004	152	0.57 ± 2.02	0.001
Verbal Memory						
RAVLT – I-V (Sum Across Trials)	145	1.80 ± 7.99	0.008	145	0.95 ± 8.81	0.196
RAVLT – VII (Delayed Recall)	144	0.42 ± 2.54	0.047	147	0.21 ± 2.71	0.346
RAVLT – Recognition Memory	144	0.17 ± 2.44	0.413	145	0.22 ± 2.48	0.286
Visuospatial Memory						
BVMT-R – Total Recall	153	0.82 ± 6.06	0.095	149	0.90 ± 5.30	0.040
BVMT-R – Delayed Recall	151	0.06 ± 2.69	0.797	147	-0.07 ± 2.17	0.704
BVMT-R – Recognition Discrimination Index	149	0.08 ± 1.29	0.446	145	-0.09 ± 1.44	0.454
Language						
BNT - Spontaneous with semantic cue	154	1.25 ± 4.00	<0.001	149	1.28 ± 4.04	<0.001
D-KEFS Verbal Fluency - Condition 1: Letter Fluency	136	-0.05 ± 2.13	0.778	138	0.13 ± 2.31	0.508
Design Fluency						
D-KEFS Design Fluency - Total Composite	150	1.29 ± 3.14	<0.001	146	1.23 ± 2.43	<0.001

[1] Statistical significance of the change from the Baseline score per the paired t-test.

[2] Lower mean values indicate better performance.

Analysis includes subjects (N) with assessments available at both Baseline and Open Label time points.

WAIS-III = Wechsler Adult Intelligence Scale; RAVLT = Rey Auditory Verbal Learning Test; BVMT-R = Brief Visuospatial Memory Test-Revised; BNT = Boston Naming Test (60 item); D-KEFS = Delis-Kaplan Executive Function System.

Data as of 5/12/2011

11.2 Combined Studies: Safety Results

11.2.1 Serious Adverse Events

Safety data were combined from the Pivotal, Feasibility and Long-term Treatment studies. All SAEs that occurred in ≥ 2.5% of implanted subjects are presented in **Table 30** categorized by MedDRA Preferred Term. The percentage of subjects and the event rate for each adverse event category is listed by the post-implant year of onset. This includes SAEs identified by the investigator as device-related and SAEs identified as not related to the device.

For the majority of categories, SAEs were more frequent in the first year after implant or were stable over time. The exceptions include EEG-monitoring (performed in hospital-based epilepsy monitoring units to provide objective information about seizure activity), implant site infection, explantation of the Neurostimulator (medical device removal), and therapeutic agent toxicity (side effects of AEDs).

Table 30: Combined Studies – SAEs in ≥ 2.5% of subjects by year

	Year 1	Year 2	Year 3	Year 4	Year 5	All Periods[1]
# of subjects entering year / Implant years within Interval	256 / 249.9	246 / 240.1	235 / 188.6	148 / 112.2	85 / 60.6	256 / 903.4
MedDRA Preferred Term	% (#) Subjects[2] Event Rate [# Events][3]					
EEG monitoring	2.3% (6) 0.024 [6]	3.7% (9) 0.046 [11]	3.0% (7) 0.042 [8]	1.4% (2) 0.018 [2]	4.7% (4) 0.083 [5]	10.5% (27) 0.039 [35]
Implant site infection	2.3% (6) 0.028 [7]	0.4% (1) 0.004 [1]	2.6% (6) 0.032 [6]	1.4% (2) 0.018 [2]	--	6.3% (16) 0.020 [18]
Complex partial seizures increased	4.7% (12) 0.052 [13]	1.2% (3) 0.012 [3]	0.4% (1) 0.005 [1]	0.7% (1) 0.009 [1]	1.2% (1) 0.017 [1]	6.3% (16) 0.021 [19]
Tonic-clonic seizures increased	2.0% (5) 0.024 [6]	2.0% (5) 0.021 [5]	1.7% (4) 0.021 [4]	1.4% (2) 0.027 [3]	--	5.5% (14) 0.020 [18]
Premature battery depletion[4]	1.6% (4) 0.016 [4]	2.4% (6) 0.025 [6]	0.4% (1) 0.005 [1]	--	--	4.3% (11) 0.012 [11]
Tonic-clonic seizures exacerbated	2.0% (5) 0.020 [5]	1.2% (3) 0.012 [3]	0.9% (2) 0.011 [2]	--	1.2% (1) 0.017 [1]	4.3% (11) 0.012 [11]
Medical device removal[5]	0.4% (1) 0.004 [1]	1.6% (4) 0.017 [4]	0.9% (2) 0.011 [2]	1.4% (2) 0.018 [2]	1.2% (1) 0.017 [1]	4.3% (11) 0.012 [11]
Death	1.6% (4) 0.016 [4]	1.2% (3) 0.012 [3]	0.4% (1) 0.005 [1]	0.7% (1) 0.009 [1]	--	3.5% (9) 0.010 [9]
Device lead damage	2.0% (5) 0.020 [5]	0.8% (2) 0.008 [2]	0.9% (2) 0.011 [2]	--	--	3.1% (8) 0.010 [9]
Therapeutic agent toxicity[6]	1.6% (4) 0.020 [5]	1.2% (3) 0.012 [3]	--	--	1.2% (1) 0.017 [1]	3.1% (8) 0.011 [10]
Device lead revision	1.6% (4) 0.016 [4]	1.2% (3) 0.012 [3]	--	--	--	2.7% (7) 0.008 [7]

[1] All study periods includes year 6 (n=41) and year 7 (n=29).
[2] % Subjects = # subjects with event / number of subjects entering interval.
[3] Event Rate = # events / implant years within interval.
[4] Occurred with battery from manufacturer that is no longer used.
[5] Elective procedures to explant the Neurostimulator (and Leads) that occurred at the time of subject withdrawal.
[6] Therapeutic agent toxicity = antiepileptic medication toxicity.
Year 1 (implant - Week 52), Year 2 (Weeks 52 - 104), Year 3 (Weeks 104 - 156), Year 4 (Weeks 156 - 208), Year 5 (Weeks 208 - 260), Year 6 (Weeks 260 - 312), Year 7 (Weeks 312 - 364)
Data as of 5/12/2011

11.2.2 Adverse Events of Particular Relevance

Adverse events of particular relevance in persons with epilepsy and in persons with an implanted medical device include intracranial hemorrhage, infection, depression and suicidality, a change in seizures, and status epilepticus. Adverse events in these categories for all subjects in all RNS System studies are discussed below.

11.2.2.1 *Hemorrhage*

SAEs related to intracranial hemorrhage (all hemorrhage categories) occurred in 12 of the 256 implanted subjects (4.7%) over the 903 implant years (**Table 31**). Hemorrhages were attributed to seizure-related head trauma in 5 of the 12 subjects. Therefore, the percentage of subjects with SAEs related to intracranial hemorrhage that were not attributed to seizure-related trauma was 2.7% (7 subjects) and the event rate was 0.8 events per 100 patient implant years.

Four subjects (1.6%) had an intracranial hemorrhage in the first 28 days and 3 of those were within the first 72 hours after implantation of the Neurostimulator and Leads. These included 2 subjects with epidural hematomas that were evacuated, one subject with a subdural hematoma that required surgical evacuation, and one subject with a small intraventricular hemorrhage diagnosed by CT who was observed in the hospital for 1 day.

After the initial month post-implant, there were 8 SAEs related to hemorrhage. Two were evacuated, and one subject had the Neurostimulator and Leads explanted at the time the subject withdrew from the study (> 13 months after the event). The remaining patients required no surgical intervention.

Nine subjects had no persistent sequelae from the intracranial hemorrhage. Three subjects had sequelae, which included one subject with worsening of a pre-existing memory deficit, one subject with a persistent right hand paresis and one subject who reported an on-going headache.

Table 31: Combined Studies – SAEs related to intracranial hemorrhage (N=256)

	First month	> 1 month	Total
	% (#) Subjects [Event rate][1]		
Intracranial Hemorrhage SAEs[2]	**1.6% (4) [0.004]**	**3.1% (8) [0.009]**	**4.7% (12) [0.013]**
Extradural hematoma	0.8% (2) [0.002]	--	0.8% (2) [0.002]
Subdural hematoma	0.4% (1) [0.001]	1.2% (3) [0.003][3]	1.6% (4) [0.004]
Cerebral hemorrhage	0.4% (1) [0.001]	1.2% (3) [0.003]	1.6% (4) [0.004]
Subarachnoid hemorrhage	--	0.4% (1) [0.001][3]	0.4% (1) [0.001]
Traumatic intracranial hemorrhage	--	0.4% (1) [0.001][3]	0.4% (1) [0.001]

[1] Event Rate = # events / implant years within period.

[2] Evacuation of hematoma (5), device explantation (1). The device explantation occurred at the time the patient withdrew from the study, which was > 13 months after the cerebral hemorrhage.

[3] Attributed to seizure-related head trauma.

Data as of 5/12/2011

The rate of SAEs related to acute or chronic hemorrhage in the RNS System studies was not higher than the rate of acute hemorrhage with implantation of intracranial electrodes to localize the seizure focus[20] and with epilepsy surgery[21], or the rate with DBS for treatment of movement disorders.[28]

11.2.2.2 *Implant Site Infection*

SAEs related to infections of the implant site occurred in 18 subjects (7.0%) over the 903 implant years, as shown in **Table 32**. In 2 of the 18 subjects, the implant site infection was attributed to seizure-related head trauma. Therefore, the percentage of subjects with serious non-seizure-related infection was 6.3% and the event rate was 2.0 events per 100 patient implant years.

All infections were treated with antibiotics with or without drainage or debridement. Eleven (4.3%) subjects had the Neurostimulator and/or Leads explanted because of infection. One of the subjects was re-implanted after the infection resolved. There were no infections of the brain, no sepsis and no permanent neurological consequences related to infection.

Table 32: Combined Studies – SAEs related to implant site infection (N=256)

	First month	> 1 month	Total[1]
% (#) Subjects [event rate][2]	2.0% (5) [0.006]	5.5% (14) [0.017]	7.0% (18) [0.022]
% (#) Subjects [event rate] explanted[3]	0.4% (1) [0.001]	2.9% (10) [0.011]	4.3% (11) [0.012]

[1] One subject had an implant site infection in the first month post-implant and in subsequent months.

[2] Two implant site infections attributed to seizure-related falls and secondarily infected scalp lacerations.

[3] One additional event resulted in neurostimulator replacement.

Data as of 5/12/2011

The rate of infections was not higher than the rate for infection with implantation of intracranial electrodes to localize the seizure focus[8,29,60] and with epilepsy surgery,[8] or the rate with DBS for treatment of movement disorders.[27,28]

11.2.2.3 *Psychiatric Adverse Events Including Depression and Suicidality*

As expected, many subjects had a history of depression and suicidality; in the Pivotal study, 50% reported a prior history of depression and 5.2% reported prior history of suicidality. According to responses on the Beck Depression Inventory (BDI-II) during the Baseline Period, 15.6% of subjects had moderate depression before implant and 9.2% endorsed suicidality (**Table 33**). Rates of depression and suicidality remained stable post-implant.

Table 33: Combined Studies – Beck Depression Inventory

	Pre-Implant	1 yr	2 yrs
Moderate depression per BDI-II[1]	15.6%	13.8%	13.0%
Suicidality per BDI-II [2]	9.2%	10.2%	8.9%

[1] BDI-II ≥ 20 [113]

[2] BDI-II Q9 > 0.

Data as of 5/12/2011

In order to fully capture any adverse event that could be representative of suicidality, suicidality was broadly defined to include the MedDRA preferred terms: suicide attempt, suicidal behavior, suicidal ideation, depression suicidal, self-injurious ideation, and suicide. SAEs related to depression or suicidality occurred in 13 subjects, including 2 subjects who committed suicide. 12 of the 13 subjects had a prior history of depression and/or suicidality. Both subjects who committed suicide had a past history of depression; one subject had experienced mild adverse events related to depression during the study.

Patients with medically intractable epilepsy have a high rate of psychiatric comorbidity.[70-72,114,115] There is no indication that treatment with the RNS System increases the risk for psychiatric conditions or exacerbates preexisting psychiatric symptoms or conditions.

11.2.2.4 *Neuropsychological Function*

Neuropsychological testing was performed in order to demonstrate that treatment with the RNS System had no negative effect on cognitive function. There was no deterioration from baseline in any of the 14 neuropsychological domains tested at the end of the evaluation period or at 1 and 2 years after implant (data provided in **Table 29**).

11.2.2.5 *Change in Seizures*

The RNS System studies used a very conservative definition of AEs related to a change in seizures. Any new type of seizure was considered an AE, whether this was a change in the phenotype (patient experience, behavior and/or appearance) of a preexisting type of seizure, or a new type of seizure, even if the seizure was milder (for example, a simple partial seizure in a patient with only complex partial seizures previously). If the subject had more frequent seizures and these seizures were longer or more severe than typical (exacerbation), then that subject was considered to have 2 AEs.

No subject withdrew from the study because of an AE related to a change in seizures. SAEs related to a change in seizures occurred in 41 of the 256 subjects (16.0%). The overall SAE event rate related to seizures was 0.077 events per year and there was no increase in the event rate over time. SAEs related to a change in seizures fell in the categories of an increase in seizure frequency (11.3%, 29/256), an exacerbation in seizures (6.6%, 17/256) and a new seizure type (1.2%, 3/256). The majority of these adverse events were considered serious because the subject was admitted for video-EEG monitoring or hospitalized to receive AEDs. Ninety percent of the SAEs related to increased seizure frequency or seizure exacerbation resolved (a new type of seizure could not, by definition, resolve).

The majority of the 30 subjects with mild or serious adverse events related to a new type of seizure were because of a milder type of seizure (80%, all mild AEs). There were only 3 SAEs related to a new seizure type and all were because of a change in phenotype.

Adverse changes in seizures are expected in any trial of an epilepsy therapy and the rate of adverse events related to changes in seizures in the RNS System studies is no greater than the rates reported in randomized controlled trials of AEDs approved for adjunctive treatment of partial onset seizures.[65-67,116]

11.2.2.6 *Status Epilepticus*

There were 16 SAEs related to status epilepticus in 8 subjects implanted with the Neurostimulator and Leads, providing an SAE rate of 3.1% and an event rate of 0.018 events per implant year. 6 episodes were convulsive and 10 were non-convulsive (note that if the type of status was not known, it was coded as convulsive). Seven subjects had 1 episode of status epilepticus and 1 subject had 9 episodes. None of the events occurred acutely at the time responsive stimulation was enabled (all events occurred during the open period at least 1 month after enabling responsive stimulation).

Three events were considered to be device-related (or device relation uncertain): one subject experienced foot twitching that spontaneously resolved; the second subject experienced multiple

seizures accompanied with aphasia, which resolved with medication; the third subject experienced recurrent seizures associated with fever and infection attributed to a tooth abscess.

One additional subject had convulsive status epilepticus after the RNS System was explanted but before the subject had withdrawn from the study; the status occurred when the patient had AEDs tapered during an EEG monitoring procedure with intracranial electrodes.

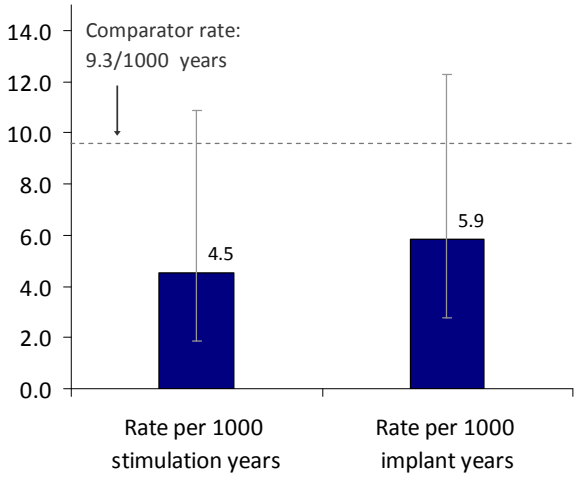
The rate of status epilepticus was not higher than is expected in a population of patients with severe partial onset seizures. [68,69]

11.2.3 Deaths and SUDEP Analysis

Data as of October 24, 2012 do not suggest that treatment with the RNS System increases the risk for SUDEP, although 1500 patient years of data are required in order to provide a confident estimate.

There were 11 deaths in the RNS System studies as of October 24, 2012 with a total follow-up of 1195 patient implant years and 1103 patient stimulation years. A brief summary of each of the deaths is provided in **Table 49** in **Appendix 15.7**. Two deaths were by suicide (one which occurred when stimulation was off). One death was due to status epilepticus in a subject who had subtherapeutic levels of AEDs. One death was due to lymphoma. Seven deaths were attributed by an independent SUDEP adjudication committee to possible, probable, or definite SUDEP; 5 of these occurred while responsive stimulation was enabled. The rate of SUDEP for subjects in the RNS System studies is presented in **Figure 29** and is compared to the background SUDEP rate for a similar patient population as estimated from the literature.[30]

Figure 29: Combined Studies – SUDEP rates



Error Bars = 95 % CI
Data as of 10/24/2012

11.2.4 Neurostimulator and Leads

SAEs requiring replacement of the Neurostimulator and/or Leads

SAEs requiring replacement of the Neurostimulator and/or Leads included premature battery malfunction, presumed Neurostimulator malfunction, Lead damage, and Lead revisions.

During the RNS System studies combined, 11/256 subjects (4.3%) had a Neurostimulator replaced due to premature battery depletion. All of these batteries were acquired from a single manufacturer prior to 2006. Since July 2006, batteries have been supplied from other manufacturers, and there have been no further battery malfunctions.

Two subjects had their Neurostimulator replaced due to presumed malfunction. One subject was assaulted and struck with a board on the head at the site of the Neurostimulator. After the assault, the subject was unable to interrogate the Neurostimulator and the Neurostimulator was replaced. However, post-implant investigation showed normal Neurostimulator function. Another subject had a replacement because of concern that the battery had depleted early; a post-implant investigation determined that the battery was functioning as expected.

Eight subjects (3.1%) had procedures to revise damaged Leads. Six subjects had Lead fractures in depth Leads placed in the hippocampus; the fracture appeared to be near the burr hole. A single patient had a titanium plate covering a prior craniectomy and required 2 separate procedures to replace Leads that appeared to be cut between the skull and the titanium plate. Another subject had a cortical strip Lead cut during a routine Neurostimulator replacement.

Seven subjects (2.7%) had procedures to revise Leads; these included adjustment of Lead location, change in Leads connected to the Neurostimulator or implant of new Leads. One subject experienced discomfort with stimulation due to the Lead location, therefore the depth Lead was explanted and a new Lead implanted. Six subjects underwent Lead revisions to change the sensing or stimulation location. Two of these subjects had a modification in the position of a Lead in order to improve placement; the Lead was not replaced. Two additional subjects had the Leads connected to the Neurostimulator changed with other Leads that were already implanted. For the last two subjects, the investigator replaced Leads that were not optimally located.

Neurostimulator Explant Procedures

The Neurostimulator was explanted in 28 of the 256 subjects over 903 patient implant years (**Table 34**). Fourteen of the procedures were elective and 14 were an intervention for a serious adverse event. The most common reasons for explantation were infection or erosion or electively for a planned epilepsy surgery (cortical resection).

Thirteen of the 14 explantations were an intervention for an infection (11) or erosion (2); 2 of these patients were re-implanted with the Neurostimulator and Leads after the infection or erosion resolved. One subject had a cerebral hemorrhage and the Neurostimulator was explanted 13 months later when the subject withdrew from the study.

Seven of the 28 Neurostimulator explants were because the subject elected to undergo an epilepsy surgery that included cortical resection. Two of the 7 subjects were re-implanted with the Neurostimulator after the epilepsy surgery. Seven additional subjects withdrew and elected to have the

Neurostimulator and Leads explanted at the time of withdrawal due to insufficient efficacy (3), to pursue other treatments (2), due to ongoing complaints (1), or for an unspecified reason (1).

Table 34: Combined Studies – Explant Procedures

Reason for procedure	# of procedures / 256 subjects
Non-elective	14
Implant site infection[1]	*9*
Implant site infection – due to seizure	*2*
Erosion[2]	*2*
Cerebral hemorrhage[3]	*1*
Elective	14
Planned epilepsy surgery[4]	*7*
Insufficient efficacy	*3*
Pursue other treatments	*2*
Ongoing complaints	*1*
No reason provided	*1*
Total	**28**

[1] One subject re-implanted after infection resolved; one other subject pending re-implant.
[2] One subject re-implanted after erosion resolved.
[3] Explantation of Neurostimulator occurred 13 months after cerebral hemorrhage.
[4] Two subjects re-implanted after epilepsy surgery.
Data as of 5/12/2011

11.3 Summary of Overall Safety

The combined safety experience in the RNS System studies demonstrates that the risks of implantation of the Neurostimulator and Leads are low, that stimulation is well-tolerated and that treatment with the RNS System is safe over time.

There were no unanticipated device-related SAEs. Adverse events in the first 4 and first 12 post-operative weeks compared favorably to comparable procedures. Stimulation was safe and well tolerated; there was no difference between subjects receiving active stimulation and subjects receiving sham stimulation in the percentage of subjects experiencing an SAE and the only difference in mild adverse events was a higher rate of AED related adverse events in the Sham group than the Treatment group. Safety is favorable over the longer-term; the overall rate of adverse events or of specific adverse events does not increase over time. The types of adverse events are consistent with known risks of medical device implantation, other epilepsy therapies, and with epilepsy. Treatment with the RNS System did not cause deterioration in any aspect of neuropsychological function. In conclusion, these results demonstrate that there is sufficient safety data to identify and quantify the risks of treatment with the RNS System.

12 RISKS VERSUS BENEFITS OF TREATMENT WITH THE RNS SYSTEM

The clinical studies demonstrate that the benefits of treatment with the RNS System outweigh the risks in a population of patients with a long history of treatment-resistant partial onset seizures. Patients participating in the RNS System Pivotal study had been challenged by epilepsy for more than 20 years on average and anticipated decades of uncontrolled seizures. Despite taking more than 2 different AEDs per day, their seizure burden was high, with a median of 9 disabling seizures per month. In addition to AEDs, over 30% had been treated with VNS, 60% had undergone implantation of intracranial electrodes to be evaluated for epilepsy surgery and one third had undergone an epilepsy resective surgery. Others were not candidates for epilepsy surgeries because the potential for benefit was low and the risks were high, or because they did not want a destructive procedure. These subjects had few options: after failure of 2 to 3 AEDs, the chance of seizure control with subsequent trials of AEDs is less than 5%.[34] If the course of their illness continues unabated, the risks for deterioration in cognition, memory, mood, quality of life and overall health are considerable. A treatment that can reduce the seizure burden can mitigate those risks.

The primary effectiveness endpoint demonstrated a statistically significantly greater reduction in seizures in the Treatment group (-37.9%) compared to the Sham stimulation group (-17.3%) during the blinded period of the trial. This effect was evident despite an implant effect, which was associated with a reduction in seizures in the Sham group that waned toward the end of the blinded evaluation period. By the end of the blinded evaluation period, the Treatment group experienced a reduction of 41.5%, whereas the Sham group experienced a reduction of 9.4%.

The Treatment group showed improvements in the secondary endpoints during the blinded evaluation period compared to the baseline (within-group analyses were not pre-specified), however there were not significant differences between Treatment and Sham. Possible explanations for the lack of significant differences in the secondary endpoints are the initial implant effect, or because binary endpoints such as responder rate do not offer as much power as the primary continuous endpoint in the pre-specified GEE analysis. In any case, the magnitude of improvement in the Treatment group would be considered clinically meaningful by many patients and their physicians.

Ultimately, what is important to patients and their physicians is that a treatment works over the long-term. The reduction in seizures with treatment with the RNS System increased over the first and second years after implant and was sustained at around 50% over additional years of follow-up. Experience over a median of 3.3 years of follow-up and of up to 7 years in some patients demonstrates the continued durability of the treatment response. Some patients had significant periods of seizure freedom; 14.5% enjoyed a seizure-free period of 6 months or more.

Pre-specified analyses were performed to determine whether there was a difference in the likelihood of a beneficial response according to the seizure onset location, whether there were one or 2 seizure foci, whether the patient had already had an epilepsy surgery or whether the patient used benzodiazepine medications for acute seizure control. There was not a difference in the likelihood of a favorable response to treatment across these subsets. The study was not powered to provide effectiveness conclusions in these subsets, however in every subset, the Treatment group had a greater seizure reduction than the Sham and in some of the groups (particularly those with the larger sample size); this difference achieved statistical significance.

Improvements in quality of life support the clinical significance of the response to treatment with the RNS System. Overall quality of life, work/driving/social function, health discouragement, seizure worry, and language were lower at baseline for these patients than expected for persons with moderate epilepsy.[109] However, at 1 and 2 years after implant, there were statistically significant group and clinically significant individual improvements in overall quality of life as well as in language, memory, attention/concentration, seizure worry, work/drive/social function and health discouragement. These are areas that are particularly impacted in persons with intractable partial onset seizures.

There is no indication that there are clinically significant adverse events related to stimulation itself. Risks associated with the implant, including infection and hemorrhage, are comparable to the risks of implantation of intracranial electrodes, epilepsy surgery and deep brain stimulation for treatment of movement disorders. SAEs related to intracranial hemorrhage occurred in 12/256 subjects (4.7%); 5/12 were attributed to seizure-related head trauma. Four of the 7 non-seizure related SAEs were post-operative. Only 1 of the 12 subjects had the device explanted; this occurred 13 months later when the subject withdrew from the study. There were neurological sequelae in 3 of the 12 subjects: 1 with mild hand weakness, 1 with worsening of a preexisting memory deficit, and 1 with on-going headache.

Patients with severe epilepsy are at high risk for depression and suicidality. The numbers of patients who entered these studies with past histories of depression and suicidality were similar to what would be predicted in the literature. The numbers of patients who met criteria at enrollment for depression and suicidality by standardized inventories are also what would be predicted and did not change from baseline over the extended post-implant follow-up. Thirteen subjects had SAEs related to depression (1) or suicidality (12, including 2 persons who died by suicide, one of whom was not receiving stimulation). 12 of these 13 patients had a prior history of depression or suicidality. Persons with a history of depression or suicidality were deliberately not excluded from these studies because to do so would exclude a large number of persons with medically intractable epilepsy who are in need of new treatment options. All patients with epilepsy, especially those with intractable partial onset seizures, should be monitored for depression and suicidality no matter what treatment they receive.

Some subjects had adverse events related to a change in seizures, although no subject withdrew from any of the studies for this reason. 16% of the subjects had SAEs because of a change in seizures – the majority of these were considered serious because the subject was admitted for video-EEG monitoring or for parenteral administration of AEDs. Thirty subjects had a serious or mild adverse event related to a new type of seizure; these were usually related to a milder type of seizure (80%), which was considered an adverse event because the RNS System studies used a conservative definition of what constituted a change in seizures. All trials of epilepsy therapies report that some patients have adverse changes in seizures. The rates of adverse events related to a change in seizures in the RNS System studies is not higher than what is reported in the literature for randomized controlled trials of AEDs.

The rate of SUDEP in subjects treated with responsive stimulation was not higher than expected in a similarly ill patient population (9.3/1000 patient years; a comparator rate requested by FDA). Based on the most recent data provided to FDA regarding deaths in the RNS System studies (as of 10/24/2012 with 1103 stimulation years, and 1195 implant years of experience), the SUDEP rate is 4.5/1000 patient stimulation years and 5.9/1000 patient implant years.

Patients choose to continue treatments that are tolerated and provide benefit. Most patients chose to continue treatment with the RNS System. Only 1.6% of subjects withdrew from implant through the end of the blinded periods; withdrawal simply requires that stimulation be programmed off. 92% of implanted subjects completed the entire two year Pivotal study, 97% of eligible subjects enrolled in the

Long-term Treatment study for up to 7 additional years of treatment, and 93% had their Neurostimulator replaced when the battery depleted.

These studies have shown that treatment with the RNS System provides the benefit of a sustained reduction in seizures in a significant percentage of patients with medically intractable partial onset seizures, is associated with meaningful improvements in quality of life, and has acceptable acute and long-term risks, especially when considering the risks of alternative and comparable procedures and the considerable risks of intractable partial onset seizures.

13 CONCLUSION

A rigorously conducted multi-center, randomized, blinded, controlled trial and extended open label follow-up over 3 clinical trials has established that treatment with the RNS System reduces seizures acutely and over the long-term, improves quality of life, is well tolerated and is acceptably safe in a population of persons with frequent and disabling partial onset seizures who have failed multiple epilepsy therapies.

Responsive stimulation reduced seizure frequency acutely and over the long-term and this effect was evident despite a transient reduction in seizures after the implant procedure, as is described in the literature.[15,16] Over the entire Blinded Evaluation Period, there was a greater reduction in seizure frequency in the Treatment group compared to the Sham stimulation group. The reduction of seizures over the Blinded Evaluation Period was 37.9% in the Treatment group, compared to 17.3% in the Sham stimulation group (GEE, $p = 0.012$). The treatment effect size of 0.29, which corresponds to an additional reduction in seizures of 25% in the Treatment compared to the Sham group, is consistent across pre-specified and post hoc GEE sensitivity analyses. The treatment effect maintains significance when subjects with potentially significant protocol deviations are excluded (i.e., the per-protocol analysis), when extreme data are excluded, and even when a number of “influential” subjects are excluded from the analysis. These sensitivity analyses demonstrate that the treatment effect is robust; the result is not dependent on specific GEE model parameters or on the inclusion of one or two specific subjects. Furthermore, the results are reproducible as demonstrated through bootstrap analyses, which show that there is a less than a 2% chance that under the null hypothesis, the results could have been achieved by chance.

The population studied in the RNS System Pivotal trial was a representative sample of patients with frequent and disabling partial onset seizures who have failed multiple epilepsy therapies, and included subgroups distinguishable by factors such as location of seizure focus or baseline seizure count. Variation in treatment effect across these subgroups, while present, was statistically not significant and in each subgroup a greater seizure reduction was observed in patients who received responsive stimulation as compared to sham stimulation. Therefore, the results of the RNS System Pivotal trial support safety and effectiveness of responsive stimulation in this patient population as a whole.

The reduction in seizures when the still-blinded Sham stimulation group first received stimulation in the Open Label Period, the on-going seizure reduction of about 50% in all patients combined over years of open-label follow-up, and the percentage of patients experiencing sustained periods of seizure freedom all support the effectiveness of responsive stimulation. The improvements in quality of life overall, as well as areas of quality of life such as cognition, seizure worry and social interaction, are of great importance to these patients so severely impacted by epilepsy.

The risks of treatment with the RNS System can be identified and quantified based on safety data from 256 implanted patients over 903 years of implant and 819 stimulation years of experience. The overall rates of SAEs were not higher than is expected in persons with epilepsy, with comparable procedures and/or with treatment with AEDs. The implantation procedure was acceptably safe, adverse events were not higher in the group receiving active stimulation compared to the group receiving sham stimulation, and adverse event rates remained stable over the open label periods of the studies. There was no adverse effect on mood or neuropsychological function. Based on the experience to date, the rate of SUDEP is not increased with responsive stimulation or with implantation of the RNS Neurostimulator and Leads.

The RNS System offers a first-of-a-kind treatment to address the unmet need for new therapies for patients with medically intractable partial onset seizures. This closed loop responsive neurostimulation system provides stimulation directly to the seizure focus only when needed. The RNS System provides one solution to the Institute of Medicine's (2012)[1] challenge to "develop medications or other treatments to reduce the burden of uncontrolled seizures." PMA approval of this device will expand treatment options available to this patient population and will provide additional experience to direct future technological and clinical innovation.

The clinical data for the RNS System have met FDA's evidentiary standard for approval of the RNS System: the probable benefits to health from the use of the RNS System outweigh any probable risks, and the evidence demonstrates that a significant portion of the target population achieved clinically significant results. With the assistance of physicians who are expert in the management and consequences of epilepsy, patients with medically intractable partial onset seizures are prepared to consider the benefits and risks, and to make an informed treatment choice.

14 REFERENCES

Refer to the "Referenced Literature" file for a full manuscript of each citation in the bibliography lists provided in **Section 14.1** (Bibliography: Executive Summary) and in **Section 14.2** (Bibliography:).

14.1 Bibliography: Executive Summary

1. IOM (Institute of Medicine), "Epilepsy Across the Spectrum: Promoting Health and Understanding." The National Academies Press available at: http://www.nap.edu/openbook.php?record_id=13379&page=R1, 2012, accessed April 30, 2012.

2. Kwan P, Arzimanoglou A, Berg AT *et al*. "Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies". *Epilepsia* 2010; 51: 1069-1077.

3. Forsgren L, Hauser WA, Olafsson E, Sander JW, Sillanpaa M, Tomson T. "Mortality of epilepsy in developed countries: a review". *Epilepsia* 2005; 46 Suppl 11: 18-27.

4. Tanriverdi T, Ajlan A, Poulin N, Olivier A. "Morbidity in epilepsy surgery: an experience based on 2449 epilepsy surgery procedures from a single institution". *J Neurosurg.* 2009; 110: 1111-1123.

5. Wong IC, Chadwick DW, Fenwick PB, Mawer GE, Sander JW. "The long-term use of gabapentin, lamotrigine, and vigabatrin in patients with chronic epilepsy". *Epilepsia* 1999; 40: 1439-1445.

6. Fountas KN, Smith JR. "Subdural electrode-associated complications: a 20-year experience". *Stereotact.Funct.Neurosurg.* 2007; 85: 264-272.

7. Hamer HM, Morris HH, Mascha EJ *et al*. "Complications of invasive video-EEG monitoring with subdural grid electrodes". *Neurology* 2002; 58: 97-103.

8. Behrens E, Schramm J, Zentner J, Konig R. "Surgical and neurological complications in a series of 708 epilepsy surgery procedures". *Neurosurgery* 1997; 41: 1-9.

9. Oh MY, Abosch A, Kim SH, Lang AE, Lozano AM. "Long-term Hardware-related Complications of Deep Brain Stimulation". *Neurosurgery* 2002; 50: 1268-1276.

10. U.S.Department of Health and Human Services, Food and Drug Administration, "Activa Tremor Control System, Summary of Safety and Effectiveness P960009." Medtronic, Inc., Minneapolis, MN available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/p960009.pdf, May, 1996

11. Beric A, Kelly PJ, Rezai A *et al*. "Complications of deep brain stimulation surgery". *Stereotact.Funct.Neurosurg* 2001; 77: 73-78.

12. Hariz MI. "Complications of deep brain stimulation surgery". *Mov Disord.* 2002; 17 Suppl 3: S162-S166.

13. Joint C, Nandi D, Parkin S, Gregory R, Aziz T. "Hardware-related problems of deep brain stimulation". *Mov Disord.* 2002; 17 Suppl 3: S175-S180.

14. Koller WC, Lyons KE, Wilkinson SB, Troster AI, Pahwa R. "Long-term safety and efficacy of unilateral deep brain stimulation of the thalamus in essential tremor". *Mov Disord.* 2001; 16: 464-468.

15. Lesser RP. "Remission of intractable partial epilepsy following implantation of intracranial electrodes". *Neurology* 2002; 58: 1317.

16. Katariwala NM, Bakay RA, Pennell PB, Olson LD, Henry TR, Epstein CM. "Remission of intractable partial epilepsy following implantation of intracranial electrodes". *Neurology* 2001; 57: 1505-1507.

17. Norman GR, Sloan JA, Wyrwich KW. "Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation". *Med Care* 2003; 41: 582-592.

18. Latini DM, Penson DF, Lubeck DP, Wallace KL, Henning JM, Lue TF. "Longitudinal differences in disease specific quality of life in men with erectile dysfunction: results from the Exploratory Comprehensive Evaluation of Erectile Dysfunction study". *J Urol.* 2003; 169: 1437-1442.

19. Pickard AS, Neary MP, Cella D. "Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer". *Health Qual.Life Outcomes.* 2007; 5: 70.

20. Wong CH, Birkett J, Byth K *et al*. "Risk factors for complications during intracranial electrode recording in presurgical evaluation of drug resistant partial epilepsy". *Acta Neurochir.(Wien.)* 2009; 151: 37-50.

21. Engel J, Jr., Wiebe S, French J *et al*. "Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology, in association with the American Epilepsy Society and the American Association of Neurological Surgeons". *Neurology* 2003; 60: 538-547.

22. Rydenhag B, Silander HC. "Complications of epilepsy surgery after 654 procedures in Sweden, September 1990-1995: a multicenter study based on the Swedish National Epilepsy Surgery Register". *Neurosurgery* 2001; 49: 51-56.

23. Voges J, Waerzeggers Y, Maarouf M *et al*. "Deep Brain Stimulation: Long-term analysis of complications caused by hardware and surgery- a single centre experience". *J Neurol.Neurosurg.Psychiatry* 2006.

24. Goodman RR, Kim B, McClelland S, III *et al*. "Operative techniques and morbidity with subthalamic nucleus deep brain stimulation in 100 consecutive patients with advanced Parkinson's disease". *J Neurol.Neurosurg.Psychiatry* 2006; 77: 12-17.

25. Pahwa R, Factor SA, Lyons KE *et al*. "Practice Parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology". *Neurology* 2006; 66: 983-995.

26. Lyons KE, Wilkinson SB, Overman J, Pahwa R. "Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures". *Neurology* 2004; 63: 612-616.

27. Deep-Brain Stimulation for Parkinson's Disease Study Group. "Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease". *N.Engl.J Med.* 2001; 345: 956-963.

28. Weaver FM, Follett K, Stern M *et al*. "Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial". *JAMA* 2009; 301: 63-73.

29. Silberbusch MA, Rothman MI, Bergey GK, Zoarski GH, Zagardo MT. "Subdural grid implantation for intracranial EEG recording: CT and MR appearance". *AJNR Am.J Neuroradiol.* 1998; 19: 1089-1093.

30. Dasheiff RM. "Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death". *J Clin Neurophysiol* 1991; 8: 216-222.

31. McCreery DB, Agnew WF, Yuen TG, Bullara L. "Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation". *IEEE Trans.Biomed.Eng* 1990; 37: 996-1001.

32. Sillanpaa M, Schmidt D. "Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study". *Brain* 2006; 129: 617-624.

33. Berg AT, Vickrey BG, Testa FM *et al*. "How long does it take for epilepsy to become intractable? A prospective investigation". *Ann Neurol.* 2006; 60: 73-79.

34. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. "Patterns of treatment response in newly diagnosed epilepsy". *Neurology* 2012; 78: 1548-1554.

35. Kwan P, Brodie MJ. "Early identification of refractory epilepsy". *N.Engl.J.Med* 2000; 342: 314-319.

36. Perucca P, Carter J, Vahle V, Gilliam FG. "Adverse antiepileptic drug effects: toward a clinically and neurobiologically relevant taxonomy". *Neurology* 2009; 72: 1223-1229.

37. Marson AG, Al-Kharusi A, Alwaidh M *et al*. "The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial". *Lancet* 2007; 369: 1000-1015.

38. Fisher RS, Vickrey BG, Gibson P *et al*. "The impact of epilepsy from the patient's perspective II: views about therapy and health care". *Epilepsy Res.* 2000; 41: 53-61.

39. Zaccara G, Franciotta D, Perucca E. "Idiosyncratic adverse reactions to antiepileptic drugs". *Epilepsia* 2007; 48: 1223-1244.

40. French JA, Kanner AM, Bautista J *et al*. "Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society". *Neurology* 2004; 62: 1252-1260.

41. French JA, Kanner AM, Bautista J *et al*. "Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society". *Neurology* 2004; 62: 1261-1273.

42. Pack AM, Walczak TS. "Bone health in women with epilepsy: clinical features and potential mechanisms". *Int Rev Neurobiol.* 2008; 83: 305-328.

43. Sheth RD, Montouris G. "Metabolic effects of AEDs: impact on body weight, lipids and glucose metabolism". *Int Rev Neurobiol.* 2008; 83: 329-346.

44. Harden CL, Meador KJ, Pennell PB *et al*. "Management issues for women with epilepsy-Focus on pregnancy (an evidence-based review): II. Teratogenesis and perinatal outcomes: Report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society". *Epilepsia* 2009; 50: 1237-1246.

45. Meador KJ, Baker GA, Browning N *et al*. "Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs". *N.Engl.J Med* 2009; 360: 1597-1605.

46. U.S.Department of Health and Human Services, Food and Drug Administration, "PMA 970003 NeuroCybernetic Prosthesis (NCP®) Pulse Generator Model 100 Physician's

Manual, Cyberonics, Inc. Webster TX." available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/p970003.pdf, July, 1997

47. Handforth A, DeGiorgio CM, Schachter SC *et al*. "Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial". *Neurology* 1998; 51: 48-55.

48. U.S.Department of Health and Human Services, Food and Drug Administration, "NeuroCybernetic Prosthesis (NCP) Vagus Nerve Stimulation System : Summary of Safety and Effectiveness Data - S050." available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/P970003S050b.pdf, July, 2005

49. Spencer SS, Berg AT, Vickrey BG *et al*. "Initial outcomes in the Multicenter Study of Epilepsy Surgery". *Neurology* 2003; 61: 1680-1685.

50. Wiebe S, Blume WT, Girvin JP, Eliasziw M. "A randomized, controlled trial of surgery for temporal-lobe epilepsy". *N.Engl.J.Med* 2001; 345: 311-318.

51. McIntosh AM, Kalnins RM, Mitchell LA, Fabinyi GC, Briellmann RS, Berkovic SF. "Temporal lobectomy: long-term seizure outcome, late recurrence and risks for seizure recurrence". *Brain* 2004; 127: 2018-2030.

52. Spencer S, Huh L. "Outcomes of epilepsy surgery in adults and children". *Lancet Neurol.* 2008; 7: 525-537.

53. Burneo JG, Steven DA, McLachlan RS, Parrent AG. "Morbidity associated with the use of intracranial electrodes for epilepsy surgery". *Can.J Neurol.Sci* 2006; 33: 223-227.

54. Wyler AR, Ojemann GA, Lettich E, Ward AA, Jr. "Subdural strip electrodes for localizing epileptogenic foci". *J.Neurosurg* 1984; 60: 1195-1200.

55. Lee WS, Lee JK, Lee SA, Kang JK, Ko TS. "Complications and results of subdural grid electrode implantation in epilepsy surgery". *Surg.Neurol.* 2000; 54: 346-351.

56. Wiggins GC, Elisevich K, Smith BJ. "Morbidity and infection in combined subdural grid and strip electrode investigation for intractable epilepsy". *Epilepsy Res.* 1999; 37: 73-80.

57. Seijo FJ, varez-Vega MA, Gutierrez JC, Fdez-Glez F, Lozano B. "Complications in subthalamic nucleus stimulation surgery for treatment of Parkinson's disease. Review of 272 procedures". *Acta Neurochir.(Wien.)* 2007; 149: 867-876.

58. Deuschl G, Schade-Brittinger C, krack P *et al*. "A randomized trial of deep-brain stimulation for Parkinson's disease". *N.Engl.J Med.* 2006; 355: 896-908.

59. Blatt DR, Roper SN, Friedman WA. "Invasive monitoring of limbic epilepsy using stereotactic depth and subdural strip electrodes: surgical technique". *Surg.Neurol.* 1997; 48: 74-79.

60. Spencer SS, Spencer DD, Williamson PD, Mattson R. "Combined depth and subdural electrode investigation in uncontrolled epilepsy". *Neurology* 1990; 40: 74-79.

61. Sindou M, Guenot M, Isnard J, Ryvlin P, Fischer C, Mauguiere F. "Temporo-mesial epilepsy surgery: outcome and complications in 100 consecutive adult patients". *Acta Neurochir.(Wien.)* 2006; 148: 39-45.

62. Schuele SU, Luders HO. "Intractable epilepsy: management and therapeutic alternatives". *Lancet Neurol.* 2008; 7: 514-524.

63. Binder DK, Podlogar M, Clusmann H *et al*. "Surgical treatment of parietal lobe epilepsy". *J Neurosurg.* 2009; 110: 1170-1178.

64. Visser-Vandewalle V, Van Der Linden C, Temel Y *et al*. "Long-term effects of bilateral subthalamic nucleus stimulation in advanced Parkinson disease: a four year follow-up study". *Parkinsonism Relat Disord.* 2005; 11: 157-165.

65. Cereghino JJ, Biton V, bou-Khalil B, Dreifuss F, Gauer LJ, Leppik I. "Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial". *Neurology* 2000; 55: 236-242.

66. Ben-Menachem E, Biton V, Jatuzis D, bou-Khalil B, Doty P, Rudd GD. "Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures". *Epilepsia* 2007; 48: 1308-1317.

67. Anhut H, Ashman P, Feuerstein TJ, Sauermann W, Saunders M, Schmidt B. "Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. The International Gabapentin Study Group". *Epilepsia* 1994; 35: 795-801.

68. Manno EM. "New management strategies in the treatment of status epilepticus". *Mayo Clin.Proc* 2003; 78: 508-518.

69. Fountain NB. "Status epilepticus: risk factors and complications". *Epilepsia* 2000; 41 Suppl 2: S23-S30.

70. Kimiskidis VK, Triantafyllou NI, Kararizou E *et al*. "Depression and anxiety in epilepsy: the association with demographic and seizure-related variables". *Ann Gen.Psychiatry* 2007; 6: 28.

71. O'Donoghue MF, Goodridge DM, Redhead K, Sander JW, Duncan JS. "Assessing the psychosocial consequences of epilepsy: a community-based study". *Br.J Gen.Pract.* 1999; 49: 211-214.

72. Jacoby A, Baker GA, Steen N, Potts P, Chadwick DW. "The clinical course of epilepsy and its psychosocial correlates: findings from a U.K. Community study". *Epilepsia* 1996; 37: 148-161.

73. Jones JE, Hermann BP, Barry JJ, Gilliam F, Kanner AM, Meador KJ. "Clinical assessment of Axis I psychiatric morbidity in chronic epilepsy: a multicenter investigation". *J Neuropsychiatry Clin.Neurosci.* 2005; 17: 172-179.

74. Blumer D. "Antidepressant and double antidepressant treatment for the affective disorder of epilepsy". *J Clin.Psychiatry* 1997; 58: 3-11.

75. Lambert MV, Robertson MM. "Depression in epilepsy: etiology, phenomenology, and treatment". *Epilepsia* 1999; 40 Suppl 10: S21-S47.

76. Kanner AM, Nieto JC. "Depressive disorders in epilepsy". *Neurology* 1999; 53: S26-S32.

77. Kanner AM, Soto A, Gross-Kanner H. "Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy". *Neurology* 2004; 62: 708-713.

78. Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. "Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy". *Neurology* 2004; 62: 258-261.

79. Nilsson L, Ahlbom A, Farahmand BY, Asberg M, Tomson T. "Risk factors for suicide in epilepsy: a case control study". *Epilepsia* 2002; 43: 644-651.

80. Rafnsson V, Olafsson E, Hauser WA, Gudmundsson G. "Cause-specific mortality in adults with unprovoked seizures. A population-based incidence cohort study". *Neuroepidemiology* 2001; 20: 232-236.

81. Christensen J, Vestergaard M, Mortensen PB, Sidenius P, Agerbo E. "Epilepsy and risk of suicide: a population-based case-control study". *Lancet Neurol.* 2007; 6: 693-698.

82. Jacoby A, Snape D, Baker GA. "Determinants of quality of life in people with epilepsy". *Neurol.Clin.* 2009; 27: 843-863.

83. Hoppe C, Elger CE, Helmstaedter C. "Long-term memory impairment in patients with focal epilepsy". *Epilepsia* 2007; 48 Suppl 9: 26-29.

84. Hermann BP, Seidenberg M, Dow C *et al*. "Cognitive prognosis in chronic temporal lobe epilepsy". *Ann Neurol.* 2006; 60: 80-87.

85. Thompson PJ, Duncan JS. "Cognitive decline in severe intractable epilepsy". *Epilepsia* 2005; 46: 1780-1787.

86. Seidenberg M, O'Leary DS, Berent S, Boll T. "Changes in seizure frequency and test-retest scores on the Wechsler Adult Intelligence Scale". *Epilepsia* 1981; 22: 75-83.

87. Hesdorffer DC, Tomson T, Benn E *et al*. "Combined analysis of risk factors for SUDEP". *Epilepsia* 2011.

88. Lhatoo SD, Sander JW. "Cause-specific mortality in epilepsy". *Epilepsia* 2005; 46 Suppl 11: 36-39.

89. Iivanainen M, Lehtinen J. "Causes of death in institutionalized epileptics". *Epilepsia* 1979; 20: 485-491.

90. Ryan CA, Dowling G. "Drowning deaths in people with epilepsy". *CMAJ.* 1993; 148: 781-784.

91. Shorvon S, Tomson T. "Sudden unexpected death in epilepsy". *Lancet* 2011.

92. Tomson T, Walczak T, Sillanpaa M, Sander JW. "Sudden unexpected death in epilepsy: a review of incidence and risk factors". *Epilepsia* 2005; 46 Suppl 11: 54-61.

93. Nilsson L, Ahlbom A, Farahmand BY, Tomson T. "Mortality in a population-based cohort of epilepsy surgery patients". *Epilepsia* 2003; 44: 575-581.

94. Poochikian-Sarkissian S, Sidani S, Wennberg RA, Devins GM. "Psychological impact of illness intrusiveness in epilepsy - comparison of treatments". *Psychol.Health Med* 2008; 13: 129-145.

95. Gilliam F. "The impact of epilepsy on subjective health status". *Curr.Neurol.Neurosci.Rep.* 2003; 3: 357-362.

96. Jones JE, Berven NL, Ramirez L, Woodard A, Hermann BP. "Long-term psychosocial outcomes of anterior temporal lobectomy". *Epilepsia* 2002; 43: 896-903.

97. Cramer JA, Van HG. "Maintenance of improvement in health-related quality of life during long-term treatment with levetiracetam". *Epilepsy Behav.* 2003; 4: 118-123.

98. Leidy NK, Elixhauser A, Vickrey B, Means E, Willian MK. "Seizure frequency and the health-related quality of life of adults with epilepsy". *Neurology* 1999; 53: 162-166.

99. Drum M, McCullagh P. "[Regression Models for Discrete Longitudinal Responses]: Comment". *Statistical Science* 1993; 8: 300-301.

100. Stokes ME, Davis CS, Koch GG. Generalized Estimating Equations. Categorical Data Analysis Using the SAS System. Cary, NC: SAS Institute, 2000: 485.

101. SAS Institute Inc., "The GENMOD Procedure." SAS Institute Inc. available at: http://support.sas.com/documentation/cdl/en/statuggenmod/61787/PDF/default/statuggenmod.pdf, 2008, accessed September 1, 2011.

102. Scott-Lennox J, Bryant-Comstock L, Lennox R, Baker GA. "Reliability, validity and responsiveness of a revised scoring system for the Liverpool Seizure Severity Scale". *Epilepsy Res.* 2001; 44: 53-63.

103. Spencer SS, Berg AT, Vickrey BG *et al*. "Health-related quality of life over time since resective epilepsy surgery". *Ann Neurol.* 2007; 62: 327-334.

104. Wiebe S, Matijevic S, Eliasziw M, Derry PA. "Clinically important change in quality of life in epilepsy". *J Neurol Neurosurg Psychiatry* 2002; 73: 116-120.

105. James KE, Bloch DA, Lee KK, Kraemer HC, Fuller RK. "An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation--a VA cooperative study". *Stat.Med* 1996; 15: 1421-1434.

106. Ballinger GA. "Using Generalized Estimating Equations for Longitudinal Data Analysis". *Organizational Research Methods* 2004; 7: 127-150.

107. Wang YG, Lin X. "Effects of variance-function misspecification in analysis of longitudinal data". *Biometrics* 2005; 61: 413-421.

108. Cook RD, Weisberg S. Assessment of Influence. Residuals and Influence in Regression. New York: Chapman and Hall, 1982: 118.

109. Loring DW, Meador KJ, Lee GP. "Determinants of quality of life in epilepsy". *Epilepsy Behav.* 2004; 5: 976-980.

110. Hessen E, Lossius MI, Gjerstad L. "Health concerns predicts poor quality of life in well-controlled epilepsy". *Seizure.* 2009; 18: 487-491.

111. Zaccara G, Messori A, Cincotta M, Burchini G. "Comparison of the efficacy and tolerability of new antiepileptic drugs: what can we learn from long-term studies?". *Acta Neurol.Scand.* 2006; 114: 157-168.

112. Zhou XH, Li CM, Yang Z. "Improving interval estimation of binomial proportions". *Philos.Transact.A Math.Phys.Eng Sci* 2008; 366: 2405-2418.

113. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation, 1996: 10-2.

114. Kanner AM. "Depression in epilepsy: a neurobiologic perspective". *Epilepsy Curr.* 2005; 5: 21-27.

115. Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. "Psychiatric comorbidity in epilepsy: a population-based analysis". *Epilepsia* 2007; 48: 2336-2344.

116. U.S.Department of Health and Human Services, Food and Drug Administration, "Keppra NDA 21-035." UCB Pharma, Inc., Smyrna, GA available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/1999/21035lbl.pdf, December 1, 1999, accessed 2003.

14.2 Bibliography: Randomized controlled trials of antiepileptic trials

Amar AP, DeGiorgio CM, Tarver WB, Apuzzo ML. "Long-term multicenter experience with vagus nerve stimulation for intractable partial seizures: results of the XE5 trial.". *Stereotact.Funct.Neurosurg.* 1999; 73: 104-108.

Anhut H, Ashman P, Feuerstein TJ, Sauermann W, Saunders M, Schmidt B. "Gabapentin (Neurontin) as add-on therapy in patients with partial seizures: a double-blind, placebo-controlled study. The International Gabapentin Study Group". *Epilepsia* 1994; 35: 795-801.

Arroyo S, Anhut H, Kugler AR *et al*. "Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures". *Epilepsia* 2004; 45: 20-27.

Barcs G, Walker EB, Elger CE *et al*. "Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy". *Epilepsia* 2000; 41: 1597-1607.

Ben-Menachem E, Manon-Espaillat R, Ristanovic R *et al*. "Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group". *Epilepsia* 1994; 35: 616-626.

Ben-Menachem E, Henriksen O, Dam M *et al*. "Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures". *Epilepsia* 1996; 37: 539-543.

Ben-Menachem E, Biton V, Jatuzis D, bou-Khalil B, Doty P, Rudd GD. "Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures". *Epilepsia* 2007; 48: 1308-1317.

Beydoun A, Uthman BM, Kugler AR, Greiner MJ, Knapp LE, Garofalo EA. "Safety and efficacy of two pregabalin regimens for add-on treatment of partial epilepsy". *Neurology* 2005; 64: 475-480.

Brodie MJ, Lerche H, Gil-Nagel A *et al*. "Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy". *Neurology* 2010; 75: 1817-1824.

Cereghino JJ, Biton V, bou-Khalil B, Dreifuss F, Gauer LJ, Leppik I. "Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial". *Neurology* 2000; 55: 236-242.

Chung S, Sperling MR, Biton V *et al*. "Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial". *Epilepsia* 2010; 51: 958-967.

Faught E, Wilder BJ, Ramsay RE *et al*. "Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. Topiramate YD Study Group". *Neurology* 1996; 46: 1684-1690.

Faught E, Ayala R, Montouris GG, Leppik IE. "Randomized controlled trial of zonisamide for the treatment of refractory partial-onset seizures". *Neurology* 2001; 57: 1774-1779.

French JA, Kugler AR, Robbins JL, Knapp LE, Garofalo EA. "Dose-response trial of pregabalin adjunctive therapy in patients with partial seizures". *Neurology* 2003; 60: 1631-1637.

French JA, Abou-Khalil BW, Leroy RF *et al*. "Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy". *Neurology* 2011; 76: 1555-1563.

French JA, Krauss GL, Biton V *et al*. "Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304". *Neurology* 2012; 79: 589-596.

French JA, Krauss GL, Steinhoff BJ *et al*. "Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: Results of randomized global phase III study 305". *Epilepsia* 2013; 54: 117-125.

Guberman A, Neto W, Gassmann-Mayer C. "Low-dose topiramate in adults with treatment-resistant partial-onset seizures". *Acta Neurol.Scand.* 2002; 106: 183-189.

Krauss GL, Serratosa JM, Villanueva V *et al*. "Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures". *Neurology* 2012; 78: 1408-1415.

Ottman R, Lipton RB, Ettinger AB *et al*. "Comorbidities of epilepsy: Results from the Epilepsy Comorbidities and Health (EPIC) survey". *Epilepsia* 2011; 52: 308-315.

Perucca P, Carter J, Vahle V, Gilliam FG. "Adverse antiepileptic drug effects: toward a clinically and neurobiologically relevant taxonomy". *Neurology* 2009; 72: 1223-1229.

Poochikian-Sarkissian S, Sidani S, Wennberg RA, Devins GM. "Psychological impact of illness intrusiveness in epilepsy - comparison of treatments". *Psychol.Health Med* 2008; 13: 129-145.

Porter RJ, Partiot A, Sachdeo R, Nohria V, Alves WM. "Randomized, multicenter, dose-ranging trial of retigabine for partial-onset seizures". *Neurology* 2007; 68: 1197-1204.

Sabsevitz DS, Swanson SJ, Hammeke TA *et al*. "Use of preoperative functional neuroimaging to predict language deficits from epilepsy surgery". *Neurology* 2003; 60: 1788-1792.

Schiller Y, Najjar Y. "Quantifying the response to antiepileptic drugs: effect of past treatment history". *Neurology* 2008; 70: 54-65.

Seidenberg M, O'Leary DS, Berent S, Boll T. "Changes in seizure frequency and test-retest scores on the Wechsler Adult Intelligence Scale". *Epilepsia* 1981; 22: 75-83.

Shorvon S, Tomson T. "Sudden unexpected death in epilepsy". *Lancet* 2011.

Spencer SS, Berg AT, Vickrey BG *et al*. "Health-related quality of life over time since resective epilepsy surgery". *Ann Neurol.* 2007; 62: 327-334.

Tanriverdi T, Ajlan A, Poulin N, Olivier A. "Morbidity in epilepsy surgery: an experience based on 2449 epilepsy surgery procedures from a single institution". *J Neurosurg.* 2009; 110: 1111-1123.

Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. "Psychiatric comorbidity in epilepsy: a population-based analysis". *Epilepsia* 2007; 48: 2336-2344.

Thompson PJ, Duncan JS. "Cognitive decline in severe intractable epilepsy". *Epilepsia* 2005; 46: 1780-1787.

U.S.Department of Health and Human Services, Food and Drug Administration, "Keppra NDA 21-035." UCB Pharma, Inc., Smyrna, GA available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/1999/21035lbl.pdf, December 1, 1999, accessed 2003.

U.S.Department of Health and Human Services, Food and Drug Administration, "POTIGA (ezogabine) Tablets Initial US Approval 2011." GlaxoSmithKline Research Triangle Park, NC 27709 available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022345s000lbl.pdf, June, 2011, accessed 2011.

Wiebe S, Blume WT, Girvin JP, Eliasziw M. "A randomized, controlled trial of surgery for temporal-lobe epilepsy". *N.Engl.J.Med* 2001; 345: 311-318.

Wong IC, Chadwick DW, Fenwick PB, Mawer GE, Sander JW. "The long-term use of gabapentin, lamotrigine, and vigabatrin in patients with chronic epilepsy". *Epilepsia* 1999; 40: 1439-1445.

Zaccara G, Messori A, Cincotta M, Burchini G. "Comparison of the efficacy and tolerability of new antiepileptic drugs: what can we learn from long-term studies?". *Acta Neurol.Scand.* 2006; 114: 157-168.

15 APPENDICES

15.1 Statistical Discussion

TABLE OF CONTENTS

List of Tables

List of Figures

1 STATISTICAL DISCUSSION

1.1 OVERVIEW

The Pivotal study is a prospective, randomized, double-blinded, concurrent sham-stimulation controlled trial. Subjects participated in a 3-month Pre-Implant Period (baseline), and all eligible subjects were implanted. At 1 month post-implant subjects were randomized 1:1 using an adaptive randomization procedure. Beginning in the 2nd month post-implant the Treatment group began to receive responsive stimulation and continued to receive responsive stimulation through the end of the study. The Sham group did not receive responsive stimulation until they entered the Open Label Period, which began in the 6th month post-implant. During the Open Label Period, which continued through 2 years post-implant, all subjects received responsive stimulation. Subject's randomization group was not revealed to the subject at any time in the study.

A total of 191 patients were implanted in the Pivotal study. All implanted subjects were randomized and included in the intent-to-treat analysis (97 subjects were randomized to the Treatment group and 94 subjects were randomized to the Sham group). 98% of all implanted subjects completed the Blinded Evaluation Period (through 5 months post-implant), and 92% of all implanted subjects completed the entire 2-year study.

The primary effectiveness endpoint compared seizure frequency during the 3rd, 4th, and 5th months post-implant (i.e., the Blinded Evaluation Period) to the seizure frequency during the 3-month Pre-Implant Period. The primary effectiveness endpoint analysis was performed using all available seizure count data collected for the Pre-Implant and Blinded Evaluation Periods; this included partial data for subjects who failed to record their seizure information during some portion of the study and for subjects who discontinued the study prior to completion. Out of the total possible number of daily seizure observations, 98% (31,434/32,088) were captured for the primary effectiveness endpoint.

The pre-specified primary effectiveness analysis, when performed in accordance with the approved statistical methods for the Pivotal study using the generalized estimating equations (GEE) method, yields a statistically significant treatment effect (effect size = -0.25, $p < 0.0001$). However, objective metrics indicated that the data did not meet the model assumptions. In other words, after initial evaluation of the data, it was apparent that the pre-specified GEE model was not appropriate for the seizure data.

In order to move forward with a scientifically valid statistical analysis, NeuroPace worked with FDA to identify modifications to the GEE model to yield an appropriate primary analysis. The modifications were made in a manner consistent with sound statistical practice and according to FDA's recommendation.

This appendix is organized into the following sections:

- **Section 1.2**: **Introduction to generalized estimating equations** reviews the main concepts of GEE, including the model parameters that need to be specified when performing a GEE analysis, the impact of misspecification of these model parameters, and the interpretation of GEE results.
- **Section 1.3: The pre-specified GEE model** provides the results of the pre-specified primary effectiveness endpoint.

- **Section 1.4**: **Modifications to the pre-specified GEE model and rationale** describes the modifications to the GEE model and discusses why the modifications are necessary to achieve a proper and efficient analysis of the data.
- **Section 1.5: Robustness of the treatment effect** provides additional sensitivity analyses that demonstrate that the treatment effect is robust to exclusion of subjects who had significant protocol deviations (the 'Per Protocol' analysis), exclusion of extreme values, missing data imputation, and reasonable modifications to the GEE analysis.

1.2 INTRODUCTION TO GENERALIZED ESTIMATING EQUATIONS

The method of generalized estimating equations (GEE) is an extension of standard linear regression for use with non-normally distributed and repeated measures data. The power and flexibility of the GEE, make it the preferred method for analysis of longitudinal non-normally distributed data such as seizure count data.[1]

Standard GEE software packages provide two sets of results (p-values) based on two methods for estimating the standard errors. These are referred to as the empirical and model-based standard errors. The empirical standard errors are often preferred because they provide statistically consistent estimates and are robust to some misspecification of the GEE analysis. However, the empirical standard errors can be highly variable and inefficient especially if the number of patients is small compared to the number of repeated measurements. The model-based standard errors allow for a scale parameter to account for over-dispersion, and may be preferable in applied work.[2] Importantly, the empirical and model-based standard errors should be similar. Large differences between the empirical and model-based standard errors indicate that the GEE model is not correctly specified or that estimates may be inefficient or both.[3]

A properly specified GEE analysis model is highly efficient and appropriately accounts for within-subject correlations as well as variability across different subject populations. Here, efficiency refers to the relative power of the analysis: a highly efficient analysis optimally uses the information in the data, whereas an inefficient analysis does not use all of the information in the data (e.g. disregards data), and can lead to incorrect interpretations of the data.

GEE analyses require proper specification of the following:

- a mean model
- a variance function
- a correlation structure

Misspecification of any of the model parameters can lead to uninterpretable results, to a loss of efficiency, or both. The sections below describe the mean model and the variance function and the impact of misspecification of these parameters.

1.2.1 Specification of the Mean Model

The mean model specifies the relationship of the variables that are expected to influence the outcome variable. For example, in this case where the outcome variable is seizure frequency, the mean model would include trial period (baseline versus post-implant) and therapy allocation (treatment versus sham). Additionally, inclusion of clinically relevant covariates in the mean model is important to minimize effect differences due to imbalance[4] and to make the analysis more precise.[5,6] Specifically, covariates that were part of the adaptive randomization should be included

to "obtain the proper significance levels,"[4] and FDA recommends including these covariates to adjust for imbalance.[7]

Misspecification of the mean model can yield un-interpretable results. For example, if the data have a U-shaped response, and the mean model requires the data to fit a straight line, the resulting estimate of the slope of the line is un-informative and does not reflect the true response in the data. Additionally, failure to adjust for known factors that influence the outcome variable, such as clinical covariates that are highly prognostic of the outcome variable or clinical covariates that are out of balance, can result in an inflated p-value.[8]

1.2.2 Specification of the Variance Function

The variance function specifies the variance or distribution of the outcome variable relative to the mean. For count data, such as seizures per month, two types of variance functions are considered: the Poisson variance function and the negative binomial variance function. Historically, the Poisson variance function was the standard model for count data. It imposes a strict mean-variance relationship, specifically that the variance is equal to the mean (var = μ). However, this assumption is often violated in practice. In fact it is difficult to find real-life Poisson data sets.[9] The negative binomial variance function, which is now considered the benchmark model to account for overdispersion on count data, allows a more general mean-variance relationship in which the variance may be larger than the mean (var = $\mu+k\mu^2$).[9] Note that the negative binomial variance function is a more general case; the Poisson variance function is simply a special case of the negative binomial variance function when k = 0.

The model-based estimators in the GEE method allow further generalization of both the Poisson and negative binomial variance functions by allowing an overdispersion parameter (ϕ). The more generalized variance functions are referred to as the *overdispersed* Poisson variance function (var =$\phi\mu$), and the *scaled* negative binomial variance function (var = $\phi(\mu+k\mu^2)$). A large overdispersion parameter (ϕ >> 1) indicates that the variance function does not adequately describe the distribution of the data.[10] Note, SAS reports the *scale parameter* which is the square root of the estimate of ϕ.

Misspecification of the variance model can significantly reduce the efficiency of the analysis,[11] thus requiring many more patients compared to an analysis using a properly specified variance model. Because the negative binomial variance function by definition includes the Poisson variance function as a special case, it leads to a more efficient use of information than the Poisson variance function.

1.3 THE PRE-SPECIFIED GEE MODEL

The primary effectiveness endpoint variable is the group-by-time interaction term in a generalized estimating equation (GEE) longitudinal regression model. The pre-specified mean model is represented by the equation:

$$\ln(E[(Y)]) = \beta_0 + \beta_1 \text{Time} + \beta_2 \text{Time*Group}$$

where Y is the daily seizure count, Time indicates the trial period (0=Pre-Implant Period, 1=Blinded Evaluation Period), and Group indicates therapy randomization (0=Sham, 1=Treatment). β_0 is the intercept, and β_1 represents the effect of time (independent of the effect of group. β_2 represents the treatment effect (the reduction in seizure frequency in the Treatment group beyond that in the Sham group during the Blinded Evaluation Period compared to the Pre-Implant Period). Additionally,

the investigational plan pre-specified that models may also include covariates that potentially influence the endpoint and are found not to be balanced between treatment groups.

The pre-specified model assumed a Poisson distribution for the daily seizure count data, and specifically called for the use of a scale parameter to address over-dispersion. This was the distribution recommended by FDA at when the study was designed. Note that model-based standard errors use the scale parameter whereas empirical standard errors do not use the scale parameter.

Use of model-based standard errors is supported in the literature when the number of patients is small compared to the number of repeated measures.[2] In the pre-specified analysis using daily seizure count data, the number of patients (191) is small compared to the number of repeated measurements (31,434 repeated measurements of daily seizure count data). In this case, empirical standard errors can be highly variable and inefficient (resulting in p-values that are too large), and the estimate can be far from robust.[2]

The pre-specified primary effectiveness analysis, when performed exactly as stated in the approved statistical methods for the pivotal investigation, yields a statistically significant treatment effect with a p-value of < 0.0001 for the group-by-time parameter estimate. The results of the pre-specified GEE model is provided in **Table 1**.

This model, which appropriately addresses the variability in the seizure data, demonstrates that there is a significant difference in seizure reduction between the Treatment and Sham groups (effect size = -0.29, empirical p-value = 0.012). Over three months of the Blinded Evaluation Period, the Treatment group experienced an overall seizure reduction of -38% whereas the Sham group experienced an overall seizure reduction of -17%.

Details and rationale regarding each of these modifications are provided in the sections below.

Table 1: GEE Results – Pre-specified primary analysis

Treatment (N = 97), Sham (N = 94)					
GEE Model Information					
Distribution	Poisson				
Link Function	Log				
Dependent Variable	Daily seizure counts				
Correlation Structure	Compound Symmetry				
Results from GEE					
Parameter	**Parameter Estimate (log scale)**	**Standard Error**		**P-Value**	
		Empirical	**Model-Based**	**Empirical**	**Model-Based**
Intercept	0.2003	0.1307	0.1245	0.1254	0.1076
Time Pre-Implant Period = 0 Blinded Evaluation Period = 1	-0.1670	0.1360	0.0376	0.2195	<0.0001
Group*Time Sham Group = 0 Treatment Group = 1	-0.2512	0.1749	0.0576	0.1510	<0.0001
Scale Parameter					2.9795
The overdispersion parameter is the square of the scale parameter.					

Data as of 5/12/2011

However, diagnostic metrics generated by standard statistical software indicated that the pre-specified GEE model was not correctly specified (i.e., the data do not fit the analysis assumptions).

- First, with a properly specified GEE analysis, the empirical and model-based standard error estimates are similar.[3] In the pre-specified analysis, the empirical standard error was 3 times the model-based standard error (0.1749 vs. 0.0576 for the group-by-time covariate). This indicates that the pre-specified GEE model is not adequately specified (i.e. does not fit the data).
- Second, the overdispersion parameter, a metric provided in standard statistical packages, should be near 1. An overdispersion parameter much greater than 1 (or much smaller than 1) is indicative of an incorrectly specified model or outliers in the data.[10] The overdispersion parameter, which is the square of the scale parameter, was nearly 9. This indicates that the daily seizure count data are highly overdispersed relative to the assumption of the Poisson distribution that the mean equals the variance.

1.4 MODIFICATIONS TO THE PRE-SPECIFIED GEE MODEL AND RATIONALE

Because trial conclusions should not be based on a statistical analysis where critical model assumptions are violated, NeuroPace sought to work with FDA to identify a modifications so that the GEE model assumptions would be appropriate for the data. The modifications were based on sound statistical principles, and were agreed upon with FDA to provide a proper and efficient analysis of the Pivotal trial data. The modifications were to 1) group seizure data by month; 2) adjust for the clinical covariates used in randomization; and 3) use a negative binomial variance function.

These modifications result in a model in which: 1) the model-based and empirical standard errors are in close agreement (0.1148 and 0.1037 for the group-by-time covariate) providing confidence that the model is properly specified; and 2) the overdispersion parameter is near 1 (overdispersion parameter = 1.5) indicating that the negative binomial distribution more accurately reflects the variance in the seizure data. These modifications are statistically and clinically justified and provide a scientifically valid and efficient estimate of the treatment effect. Results of the modified model are provided in **Table 2**.

Table 2: GEE Results – Valid primary analysis

Treatment (N = 97), Sham (N = 94)						
GEE Model Information						
Distribution		Negative Binomial				
Link Function		Log				
Dependent Variable		Seizure counts				
Correlation Structure		Compound Symmetry				
GEE Fit Criteria (QIC / QICu)		-177455 / -177470				
Results from GEE						
Parameter		**Parameter Estimate (log scale)**	**Standard Error**		**P-Value**	
			Empirical	**Model-Based**	**Empirical**	**Model-Based**
	Intercept	-0.2630	0.1932	0.2278	0.1734	0.2483
Clinical covariates	**Seizure onset zone** Mesial temporal lobe only = 0 Other = 1	0.9463	0.2353	0.2323	<0.0001	<0.0001
	Number of seizure foci Unifocal = 0 Bifocal = 1	-0.5719	0.1955	0.2237	0.0034	0.0106
	Prior surgery No prior surgery = 0 Prior surgery = 1	0.2561	0.2416	0.2453	0.2892	0.2966
	Time Pre-Implant Period = 0 Blinded Evaluation Period = 1	-0.1898	0.0847	0.0762	0.0250	0.0128
	Group*Time Sham Group = 0 Treatment Group = 1	-0.2873	0.1148	0.1037	0.0123	0.0056
Scale Parameter[1]						1.2370

[1] Computed as the square root of the normalized Pearson's chi-square.
The overdispersion parameter is the square of the scale parameter.
Data as of 5/12/2011

1.4.1 Grouping seizure data by month

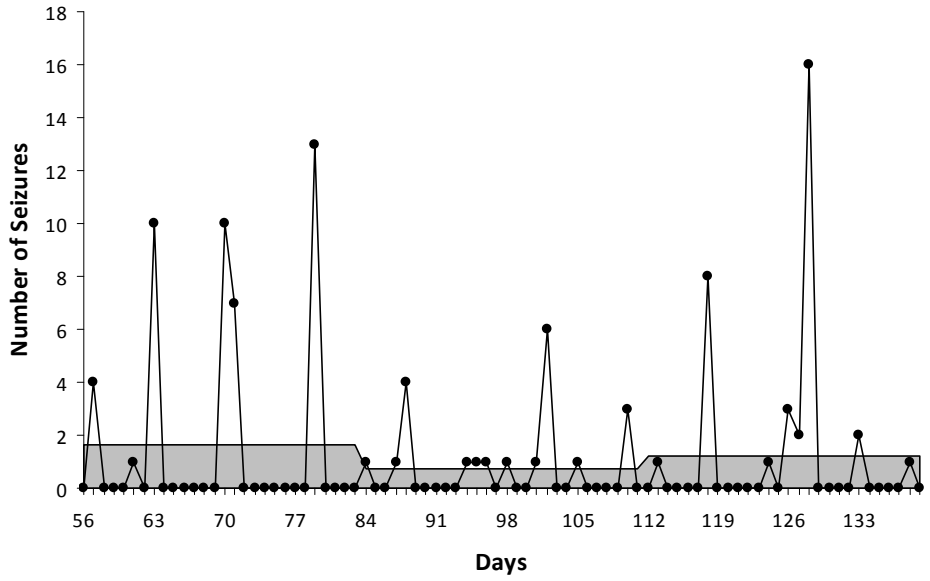
Daily seizure count data may be clustered and/or have periodicities.12 The daily seizure data observed in the Pivotal trial were highly variable with patients often having many days without seizures followed by brief periods with several seizures (an example of daily seizure count data for one subject is provided in **Figure 1**). These daily seizure data are over-dispersed and do not meet the distributional assumptions of the pre-specified GEE analysis.

Grouping seizure data by monthly intervals has been shown to reduce the effects of over-dispersion and allow for choice of an appropriate model.[13] FDA also recommended using monthly seizure count data because daily seizure count data are problematic: they increase the number of repeated observations per subject and introduces a substantial number of zero observations.

Daily seizure count data are highly variable, making it difficult to specify an appropriate statistical model that will permit valid and efficient analyses. Averaging data by month facilitates choice of an appropriate model.

Therefore, to allow for valid statistical analysis, facilitate clinical interpretation, and per FDA recommendation, daily counts were grouped into monthly intervals. The average counts per month are shown by the gray shaded region in **Figure 1**.

Figure 1: Daily seizure count example for patient 2922357



Data as of 5/12/2011

1.4.2 Adjusting for clinical covariates used in randomization

The inclusion of clinically relevant covariates is recognized as an important process in analyses of variance to minimize effect differences due to imbalance[4] and to make the analysis more precise.[5,6] Specifically, covariates that are part of the adaptive randomization should be included to obtain the proper significance levels,[4] and is recommended by FDA to adjust for imbalance.[7] In fact, failure to include randomization covariates may result in an over-estimation of the p-value, potentially resulting in Type II error.[8] Stated simply, failure to include appropriate covariates means systematic variation that is due to known clinical factors – such as seizure onset zone – will be treated essentially as noise, artificially increasing the standard error estimates and reducing or potentially concealing the significance of real effects.

FDA guidance and statistical literature strongly support inclusion of randomization covariates in order to have the analysis match the design, to increase precision by explaining the variability in the outcome measure, and to adjust for any residual imbalance between the active and control groups.

Three clinical characteristics were identified *a priori* to be used in the adaptive randomization process:

- Seizure onset location: Whether seizures arise in the mesial temporal lobe or from another location
- Number of seizure foci: Whether seizures arise from one or two locations in the brain
- Prior therapeutic surgery: Whether the subject has undergone brain surgery for epilepsy

These characteristics are highly prognostic of seizure frequency (**Table 3**), therefore inclusion of these covariates is important to adjust for the high variation in seizure counts across different subject populations. Additionally, one of the randomization covariates was moderately out of balance between the groups (p = 0.089, **Table 4**), therefore inclusion of this covariate is necessary to adjust for potential imbalance between the Treatment and Sham groups.

After FDA had reviewed the data, FDA specifically recommended that the analysis should adjust for the covariates used in randomization because the trial used a minimization approach to randomization. Therefore, the clinical characteristics used in randomization were included in the GEE analysis model.

Table 3: Pre-Implant Period seizure frequency by subset

Characteristics used as Strata in Adaptive Randomization Algorithm	**% (n/N)**	**Pre-Implant Seizure Frequency** (Mean ± SD, seizures/month)
Seizure Onset Zone		
Mesial Temporal Lobe	50% (95/191)	15.81 ± 26.75
Other	50% (96/191)	52.39 ± 79.27
Number of Seizure Foci		
Unifocal onset	45% (85/191)	53.79 ± 84.65
Bifocal onset	55% (106/191)	18.49 ± 25.33
Prior Therapeutic Surgery for Epilepsy		
Prior Surgery	32% (62/191)	56.38 ± 85.30
No Prior Surgery	68% (129/191)	23.53 ± 43.21

Data as of 5/12/2011

Table 4: Clinical characteristics used in randomization

Characteristic	**All Implanted (N=191)**	**By Randomization Group**		
		Treatment (N=97)	**Sham (N=94)**	**p-value[1]**
Seizure onset location - Mesial Temporal Lobe Only (v. other)	50% (95/191)	49% (48/97)	50% (47/94)	0.943
Number of seizure foci - Bifocal (v. unifocal)	55% (106/191)	49% (48/97)	62% (58/94)	0.089
Prior therapeutic surgery for epilepsy	32% (62/191)	35% (34/97)	30% (28/94)	0.437

[1] p-value per chi-square test

Data as of 5/12/2011

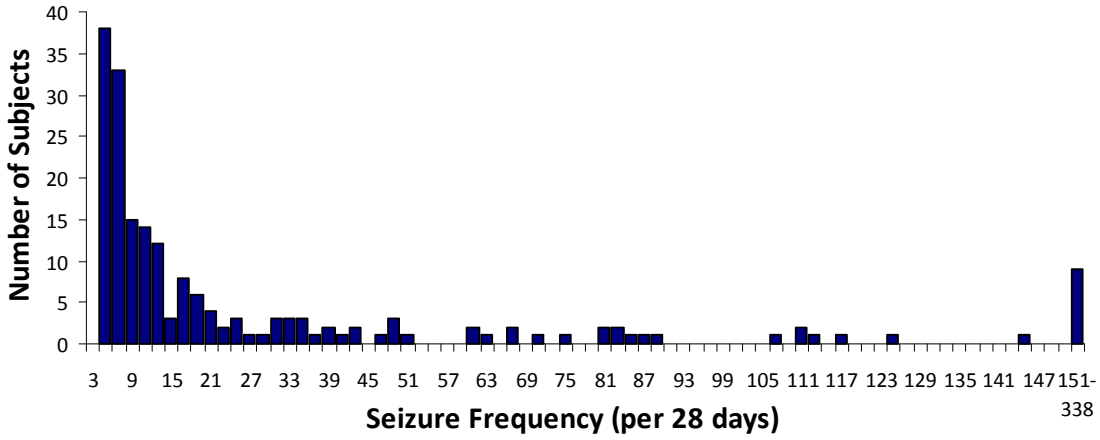
1.4.3 Using a negative binomial variance function

The pre-specified GEE model assumed an overdispersed Poisson variance function as originally recommended by FDA. However, the variability in the seizure data collected in the study is not consistent with the overdispersed Poisson variance function. There is considerable variability in the baseline seizure frequency across subjects (**Figure 2**), and the seizure data do not meet the strict requirement that the variance is a linear function of the mean (i.e., var = $\phi\mu$, where ϕ is the overdispersion parameter and μ is the mean). Rather, the study data are consistent with the more general negative binomial variance function, which is parameterized so that the variance is a

quadratic function of the mean (i.e., var = $\phi(\mu+k\mu^2)$, where k is the negative binomial dispersion parameter). The negative binomial variance function is the benchmark model to account for overdispersion in count data.[9] Note that the overdispersed Poisson variance function is simply a special case of the negative binomial variance function when $k = 0$.

The negative binomial variance function is the benchmark model to account for overdispersion in count data. The overdispersed Poisson variance function is a restrictive special case of the negative binomial variance function.

Figure 2: Pivotal Study – Pre-Implant Seizure Frequency



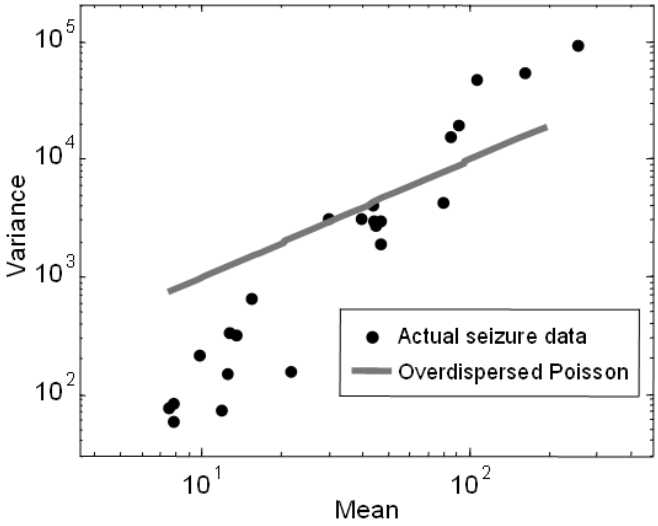
Data as of 5/12/2011

Historically, the overdispersed Poisson variance function was often cited as a reasonable assumption for modeling overdispersion. However, these publications should be considered in context. Prior to 2001, the negative binomial GEE regression was not available in commercial statistical packages.[14] As such, historical interest in approximating overdispersion with the overdispersed Poisson model was likely due to absence of viable software for negative binomial GEE regression.

Importantly, there are limitations to the type and amount of overdispersion that can be addressed with the overdispersed Poisson variance function. Breslow[15] simulated data from negative binomial distributions with $k = 0.0$, 0.2, and 0.5. Breslow's results demonstrate that the overdispersed Poisson standard errors – while somewhat robust for small k – begin to perform poorly under both the null hypothesis and the alternative hypothesis when the overdispersed Poisson model is used to draw inferences for negative binomial data with $k \geq 0.5$. For comparison, the estimate of k in the Pivotal trial seizure data is approximately 3 times that value ($k = 1.47$, standard error = 0.071).

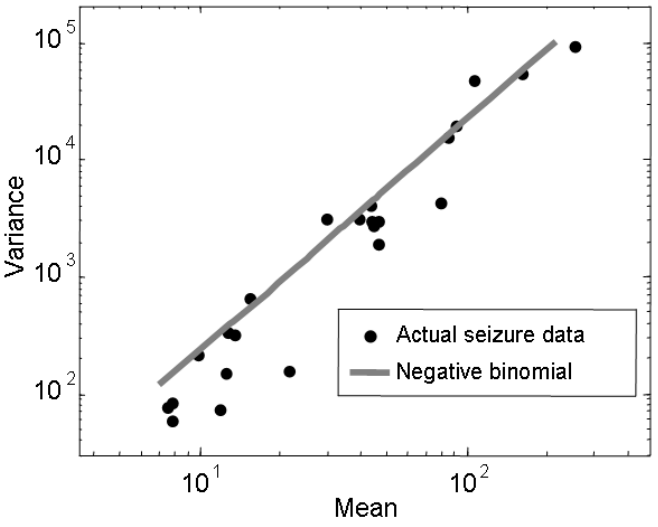
To demonstrate the inadequacy of the overdispersed Poisson variance function for the seizure count data, the actual and modeled mean-variance relationships for the seizure data are plotted in **Figure 3**, where each dot represents the actual mean and variance of the seizure data for a given data bin, and the line represents the best possible fitted mean-variance relationship when using an overdispersed Poisson variance function. Because the overdispersed Poisson variance function defines a strictly linear relationship between the mean and variance, the line in the figure below (on a log-log plot) is the best fit that can be made; it cannot be improved or "rotated" to better fit the actual seizure count data.

Figure 3: Actual vs. modeled mean-variance relation for the overdispersed Poisson model (var = $\phi\mu$)



The actual mean-variance relationship (dots) is shown with the overdispersed Poisson model-fitted mean-variance relationship (line). Due to the restrictive linear mean-variance relationship defined by the overdispersed Poisson variance function, the fit to the raw data cannot be improved.

Figure 4: Actual vs. modeled mean-variance relation for the scaled negative binomial model (var = $\phi(\mu+k\mu^2)$)



The actual mean-variance relationship (dots) is shown with the scaled negative binomial model-fitted mean-variance relationship (line). The fit of the line is substantially improved as compared to the fit when using the overdispersed Poisson variance function.

In contrast, when the data are modeled using the scaled negative binomial variance function, which is the more general variance function, the fit is dramatically improved (**Figure 4**). The scaled negative binomial variance function, through specification of *k*, allows a quadratic relationship

between the variance and the mean thereby allowing the modeled variance function to better approximate the actual data.

In other words, the negative binomial allows the variance to potentially be much greater than the mean, and is therefore often used to model overdispersed count data.[1,13,16,17] Additionally, the negative binomial distribution is specifically recommended when the overdispersion parameter estimated using the overdispersed Poisson variance function is much greater than 1 (SAS GENMOD documentation).[10] The overdispersion parameter in the pre-specified analysis was 8.9.

Using an inadequate variance function can significantly reduce the efficiency of an analysis.[1,11] In this case, using the overdispersed Poisson variance function reduces the efficiency of the analysis by over 70% relative to using the negative binomial distribution function. Bootstrap analyses demonstrate that the inflated standard error estimate for the treatment effect that results from using the overdispersed Poisson variance function with the Pivotal trial seizure data is as large as the standard error estimate observed when using only 54 of the 191 subjects and the more appropriate scaled negative binomial variance function. In other words, performing the analysis using the overdispersed Poisson variance function is like performing the analysis using less than 30% of the available data.

1.4.4 Summary of GEE Model Modifications

To summarize, while the pre-specified primary effectiveness endpoint analysis yielded a highly statistically significant result, modifications to the analysis were required because critical assumptions of the pre-specified analysis were not met. These modifications, which were based on sound statistical practice and per FDA recommendation, were to group seizure data by month, include covariates used in randomization, and use a negative binomial distribution.

Grouping seizure data by month is necessary in order to allow for a valid statistical analysis; daily data are problematic because of the large number of repeated observations per subject and the substantial number of zero observations. It is also necessary to adjust for the clinical covariates used in randomization, which are highly prognostic of the outcome variable, in order to make the estimate more precise and to adjust for imbalance between the Treatment and Sham groups. One of the randomization covariates was not in balance (number of seizure foci, $p = 0.089$). Finally it is necessary to assume a negative binomial variance function. The seizure data do not meet the distributional assumptions of the overdispersed Poisson variance function.

The modifications are founded on statistical literature and statistical principles. Additionally, diagnostic metrics indicate that the modifications result in an appropriate analysis of the study data and that the assumptions are valid: 1) the model-based and empirical standard errors are in close agreement providing confidence that the model is properly specified and 2) the overdispersion parameter is near 1 indicating that the negative binomial distribution reflects the variance in the seizure data.

In collaboration with FDA, a set of modifications to the pre-specified GEE model was identified as being necessary to allow proper and efficient analysis of the Pivotal trial data. These modifications are in accord with sound statistical principles, are clinically and statistically justifiable, and are supported by quantitative goodness-of-fit measures.

1.5 ROBUSTNESS OF THE TREATMENT EFFECT

Robustness is a property of an analysis which demonstrates that inferential decisions are not changed by relaxing selected assumptions used in the analysis. However, testing robustness using models that violate the critical assumptions described above is statistically unsound. Below is a demonstration of the robustness of the treatment effect supported by sensitivity analyses that show that the magnitude and statistical significance of the seizure reduction in the Treatment compared to Sham groups is not altered when the few patients with potentially significant protocol deviations are excluded, or when extreme data are excluded. Additionally, the treatment effect is not sensitive to imputation of missing data. Moreover, the results are consistent across appropriate GEE models, and reproducible as demonstrated through bootstrap analyses, and statistical significance is maintained with exclusion of a number of influential subjects.

1.5.1 Pre-specified Per-Protocol analysis

As pre-specified in the investigational plan, the primary effectiveness endpoint analysis was repeated excluding data from subjects with protocol deviations that may seriously affect the integrity of the data collected, e.g. a "per-protocol" analysis.

Nine such subjects were identified: 6 due to medication changes during the Pre-Implant or Blinded Evaluation Periods, 2 due to inadequate pre-implant seizure counts, and 1 due to removal of hippocampal tissue during the RNS System implant procedure. The primary effectiveness endpoint analysis repeated excluding data from these 9 subjects (i.e., the analysis of the Per-Protocol population) shows that the treatment effect was materially unchanged (effect size = -0.27) and remained significant ($p = 0.027$), demonstrating that removing these subjects does not change the conclusions of the primary analysis.

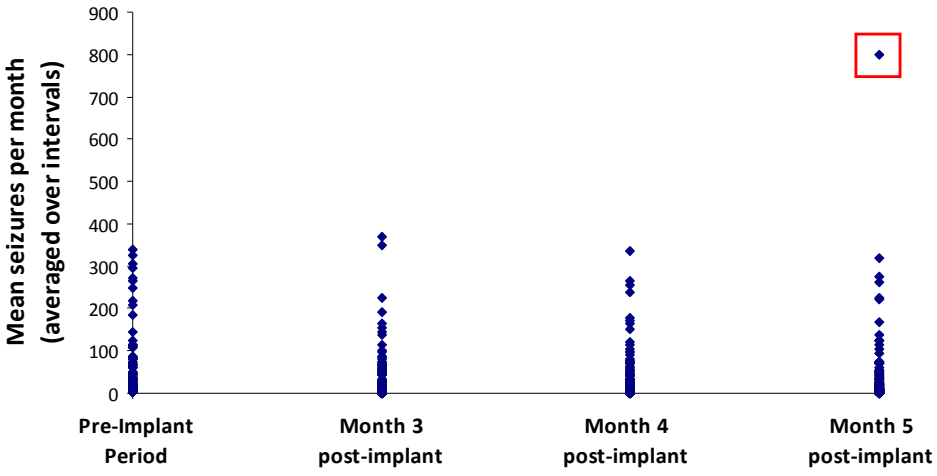
1.5.2 Exclusion of extreme data

Although there were no subjects identified as outliers based on the clinical assessment, the data were examined with respect to extreme data. There was one subject who had a high seizure frequency during the third month of the Blinded Evaluation Period. Therefore sensitivity analyses were performed evaluating the effect of this data point and this subject on the results. The treatment effect is robust to the exclusion of the most extreme data point as well as exclusion of the subject with the most extreme data.

A per subject scatter plot of the monthly seizure frequency for each of the intervals that are used in the primary effectiveness analyses (the Pre-Implant Period and each of the 3 months of the Blinded Evaluation Period) revealed one data point in the third month of the Blinded Evaluation Period that was extreme, with a total seizure count for that month equal to 799 (**Figure 5**, data point identified with a box). Although the data point was high, the seizure frequency did not appear to be qualitatively different than other seizure frequency data reported for this subject during other periods of the trial. Thus, this data point was not considered to be an outlier.

Nevertheless, sensitivity analyses were conducted to assess whether or not this subject and this data point had a large influence on the outcome by (1) removing the single data point and (2) removing all of the subject's data from the analysis. In both cases, with the single data point removed and with the subject removed, the treatment effect (Group-by-Time interaction) remained significant ($p = 0.0213$ and $p = 0.0372$, respectively).

Figure 5: Pivotal Study – Mean seizures per month



Data as of 5/12/2011

1.5.3 Pre-specified missing data analyses

Analyses were also conducted as pre-specified to assess the impact of missing data on the primary effectiveness endpoint. Results of the missing data analyses demonstrate that the missing data do not bias the results, and the treatment effect was significant for all methods of data imputation.

Out of a maximum possible number of observations for the primary effectiveness endpoint analysis of 32,088 (191 subjects * [84 observations in the Pre-Implant Period + 84 observations in the Blinded Evaluation Period]), a total of 31,434 data points were collected. Therefore only 2% of the observations were missing.

Missing data were imputed using three different methods. For subject data that were 'intermittent' missing, the seizure count for each missed day was imputed by averaging the seizure counts of the latest and earliest non-missed days before and after the missed day (respectively) during the Pre-Implant and Blinded Evaluation Periods. For subject data that were truncated, analyses were performed using two different methods to account for truncated data as specified in the investigational plan. In the first method, data were analyzed using a multiple imputations (MI) procedure, where missing seizure count data were imputed with randomly chosen values from non-missing observations of subjects within the same stratum (as defined by a propensity score). In the second method, truncated missing data were imputed using the last observed value "carried forward" (LOCF).

Table 5 summarizes the parameter estimate for the treatment effect (the Group-by-Time interaction term in the primary GEE model) using the different data imputation methods and compares results to the results of the primary effectiveness endpoint analysis with no imputation.

Results of the missing data analyses demonstrate that the missing data do not bias the results. In all cases, imputation of missing data did not change the estimate of the treatment effect by more than 5%, and in all cases the p-value remained statistically significant ($p < 0.02$).

Table 5: Pivotal Study – Summary of Treatment Effect estimate with missing data imputed

	No Imputation (Primary GEE)	With Missing Data Imputed		
		Intermittent missing only	Intermittent missing and LOCF	Intermittent missing and MI
Estimate	-0.2873	-0.2917	-0.2764	-0.3012
Standard Error	0.1148	0.1146	0.1153	0.1125
P-value	**0.0123**	**0.0109**	**0.0165**	**0.0074**

Data as of 5/12/2011

1.5.4 Pre-specified GEE sensitivity analyses

The inclusion of clinically relevant covariates is recognized as an important process in analyses of variance to minimize effect differences due to imbalance (Friedman et al. and to make the analysis more precise.[5,5,6] Alternative models with the inclusion and exclusion of different sets of clinically relevant covariates as pre-specified are presented in **Table 6** in order of goodness-of-fit using the quasi-likelihood under the independence model criterion (QICu) from best to worst. The covariates considered are the clinical characteristics used in the adaptive randomization process, the clinical characteristics found to be out of balance between the Treatment and Sham groups, and the main effect of group, which adjusts for any differences in baseline seizure frequency between the Treatment and Sham groups. Note: for comparative purposes the results from the modified primary endpoint model are presented in row C in **Table 6**.

Across all of these models, the effect size of the treatment effect remains consistent. There is an effect size of about -0.29, which corresponds to an additional reduction in seizure frequency in the Treatment group of 25% beyond the reduction in the Sham group, corresponding to a total reduction in seizure frequency in the Treatment group of approximately 38%. Additionally, with the exception of the single model that provides the worst fit, the treatment effect maintains significance (**Table 6**).

The single model that does not reach significance includes only one clinical covariate, which is the randomization characteristic that is least predictive of baseline seizure frequency (prior resection).

Table 6: Pre-specified GEE sensitivity analyses
(in order of goodness-of fit from best to worst)

	Covariate description	Clinical Covariates	GroupxTime Estimate	Empirical p-value	Scale Factor	QICu
A	Randomization covariates + Group	Onset zone Number of foci Prior resection Group	-0.275	0.018	1.23	-179533
B	Randomization covariates significant in model	Onset zone Number of foci	-0.293	0.013	1.23	-178449
C	Randomization covariates	Onset zone Number of foci Prior resection	-0.287	0.012	1.24	-177470
D	Randomization covariates and covariates out of balance	Onset zone Number of foci Prior resection Prior IEEG	-0.290	0.011	1.24	-176668
E	Covariates out of balance	Number of foci Prior IEEG	-0.305	0.012	1.28	-166069
F	Number of foci only	Number of foci	-0.286	0.027	1.31	-157285
G	Onset zone only	Onset zone	-0.289	0.025	1.32	-155406
H	Prior resection only	Prior resection	-0.240	0.056	1.49	-122309

All models use seizure data grouped by month, include the time and group-by-time covariates, and assume a compound symmetry correlation structure and the scaled negative binomial variance function. Results are ordered by goodness-of-fit using the quasi-likelihood under the independence model criterion (QICu) from best to worst fit, where smaller (more negative QICu) indicates better fit.

Group = therapy allocation (Treatment or Sham)

IEEG = intracranial electroencephalography

1.5.5 Summary of sensitivity analyses

Sensitivity analyses of the primary effectiveness endpoint demonstrate that the treatment effect is robust (**Table 7**). The treatment effect is statistically significant when analyzed for the intent-to-treat population using the pre-specified as well as the agreed-upon modified primary analysis. The treatment effect maintains statistical significance when subjects with significant protocol deviations are excluded (a pre-specified sensitivity analysis). The treatment effect maintains statistical significance when extreme data are excluded. Furthermore, the treatment effect is robust to missing data imputation (a pre-specified sensitivity analysis). Additionally the treatment effect is statistically significant when the model is modified to include the 'Group' covariate and covariates that were out of balance (both pre-specified sensitivity analyses).

Table 7: Summary of primary and sensitivity analyses

Analysis Description		N	Treatment Effect p-value[1]
Pre-specified primary analysis		191	< 0.0001
Agreed upon modified analysis		191	0.012
Per protocol analysis		182	0.027
Exclusion of extreme data	Removing data point	191	0.021
	Removing subject	190	0.037
Missing data imputation	Intermittent missing	191	0.011
	LOCF	191	0.017
	Multiple imputations	191	0.007
Adjusting for covariates[2]	Inclusion of 'Group' covariate	191	0.018
	Covariates out of balance	191	0.012

[1] The p-value for the pre-specified primary analysis refers to the model-based p-value as pre-specified; all others refer to the empirical p-value per FDA preference.
[2] Refer to Table 6 for a complete list of the analyses adjusting for different covariates.

1.5.6 Post hoc bootstrap analysis

Bootstrap analyses are powerful methods to assess the accuracy and reproducibility of statistical results using minimal assumptions. As suggested by FDA, a *post hoc* bootstrap analysis was conducted to assess the likelihood that the results observed in the Pivotal study could have occurred by chance. The bootstrap analysis showed that there was < 2% probability that under the null hypothesis the results of the Pivotal study could have occurred by chance.

The bootstrap analyses were performed by creating 2500 simulated clinical trials under the null hypothesis. For each simulated trial, 97 patients were randomly resampled from the entire population of 191 patients in the RNS System Pivotal study, with replacement and without regard for their original therapy status, and assigned to the treatment group in the simulated trial. Similarly, 94 patients were randomly resampled from the entire population and assigned to the sham group in the simulated trial. This yielded a set of 2500 simulated trials under the null hypothesis, each with the same number of treatment and sham patients as the original clinical trial. In these simulated trials, no systematic treatment effect would be expected and non-zero estimates of the treatment effect parameter would arise only due to random sampling variability. In other words, if the results from this study were consistent with random sampling, one would expect a large proportion of the simulated trials to have a treatment effect as large as or larger than the result observed in the study.

For each simulated trial, a treatment effect was estimated using the GEE model of our modified primary effectiveness analysis. These estimates were examined to determine the empirical distribution of treatment effect estimates that would arise due to random sampling variability. To evaluate consistency of the result, a total of five sets of 2500 trials were generated and analyzed, using a different random seed for each set. Results are shown in **Table 8**.

Table 8: Results of bootstrap samples of the Treatment Effect under the null hypothesis

Seed	Samples	Parameter Estimate for Treatment Effect Mean (SD)	Normality *p*-value[1]	Samples with estimate ≤ -0.287 % (# Samples)	Normal probability[2] of estimate ≤ -0.287	
					Z	Pct(Z ≤ -0.287)
14426	2500	0.000494 (0.1301)	0.292	**1.16% (29)**	-2.21	1.36%
29751	2500	0.001409 (0.1257)	0.508	**1.04% (26)**	-2.29	1.10%
53801	2500	-0.000420 (0.1324)	0.157	**1.64% (41)**	-2.16	1.54%
57862	2500	-0.000101 (0.1310)	0.640	**1.44% (36)**	-2.19	1.43%
69598	2500	0.000745 (0.1278)	0.080	**1.68% (42)**	-2.25	1.22%

[1] Anderson-Darling Test
[2] Z = (-0.287 - Mean) / SD

It is apparent from these results that, when patients are drawn at random from the trial in a way that favors the null hypothesis, the probability of an observation having a value at least as extreme as -0.287 is less than 0.02 (2%) whether it is computed empirically from the samples or parametrically as a normal random variable. The five bootstrap analyses are consistent and demonstrate the reproducibility of the results.

In summary, this analysis provides strong evidence supporting the robustness of the treatment effect; the treatment effect size observed in the Pivotal trial would not be expected under random sampling (i.e., by chance).

1.5.7 Post hoc analysis excluding influential subjects

FDA performed a *post hoc* sensitivity analysis selectively removing two Sham subjects identified by FDA as influential using a metric called cluster-level Cook's distance. Cook's distance estimates the level of influence of each subject on the overall result. Importantly, these two subjects were not outliers based on a standard definition of outlier using Cook's distance (i.e., a value > 1).[18] These subjects have a Cook's distance of 0.11 and 0.10). Additionally, these subjects were not clinical or statistical outliers: these two subjects were not those with the highest seizure frequency, nor were they the two subjects who had the largest percent change in seizure frequency.

FDA concluded from this analysis that the primary effectiveness endpoint result appears to be sensitive to the inclusion of these two subjects because their removal results in a loss of statistical significance in the empirical but not the model-based p-value. While it is not recommended that subjects be removed from an analysis, as a diagnostic exercise, NeuroPace further extended the sensitivity analysis. Extension of this analysis by sequential elimination of other subjects (with re-fitting of the model after each deletion to account for the impact of the removal of one patient on the fit for the remaining subjects) demonstrates that the statistical significance of the treatment effect is not dependent solely on the inclusion of influential subjects.

The properly executed deletion of influential subjects shows no evidence of a lack of robustness. Statistical significance is maintained in both the empirical and model-based p-values with deletion of the top 1, 3, 4, 5, 6, 7, and 8 most influential subjects. Loss of statistical significance in only the empirical p-value only with deletion of two influential subjects but not with deletion of other influential subjects simply reflects the variability inherent in sampling of real data.

Table 9: Sequential exclusion of most influential patients

# Patients excluded	Empirical p-value	Model-based p-value
None (original)	0.012*	0.006*
1	0.037*	0.012*
2	0.086	0.029*
3	0.012*	0.004*
4	0.026*	0.006*
5	0.014*	0.003*
6	0.032*	0.011*
7	0.024*	0.006*
8	0.045*	0.016*
9	0.081	0.039*
10	0.141	0.085

* Statistically significant results ($p < 0.05$)

This analysis demonstrates that the statistical significance of the treatment effect is not dependent solely on the inclusion of two influential subjects. Rather, the statistical significance of the treatment response is robust to the removal of several of the most influential subjects.

2 REFERENCES

Refer to the CD file titled “Referenced Literature” for a full manuscript of each citation in the bibliography list below.

Reference List

1. Ballinger GA. "Using Generalized Estimating Equations for Longitudinal Data Analysis". *Organizational Research Methods* 2004; 7: 127-150.

2. Drum M, McCullagh P. "[Regression Models for Discrete Longitudinal Responses]: Comment". *Statistical Science* 1993; 8: 300-301.

3. Stokes ME, Davis CS, Koch GG. Generalized Estimating Equations. Categorical Data Analysis Using the SAS System. Cary, NC: SAS Institute, 2000: 485.

4. Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials. New York: Springer-Verlag, 1998: 61-81 and 284-322.

5. Neter J, Wassermann W, Kutner MH. Analysis of Covariance. Applied linear statistical models: regression, analysis of variance, and experimental designs. Homewood, IL: Richard D. Irwin, 1990: 861.

6. Pocock SJ, Assmann SE, Enos LE, Kasten LE. "Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems". *Stat.Med* 2002; 21: 2917-2930.

7. U.S.Department of Health and Human Services, Food and Drug Administration, "Statistical Guidance for Clinical Trials of Non Diagnostic Medical Devices." available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm106757.htm, January, 1996

8. Kernan WN, Viscoli CM, Makuch RW, Brass LM, Horwitz RI. "Stratified randomization for clinical trials". *J Clin.Epidemiol.* 1999; 52: 19-26.

9. Morel J, Nagaraj Neerchal N. Overdispersion Models in SAS. Cary, NC: SAS Institute, 2012: 172-7.

10. SAS Institute Inc., "The GENMOD Procedure: SAS/STAT® 9.2 User's Guide, 1971." SAS Institute Inc. available at: http://support.sas.com/documentation/cdl/en/statuggenmod/61787/PDF/default/statuggenmod.pdf, 2008, accessed September 1, 2011.

11. Wang YG, Lin X. "Effects of variance-function misspecification in analysis of longitudinal data". *Biometrics* 2005; 61: 413-421.

12. Balish M, Albert PS, Theodore WH. "Seizure frequency in intractable partial epilepsy: a statistical analysis". *Epilepsia* 1991; 32: 642-649.

13. Troconiz IF, Plan EL, Miller R, Karlsson MO. "Modelling overdispersion and Markovian features in count data". *J Pharmacokinet.Pharmacodyn.* 2009; 36: 461-477.

14. Horton NJ, Lipsitz SR. "Review of Software to Fit Generalized Estimating Equation Regression Models". *The American Statistician* 1999; 53: 160-169.

15. Breslow N. "Tests of Hypotheses in Overdispersed Poisson Regression and Other Quasi-Likelihood Models". *Journal of the American Statistical Association* 1990; 85: 565-571.

16. Gardner W, Mulvey EP, Shaw EC. "Regression analyses of counts and rates: Poisson, overdispersed Poisson, and negative binomial models". *Psychol.Bull.* 1995; 118: 392-404.

17. Diggle PJ, Heagerty P, Liang K, Zeger SL. Marginal Models. Analysis of Longitudinal Data. New York: Oxford University Press, 2002: 141-68.

18. Cook RD, Weisberg S. Assessment of Influence. Residuals and Influence in Regression. New York: Chapman and Hall, 1982: 118.

15.2 RNS System Pivotal Clinical Investigation Protocol

[See external file: file extracted from section 10.6 of original PMA submission]

15.3 RNS System Feasibility Clinical Investigation Design and Results

RNS System Feasibility Clinical Investigation

The Feasibility study was a prospective clinical study conducted at 12 Comprehensive Epilepsy Centers in the U.S. to demonstrate adequate safety and provide evidence of effectiveness for the RNS System to support the commencement of the Pivotal Clinical Investigation. In addition, the study demonstrated that subjects could be randomized to active or sham stimulation while adequately maintaining the treatment blind. The effectiveness data in this primarily open label study were used only in the analyses to provide evidence of sufficient effectiveness to support commencement of the Pivotal study. The first subject was implanted in February 2004 and the last subject completed the open label period in December 2007.

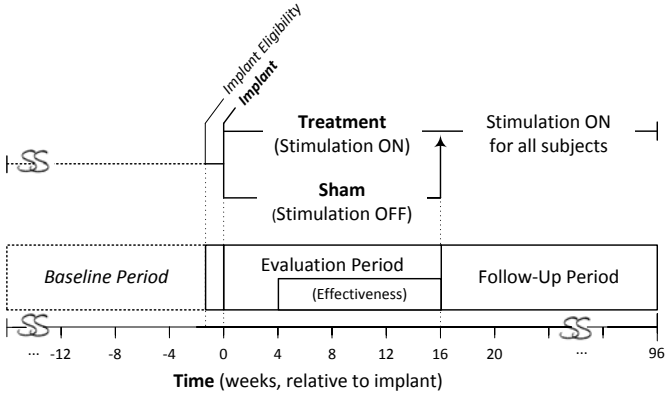
Feasibility Study Design

Subjects were 18-65 years of age with medically intractable partial onset seizures and a minimum of 4 simple partial seizures (motor or sensory), complex partial seizures, and/or secondarily generalized seizures in each of the previous three months. Subjects were required to be on a stable antiepileptic medication regimen and to have previously undergone diagnostic testing that localized one or two epileptogenic region(s). Subjects with psychogenic or non-epileptic seizures, status epilepticus, active psychosis, severe depression, or suicidal ideation within the preceding year were excluded.

The first four subjects implanted at a clinical site participated in an open label protocol (all subjects received responsive stimulation, N=42). In order to demonstrate that a blind could be successfully maintained, subsequent subjects at that site participated in a randomized, double-blind, concurrent sham-stimulation control protocol in which the Treatment group received stimulation and the Sham group did not (N=23).

At completion of the 12 week Evaluation Period, subjects transitioned to a Follow-Up Period and were able to receive responsive stimulation. The Follow-Up Period continued through 2 years post-implantation (**Figure 30**). Subjects who completed the Feasibility study were able to continue to be treated with the RNS System by enrolling in the Long-term Treatment study.

Figure 30: Feasibility Study – Design



The first four subjects implanted at each investigational site entered the Treatment group; subsequent subjects were randomized to either the Treatment or Sham group.

Feasibility Subject Population

Sixty-five of the 70 subjects who enrolled in the study were implanted with the RNS Neurostimulator and Leads and completed the Evaluation Period (16 weeks post-implant); 59 subjects completed the

study (24 months). Subject disposition is presented in **Table 35** and subject demographics are presented in **Table 36**.

Table 35: Feasibility Study – Subject disposition

	N
Total Enrolled	**70**
Withdrawn (pre-implant)	5
Total Implanted	**65**
Completed Evaluation Period (>4 months[1] post-implant)	65
Withdrew >12 months post-implant (including 1 death)	6
Completed study	59
Continued follow-up in Long-term Treatment Trial	**57**

[1] Month = 28 days

Table 36: Feasibility Study – Subject demographics

Subject Characteristic	Mean ± SD (min-max) or % (n/N)
Age (years)[1]	31 ± 10 (18 - 56)
Gender (Female)	52% (34/65)
Duration of epilepsy (years)[1]	17 ± 10 (2 - 42)
Number of lifetime AEDs	8 ± 3 (2 - 15)
Prior therapeutic epilepsy surgery	37% (24/65)
Prior intracranial monitoring	82% (53/65)

[1] Due to hospital confidentiality requirements some institutions did not provide subject date of birth.

Feasibility Safety Results

The primary safety endpoint for the Feasibility study was met. The serious adverse event (SAE) rates (whether related to the device or not) during the Acute Period (initial implant procedure and the following month) and the Short-Term Chronic Period (initial implant procedure and the following three months) were not worse than the rate of SAEs with implantation and treatment with deep brain stimulation (DBS) for movement disorders, which was the pre-specified historical control (**Table 37**). In addition, there were no unanticipated device-related serious adverse events.

Table 37: Feasibility Study – Primary safety endpoint analysis

Period	SAE Rate		
	RNS System	Comparator[1]	Met primary safety endpoint?
	% subjects with ≥ 1 SAE (n/N) [upper 95% CI[2]]		
Acute: Surgery – 4 weeks	6.2% (4 /65) [13.0%]	19% [28%]	Yes, upper limit for RNS System is less than that of the comparator (13.0% < 28%)
Short-Term Chronic: Surgery – 12 weeks	9.2% (6 /65) [16.9%]	36% [46%]	Yes, upper limit for RNS System is less than that of the comparator (16.9% < 46%)

[1] Protocol-specified literature based endpoint: SAE rate associated with DBS for movement disorders.[8-14]

[2] Upper limit of the one-sided 95% confidence interval, estimated using the Score Interval (also known as the Wilson Interval.[112] Upper limits for literature comparators were pre-specified in the protocol, estimated using the Score Interval based on a sample size of 65.

Data regarding adverse events in the Open Label Period of the Feasibility study are provided in **Section 11.2**. Effectiveness was assessed by the responder rate, defined as the percentage of subjects experiencing a 50% or greater reduction in mean frequency of disabling seizures after treatment with

the RNS System compared to the pre-implant Baseline Period. Preliminary evidence for effectiveness was demonstrated by a responder rate of 24% for the 51 subjects in the active Treatment group, which was greater than the 13% required to establish non-futility of continuing to a pivotal investigation. In addition, there were statistically significant reductions in seizure frequency in the Treatment group compared to the pre-implant baseline ($p < 0.001$ Wilcoxon signed rank test).

The blind was effectively maintained: of the 23 randomized subjects, 30% of the subjects declined to guess, 35% of the subjects guessed incorrectly, and 35% of the subjects guessed correctly.

15.4 Long-term Treatment Clinical Investigation Summary

The on-going Long-term Treatment Clinical Investigation is a multi-center prospective open label clinical study to assess the ongoing safety and to evaluate the long-term effectiveness of the RNS System. Additionally, the Long-term Treatment study provides additional data to estimate the rate of Sudden Unexplained Death in Epilepsy (SUDEP). Subjects who had completed the Feasibility or Pivotal clinical investigation were potential candidates for the LTT study; 97% chose to enroll.

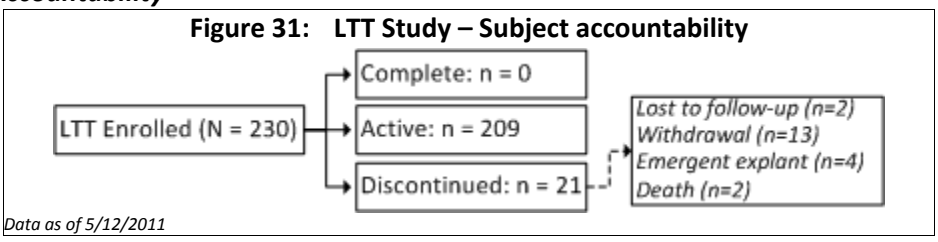
LTT Study – Study Design

Subjects were eligible to enroll in the LTT study if they completed either the Feasibility or Pivotal studies, had the RNS System implanted, elected to continue to receive responsive stimulation, and were able to attend scheduled study appointments. They were not eligible if they had an active psychiatric illness or if they had been diagnosed during the Feasibility or Pivotal studies with psychogenic or non-epileptic seizures, or primarily generalized seizures.

Subjects continue to receive responsive stimulation during the LTT study for up to an additional 7 years beyond the originating study. Safety and effectiveness data are collected at 6-month intervals, and data regarding quality of life are collected at yearly intervals. Antiepileptic drug adjustments are permitted as medically necessary. As of May 12, 2011, 230 subjects had enrolled in the LTT study. This represents 97% of the subjects who were eligible to enroll.

LTT Study – Accountability

Figure 31: LTT Study – Subject accountability



Data as of 5/12/2011

LTT Study – Demographics

Table 38: LTT Study – Demographic and baseline characteristics

Characteristic	All (N = 230)
	% (n/N) or Mean ± SD (min-max)
Participated in Feasibility Study[1]	25% (57/230)
Participated in Pivotal Study[1]	75% (173/230)
Female	50% (115/230)
Age (years)[2]	36.6 ± 11.5 (20 - 68)
Duration of epilepsy (years) [2,3]	22.2 ± 11.5 (3 - 60)
Number of AEDs taken (at LTT enrollment)	3.0 ± 1.1 (0 - 8)
Mean seizure frequency during Pre-Implant Period of originating study (seizures/month)	49.1 ± 181.2 (0 - 2320) median = 9.7

[1] Study during which subject received first implantation of the RNS System.

[2] Some institutions did not provide subject date of birth.

[3] Duration of epilepsy is based on the age at enrollment into the LTT study and the "age of onset". entered in the originating study.

Data as of 5/12/2011

15.5 Post-Approval Study Plans

NeuroPace intends to continue the Long-term Treatment study and to begin a post-approval safety study to assess the one-year safety of treatment with the RNS System in patients with medically intractable partial seizures who are being treated by physicians who are newly trained in the implantation and management of the RNS System.

1. Subjects who have participated in the RNS System Feasibility or Pivotal studies have already enrolled in the on-going Long-term Treatment study, which provides an additional 7 years of prospective open label follow-up. After approval, NeuroPace will continue the Long-term Treatment study to gather additional data on safety and efficacy and to collect additional patient years of data in order to provide a confident estimate of the rate of Sudden Unexplained Death in Epilepsy (SUDEP). When combined with data from their initiating study, subjects who complete the Long-term Treatment Study will have accumulated 9 years of post-implant follow-up data.
2. The proposed Post-Approval Safety Study is a prospective, non-randomized, multicenter study to collect one year of safety data on patients newly implanted with the RNS System who are being treated by physicians newly trained on implantation and management of the RNS System. The objective is to demonstrate that the safety experience for patients treated with newly trained physicians is comparable to the safety experience in the RNS System Pivotal study. Other objectives are to describe the rate of adverse events of special relevance to persons with epilepsy and persons implanted with a medical device, to assess changes in quality of life at the end of the first post-implant year, to assess patient and physician satisfaction with RNS System treatment, and to gather additional patient years of data to contribute to the estimate of the rate of Sudden Unexplained Death in Epilepsy (SUDEP).

Primary Endpoint

To demonstrate that the total serious adverse event (SAE) rate (device-related and not device-related) at one year for patients treated by physicians newly trained in implantation and use of the RNS System is not worse than the total SAE rate observed in the first year of the RNS System Pivotal trial, which was 39% (74/191). The SAE rate is defined as the proportion of subjects experiencing one or more serious adverse events.

This endpoint will be evaluated in terms of success rates (that is, the proportion of subjects who did not experience an SAE during the first year post-implant), where the endpoint is met if the ratio of the expected success rate during the post approval study to the expected success rate during the pivotal study exceeds the “non-inferiority” limit of the ratio, which in this study is chosen to be 0.75.

Supporting Analyses

1. Evaluate the rate of the following SAEs of special relevance at 1 year after implantation: implant or incision site infection, intracranial hemorrhage, suicidality, and depression. SAE rates for implant or incision site infection and for intracranial hemorrhages will be calculated by spontaneously reported adverse events reported by the investigator on case report forms. The Columbia Suicidality Inventory and the Beck Depression Inventory-II will be administered in order to provide additional assessments of depression and suicidality.
2. Assess changes in quality of life with treatment with the RNS System. Group and individual changes in the QOLIE-89 will be evaluated before implantation and at 1 year after implant.

3. Evaluate patient and physician satisfaction with treatment with the RNS System. Patient and physician satisfaction surveys will be administered at 3, 6 and 12 months after implantation
4. Gather additional patient stimulation years to combine with data from the Feasibility, Pivotal and Long-term Treatment trials to provide a confident estimation of the SUDEP rate in patients being treated with the RNS System. Data regarding SUDEP across all investigations will be pooled and the SUDEP rate will be calculated as the ratio of the number of possible, probable, and definite SUDEP events in subjects programmed to receive stimulation divided by the number of patient stimulation years, with 95% confidence interval calculated according to patient stimulation years of follow-up.

Subjects

A single group of subjects will be enrolled in the Post-Approval Safety Study. A second group of subjects, the implanted Pivotal Study cohort at one year of follow-up, will serve as the comparator group for the primary safety analysis.

Enrollment Criteria

Key Inclusion Criteria:

- 18 to 70 years of age.
- Disabling seizures (simple partial motor, complex partial and/or generalized tonic clonic seizures).
- Failed treatment with a minimum of two antiepileptic medications (used in appropriate doses) with adequate monitoring of compliance and the effects of treatment, as determined by the physician investigator.
- Has undergone diagnostic testing as part of his/her standard care that has identified one or two epileptogenic regions.

Key Exclusion Criteria:

- Diagnosed with primarily generalized seizures or has been diagnosed with psychogenic or non-epileptic seizures in the preceding 2 years.
- Diagnosed with active psychosis, major depression or suicidality in the preceding 2 years. Subjects with post-ictal psychiatric symptoms are not excluded. The screening version of the Columbia Suicide Severity Rating Scale will be used to assess pre-enrollment suicidality.
- In the opinion of the investigator, subject has a clinically significant or unstable medical condition (including alcohol and/or drug abuse) or a progressive central nervous system disease.
- English is not the primary language spoken.

Study Design

Subjects will be enrolled prior to implantation of the Neurostimulator and Leads. Study visits and procedures at each visit are provided in the Table below.

Table 39: Post Approval Safety Study Schedule

Procedure	Enroll	Device Implant	Visit (months post-implant)					
			2 wks	1	2	3	6	12
Screening[1]	X							
Informed consent	X							
Demographics and medical history	X							
Adverse event monitoring		X	X	X	X	X	X	X
Patient and physician satisfaction surveys						X	X	X
QOLIE-31	X							X
Beck Depression Inventory (BDI-II)	X					X	X	X
Columbia Suicide Severity Rating Scale	X					X	X	X

[1] Subjects will be screened for suicidality prior to enrollment.

Investigational sites

The study will be conducted at 20 Level IV Comprehensive Epilepsy Centers as defined by the National Association of Epilepsy Centers (NAEC). The principal investigators at the participating centers will not have previously participated in an RNS System trial. Each Center will be required to have an active epilepsy surgery program, including the capacity to perform video-EEG monitoring with scalp and intracranial electrodes, and MRI imaging. In addition, each site is required to have a neurologist serving as principal investigator who is expert in epilepsy and EEG, and a neurosurgeon experienced in stereotactic placement of intracranial electrodes.

The goal is for each investigational center to enroll an average of 10 patients, for a total study enrollment of 200 subjects. This provides sufficient power for the primary endpoint analysis and, when combined with data from the 32 Comprehensive Epilepsy Centers that participated in the pre-market trials, provides clinical experience at a meaningful percentage of Level IV Epilepsy Centers in the United States.

15.6 Physician Training

NeuroPace will ensure appropriate use of the RNS System by initially providing the RNS System only to neurologists and neurosurgeons with appropriate expertise and by additionally providing detailed modular training on the RNS System.

The RNS System will initially be available only to neurologists and neurosurgeons associated with a Level IV Comprehensive Epilepsy Center as identified by the National Association of Epilepsy Centers (NAEC). According to the NAEC,

> *"Fourth level epilepsy centers serve as a regional or national referral facilities for intractable epilepsy patients. These centers should provide the more complex forms of intensive neurodiagnostic monitoring, as well as more extensive medical, neuropsychological and psychosocial treatment. Fourth level centers also offer a complete evaluation for epilepsy surgery including intracranial electrodes and provide a broad range of surgical procedures for epilepsy. Many level 4 centers are actively involved in clinical trials and are well aware of trials conducted in other level 4 centers to make patient referrals."* [1]

The neurologists/epileptologists and neurosurgeons associated with these centers are highly experienced in the medical and surgical care of persons with medically intractable partial onset seizures. The neurosurgical techniques involved in implantation of the RNS Neurostimulator and Leads are comparable to those used for the implantation of intracranial electrodes for localization of the seizure focus (performed in order to determine whether the patient is a candidate for epilepsy surgery), as well as epilepsy surgery procedures. Epileptologists at Level IV centers are experienced in diagnostic assessments of epilepsy patients with EEG recorded from the scalp and from intracranial electrodes and will use this expertise to define the seizure focus and the electrographic activity to be detected by the RNS Neurostimulator for each patient.

NeuroPace will provide detailed modular training to physicians prior to use of the RNS System. Training includes patient selection, implantation of the Neurostimulator and Leads, and Neurostimulator programming. In addition, NeuroPace Field Clinical Engineers will attend the first 5 implant surgeries as well as subsequent surgeries as requested by the neurosurgeon. Field Clinical Engineers will also provide on-site support for initial and subsequent Neurostimulator programmings as requested.

[1] National Association of Epilepsy Centers "Guidelines for essential services, personnel, and facilities in specialized epilepsy centers" January 12, 2010. http://www.naec-epilepsy.org/spec_care/documents /NAEC-FinalGuidelineswithruralcenterrevision.pdf

15.7 Additional Data Tables and Figures

Table 40: Clinically significant changes in QOLIE-89 summary and subscale scores at 1 and 2 years

Overall / Primary Scale	1 year Post-Implant			2 years Post-Implant		
	N	% subjects improved[1] (# subjects)	% subjects worsened[1] (# subjects)	N	% subjects improved[1] (# subjects)	% subjects worsened[1] (# subjects)
QOLIE Overall Score	**166**	**38% (63)**	**12.7% (21)**	**154**	**44.2% (68)**	**16.2% (25)**
Attention/Concentration	167	45.5% (76)	10.2% (17)	155	43.2% (67)	11.0% (17)
Seizure Worry	167	43.7% (73)	13.8% (23)	155	52.3% (81)	16.1% (25)
Memory	165	40.6% (67)	13.9% (23)	153	42.5% (65)	18.3% (28)
Role Limitation - Physical	165	40.0% (66)	24.8% (41)	153	44.4% (68)	21.6% (33)
Health Discouragement	165	40.0% (66)	12.7% (21)	153	43.1% (66)	13.7% (21)
Language	164	39.6% (65)	15.9% (26)	152	42.1% (64)	17.1% (26)
Overall Quality of Life	167	37.7% (63)	21.0% (35)	155	34.8% (54)	22.6% (35)
Energy / Fatigue	167	35.3% (59)	19.2% (32)	155	31.6% (49)	20.6% (32)
Work / Driving / Social Function	167	34.7% (58)	18.0% (30)	155	42.6% (66)	20.6% (32)
Medication Effects	167	34.7% (58)	28.1% (47)	155	34.8% (54)	23.2% (36)
Physical Function	165	31.5% (52)	24.2% (40)	153	23.5% (36)	25.5% (39)
Social Support	165	30.3% (50)	24.2% (40)	153	35.9% (55)	32.7% (50)
Role Limitations - Emotional	165	27.9% (46)	26.7% (44)	153	30.1% (46)	29.4% (45)
Health Perceptions	165	27.9% (46)	17.0% (28)	153	25.5% (39)	20.9% (32)
Emotional Well-Being	167	27.5% (46)	24.6% (41)	155	32.3% (50)	25.2% (39)
Social Isolation	165	25.5% (42)	24.2% (40)	153	25.5% (39)	26.8% (41)
Pain	165	23.0% (38)	29.1% (48)	153	26.1% (40)	30.7% (47)

[1] Clinically significant change is defined as ≥ 5 point increase in T-score relative to baseline (equivalent to 0.5 SD).

Data as of 5/12/2011

Table 41: Pivotal Study – Change in proportion of seizure-free days: Blinded Evaluation Period, Treatment vs. Sham

Period	Group	Change in Proportion of Seizure-Free Days			
		N[1]	Mean +/- SD	Within Group P-value[2]	Across Group P-value[3]
Entire Blinded Evaluation Period (BEP)	Treatment	96	0.08 +/- 0.19	<0.0001	0.5
	Sham	93	0.06 +/- 0.14	0.0001	
BEP 1 (Post-op Month 3)	Treatment	96	0.06 +/- 0.20	0.003	0.9
	Sham	93	0.07 +/- 0.17	0.0003	
BEP 2 (Post-op Month 4)	Treatment	95	0.09 +/- 0.17	<0.0001	0.2
	Sham	90	0.05 +/- 0.18	0.006	
BEP 3 (Post-op Month 5)	Treatment	95	0.10 +/- 0.18	<0.0001	**0.048**
	Sham	91	0.05 +/- 0.17	0.007	

[1] N represents the number of subjects for which any seizure data are available for that time period.

[2] By paired t-test.

[3] By two-sample t-test.

Data as of 5/12/2011

Table 42: Pivotal Study – Responder rates: Blinded Evaluation Period, Treatment vs. Sham

	% Responders (n/N) [2]		P-value[1]
	Treatment	Sham	
Entire Blinded Evaluation Period (BEP)	**29% (28/96)**	**27% (25/93)**	**0.727**
BEP 1 (Post-op Month 3)	34% (33/96)	39% (36/93)	0.536
BEP 2 (Post-op Month 4)	39% (37/95)	31% (28/90)	0.264
BEP 3 (Post-op Month 5)	34% (32/95)	30% (27/91)	0.557

[1] P-value per z-statistic.

[2] N represents the number of subjects for whom any seizure data are available in that time period.

Data as of 5/12/2011

Table 43: Pivotal Study – Mean change in Liverpool Seizure Severity Scale scores: Blinded Evaluation Period, Treatment vs. Sham

	Liverpool Scaled[1] Score		
Period	Treatment (N = 95)[2] (mean ± SD)	Sham (N = 93)[2] (mean ± SD)	Across Group P-value[4]
Pre-Implant	43.817 +/- 18.111	45.092 +/- 18.691	--
Entire Blinded Evaluation Period	39.110 +/- 19.689	39.228 +/- 19.358	
Change	-4.707 +/- 12.911	-5.864 +/- 15.178	0.574
Within-Group P-value[3]	< 0.001	< 0.001	

[1] Scaled score (ICTAL) per Scott-Lennox et al., 2001.

[2] Includes subjects who have at least one observation in both the Pre-Implant and Blinded Evaluation Periods.

[3] By paired t-test.

[4] By two-sample t-test.

Data as of 5/12/2011

Table 44: Pivotal Study – Change in mean seizure frequency, Sham group: Open Label weeks 24-36 vs. Pre-Implant and Blinded Evaluation Periods

	Seizure Frequency[1] (mean ± SD, seizures/month)	
Time Period	Open Label to Pre-Implant Comparison (N = 91)	Open Label to Blinded Evaluation Comparison (N = 91)
Pre-Implant	35.725 ± 68.037	--
Blinded Evaluation (Months 2-5)	--	30.442 ± 67.082
Open Label (Months 6-9)	27.964 ± 62.014	27.964 ± 62.014
Change	-7.761 ± 35.498	-2.478 ± 27.333
P-value[2]	0.04	0.39

[1] Calculations include those subjects who were randomized to the Sham group for the Blinded Evaluation Period and who had had the opportunity to complete the 36-week study appointment(s) by 5/12/2011.

[2] P-value based on paired t-test.

Data as of 5/12/2011

Figure 32: Pivotal Study – Seizure frequency percent change by subject: most recent 3 months of the Open Label Period

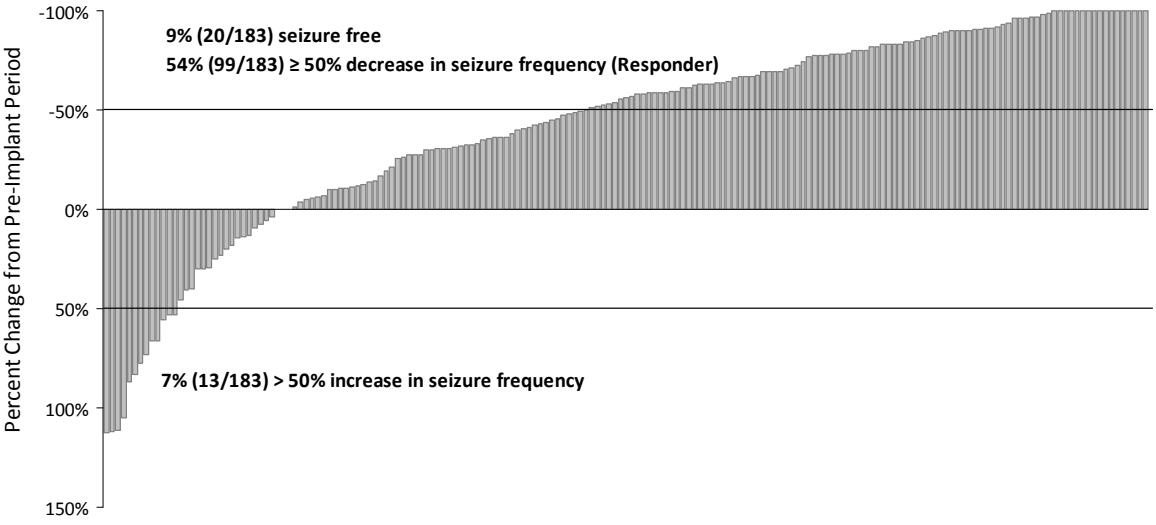


Figure includes all patients with at least 3 months of data in the Open Label Period, N=183.

Table 45: Pivotal Study – Change in QOLIE-89 overall score at the end of Blinded Evaluation Period, Treatment vs. Sham

Post-Implant period	QOLIE-89 Overall Score (T-Score)					
	N[1]	Baseline (mean ± SD)	Post-Implant Time point (mean ± SD)	Change from Baseline (mean ± SD)	Change from Baseline P-value[2]	Difference in Change Between Groups p-value3
Treatment	93	45.75 ± 9.54	47.78 ± 9.81	2.04 ± 9.43	0.04	0.916
Sham	87	44.87 ± 9.68	47.05 ± 10.24	2.18 ± 9.35	0.032	
All Subjects	180	45.32 ± 9.59	47.43 ± 10.00	2.11 ± 9.37	0.003	--

[1] Analysis includes subjects (N) with assessments available at both Baseline and Post-Implant time points.
[2] Paired t-test.
[3] Two-sample t-test.
Data as of 5/12/2011

Table 46: Pivotal Study – Change in QOLIE-89 overall score: 20 weeks, 1 and 2 years

Post-Implant period	QOLIE-89 Overall Score (T-Score)				
	N[1]	Baseline (mean ± SD)	Post-Implant Time point (mean ± SD)	Change from Baseline (mean ± SD)	Change from Baseline P-value[2]
20 Weeks	180	45.32 ± 9.59	47.43 ± 10.00	2.11 ± 9.37	0.003
1 Year	166	45.42 ± 9.52	49.00 ± 10.50	3.57 ± 8.89	<0.001
2 Years	154	45.28 ± 9.93	49.27 ± 10.31	3.99 ± 10.37	<0.001

[1] Analysis includes subjects (N) with assessments available at both Baseline and Post-Implant time points.
[2] Paired t-test.
Data as of 5/12/2011

Table 47: Pivotal Study – Mild and serious adverse events in ≥ 2.5% of subjects in either group: Blinded Periods (Treatment and Sham)

MedDRA Preferred Term	Treatment (N=97)		Sham (N=94)	
	% Subjects	# Events [# device-related[1]]	% Subjects	# Events [# device-related[1]]
Nasopharyngitis	10.3% (10)	12 [0]	11.7% (11)	12 [0]
Headache	7.2% (7)	9 [4]	13.8% (13)	17 [6]
Skin laceration (due to seizure)	8.2% (8)	8 [1]	5.3% (5)	7 [0]
Contusion (due to seizure)	9.3% (9)	10 [0]	3.2% (3)	3 [0]
Depression	7.2% (7)	8 [1]	5.3% (5)	5 [2]
Dysesthesia	4.1% (4)	4 [3]	7.4% (7)	7 [3]
Influenza	7.2% (7)	8 [0]	3.2% (3)	3 [0]
Implant site pain	4.1% (4)	4 [3]	5.3% (5)	5 [2]
Adverse drug reaction	4.1% (4)	4 [0]	3.2% (3)	3 [0]
Complex partial seizures	2.1% (2)	2 [1]	5.3% (5)	5 [2]
Complex partial seizures increased	4.1% (4)	4 [2]	3.2% (3)	4 [2]
Therapeutic agent toxicity	--	--	6.4% (6)	6 [0]
Upper respiratory tract infection	2.1% (2)	2 [0]	4.3% (4)	4 [0]
Vomiting	3.1% (3)	4 [0]	3.2% (3)	3 [0]
Head injury	1.0% (1)	1 [0]	4.3% (4)	4 [1]
Implant site paresthesia	2.1% (2)	2 [1]	3.2% (3)	3 [2]
Simple partial seizures (sensory)	3.1% (3)	4 [3]	2.1% (2)	4 [4]
Abdominal pain	3.1% (3)	3 [0]	1.1% (1)	1 [0]
Balance disorder	--	--	4.3% (4)	4 [1]
Dizziness	1.0% (1)	1 [0]	3.2% (3)	3 [2]
Muscle twitching	3.1% (3)	3 [3]	1.1% (1)	1 [0]
Pain of skin	4.1% (4)	4 [0]	--	--
Peripheral nerve injury	1.0% (1)	1 [0]	3.2% (3)	3 [0]
Pharyngitis	1.0% (1)	1 [0]	3.2% (3)	3 [0]
Tremor	3.1% (3)	3 [1]	1.1% (1)	1 [0]
Excoriation (due to seizure)	3.1% (3)	3 [0]	--	--
Joint injury (due to seizure)	--	--	3.2% (3)	3 [0]
Laceration (due to seizure)	3.1% (3)	4 [0]	--	--

Blinded Periods include the Stimulation Optimization and Blinded Evaluation Periods.
With the exception of Therapeutic agent toxicity (p = 0.013), differences between Treatment and Sham groups not significant (all p-values > 0.05 per Fisher's exact test).
[1] Device-related includes events categorized as device relation uncertain.
Data as of 5/12/2011

Table 48: Combined Studies – Device-related SAEs by year[1]

	Year 1	Year 2	Year 3	Year 4	Year 5	All Study Periods[2]
# of subjects entering year / Implant years within Interval	256 / 249.9	246 / 240.1	235 / 188.6	148 / 112.2	85 / 60.6	256 / 903.4
MedDRA SOC MedDRA Preferred Term	% Subjects[3] Event rate[4]					
Injury, poisoning and procedural complications						
Premature battery depletion	1.6% (4) 0.016 [4]	2.4% (6) 0.025 [6]	0.4% (1) 0.005 [1]	--	--	4.3% (11) 0.012 [11]
Device lead damage	2.0% (5)	0.4% (1)	0.9% (2)	--	--	2.7% (7)

Table 48: Combined Studies – Device-related SAEs by year[1]

	Year 1	Year 2	Year 3	Year 4	Year 5	All Study Periods[2]
	0.020 [5]	0.004 [1]	0.011 [2]			0.009 [8]
Device lead revision	0.4% (1) 0.004 [1]	1.2% (3) 0.012 [3]	--	--	--	1.6% (4) 0.004 [4]
Implant site erosion	0.4% (1) 0.004 [1]	0.4% (1) 0.004 [1]	--	0.7% (1) 0.009 [1]	--	1.6% (4) 0.004 [4]
Extradural hematoma	0.8% (2) 0.008 [2]	--	--	--	--	0.8% (2) 0.002 [2]
Skin laceration (dts)	0.4% (1) 0.004 [1]	0.4% (1) 0.004 [1]	--	--	--	0.8% (2) 0.002 [2]
Subdural hematoma (dts)	0.4% (1) 0.004 [1]	0.4% (1) 0.004 [1]	--	--	--	0.8% (2) 0.002 [2]
Device electrical finding[5]	--	--	--	0.7% (1) 0.009 [1]	--	0.4% (1) 0.001 [1]
Device malfunction[6]	--	--	--	0.7% (1) 0.009 [1]	--	0.4% (1) 0.001 [1]
Head injury (dts)	--	--	0.4% (1) 0.005 [1]	--	--	0.4% (1) 0.001 [1]
Intracranial hypotension	--	0.4% (1) 0.004 [1]	--	--	--	0.4% (1) 0.001 [1]
Procedural headache	0.4% (1) 0.004 [1]	--	--	--	--	0.4% (1) 0.001 [1]
Subdural hematoma	0.4% (1) 0.004 [1]	--	--	--	--	0.4% (1) 0.001 [1]
Suture related complication	--	0.4% (1) 0.004 [1]	--	--	--	0.4% (1) 0.001 [1]
Nervous system disorders						
Tonic-clonic seizures increased	1.2% (3) 0.012 [3]	1.6% (4) 0.017 [4]	0.9% (2) 0.011 [2]	0.7% (1) 0.009 [1]	--	3.9% (10) 0.011 [10]
Complex partial seizures increased	2.7% (7) 0.032 [8]	0.8% (2) 0.008 [2]	--	--	--	3.1% (8) 0.011 [10]
Cerebral hemorrhage	0.4% (1) 0.004 [1]	--	1.3% (3) 0.016 [3]	--	--	1.6% (4) 0.004 [4]
Complex partial seizures exacerbated	0.8% (2) 0.008 [2]	--	0.4% (1) 0.005 [1]	--	--	1.2% (3) 0.003 [3]
Headache	0.4% (1) 0.004 [1]	0.4% (1) 0.004 [1]	--	--	--	0.8% (2) 0.002 [2]
Hydrocephalus	0.8% (2) 0.008 [2]	--	--	--	--	0.8% (2) 0.002 [2]
Nonconvulsive status epilepticus	0.8% (2) 0.008 [2]	--	--	--	--	0.8% (2) 0.002 [2]
Postictal state	0.8% (2) 0.008 [2]	--	--	--	--	0.8% (2) 0.002 [2]
Simple partial seizures increased (sensory)	0.4% (1) 0.004 [1]	--	0.4% (1) 0.005 [1]	--	--	0.8% (2) 0.002 [2]
Tonic-clonic seizures exacerbated	0.4% (1) 0.004 [1]	0.4% (1) 0.004 [1]	--	--	--	0.8% (2) 0.002 [2]
Acquired epileptic aphasia	0.4% (1) 0.004 [1]	--	--	--	--	0.4% (1) 0.001 [1]

Table 48: Combined Studies – Device-related SAEs by year[1]

	Year 1	Year 2	Year 3	Year 4	Year 5	All Study Periods[2]
Apraxia	0.4% (1) 0.004 [1]	--	--	--	--	0.4% (1) 0.001 [1]
Complex partial seizures	--	--	0.4% (1) 0.005 [1]	--	--	0.4% (1) 0.001 [1]
Confusional state	0.4% (1) 0.004 [1]	--	--	--	--	0.4% (1) 0.001 [1]
Convulsive status epilepticus	--	0.4% (1) 0.004 [1]	--	--	--	0.4% (1) 0.001 [1]
Dysphemia	0.4% (1) 0.004 [1]	--	--	--	--	0.4% (1) 0.001 [1]
Simple partial seizures (sensory)	0.4% (1) 0.004 [1]	--	--	--	--	0.4% (1) 0.001 [1]
Simple partial seizures increased (motor)	0.4% (1) 0.008 [2]	--	--	--	--	0.4% (1) 0.002 [2]
Infections and infestations						
Implant site infection	2.3% (6) 0.028 [7]	0.4% (1) 0.004 [1]	2.1% (5) 0.027 [5]	1.4% (2) 0.018 [2]	--	5.9% (15) 0.019 [17]
Stitch abscess	--	--	0.4% (1) 0.005 [1]	--	--	0.4% (1) 0.001 [1]
Surgical and medical procedures						
Medical device removal	0.4% (1) 0.004 [1]	1.2% (3) 0.012 [3]	0.9% (2) 0.011 [2]	0.7% (1) 0.009 [1]	1.2% (1) 0.017 [1]	3.5% (9) 0.010 [9]
Cranioplasty	--	--	--	0.7% (1) 0.009 [1]	--	0.4% (1) 0.001 [1]
General disorders and administration site conditions						
Death	0.4% (1) 0.004 [1]	0.4% (1) 0.004 [1]	--	0.7% (1) 0.009 [1]	--	1.2% (3) 0.003 [3]
Implant site discharge	0.4% (1) 0.004 [1]	--	--	--	--	0.4% (1) 0.001 [1]
Implant site pain	--	0.4% (1) 0.004 [1]	--	--	--	0.4% (1) 0.001 [1]
Investigations						
EEG monitoring	0.4% (1) 0.004 [1]	--	0.9% (2) 0.011 [2]	--	1.2% (1) 0.017 [1]	2.0% (5) 0.006 [5]
Psychiatric disorders						
Depression suicidal	0.8% (2) 0.008 [2]	--	--	--	1.2% (1) 0.017 [1]	1.2% (3) 0.003 [3]
Agitation	--	--	0.4% (1) 0.005 [1]	--	--	0.4% (1) 0.001 [1]
Suicidal ideation	--	--	0.4% (1) 0.005 [1]	--	--	0.4% (1) 0.001 [1]
Suicide attempt	0.4% (1) 0.004 [1]	--	--	--	--	0.4% (1) 0.001 [1]
Summary of SAEs by Year[7]	15.6% (40) 0.244 [61]	12.2% (30) 0.125 [30]	8.1% (19) 0.127 [24]	6.1% (9) 0.080 [9]	3.5% (3) 0.050 [3]	32.8% (84) 0.146 [132]

[1] Device-related includes events categorized as device relation uncertain.

[2] Row totals may not sum to totals in this column because some subjects may have had SAEs in more than one period. Events beyond year 5 are only included in the total.

Table 48: Combined Studies – Device-related SAEs by year[1]

	Year 1	Year 2	Year 3	Year 4	Year 5	All Study Periods[2]

[3] % Subjects = # subjects with event / number of subjects entering interval.
[4] Event Rate = # events / implant years within interval.
[5] Device electrical finding: the battery appeared to be depleting faster than anticipated so was replaced. However, when explanted, the NeuroPace product investigation determined that the device performed as designed.
[6] Device malfunction: subject was unable to interrogate the Neurostimulator after being assaulted in the head so the Neurostimulator was replaced. Post-implant investigation showed normal Neurostimulator function.
[7] Column totals may not sum to totals in this row because some subjects may have had >1 one SAE type
Year 1 (implant - Week 52), Year 2 (Weeks 52 - 104), Year 3 (Weeks 104 - 156), Year 4 (Weeks 156 - 208), Year 5 (Weeks 208 - 260)
Data as of 5/12/2011

Table 49: Combined Studies – Subject deaths and SUDEP classification

(Feb. 2004 - Oct. 2012)

Pt	Study	Days Implanted	Device Relation	Circumstances of death	Cause of Death[1]	Stimulation Status at Time of Death
A	Pivotal	324	No	The subject was found dead face down in bed.	Definite SUDEP	Enabled
B	Pivotal	351	No	The subject was found unconscious and pulseless following a generalized tonic clonic seizure. The subject was resuscitated and placed on life support for 1 day.	Definite SUDEP	Enabled
C	Feasibility	473	Uncertain	The subject was found dead on the living room floor.	Definite SUDEP	Enabled
D	LTT	856	No	The subject was found dead at home.	Definite SUDEP	Disabled
E	Pivotal	36	No	The subject was found dead face down in bed.	Possible SUDEP	Disabled
F	Pivotal	594	No	The subject was found dead in a non-ignited fire pit.	Possible SUDEP	Enabled
G	Pivotal	230	Uncertain	The subject was found dead with a close contact gun shot wound to the head.	Not SUDEP (Suicide)	Enabled
I	LTT	1139	Uncertain	The subject was found dead surrounded by alcohol and pill bottles. Toxicology results indicated lethal levels of oxycodone and acetaminophen.	Not SUDEP (Suicide)	Disabled[2]
H	Pivotal	371	No	Subject died in the hospital due to cardiopulmonary arrest as a consequence of metastatic B-cell lymphoma.	Not SUDEP (Lymphoma)	Enabled
J	LTT	1295	Uncertain	The subject was found in convulsive status epilepticus. Following admission to ICU, subject died of cardiac arrest as a consequence of multisystem organ failure.	Not SUDEP (Status epilepticus)	Enabled
K	LTT	1277	No	The subject was found dead face down in bed.	Probable SUDEP	Enabled

[1] All deaths adjudicated by an external SUDEP committee.
[2] Neurostimulator programmed to have stimulation enabled, however battery was depleted at the time of death.
Data as of 10/24/2012

Table 50: Pivotal Study - Neuropsychological measures: Change in summary scores at end of Blinded Evaluation Period relative to Baseline, Treatment vs Sham

Test	Treatment		Sham		p-value[1]
	N	Mean ± SD	N	Mean ± SD	
Visual Motor Speed					
Trailmaking - Part A[2]	91	0.87 ± 14.61	86	-0.37 ± 14.97	0.578
Trailmaking - Part B[2]	90	-6.02 ± 52.72	85	-6.06 ± 33.49	0.996
Motor Speed / Dexterity					
Grooved Pegboard - Dominant[2]	89	-1.24 ± 14.95	79	-2.19 ± 22.80	0.746
Grooved Pegboard - Nondominant[2]	88	-1.89 ± 18.81	76	1.32 ± 27.31	0.378
Auditory Attention					
WAIS-III Digit Span	90	-0.21 ± 1.55	86	0.09 ± 1.48	0.185
General Verbal Ability					
WAIS-III Information	91	0.11 ± 1.14	83	0.12 ± 1.17	0.952
General Visuospatial Ability					
WAIS-III Block Design	90	-0.03 ± 2.06	84	0.31 ± 1.62	0.227
Verbal Memory					
RAVLT – I-V (Sum Across Trials)	86	-1.94 ± 9.20	84	-0.21 ± 10.01	0.243
RAVLT - VII (Delayed Recall)	86	-0.10 ± 2.75	84	0.01 ± 2.33	0.766
RAVLT - Recognition Memory	86	-0.21 ± 2.69	83	0.23 ± 3.12	0.329
Visuospatial Memory					
BVMT-R – Total Recall	90	1.94 ± 6.16	85	2.00 ± 5.95	0.952
BVMT-R - Delayed Recall	87	0.24 ± 2.75	85	0.32 ± 2.26	0.832
BVMT-R - Recognition Discrimination Index	88	0.14 ± 1.42	83	-0.07 ± 1.24	0.309
Language					
BNT - Spontaneous with semantic cue	90	0.70 ± 4.37	84	1.36 ± 3.89	0.297
D-KEFS Verbal Fluency - Condition 1: Letter Fluency	83	-0.06 ± 1.69	77	0.53 ± 2.32	0.065
Design Fluency					
D-KEFS Design Fluency - Total Composite	89	0.49 ± 2.32	80	0.40 ± 2.40	0.795

[1] Statistical significance of the between-group difference in change in score (at 20 weeks relative to pre-implant) between Treatment and Sham groups per two-sample t-test.

[2] Lower mean values indicate better performance.

Analysis includes subjects (N) with assessments at both Baseline and end of Blinded Evaluation Period time points.

WAIS-III = Wechsler Adult Intelligence Scale; RAVLT = Rey Auditory Verbal Learning Test; BVMT-R = Brief Visuospatial Memory Test-Revised; BNT = Boston Naming Test (60 item); D-KEFS = Delis-Kaplan Executive Function System

Table 51: Pivotal Study – Change in affective status: Blinded Evaluation Period (Treatment and Sham)

Survey	Summary Score[1] at Time Point, Mean ± SD				
	N[2]	Baseline	End of Blinded Evaluation (20 Weeks)	Change from Baseline	Difference in Change Between Groups P-value[3]
Beck Depression Inventory (BDI-II)					
Treatment	94	10.54 ± 8.41	9.16 ± 7.88	-1.38 ± 8.02	0.768
Sham	89	10.90 ± 8.09	9.87 ± 10.31	-1.03 ± 7.99	
Profile of Mood States (POMS)					
Treatment	94	27.94 ± 30.02	23.81 ± 29.70	-4.13 ± 31.30	0.308
Sham	87	26.66 ± 34.66	27.34 ± 39.15	0.69 ± 32.02	
Center for Epidemiological Studies Depression Scale (CES-D)					
Treatment	94	15.13 ± 9.59	14.14 ± 8.95	-0.99 ± 9.20	0.492
Sham	89	14.94 ± 9.00	14.91 ± 10.09	-0.03 ± 9.59	

[1] Total Mood Disturbance Score.
[2] Analyses include subjects (N) with assessments available at both time points.
[3] Two-sample t-test.
Data as of 5/12/2011

Table 52: Pivotal Study – Change in affective status: 1, 1.5 and 2 Years

	1 Year	1.5 Year	2 Years
	Summary Score at Time Point, Mean ± SD		
Beck Depression Inventory (BDI-II)			
N[1]	169	158	155
Baseline	10.54 ± 7.96	10.54 ± 7.63	10.57 ± 8.35
Post-Implant Time Point	8.99 ± 9.81	9.07 ± 9.33	8.66 ± 8.92
Change from Baseline	-1.55 ± 9.55	-1.47 ± 8.39	-1.90 ± 8.85
P-value[2]	0.036	0.029	0.008
Profile of Mood States (POMS)[3]			
N[1]	168	154	156
Baseline	26.90 ± 31.84	28.34 ± 31.77	27.80 ± 33.02
Post-Implant Time Point	22.34 ± 34.61	23.95 ± 35.78	21.99 ± 36.48
Change from Baseline	-4.56 ± 33.60	-4.39 ± 33.12	-5.81 ± 35.05
P-value[2]	0.080	0.102	0.040
Center for Epidemiological Studies Depression Scale (CES-D)			
N[1]	168	158	159
Baseline	14.87 ± 9.13	15.03 ± 9.08	14.99 ± 9.47
Post-Implant Time Point	13.55 ± 10.01	14.42 ± 9.92	13.91 ± 10.63
Change from Baseline	-1.32 ± 9.83	-0.61 ± 10.01	-1.09 ± 11.18
P-value[2]	0.085	0.442	0.222

[1] Analyses include subjects (N) with assessments available at both time points.
[2] Comparison of change from Baseline for entire subject population per paired t-test.
[3] Total Mood Disturbance Score.
Data as of 5/12/2011

Table 53: Pivotal Study – Schedule of appointments and activities

	Weeks Pre-Implant				Implant**	Weeks Post Implant																					
	Initial	4	8	12		2	4	5	6	7	8	12	16	20	24	28	32	36	40	44	48	52	56	68	80	92	104
																		☎	☎		☎	☎					
Baseline Activities (Pre-Implant)*																											
Consent Subject	X																										
Physical Exam	X																										
Neurological Exam	X			X																							
Review Medical History	X																										
Review Medications		X	X	X																							
Complete My Seizures Table	X																										
Collect Seizure Data		X	X	X																							
Administer Mood Surveys	X																										
Neuropsychological Eval.***				X																							
Confirm Eligibility for Implant				X																							
Assessment Protocol Activities (Post-Implant)																											
Neurological Exam							X				X	X	X	X	X	X	X			X			X	X	X	X	X
Review Medications							X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events							X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neuropsychological Eval.														X									X				X
Update My Seizures Table							when applicable																				
Administer Mood Surveys														X									X		X		X
Collect Seizure Data							X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Perform Therapy Assessment														X													
Conclude Participation																											X
Treatment Protocol Activities (Post-Implant)																											
Surgery & Hospitalization					X	when applicable																					
Synchronize Programmer						X	X	X	X	X	X	X	X	X	X	X	X			X			X	X	X	X	X
Review Adverse Events						X	X	X	X	X	X	X	X	X	X	X	X			X			X	X	X	X	X

*Baseline appointments continue to follow the same schedule until date of qualification for implant or until the subject is withdrawn.

**Implant must take place within 28 days of data of qualification.

***Initial Neuropsychological Evaluation must be administered between the date of qualification and the implant surgery.

☎ Telephone appointments were used to collect safety and seizure data in between office appointments.

15.8 Summary of Safety and Effectiveness Data

[See external file]

15.9 Labeling – User Manual

[See external file]

15.10 Labeling – Patient Manual

[See external file]