
10.6 Pivotal Clinical Study

The RNS™ System Pivotal Clinical Investigation provides valid scientific evidence providing reasonable assurance of the safety and effectiveness of the RNS™ System for its proposed intended use 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 antiepileptic medications. As pre-specified in IDE G030126, this PMA application is based upon the primary safety and effectiveness endpoint data from the Pivotal study. The safety data from the Pivotal study (N = 138) along with the safety data from the Feasibility study (N = 64) are used for the Pooled Safety Analysis providing more than 12 months of safety data sufficient to provide a reasonable assurance of safety for the indication for use as requested by the FDA. A total of 240 subjects were enrolled in the Pivotal study, 191 subjects have been implanted with the RNS™ Neurostimulator and Leads, of whom 187 have completed the Blinded Evaluation Period upon which the primary effectiveness endpoint to support this PMA is based. In addition, as of the data cutoff date for this PMA application (October 16, 2009), 56 subjects have completed the Open Label Period (24 months).

The RNS™ System Pivotal Clinical Investigation is a multi-center, prospective, randomized, double-blinded, sham-stimulation controlled pivotal study designed to assess safety and to demonstrate that the RNS™ System is effective for its intended use. After qualifying for implant over a 3-month (12-week) period (Pre-Implant Period), subjects were implanted with the RNS™ Neurostimulator and NeuroPace® Leads. Following a 4-week post-operative recovery period, subjects were randomized 1:1 to receive active (Treatment group) or sham responsive stimulation (Sham group). Subjects and the investigators collecting seizure data and other outcome data were blind to therapy allocation. Another group of investigators programmed the Neurostimulator but did not collect any of the outcome data. At 20 weeks (5 months) post-implant, subjects entered an open label period to complete 2 years post-implant. All subjects are able to receive active responsive stimulation during this period.

The primary effectiveness objective for this investigation is to demonstrate a significantly greater reduction in the frequency of total disabling seizures in the Treatment group compared to the Sham group during the Blinded Evaluation Period relative to the Pre-Implant Period of the investigation. Disabling seizures include simple partial motor seizures, complex partial seizures and generalized tonic-clonic seizures.

The primary safety objective is to establish that the RNS™ System serious adverse event (SAE) rate during the surgical procedure and the following 84 days (12 weeks) is no worse than the historical SAE rate for comparable procedures.

The data and analyses presented for the RNS™ System Pivotal Clinical Investigation demonstrate that the primary safety and effectiveness endpoints have been met. Experience in this trial indicates that responsive stimulation reduces seizure frequency. This is demonstrated by the statistically significantly greater reduction in mean seizure frequency in the Treatment group compared to the Sham group during the Blinded Evaluation Period, and by favorable changes in seizure frequency and severity in the Treatment group compared to the Pre-Implant Period. Subjects in the Sham group experienced a reduction in seizure frequency in the Open Label Period when responsive stimulation was enabled. Effectiveness for all subjects was sustained over the longer-term; seizure reductions persisted throughout the 2 year post-implant follow-up. Responsive stimulation therapy was safe and well tolerated over the short and longer-term. The rate of serious adverse events compared favorably to comparable procedures and there was no statistically significant difference between the Treatment and Sham groups during the randomized, blinded portion of the trial in the rate of any adverse event.

These results demonstrate that the RNS™ System is safe and 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 antiepileptic medications.

10.6.1 Pivotal – Regulatory Overview

The RNS™ System Pivotal Clinical Investigation (IDE G030126) was granted FDA conditional approval on September 15, 2005, and full approval on November 23, 2005 limiting the Pivotal study to 28 institutions and 240 subjects. A correction to the approval letter was issued on December 5, 2005 to specifically include the Long-Term Treatment Clinical Investigation and raise the LTT subject limit to 280 subjects. This LTT study subject limit was approved at 280 subjects to account for discontinuations; in other words enrollment of fewer subjects than the total enrollment approved for the Feasibility (80) and Pivotal studies (240). On August 23, 2007 FDA granted expansion of the study to 29 institutions (retaining the 240 subject limit). On December 17, 2007, the FDA approved the replacement of a maximum of three low enrolling investigational sites. On May 29, 2008, FDA clarified that the investigation was limited to 32 institutions of which only 29 sites were to be active to enrollment at the same time. As of October 16, 2009, 35 clinical sites received IRB approval for the Pivotal study of which 32 were opened to enrollment and enrolled subjects and 31 have implanted subjects. Only 29 investigational sites were active to enrollment at any given point in time. The first IRB approval for the Pivotal study was received November 11, 2005. No IRB withdrew approvals during the course of the investigation. The first subject was enrolled on December 29, 2005. The first subject in the Pivotal study received an RNS™ System implant on May 03, 2006. On November 17, 2008, the 240th subject was enrolled, and on November 18, 2008 NeuroPace notified the investigative sites that since the 240 subject limit had been reached, the study was closed to further enrollment. Eligible subjects completing the Pivotal study are given the opportunity to continue in the Long-Term Treatment study.

Subjects participating in this study are followed for two years post-implant, with the primary endpoint analysis occurring at the end of the 12-week Blinded Evaluation Period beginning 8 weeks post-implant and ending 20 weeks post-implant. A total of 240 subjects were enrolled in the Pivotal study to ensure that a minimum of 180 subjects completed the Blinded Evaluation Period to provide an adequate sample size for the primary endpoint analysis.

The Pivotal study is being conducted in the United States. As of October 16, 2009, the Pivotal study is ongoing, with actively participating subjects at 28 investigational sites (many of the same clinical sites that participated in the Feasibility study continued to participate in the Pivotal study). The Blinded Evaluation Period of the Pivotal study has been completed and the Open Label Period is continuing. As indicated in IDE G030126, the Pivotal clinical investigation was to be considered complete (with regard to the primary safety and effectiveness endpoints) when 180 subjects completed the Blinded Evaluation Period of the Pivotal study and when 12 months of safety data sufficient to provide a reasonable assurance of safety for the indication for use were collected from the RNS™ System Clinical Investigations in epilepsy

combined. Over 180 subjects have now completed the Blinded Evaluation Period of the Pivotal study. More than 12 months of safety data are available for over 180 subjects from the Feasibility and Pivotal investigations combined.

The Pivotal clinical study report titled *RNS™ System Pivotal Clinical Investigation Primary Endpoint Clinical Study Report* is provided in **Appendix 10.14.3.2** of this PMA application. Note that this report is referred to as the *Pivotal clinical study report* in italic font throughout the PMA application. This report includes a detailed description of the study protocol and safety and effectiveness results (including pre-specified and modified analyses) supporting the Pivotal study primary and secondary endpoints. This report also includes multiple appendices providing study information such as: modified primary effectiveness endpoint analyses including statistical rationale and considerations; additional pre-specified and not pre-specified effectiveness analyses; site poolability analyses; additional effectiveness statistical analysis listings, tables and figures; adverse event data summary figures and tables; data from mood and behavioral inventories and neuropsychological functioning assessments; listings and narratives for deaths and serious adverse events; additional safety analyses; discussion of missing and excluded data; lists summarizing malfunctions and product complaint reports; subject data listings; and study information such as a discussion of investigational plan amendments, a copy of the current investigational plan, copies of committee charters, sample consent form, and the list of investigators. Changes to the Pivotal study investigational plan (protocol) are summarized in **Section 10.6.10.1.1** of this PMA application.

Analyses presented in the clinical study report and the following PMA application sections (**Sections 10.6, 10.7, and 10.8**) were performed using study data as of October 16, 2009. These data were monitored and verified by NeuroPace personnel and the study database was locked on November 18, 2009. Clinical data beyond the data cut off date continue to be monitored and verified.

Longer-term follow-up of investigational subjects completing the Pivotal study is managed under a separate investigational plan and protocol, the RNS™ System Long-Term Treatment (LTT) Clinical Investigation. Eligible subjects completing the Pivotal study are given the opportunity to continue in the 5 year LTT study so that additional data safety and effectiveness data can be collected. A preliminary report for the LTT study is presented in **Section 10.7** of this PMA application.

In addition, NeuroPace has completed a pooled safety analysis specifically to support this PMA application. The RNS™ System Pooled Safety Analysis presented in **Section 10.8** of this PMA application provides further evidence supporting the ongoing safety of the RNS™ System. This analysis was conducted specifically to provide more than 12 months of safety data pooled from the Feasibility, Pivotal, and LTT clinical investigations in epilepsy to support the ongoing safety of the RNS™ System for the purposes of this PMA application.

10.6.1.1 Pivotal – Study Status and Follow-up

The first IRB approval for the Pivotal study was received November 11, 2005 and the first subject was enrolled on December 29, 2005. The first subject in the Pivotal study received an RNS™ System implant on May 03, 2006. The Pivotal study was closed to further enrollment following enrollment of the 240th subject on November 17, 2008. The final implant procedure was performed on May 20, 2009.

As of the data cut-off date (October 16, 2009), all implanted subjects (n = 191) had the opportunity to complete the Blinded Evaluation Period and are included in the primary safety and effectiveness analysis. 187 subjects have completed the Blinded Evaluation Period. Seven subjects (7/191) withdrew from the study after implant. 123 subjects continue to be followed in the Open Label Period. Fifty-six subjects have completed the Pivotal study (through 2 years post-implant) as of the cut-off date and all have enrolled in the Long-Term Treatment Clinical Investigation. No subject was lost to follow-up. One additional subject withdrew from the Pivotal study and subsequently enrolled in the LTT study. Participating subjects have completed a total of over 275 patient years of implant experience and 225 patient years of stimulation.

As of the cutoff date, there were 5 deaths in the Pivotal study; 4 due to possible or definite SUDEP (3 occurred in subjects in whom the Neurostimulator was programmed to provide responsive stimulation) and 1 due to suicide. An additional death attributed to lymphoma occurred on February 24, 2010, after the data cutoff date, is being reported for completeness.

10.6.2 Pivotal – Study Objectives

The primary objective of the Pivotal study 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 antiepileptic medications.

10.6.3 Pivotal – Study Design and Choice of Control

The RNS™ System Pivotal Clinical Investigation is a randomized, double-blinded, multi-center, concurrent sham-stimulation controlled clinical investigation of individuals (18 – 70 years of age) with medically intractable epilepsy conducted in the United States.

In order to address the primary study objectives, up to 240 subjects were to be enrolled to ensure that 180 subjects completed the Blinded Evaluation Period to provide an adequate sample size for the primary endpoint analysis.

Safety is primarily measured by adverse events. Effectiveness is primarily measured by changes in frequency of total disabling seizures within and across the Treatment and Sham (sham-stimulation control) groups.

The concurrent sham stimulation control group is not technically a placebo control. Subjects in the Sham group underwent a surgical procedure that included general anesthesia, a craniectomy and implantation of the Neurostimulator and Leads. Seizures can change for a limited period of time as a result of brain surgical procedures (Lesser, 2002; Katariwala et al., 2001) therefore the Sham group is not considered a placebo control. However, the Sham control (responsive stimulation programmed OFF) is essential to maintain the treatment blind.

In order to maintain the blind, the study design included two protocols (Assessment and Treatment) performed by separate clinicians. The clinicians conducting the Assessment Protocol are responsible for monitoring the subject's seizures and overall health. The clinicians conducting the Treatment Protocol manage the implanted RNS™ System. The Treatment Protocol team is aware of the subject's therapy allocation during the Blinded Evaluation Period, whereas the subject and the clinician conducting the Assessment Protocol are blinded.

The investigation lasted for up to 60 weeks prior to implant and two years following implant (104 weeks). The study design included five distinct time periods as presented in the schematic of the study design and trial flow presented in **Figure 10-8**: Baseline Period (12 weeks minimum, 60 weeks maximum), Post-Operative Stabilization Period (4 weeks), Stimulation Optimization Period (post-randomization, 4 weeks), Blinded Evaluation Period (12 weeks), and the Open Label Evaluation Period (84 weeks).

Time periods used in the safety and effectiveness analyses (Analysis Periods) are also presented in **Figure 10-8**.

Trial Flow

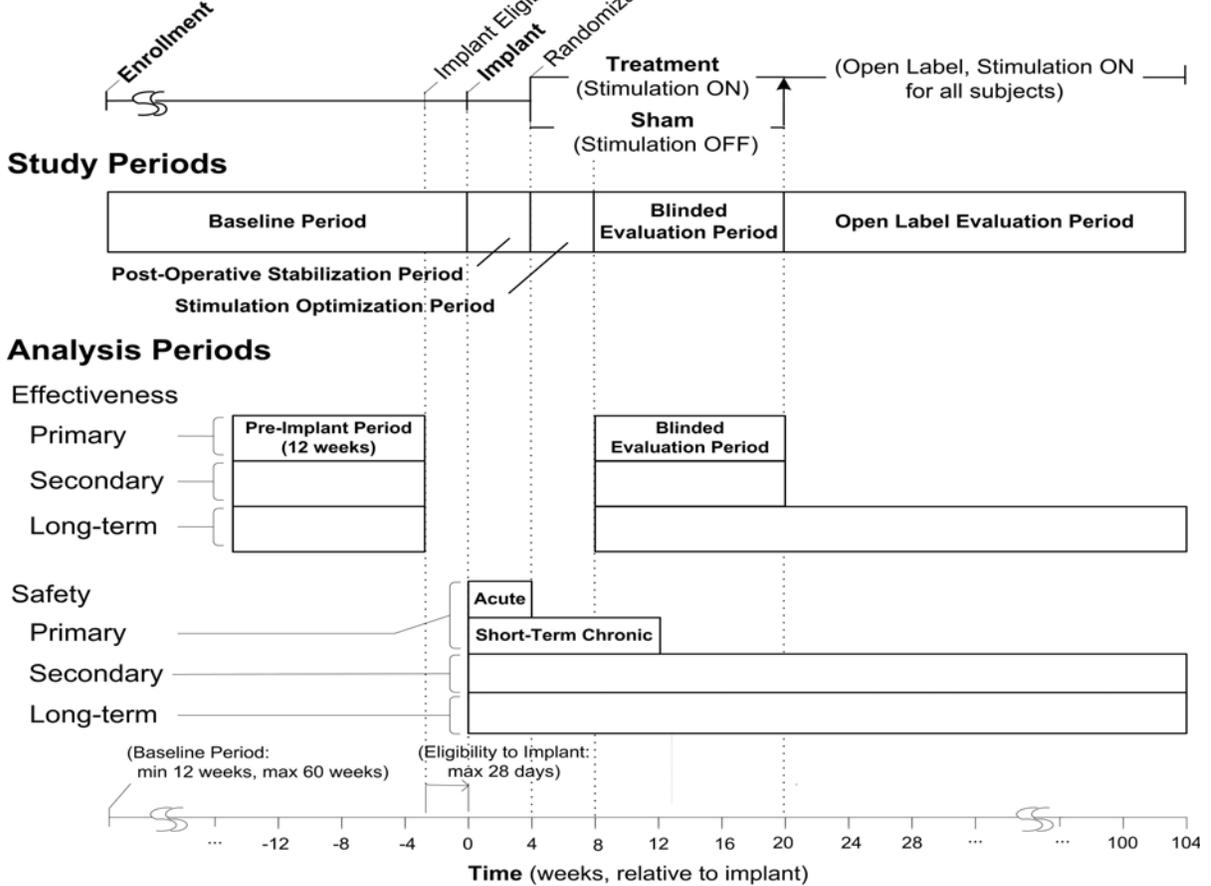


Figure 10-8: Pivotal Study – Trial Flow and Periods

Enrollment into the investigation began when the clinician determined that the subject met the inclusion and exclusion criteria and the subject (or legal guardian) signed the informed consent. Enrollment was confirmed once the relevant electronic case report forms (Inclusion and Exclusion Criteria and Consent Information) had been entered into the Patient Data Management System. Subjects that met enrollment criteria entered the Baseline Period. Seizure frequency and severity, and antiepileptic medications, were monitored and recorded during the entire study. Subjects or their caregivers kept a seizure diary throughout the entire study. To qualify for implantation with the RNS™ Neurostimulator and Leads, the subjects were required to remain on a stable antiepileptic drug (AED) regimen while having an average of three or more disabling seizures (motor partial seizures, complex partial seizures and/or secondarily generalized seizures) per 28 days over three consecutive 28-day periods during the Baseline Period, with no 28-day period with less than two seizures. Concomitant antiepileptic medication therapy is further described in **Section 10.6.5.3** of this PMA application.

Upon demonstrating the required seizure frequency and stable antiepileptic medications over 3 consecutive months (12 weeks) of the Baseline Period, subjects qualified for RNS™ Neurostimulator and Leads implantation. Per protocol, the surgical procedure was performed within one month (4 weeks) following the date that the subject met the implant criteria (date of qualification). If more than one month elapsed from the date of qualification to the date for implantation, and the subject failed to meet the implant criteria during that month, the qualification period had to be restarted. The 3-month (12-week) period preceding the date of qualification was defined as the Pre-Implant Period and data from this period are used as baseline data in the endpoint analyses.

Subjects meeting the requisite number of seizures while maintaining a stable antiepileptic drug regimen were implanted with the RNS™ Neurostimulator and Leads. The RNS™ Neurostimulator was cranially implanted and connected to one or two NeuroPace® Leads (subdural Cortical Strip and/or Depth Leads). The investigational team determined the placement of the Leads based on prior localization of the epileptogenic focus.

During the Post-Operative Stabilization Period (0 – 4 weeks post-implant), the Neurostimulator was programmed to enable detection of epileptiform activity for all subjects. Stimulation was not enabled in any subject. Following the 4 weeks of post-operative recovery, subjects were randomized on a one-to-one basis to the Treatment group (responsive stimulation programmed ON) or Sham group (responsive stimulation programmed OFF) at the Week 4 (post-implant) office appointment. Therapy allocation was achieved with a stratified adaptive randomization algorithm to balance variables that might influence response to responsive stimulation. Therapy allocation randomization method is further described in **Section 10.6.5.1** of this PMA application.

Subjects randomized to the Treatment group received responsive stimulation (i.e., Neurostimulator was programmed to both detect and deliver stimulation in response to detected epileptiform activity) during the Stimulation Optimization and Blinded Evaluation Periods. Subjects randomized to the Sham group did not receive responsive stimulation during the Stimulation Optimization and the Blinded Evaluation Periods (Neurostimulator was programmed only for detection). A Remote Monitor provided to the subject was used as directed by the subject's physician. It is recommended that the subject interrogate the RNS™ Neurostimulator and upload the data to the Patient Data Management System (PDMS) at least once a week throughout the investigation.

Over the next month (Stimulation Optimization Period), all subjects were seen on a weekly basis by the Treatment Protocol investigator. For those subjects randomized to the Treatment group, responsive stimulation (i.e., stimulation in response to detected epileptiform activity) was enabled and settings were optimized during weekly visits over the following month (4 weeks). For those subjects randomized to the Sham group, responsive stimulation was not enabled

during the Stimulation Optimization Period and the Blinded Evaluation Period; however, these subjects were seen on the same schedule as subjects in the Treatment group for simulated programming visits to maintain the treatment blind. Responsive stimulation treatment is further described in **Section 10.6.5.4** of this PMA application.

The 12-week Blinded Evaluation Period of the study lasted until 5 months (20 weeks) post-implant. During this time, subjects continued to maintain stable antiepileptic medications. Subjects in the Treatment group received responsive stimulation and subjects in the Sham group did not. Blinding was achieved by having separate investigators conducting Assessment and Treatment Protocols. Both the subject and the investigator conducting the Assessment Protocol were blinded to whether responsive stimulation therapy was enabled or disabled through the Blinded Evaluation Period of the clinical investigation. Blinding is further described in **Section 10.6.5.2** of this PMA application.

Following completion of the Blinded Evaluation Period at 5 months (20 weeks) post-implant, all subjects transitioned into the Open Label Evaluation Period during which all subjects (from both the Treatment and Sham groups) receive responsive stimulation and antiepileptic medications can be adjusted as needed. Responsive stimulation therapy was enabled (turned ON) for Sham group subjects and managed in an open label fashion for all Pivotal study subjects for the remainder of the study.

Subjects are followed in the Pivotal study (office/telephone appointments) for 2 years (104 weeks) post-implant. Throughout study participation (both before and after implantation), safety data are monitored continuously. Subjects record effectiveness data (seizure frequency and severity) using a daily seizure diary. These safety and effectiveness data are reviewed and documented by the study investigator at study appointments scheduled every month (4 weeks) for the first year (through 56 weeks) post-implant, then every 3 months (12 weeks) until the end of the investigation (through 104 weeks post-implant). The time periods of the study and associated protocol activities, including subject assessments, are described in more detail in **Section 10.6.6** of this PMA application.

Subjects' therapy allocation during the Stimulation Optimization and Blinded Evaluation Periods was not disclosed to either the clinician conducting the Assessment Protocol or the subject; this information will remain confidential until the end of the Pivotal clinical investigation.

Long-term follow-up of investigational subjects completing the Pivotal study is managed under a separate investigational plan and protocol, the RNS™ System Long-Term Treatment (LTT) Clinical Investigation. The LTT study was designed to gather additional longer-term safety and effectiveness data on subjects who had completed the Pivotal study. An overview of the LTT study and a summary of the preliminary report are provided in **Section 10.7** of this PMA application.

10.6.4 Pivotal – Trial Population

The trial population in the RNS™ System Pivotal Clinical Investigation consisted of individuals of either gender (18 - 70 years of age) with medically intractable partial onset epilepsy reporting an average of three or more disabling seizures (motor simple partial seizures, complex partial seizures and/or secondarily generalized seizures) per month (28 days) over the three most recent consecutive months, with no month with less than two seizures.

The inclusion/exclusion criteria for the Pivotal study were designed to ensure that enrolled subjects were able to provide reliable seizure counts, had a favorable risk-benefit ratio for receiving the RNS™ Neurostimulator and Leads, and had the profile of a subject that could adhere to the requirements of a clinical investigation. The key criteria for enrollment are summarized as follows:

Pivotal – Abbreviated Inclusion Criteria for Enrollment

- Subjects of either gender (18-70 years of age) with disabling motor simple partial seizures, complex partial seizures, 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 or mobility.
- Subject reports an average of three or more disabling seizures per month over the three most recent consecutive months, with no month with less than two seizures.
- Subject 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.
- Subject has remained on the same antiepileptic medication(s) over the 3 months preceding enrollment.
- Subject has undergone diagnostic testing as part of his/her standard care that has identified no more than two epileptogenic regions.

Note: A subject was still eligible to participate if antiepileptic medication(s) were temporarily discontinued for the purposes of diagnostic or medical procedures during the 3 months preceding enrollment.

Pivotal – Abbreviated Exclusion Criteria for Enrollment

- Subjects who have been diagnosed with primarily generalized seizures or have been diagnosed with psychogenic or non-epileptic seizures in the preceding year are excluded.
- Subjects who have been diagnosed with active psychosis, major depression or suicidal ideation in the preceding year. Subjects with post-ictal psychiatric symptoms are not excluded.
- In the opinion of the investigator, subjects who have a clinically significant or unstable medical condition (including alcohol and/or drug abuse) or a progressive central nervous system disease are excluded.

Pivotal – Key Inclusion Criteria for RNS™ Neurostimulator and NeuroPace® Leads Implantation

In order to qualify to be implanted with the RNS™ Neurostimulator and Leads, subjects must meet the following criteria during the Baseline Period:

- Over 3 consecutive months (12 weeks) of the Baseline Period, subject had an average of three or more disabling partial seizures per month, with no month with less than two seizures.
- Subject remained on the same antiepileptic medication(s) over these same three months (other than acute, intermittent use of benzodiazepines as rescue medications).

The three months during which the subject demonstrated eligibility for implant is defined as the “Pre-Implant Period”. (Refer to **Figure 10-8** for a summary of study design and trial flow.)

A complete list of inclusion and exclusion criteria are presented in Section 9.3 of the *Pivotal clinical study report* provided in **Appendix 10.14.3.2** of this PMA application.

Withdrawal of Subjects

Withdrawal is defined as premature discontinuation of the subject, which may occur at any time. Subjects were permitted to withdraw consent prior to implantation with the RNS™ Neurostimulator and Leads and exit the investigation. Similarly, if at the end of the twelfth 28-day period during the Baseline Period the subject had not met the seizure frequency criteria, the subject was to be withdrawn from the investigation.

Subjects withdrawing after implant with the RNS™ System are provided with the option to keep the Neurostimulator implanted (responsive stimulation and detection programmed disabled) or have it explanted. The Neurostimulator and Leads were designed to remain implanted whether responsive stimulation and detection are enabled or disabled.

10.6.5 Pivotal – Treatments

10.6.5.1 Pivotal – Therapy Allocation - Randomization Methods

Subjects implanted with the RNS™ Neurostimulator and Leads were randomized 1:1 to the Treatment group (responsive stimulation enabled) or to the Sham group (responsive stimulation disabled). To ensure equal representation in the two therapy groups, adaptive randomization was used to balance variables that might influence the clinical response to responsive stimulation. These variables (listed in order of priority) were:

- 1) investigational site
- 2) seizure onset zone location (partial onset seizures of mesial temporal origin versus partial onset seizures arising from any other region of the cortex)
- 3) number of seizure foci (unifocal versus bifocal)
- 4) previous resection (whether the subject had previously undergone a therapeutic epilepsy surgery)

Subjects were randomized at the start of the Stimulation Optimization Period (Week 4 post-implant). (Refer to **Figure 10-8** for a summary of study design and trial flow.) Subjects were randomized one at a time, so that the allocations of preceding subjects were taken into account when performing adaptive randomization for the next subject. The NeuroPace research department was responsible for maintaining the randomization code. Implementation of the adaptive randomization method is described in further detail in Section 9.4.3 of the *Pivotal clinical study report* provided in **Appendix 10.14.3.2** of this PMA application.

Administration of the allocation occurred at NeuroPace, and was communicated to the clinician conducting the Treatment Protocol through the Programmer. The therapy group allocation was concealed from the subject and Assessment Protocol clinicians in order to maintain the double blind. All randomized subjects were to be included in the intent-to-treat population for effectiveness analyses.

10.6.5.2 Pivotal – Blinding

Blinding was achieved by having separate investigators conducting Assessment and Treatment Protocols. Both the subject and the investigator conducting the Assessment Protocol were blinded to whether responsive stimulation therapy was enabled or disabled through the Blinded Evaluation Period. (Refer to **Figure 10-8** for a summary of study design and trial flow.) The clinicians conducting the Assessment Protocol evaluate the subject's condition and monitor and collect seizure data. The clinicians conducting the Treatment Protocol are knowledgeable in the use of the RNS™ System and by necessity were aware of the subject's assigned therapy allocation. Epileptiform activity detection settings were adjusted for subjects in both groups in order to optimize

detection. For those subjects randomized to the Treatment group, the clinician conducting the Treatment Protocol adjusted the RNS™ Neurostimulator responsive stimulation settings according to the subject's clinical response. The Treatment Protocol clinician performed simulated adjustment of the programmed settings in the Sham subjects at the same intervals as the Treatment group, but did not enable responsive stimulation therapy in the Sham group subjects.

At the conclusion of the Blinded Evaluation Period, subjects were asked whether they thought their Neurostimulator had been delivering therapy. The results were analyzed to ascertain the degree of subject blinding achieved, and to determine if there were any systematic reasons that compromised the blind. Subjects and the Assessment Protocol clinicians were not told whether the subject had been in the Treatment or Sham group during the Blinded Evaluation Period.

10.6.5.3 Pivotal – Concomitant Therapy

Information regarding antiepileptic medications (AEDs) and other medications taken by the subject is collected throughout the investigation.

During the Baseline Period, subjects were required to remain on the same antiepileptic medications for three consecutive months (12 weeks) to qualify for implantation with the RNS™ Neurostimulator and Leads. Any significant change in antiepileptic medications for seizure control (dose, new AED, or stopped AED) required that the 3-month (12-week) qualifying period (Pre-Implant Period) begin again. Minor adjustments to daily dose to maintain target blood serum levels or for toxicity were acceptable. Acute, intermittent use of benzodiazepines for seizure clusters or prolonged seizures was also acceptable.

During the Post-Operative Stabilization, Stimulation Optimization and Blinded Evaluation Periods, any significant change (dose, new AED, or stopped AED) for seizure control was a protocol deviation. Minor adjustments to daily dose to maintain target blood serum levels or for toxicity were acceptable. Acute, intermittent use of benzodiazepines for seizure clusters or prolonged seizures was also acceptable.

During the Open Label Evaluation Period AED adjustments (dose/type) are permitted to be made as needed. (Refer to **Figure 10-8** for a summary of study design and trial flow.)

10.6.5.4 Pivotal – Description of RNS™ System Operator Technique

A brief description of the RNS™ System is provided above in **Sections 10.2** and **10.2.2** and a complete description is provided in **Section 3 Device Description** of this PMA application; the RNS™ System operation is discussed in further detail in **Sections 3.2** and **3.3**.

10.6.5.4.1 PIVOTAL – PRE-PROCEDURE EXAMINATION AND TESTS

All subjects underwent a standard physical examination, a full neurological examination, a neuropsychological evaluation, and completed various mood and behavioral surveys prior to surgery. Subjects also completed a medical history.

10.6.5.4.2 PIVOTAL – RNS™ SYSTEM IMPLANT PROCEDURE

The RNS™ Neurostimulator and NeuroPace® Depth and/or Cortical Strip Leads were implanted under general anesthesia in an operating room by a neurosurgeon. The surgical procedure required a craniectomy within which a Ferrule was attached and the Neurostimulator was seated. Depth and/or subdural Cortical Strip Leads were placed via the craniectomy, or through a separate craniectomy or burr hole, depending on the location and orientation of the Leads. The Depth and/or subdural Cortical Strip Leads were placed in order to optimally record from the epileptogenic region, as identified previously by the investigational team at each site. Although the Neurostimulator can be connected to two Leads containing 4 electrode contacts each, the investigational sites had the option to implant up to 4 Leads (only two of which may be Depth Leads) with the proximal portion of the third and fourth Leads externalized to the dura and capped. If, at a later date, epileptiform activity detection or stimulation response was not adequate with the 2 Leads initially selected, the third and/or fourth Lead could be connected to the Neurostimulator in place of the first and second Lead, without penetrating the dura.

10.6.5.4.3 PIVOTAL – NEUROSTIMULATOR PROGRAMMING

Following surgical implantation of the RNS™ Neurostimulator and NeuroPace® Leads, per the investigational plan, the Treatment Protocol investigator was permitted to adjust the Neurostimulator programming according to the subject's clinical response. Reprogramming occurred at study visits that were scheduled at regular intervals within the Treatment Protocol.

Throughout the study and per the Treatment Protocol, the Treatment physician is advised to interrogate the Neurostimulator, review the device data such as Lead impedance, battery voltage, number of detections and

stimulations, and stored ECoGs. The physician may then program new detection and/or stimulation settings depending on the review of the device data and the patient's clinical response. In most cases, Neurostimulator programming occurs at each visit.

The range of available settings in the RNS™ Neurostimulator for the programmable responsive stimulation parameters is presented in **Table 10-19**. The protocol (Section 7.3.2 of the investigational plan, which is included in Appendix 15.7.2 of the *Pivotal clinical study report* provided in **Appendix 10.14.3.2** of this PMA application) advised programming the Neurostimulator to initial settings of 200 Hz, 160 μs, and 100 ms burst duration, and then adjusting settings according to the patient's clinical response.

Table 10-19: Pivotal Study – Range of RNS™ Neurostimulator Programmable Stimulation Parameters

	Minimum	Maximum
Frequency (Hz)	1 Hz	333 Hz
Burst Duration (ms)	10 ms	5000 ms
Pulse width (μs)	40 μs	1000 μs
Current	0.5 mA	12 mA

The expectation is that in clinical practice, patient visits will occur with similar frequency as the appointment schedule in the Pivotal trial. In addition, it is expected that Neurostimulator programming will occur with similar frequency, depending on the patient's clinical response. Adjustment of stimulation parameters is recommended at intervals of 4-6 weeks to allow sufficient time to assess the patient's clinical response.

10.6.5.4.4 PIVOTAL – NEUROSTIMULATOR REPLACEMENTS AND LEAD REVISION PROCEDURES

Neurostimulator replacement procedures are conducted either under general or local anesthesia, as an in-patient or out-patient procedure according to the Neurosurgeon's preference. A scalp incision is made at the site of the RNS™ Neurostimulator implant and the Neurostimulator and Ferrule are exposed. The NeuroPace® Leads are then disconnected from the Neurostimulator and the Neurostimulator removed from the Ferrule. The Leads are connected to the replacement Neurostimulator. The Neurostimulator is secured within the Ferrule and the incision is closed.

Lead revisions include procedures to adjust placement of already implanted Leads, to change connection of already implanted Leads to the Neurostimulator, to remove Leads, and to implant new Leads. The procedure for implantation of Depth and Cortical Strip Leads is described above in **Section 10.6.5.4.2**. Depth Leads are removed by simple withdrawal. Cortical Strip Leads require varying degrees of dissection of adhesions prior to removal.

10.6.5.4.5 PIVOTAL – NEUROSTIMULATOR EXPLANT PROCEDURES

As with the Neurostimulator replacement procedures, Neurostimulator explant procedures are conducted either under general or local anesthesia, as an in-patient or out-patient procedure according to the Neurosurgeon's preference. A scalp incision is made at the site of the Neurostimulator implant and the Neurostimulator and Ferrule are exposed. The Leads are then disconnected from the Neurostimulator and the Neurostimulator removed from the Ferrule. The Ferrule can be left in place or removed. The craniectomy defect is filled by inserting a NeuroPace® Cranial Prosthesis into the Ferrule or according to the Neurosurgeon's preference and the scalp incision is closed.

10.6.6 Pivotal – Protocol and Subject Assessments

A summary of the study appointment schedule and activities performed at each appointment is presented in **Table 10-20**. Protocol appointments are scheduled based on the day of the initial office appointment for the Baseline Period and on the day of implant for the remaining periods. (Refer to **Figure 10-8** for a summary of study design and trial flow.)

In order to maintain the blind for the physician responsible for collecting the effectiveness and safety outcome data, the trial is conducted by two investigator teams at each site. The Assessment Protocol team is blinded to the subject's treatment allocation and is therefore not involved in managing the RNS™ System. The Assessment Protocol team saw the subject at the first study visit and continues to follow the subject throughout the trial. The Assessment Protocol team collects all the seizure frequency and severity data and captures them in the study case report forms, as well as the neuropsychological and affective status (behavioral surveys) inventories, and the quality of life inventory. The Treatment Protocol began at the time that the subject was implanted with the RNS™ Neurostimulator and Leads. This investigator is by necessity not blinded to treatment status and is responsible for programming the Neurostimulator. Both investigator teams collect data on adverse events.

Clinicians conducting the Assessment Protocol interact with the subject during required scheduled office and telephone appointments, and during unscheduled telephone and office appointments as needed. All neuropsychological evaluations and behavioral surveys are conducted within the Assessment Protocol.

Clinicians conducting the Treatment Protocol interact with the subject during regularly scheduled office appointments and, as needed, by telephone and additional office appointments.

Subjects and the Assessment Protocol clinicians are not told whether the subject had been randomized to the Treatment or Sham group for the Stimulation Optimization and Blinded Evaluation Periods. At the conclusion of the Blinded Evaluation Period, subjects were asked whether they thought their Neurostimulator had been delivering therapy. The results were analyzed to ascertain the degree of subject blinding achieved, and to determine if there were any systematic reasons that compromised the blind.

Table 10-20: Pivotal Study – Study Appointment Schedule

Study Periods	Baseline			Post-Op Stabilization	Stimulation Optimization	Blinded Evaluation	Open Label Evaluation																				
	Initial Visit	Weeks Pre-Implant ¹			Implant ²	Weeks Post-Implant																					
Study Appointment Time Points		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
ACTIVITIES																											
Assessment Protocol																											
Consent	X																										
Physical Exam	X																										
Medical History	X																										
My Seizures Table	X																										
Neurological Exam	X			X			X			X	X	X	X	X	X	X			X			X	X	X	X	X	
Review of Medications		X	X	X			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review of Adverse Events		X	X	X			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Seizure Data (Diary/Severity)		X	X	X			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
My Seizures Table (Review/Update)		<i>As needed</i>				<i>As needed</i>																					
Affective Status/Quality of Life Surveys	X												X									X		X		X	
Neuropsychological Evaluation ³				X									X									X				X	
Therapy Blind Lifted ⁴													X														
Treatment Protocol																											
Surgery & Hospitalization					X																						
RNS™ System Activity Review						X	X	X	X	X	X	X	X	X	X	X			X			X	X	X	X	X	
Review of Adverse Events						X	X	X	X	X	X	X	X	X	X	X			X			X	X	X	X	X	
Remote Monitor Uploads						<i>As prescribed by physician</i>																					

¹ Baseline appointments continued to follow the schedule of two telephone appointments and then an office appointment. If the subject did not meet the seizure frequency criteria by the end of the twelfth 28-day period, the subject was to be withdrawn from the investigation. However, if monthly seizure count criteria were met during the twelfth 28-day period, the subject was permitted to continue to participate for up to two more 28-day periods so long as the subject continued to meet the seizure count criteria in each of those periods.

² Implant must have taken place within 28 days of the date of qualification for the RNS™ System implant.

³ The first (baseline) Neuropsychological Evaluation took place after qualification for implant and before RNS™ System implant surgery.

⁴ The therapy allocation may be lifted no earlier than the 20-week appointment. Note that therapy allocation during the Blinded Evaluation Period is not revealed to the subject and the Assessment Protocol team until after the Pivotal clinical investigation is complete.

10.6.7 Pivotal – Effectiveness and Safety Endpoints and Analyses

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 antiepileptic medications.

The assessments used to assess safety and to demonstrate effectiveness are described below. The information in **Section 10.6.7** is organized as follows:

- Section 10.6.7.1 Pivotal – Sample Size Calculations**: This section provides explanation how the Pivotal study sample size was originally determined.
- Section 10.6.7.2 Pivotal – Effectiveness Objectives, Assessments and Statistical Methods**: This section provides a discussion of the study effectiveness objectives; assessment variables and endpoints; and statistical methodology. All pre-specified methods as presented in the investigational plan as well as any modifications to the pre-specified methods and methods for additional analyses that were not pre-specified.
- Section 10.6.7.3 Pivotal – Safety Objectives, Assessments and Statistical Methods**: This section provides a discussion of the study safety objectives; assessment variables and endpoints; and statistical methodology. Statistical methods include all pre specified methods as presented in the investigational plan; there were no modifications to the pre-specified methods.
- Section 10.6.7.4 Changes in Planned Analyses**: This section provides a brief summary and cross references to the location of the pre-specified, modified, and additional analyses.

Results of the Pivotal study effectiveness and safety endpoint analyses are provided in **Section 10.6.8**.

10.6.7.1 Pivotal – Sample Size Calculations

The trial was designed to have 80% power should the responder rate in the Treatment group be equal to or greater than 40%, given an assumed 20% responder rate in the Sham-stimulation subject group, at an over-all 2-sided Type 1 error of 0.05. To meet these criteria, 180 subjects were required in the Blinded Evaluation Period. Assuming approximately 10% of subjects would not be compliant (including subjects who did not complete the Blinded Evaluation Period), approximately 200 subjects were to be randomized, 100 each into the Treatment and Sham groups. Assuming a 20% dropout rate in the Baseline Period, a minimum of 240 subjects were planned to be enrolled in the investigation.

10.6.7.2 Pivotal – Effectiveness Objectives, Assessments and Statistical Methods

The primary effectiveness objective for this investigation is to demonstrate a significantly greater reduction in the frequency of total disabling seizures in the Treatment group compared to the Sham group during the Blinded Evaluation Period relative to the Pre-Implant Period of the investigation.

Primary and secondary endpoint analyses of effectiveness were performed on seizure counts and severity data collected by subjects in a daily diary and entered by the Assessment Protocol physicians onto case report forms.

Subjects or their caregivers keep a seizure diary throughout the entire study. A new diary is provided at every appointment. Each monthly diary includes one page per day for documenting the number and type of each seizure experienced each day. The final page of the diary includes the 12-item Liverpool Seizure Severity Scale questionnaire, which the subject completes based entirely upon the most severe seizure experienced by the subject during that 1-month (28-day) period. Monthly, at each study appointment (**Table 10-20** above), the Assessment Protocol physician discusses the diary with the subject and enters the seizure frequency and severity data into case report forms.

Primary and secondary effectiveness endpoint analyses used seizure data collected during the 3-month Blinded Evaluation Period (Weeks 8 - 20 post-implant) and from the 3-month Pre-Implant Period (the 12 consecutive weeks leading up to the subject's qualification for RNS™ System implant).

The following describes the statistical methods used for the analysis of the effectiveness data presented in this PMA application. Statistical methods include all pre-specified methods as presented in the investigational plan as well as any modifications to the pre-specified methods and methods for additional analyses that were not pre-specified.

10.6.7.2.1 PIVOTAL – PRIMARY EFFECTIVENESS ENDPOINT

The pre-specified primary effectiveness endpoint variable is the group-by-time interaction term in a generalized estimating equation (GEE), longitudinal regression model, where group refers to active stimulation (Treatment) or sham stimulation (Sham) and time refers to the Pre-Implant Period or Blinded Evaluation Period.

The primary effectiveness endpoint is met when the group-by-time interaction term is significant in the model. A significant group-by-time interaction term demonstrates a significantly greater reduction in seizure frequency in the Treatment group than the Sham group during the Blinded Evaluation Period compared to the Pre-Implant Period.

10.6.7.2.1.1 Primary Effectiveness Endpoint Hypothesis and Statistical Methods

Seizure frequency data recorded by subjects on a daily basis during the Pre-Implant and Blinded Evaluation Periods were used in the primary effectiveness analysis. As pre-specified in the investigational plan, to account for both between-subject and within-subject variation in seizure frequency data when comparing the Treatment (active stimulation) and Sham (sham stimulation) groups, a generalized estimating equation (GEE), longitudinal Poisson model was applied to the data. The longitudinal Poisson regression model presented in the Investigational Plan was represented by the following equation:

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

where the dependent variable, Y , is daily seizure counts, which is modeled to be linear on the log scale. The primary effectiveness endpoint variable is the *Group-by-Time* interaction term in the GEE model, where *Group* indicates the therapy randomization group (0 = Sham, 1 = Treatment), and *Time* indicates the trial period (0 = Pre-Implant Period, 1 = Blinded Evaluation Period). The significance of the Treatment Effect (any reduction in seizure frequency in the Treatment group beyond that in the Sham group) is quantified by the estimate of the *Group-by-Time* interaction parameter, β_2 , where the null and alternative hypotheses are as follows:

$$\begin{aligned} H_0: \beta_2 &= 0 \\ H_1: \beta_2 &\neq 0 \end{aligned}$$

The logarithmic link was specified, and the “scale” parameter was not to be fixed at unity to allow for over-dispersion of variance. Additional models including covariates that potentially influence the endpoint and covariates that were found not to be balanced between the groups were to be included in the model.

The results for the primary effectiveness analysis as pre-specified in the investigational plan are presented in **Section 10.6.8.8.1.2.1** of this PMA application. However, these results could not be reliably interpreted nor provide valid conclusions regarding the effect of treatment because the model is poorly specified. Therefore modifications to the primary effectiveness endpoint analysis methods were required to allow results to be appropriately interpreted and accurate conclusions to be drawn.

The modifications to the methods were to group seizure count data by month rather than using daily seizure count data, to model data with a negative binomial distribution rather than assume a Poisson distribution, and to include clinically-relevant characteristics as covariates to account for differences in seizure frequency across patient populations. The characteristics included in the model had been identified *a priori* as clinically

important factors and were variables used in the randomization strata. The covariates are:

- Seizure onset zone location (subjects with seizure onsets exclusively in the mesial temporal lobe versus any other region(s) of the cortex)
- Number of seizure foci (unifocal versus bifocal)
- Prior therapeutic epilepsy surgery (resection, subpial transection and/or corpus callosotomy, versus no such surgery)

These modifications account for the day-to-day variability in seizure count data within subjects, and variability in seizure count data between subjects, and allow for reliable and valid statistical inferences to be drawn from the results.

The modified model is described in **Section 10.6.8.8.1.2.2** of this PMA application. Additional detail and discussion regarding model modifications and rationale is provided in Appendix 15.1.1.2 of the *Pivotal clinical study report* provided in **Appendix 10.14.3.2** of this PMA application.

10.6.7.2.1.1 Statistical Considerations and Adjustment for Confounders

Pre-specified statistical considerations for the primary effectiveness endpoint analyses include adjustment for covariates found to be out of balance, and assessment of missing data, treatment failures, and extreme values. A summary of these analyses and statistical considerations is presented in **Section 10.6.8.8.1.2.4** of this PMA application.

Covariates Found to Be Out of Balance between Treatment Groups

Per the investigational plan, demographic and baseline characteristics of interest were evaluated for balance between the Treatment and Sham groups (refer to **Table 10-24** and **Table 10-25**). All demographic and baseline characteristics found to be out of balance ($p < 0.05$) and those found to have a trend towards imbalance ($p < 0.1$) were considered as additional covariates in the GEE model for the primary effectiveness analysis. The covariates were to be included in the final GEE model if they were found to be out of balance and significant as a main effect in the model at $p < 0.05$.

Additionally, as pre-specified in the investigational plan, the baseline seizure frequency was evaluated for potential differences by group (Treatment and Sham). This was done by including “Group” as an additional covariate in the GEE model for the primary effectiveness analysis. The “Group” covariate was to be included in the final GEE model if the covariate was found to be significant in the model.

Other covariates not pre-specified were identified as possible characteristics of interest (prior vagus nerve stimulator and age). Although these characteristics were not found to be out of balance between the Treatment and Sham groups, these characteristics were considered as additional covariates in the GEE model. If the covariates were found to be significant as a main effect, the covariate was to be further evaluated for possible interaction with the Treatment Effect by including an interaction term in the GEE model.

Missing Data Considerations

The GEE method does not require imputing missing data points, therefore the primary effectiveness endpoint analysis included all subjects on an intent-to-treat basis using all available data. However, sensitivity analyses were performed per the investigational plan to assess the impact of missing data on the primary effectiveness endpoint.

First, for subject data that was 'intermittent' missing (e.g., missed observations within the Pre-Implant or Blinded Evaluation Period), the missing data were imputed by averaging the outcome value of the latest non-missing day before the missed day and the earliest non-missed day after the missed day.

Secondly, for subjects who withdrew or died, a multiple imputation strategy was performed using a logistic propensity score method. Logistic regression was used to obtain estimates of the probability of having a missing value on a given day. For each day with missing values the covariates in the logistic regression included the baseline covariates: seizure onset zone, number of seizure foci and prior surgery, as well as the seizure frequency from prior days during the Blinded Evaluation Period. The propensity scores resulting from the logistic regression for a given day were stratified by quartile and the missing values were imputed using observed values within the same stratum selected by performing an approximate Bayesian bootstrap.

This process was repeated 200 times to produce 200 complete datasets. The primary GEE regression model was applied to the 200 datasets and the results were combined using Proc MIANALYZE in SAS.

A further sensitivity analysis was performed where seizure count data were carried forward as an imputation of subsequent missing data (e.g., last observation carried forward). The resulting complete data set was subjected to the primary GEE regression model.

Treatment Failures (Per-Protocol Analysis)

As pre-specified in the investigational plan, the primary effectiveness endpoint analysis was repeated excluding subjects with protocol

deviations that seriously affect the integrity of the data collected. Subject adherence to the protocol was examined to determine whether any subject deviated from the protocol in such a manner as to make it reasonable to repeat analyses with these subjects excluded. This examination was conducted by persons blinded to treatment allocation and before any analyses were performed. The population of the subjects included in the analysis is called the Per-Protocol Population. The specific protocol deviations of the subjects excluded from the Per-Protocol Population are described in **Section 10.6.8.2**, and results of the Per-Protocol Population analysis are summarized in **Section 10.6.8.8.1.2.4** [see subsection titled ***Treatment Failures (Per-Protocol Population Analysis)***] of this PMA application.

Outliers and Extreme Values

Data for the primary effectiveness analysis were examined with respect to extreme values. Sensitivity analyses were conducted removing any extreme observations as well as the subjects with extreme observations.

10.6.7.2.2 PIVOTAL – SECONDARY EFFECTIVENESS ENDPOINT ANALYSES AND STATISTICAL METHODS

The objective of the secondary endpoint analyses is to provide supportive evidence for the superiority of the clinical response in the Treatment group relative to the Sham group during the Blinded Evaluation Period. Per the investigational plan, the pre-specified secondary effectiveness comparisons were responder rates, change in mean seizure frequency, proportion of seizure-free days and change in seizure severity. These metrics were evaluated for the entire 3-month Blinded Evaluation Period. The responder rate, change in mean seizure frequency and proportion of seizure-free days were also evaluated for each of the three months separately.

10.6.7.2.2.1 Responder Rates (Secondary Endpoint)

The objective is to compare the responder rate (proportion of subjects who are responders) in the Treatment group during Blinded Evaluation Period of the trial to the responder rate in the Sham group. A responder is defined as a subject having a 50% or greater reduction in mean disabling seizure frequency during the Blinded Evaluation Period compared to the Pre-Implant Period. The null and alternative hypotheses are as follows:

$$H_0: \pi_0 = \pi_S$$

$$H_1: \pi_0 \neq \pi_S,$$

where π_0 is the expected rate of the Treatment group and π_S is the expected Sham rate.

Responder status was calculated by first taking the average seizures per day across the 3-month Pre-Implant and Blinded Evaluation Periods per subject. The percent change was then computed by subtracting the subject's average frequency in the Pre-Implant Period from the average for the Blinded Evaluation Period and then divided by the subject's average frequency in the Pre-Implant Period. If the resulting percent change was less than or equal to -50% (i.e., a 50% or greater reduction in seizures) the patient was categorized as a responder.

The responder rates for Treatment versus Sham groups were statistically compared using the Z-statistic

$$Z = \frac{|p_o - p_s|}{\sqrt{p(1-p)(1/n + 1/k)}}$$

where p is the pooled responder rate, p_o and p_s are the corresponding rates for the Treatment group and the Sham group, respectively. The sample size in the Treatment group equals n and the Sham group equals k .

Responder rates are presented and compared for the entire Blinded Evaluation Period as well as for each month of the Blinded Evaluation Period. Additionally, although not pre-specified, responder rates by other percent decreases from baseline (deciles) are presented.

10.6.7.2.2 Change in Mean (Average) Seizure Frequency (Secondary Endpoint)

The objective is to compare the change in mean (average) frequency of disabling seizures during the Blinded Evaluation Period relative to the Pre-Implant Period experienced by the Treatment group relative to the change experienced by the Sham group. The null and alternative hypotheses are as follows:

$$\begin{aligned} H_0: \mu_o &= \mu_s \\ H_1: \mu_o &\neq \mu_s \end{aligned}$$

where μ_o is the change in seizure frequency of the Treatment group and μ_s is the change in seizure frequency of the Sham group.

The change in mean frequency of disabling seizures from the Blinded Evaluation Period compared to the Pre-Implant Period was calculated for each subject and then averaged across groups (Treatment and Sham). Per the investigational plan, the two-sample t-test was used to compare the two groups (Treatment vs. Sham). Additionally, the paired t-test was used to assess within group changes during the Blinded Evaluation Period compared to the Pre-Implant Period. The analyses were performed for the

entire Blinded Evaluation Period as well as for each month of the Blinded Evaluation Period.

10.6.7.2.2.3 Proportion of Seizure-Free Days (Secondary Endpoint)

The objective is to compare the change in proportion of seizure-free days during the Blinded Evaluation Period relative to the Pre-Implant Period experienced by the Treatment group with the change experienced by the Sham group.

Each day, a subject either experiences at least one total disabling seizure (coded as no) or experiences a day with no total disabling seizures (coded as yes). This was abstracted daily during the Pre-Implant and Blinded Evaluation Periods.

Per the investigational plan, a GEE model was used to investigate the significance of group membership (Treatment versus Sham). On the logistic scale, the dependent variable, Y, is a yes/no seizure-free day and the independent variables are time (an indicator of the Pre-Implant versus the Blinded Evaluation Period), the interaction of time with treatment group membership, and covariates that might be predictive of outcome.

The analysis was performed for each month of the Blinded Evaluation Period. The GEE model on the logistic scale is represented by the equation:

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

Time is coded as 0 for Pre-Implant and 1 for the Blinded Evaluation Period. Group is coded as 0 for Sham and 1 for Treatment. The variable of interest is the Group-by-Time interaction term in this model, which represents the Treatment Effect and is estimated by β_2 . A working compound symmetry correlation structure of the within subject counts reported over time was used.

Additionally, the paired t-test was used to assess change from each month of the Blinded Evaluation Period compared to the Pre-Implant Period, and the 2-sample t-test was used to compare two groups (Treatment vs. Sham).

10.6.7.2.2.4 Change in the Liverpool Seizure Severity Inventory (Secondary Endpoint)

The objective is to compare the change in seizure severity as measured by the Liverpool Seizure Severity Inventory during the Blinded Evaluation Period relative to the Pre-Implant Period experienced by the Treatment group with the change experienced by the Sham group. Seizure severity was measured by the Liverpool Seizure Severity Scale 2.0 scaled summary

score (Scott-Lennox et al., 2001). The expected result is that the Treatment group will have a greater reduction in seizure severity as measured by this inventory compared to the Sham group.

Change in individual subjects' Liverpool score during the Blinded Evaluation Period compared to the Pre-Implant Period is the outcome variable. The Liverpool Seizure Severity score was collected for each 28-day period throughout the study, thus three scores for each time period (Pre-Implant and Blinded Evaluation) for each subject are expected. To calculate the change in severity per subject, the three scores for each time period were first averaged. Secondly, change per subject was calculated as the difference between these two scores (Blinded Evaluation Score minus Pre-Implant Score). The paired t-test was used to assess change from the Pre-Implant Period, and the 2-sample t-test was used to compare two groups (Treatment vs. Sham).

10.6.7.2.3 PIVOTAL – SUBSET ANALYSES

Four subset analyses were pre-specified in the investigational plan: seizure location (seizure onset zone), number of seizure foci, previous resection, and antiepileptic medication changes. The subset analyses were included to evaluate whether these variables could potentially affect the clinical outcome to treatment with the RNS™ System.

As pre-specified in the investigational plan, for each subset analysis, summary statistics including the mean and standard deviation of seizure frequencies are presented to describe differences between subsets for all study subjects combined and for the Treatment and Sham groups separately. The Fisher's exact test was used to assess qualitative differences in the responder rates in the Treatment group across subsets within a stratification; the possible impact of each of these factors on the clinical response was assessed quantitatively using GEE analyses with interaction terms.

Seizure Onset Zone

Subjects were stratified into two subsets, those with partial onset seizures of mesial temporal origin only versus partial onset seizures arising from any other region(s) of the cortex.

Number of Seizure Foci

Subjects were stratified into two subsets, those with unifocal epileptogenic onsets and those with bi-focal onsets.

Previous Resection

Subjects were stratified into two subsets, those with previous therapeutic surgery for epilepsy (including resection, subpial transection and/or corpus callosotomy) and those with no such surgery.

Antiepileptic Medication Changes / Benzodiazepine Use

The effect of the use of acute (rescue) benzodiazepines for seizure control was assessed by stratifying subjects into two subgroups, those who used acute benzodiazepines as rescue medication for seizures during the Pre-Implant Period and those who did not. Any use of rescue benzodiazepines during the Pre-Implant Period through implant was included.

The investigational plan also pre-specified subset analyses based on changes in antiepileptic medications. Summary statistics are presented for the subjects who had changes to their antiepileptic medication regimen during the Pre-Implant Period through the Blinded Evaluation Period. Note that any significant changes to the antiepileptic medication regimen (e.g., dose, discontinued antiepileptic medication, or new antiepileptic medication) that occurred anytime from the beginning of the Pre-Implant Period through the end of the Blinded Evaluation Period were considered protocol deviations. Therefore the subjects who had antiepileptic medication changes were excluded from analyses of the Per-Protocol Population. Protocol deviations are discussed in **Section 10.6.8.2** of this PMA application. Results of the analyses of the Per-Protocol Population are summarized in **Section 10.6.8.8.1.2.4** [see subsection titled ***Treatment Failures (Per-Protocol Population Analysis)***].

10.6.7.2.4 PIVOTAL – LONG-TERM (OPEN LABEL) EFFECTIVENESS ANALYSES AND STATISTICAL METHODS

The objective of the long-term effectiveness analyses is to demonstrate a persistent reduction in disabling seizures during the Open Label Evaluation Period through 104 weeks (2 years) post-implant, and to evaluate the change in seizure frequency in the Sham group once responsive stimulation is enabled in the Open Label Period. The following long-term (Open Label) analyses were pre-specified in the investigational plan.

The Open Label Evaluation Period of the trial begins at 5 months (20 weeks) post-implant and continues to 2 years post-implant. At the time of the data cutoff for this report (October 16, 2009), 56 subjects had completed the Open Label Evaluation Period. Therefore all analyses of the Open Label Evaluation Period are preliminary; a final analysis will be conducted following completion of the Pivotal study (subjects through 2 years post-implant).

10.6.7.2.4.1 Responder Rates (Open Label)

The objective is to present each subject's responder rate (seizure frequency data) for the Open Label Evaluation Period. The responder rate will be calculated for the Blinded Evaluation Period and every subsequent 3-month period for a total of 8 times during the study: weeks 8-20 post-implant

(Blinded Evaluation Period) and weeks 20-32, 32-44, 44-56, 56-68, 68-80, 80-92, and 92-104 post-implant (the first through seventh 3-month periods of the Open Label Evaluation Period, respectively).

Each subject's responder status (yes/no) was calculated eight times, including weeks 8-20 post-implant (Blinded Evaluation Period) and weeks 20-32, 32-44, 44-56, 56-68, 68-80, 80-92, and 92-104 post-implant (the first through seventh 84-day periods of the Open Label Evaluation Period, respectively).

Per the investigational plan, a GEE model was to be used investigate the change in responder status during the extended follow-up period. On the logistic scale, outcome (yes/no responder) was to be modeled as follows:

$$\text{Logit (probability of being a responder)} = \beta_0 + \beta_1 \text{Group} + \beta_2 \text{Time} + \beta_3 \text{Group} * \text{Time},$$

where Group is an indicator of treatment group membership, and Time identifies each of the 8 time points.

At the time of the data cutoff, there were not sufficient number of subjects to enable meaningful GEE analyses. Summary statistics of the responder rate by group (Treatment and Sham) for each 3-month period are provided for all available data. Additionally, the responder rate based on the most recent 3-month period for all subjects in the Open Label Evaluation Period (representing the last observation for each subject) is presented.

10.6.7.2.4.2 Daily Seizure Frequency (Open Label)

The objective is to present daily seizure frequency during the Open Label Period relative to the Pre-Implant Period experienced by each group (Treatment and Sham). Daily seizure frequency counts during each of the eight 3-month periods of the Open Label Evaluation Period (as described for the responder rate analysis in **Section 10.6.7.2.4.1**, above) will be compared to the Pre-Implant Period for the Treatment and Sham groups.

Per the investigational plan, the daily seizure frequency data during the two-year follow-up period were to be analyzed using a GEE model with an identity link with the same form of model as described above in **Section 10.6.7.2.4.1**. At the time of the data cutoff, there were not sufficient number of subjects to enable meaningful GEE analyses. Summary statistics (mean and standard deviation) for the seizure frequency and change in seizure frequency during each 3-month period are provided for all available data by group (Treatment and Sham).

10.6.7.2.4.3 Change in Seizure Frequency of the Sham Group (Open Label)

The objective is to examine the change in the average seizure frequency in the Sham group once responsive stimulation therapy is enabled in that group during the Open Label Period. Average seizure frequency in the Sham group during 3 months of the Open Label Evaluation Period (starting one month after stimulation is enabled) will be compared to the average (mean) seizure frequency for those same subjects during the 3-month Blinded Evaluation Period and also compared to the 3-month Pre-Implant Period.

An analysis of the change in seizure frequency during the Open Label Evaluation Period was conducted for those subjects who had been randomized to the Sham group during the Blinded Evaluation Period. After completion of the Blinded Evaluation Period, it was anticipated that these subjects would have therapy enabled and stimulation optimized over the next month. Therefore the subsequent 3 months (months 6 - 9 post-implant) were used in this analysis as pre-specified in the investigational plan.

Per the investigational plan, the difference in the average seizure frequency during these 3 months of the Open Label Evaluation Period from that in the Blinded Evaluation Period was calculated for each subject. The difference in overall averages between the two periods is the outcome of interest and was assessed for statistical significance using a paired one-sample t-test. Additionally, the average seizure frequency during the 3 months of the Open Label Evaluation Period was compared to the 3 month Pre-Implant Period. Statistical significance of the difference was assessed using the paired one-sample t-test.

10.6.7.2.4.4 Quality of Life (Open Label)

The objective is to evaluate quality of life before implant of the RNS™ System and at one year post-implant. Quality of life in individual subjects as measured with the Quality of Life in Epilepsy inventory (QOLIE-89) will be summarized to provide a descriptive analysis for each treatment group for the Baseline (administered at the time of enrollment), Blinded Evaluation, and Open Label Evaluation Periods. The objective is to evaluate quality of life before implant and at one year post-implant. For Spanish-speaking subjects, the validated Spanish version of the QOLIE-31-P was substituted for the QOLIE-89.

Descriptive statistics are provided for each group for the Baseline (administered at the time of enrollment), Blinded Evaluation, and Open Label Evaluation Periods. Average changes in the QOLIE overall score between Baseline and the later assessment periods were compared between the Treatment and Sham groups using the 2-sample t-test.

Additionally results for the QOLIE overall score and primary scale scores are presented for the Treatment and Sham groups combined, with comparisons to Baseline using the paired one-sample t-test.

10.6.7.2.5 PIVOTAL – ADDITIONAL ANALYSES

10.6.7.2.5.1 Additional Analyses (Pre-Specified)

Additional exploratory effectiveness analyses of the Blinded Evaluation Period as proposed in the investigational plan included incorporating quartiles as indicator variables in an additional GEE model and analyses of seizure subtypes.

Per the investigational plan, an exploratory analysis of baseline seizure frequency was conducted by including quartiles of baseline seizure frequency (e.g., 25%, 50%, and 75% based on the Pre-Implant Period seizure frequencies across subjects) as indicator variables in the primary GEE model. Given the sample size per quartile per treatment group was relatively small, exploratory analyses were also conducted using tertiles.

Summary statistics by seizure subtype are provided describing the mean seizure frequencies during the Pre-Implant and Blinded Evaluation Periods. The 2-sample t-test was performed to compare the Treatment and Sham groups. Summary statistics of the mean percent change by seizure subtype are also presented for the entire Blinded Evaluation Period and separately for each month of the Blinded Evaluation Period. Percent change by seizure subtype was calculated by for each subject based on the difference in the mean seizure frequency of that subtype during the specified month(s) of the Blinded Evaluation Period from the mean seizure frequency of that subtype during the Pre-Implant Period normalized (divided) by the mean seizure frequency of that subtype during the Pre-Implant Period. Only subjects who reported seizures of that subtype during the Pre-Implant Period are included in each seizure subtype mean percent change analysis.

Results for additional exploratory analyses as pre-specified are presented in Appendix 15.1.3 of the *Pivotal clinical study report* provided in **Appendix 10.14.3.2** of this PMA application.

10.6.7.2.5.2 Additional Analyses (Not Pre-Specified)

The percent change during each month of the Blinded Evaluation Period was calculated for each subject based on the difference in the mean seizure frequency during the specified month of the Blinded Evaluation Period from the mean seizure frequency during the Pre-Implant Period normalized (divided) by the mean seizure frequency during the Pre-Implant Period. The median of the mean percent change by month was presented separately for the Treatment and Sham groups.

Additional exploratory analyses that were not pre-specified included evaluating subgroups of patients for potential differences in the Treatment Effect during the Blinded Evaluation Period:

- Awareness of Side Effects: Subjects were stratified into two subsets based on blinding assessment; subjects who had reported “awareness of side effects” versus those who did not report an “awareness of side effects”.
- Time in Baseline to Meet Seizure Criteria: Subjects were stratified into two subsets based on the time from enrollment to meeting the seizure criteria to be eligible for implant; those who met seizure criteria to be eligible for implant (an average of 3 seizures per month for three consecutive months) within the first three months of enrollment versus those who did not.
- Implantation Effect: Subjects were stratified into two subsets by median split based on seizure frequency percent change during the first month post-implant (prior to enabling stimulation in either group).

Summary statistics were provided, and if applicable, sensitivity analyses of the primary effectiveness endpoint were performed excluding subgroups of patients.

Additionally, an exploratory analysis that was not pre-specified was performed to evaluate differences in seizure frequency percent change with respect to changes in antiepileptic medications during the Open Label Evaluation Period. Antiepileptic medication changes were allowed per protocol during the Open Label Evaluation Period. All antiepileptic medication changes were reviewed on a per-subject basis to determine whether a subject had no change in antiepileptic medications, increased antiepileptic medications, decreased antiepileptic medications, or a combination of both increased and decreased antiepileptic medications at the time of the data cutoff as compared to the start of the Pre-Implant Period. Subjects were categorized into one of four categories as follows:

- No change in antiepileptic medications: No changes in antiepileptic medications, daily dosage of all subject’s antiepileptic medications are within 25% of the dose at the start of the Pre-Implant Period.
- Increased antiepileptic medications: a new antiepileptic medication was added or there was a greater than 25% increase relative to the start of the Pre-Implant Period.
- Decreased antiepileptic medications: either an antiepileptic medication was stopped AED or there was a greater than 25% decrease relative to the start of the Pre-Implant Period.
- Combination: one or more antiepileptic medications were increased or added while one or more were decreased or discontinued.

For this analysis, each subject's seizure frequency percent change from the Pre-Implant Period was calculated based on their mean seizure frequency over the most recent 3 months in the Open Label Evaluation Period. Only subjects who have been in the Open Label Evaluation Period for at least 3 months are included in this analysis.

Results for additional exploratory analyses that were not pre-specified are summarized in **Section 10.6.8.8.4** of this PMA application.

10.6.7.2.6 *PIVOTAL – POOLABILITY ACROSS INVESTIGATIONAL SITES*

For the primary and secondary endpoints, baseline information for all subjects is provided for each participating institution and for all institutions combined. This information was used to assess whether or not the data could be pooled. The analysis investigating site differences includes combining small sites and including sites as indicator variables in the analysis. The analysis of variance (ANOVA) was the statistical assessment method. Results and discussion of poolability across investigational sites are presented in **Section 10.6.8.8.1.2.5** of this PMA application.

10.6.7.3 Pivotal – Safety Objectives, Assessments and Statistical Methods

The primary safety objective is to establish that the RNS™ System serious adverse event (SAE) rate during the surgical procedure and the following 28 days (4 weeks, Acute Period) is 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 (12 weeks, Short-Term Chronic Period) is no worse than the historical SAE rate for deep brain stimulation (DBS) for movement disorders.

Assessments of safety were made primarily through analyses of reported adverse events. Secondary safety assessments also included summary scores from standardized inventories of neuropsychological functioning (assessing a variety of domains including visual and verbal memory, cognitive flexibility, and others) and summary scores of validated surveys of affective status [Beck Depression Inventory (BDI-II), Profile of Mood States (POMS), Center for Epidemiological Studies Depression Scale (CES-D)].

Adverse event data are collected during the RNS™ System Pivotal Clinical Investigation on all enrolled subjects for the entire study in accordance with reporting requirements outlined in the investigational plan. At each study appointment (see **Table 10-20** above for required appointment schedule), investigators use case report forms (CRFs) to report any new adverse events experienced by the subject since the previous appointment, and to provide any updated information regarding previously-reported ongoing adverse events. The CRFs were designed to capture the date of onset, date reported, severity, relationship to the device, expectedness (if related to the device), event description, interventions applied, and resolution status (resolved, ongoing).

Adverse events are classified by the reporting investigator according to the definitions provided in the investigational plan and presented in **Table 10-21**. These definitions are used by the investigators when identifying an adverse event, assessing severity, and determining device relation. All determinations of severity, device relation, and resolution were made by the investigator and not by the sponsor.

Table 10-21: Pivotal Study – 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.

Table 10-21: Pivotal Study – Adverse Event Classification Definitions

Term	Definition
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 a NeuroPace investigational device.
Not Device-Related	The event is not related to a NeuroPace investigational device.
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.

These definitions are virtually identical to the definitions used in the Feasibility study (see **Section 10.5.8.6.2**, above); the same definitions were used across all three RNS™ System clinical investigations in epilepsy (Feasibility, Pivotal and LTT studies).

All serious adverse events and deaths (device-related and not device-related) were to be reported by the investigator to the sponsor and to the local IRB within the time periods described in the Pivotal study investigational plan. Investigators were also responsible for any other reporting obligations required by their IRB. The sponsor informed the Data Monitoring Committee (DMC) of all serious adverse events as described in **Section 10.6.10.3** of this PMA application and described in detail in Section 6.3.1 of the *Pivotal clinical study report* provided in **Appendix 10.14.3.2** of this PMA application.

In order to maintain the study blind, the Treatment and Assessment Protocol investigators independently reported adverse events throughout the study. It was anticipated that this would result in duplicate reporting of some adverse events. In order to ensure accurate summary and analysis of reported adverse

events, all reported adverse events were reviewed by NeuroPace to identify any such duplicates. The safety analyses were performed on the dataset containing all reported unique (i.e., non-duplicate) adverse events.

To facilitate analysis and reporting of adverse event data, the Medical Dictionary for Regulatory Activities (MedDRA®) terminology is applied by NeuroPace to categorize every reported adverse event. Methodology is consistent with the MedDRA® Term Selection: Points to Consider document. Events were grouped by System Organ Classification (SOC), High Level Group Term (HLGT), High Level Term (HLT), Preferred Term (PT), and Low Level Term (LLT) according to diagnosis and/or event description as provided by the investigator in the case report form for the specific event.

MedDRA code assignments were made without knowledge of subject randomization status. The Chief Medical Officer of NeuroPace reviews/verifies that the selected MedDRA coding accurately represents each of the reported unique adverse events.

This section describes the statistical methods used for the analysis of the safety data presented in this PMA application. Statistical methods include all pre-specified methods as presented in the investigational plan. There were no modifications to the pre-specified methods.

10.6.7.3.1 PIVOTAL – PRIMARY SAFETY ENDPOINT

As pre-specified in the investigational plan, the primary safety endpoint variable is the serious adverse event (SAE) rate in all implanted subjects calculated for the two timeframes. For the Acute Period [during the surgical procedure and the following 28 days (4 weeks)] the SAE rate is not expected to exceed 15%, which is comparable to the combined risks (SAE rate) associated with implantation of intracranial electrodes for localization procedures and epilepsy resective surgery. To demonstrate this, based on a sample size of 180 subjects, the upper limit of the one-sided 95% confidence interval for the RNS™ System SAE rate will not exceed 20%. And for the Short-Term Chronic Period [during the surgical procedure and the following 84 days (12 weeks)] the RNS™ System SAE rate is not expected to exceed 36%, which is historical SAE rate for deep brain stimulation (DBS) for movement disorders. To demonstrate this, based on a sample size of 180 subjects, the upper limit of the one-sided 95% confidence interval for the RNS™ System SAE rate will not exceed 42%.

10.6.7.3.1.1 Primary Safety Endpoint Hypotheses and Statistical Methods

The primary safety endpoint variable is the serious adverse event (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. The SAE rate includes all SAEs, whether reported by the investigator as device-related or not. Safety data as described in **Section 10.6.7.3** (above) were used in the primary safety analysis. Definitions are provided in **Table 10-21** (above).

Acute

For the surgical procedure and the following month (28 days), the RNS™ System SAE rate is not expected to exceed 15%, which is the combined SAE rate associated with implantation of intracranial electrodes for localization procedures and epilepsy resective surgery (Tanriverdi et al., 2009; Wong et al., 2009; Fountas and Smith, 2007; Hamer et al., 2002; Behrens et al., 1997). 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%. The null and alternative hypotheses are as follows:

H_0 : The expected (RNS™ System SAE rate) > 20%

H_1 : The expected (RNS™ System SAE rate) ≤ 20%

Short-Term Chronic

For the surgical procedure and the following three months (84 days), the RNS™ System SAE rate is not expected to exceed 36%, which is the DBS rate (Oh et al., 2002; Summary of Safety and Effectiveness, Activa Tremor Control System P960009; Beric et al., 2001; Behrens et al., 1997; Hariz, 2002; Joint et al., 2002; Koller et al., 2001). 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 null and alternative hypotheses are as follows:

H_0 : The expected (RNS™ System SAE rate) > 42%

H_1 : The expected (RNS™ System SAE rate) ≤ 42%

10.6.7.3.2 PIVOTAL – SECONDARY SAFETY ENDPOINT ANALYSES AND STATISTICAL METHODS

The objective of the secondary safety endpoints is to evaluate the occurrence of adverse events and to describe changes in affective status and neuropsychological functioning from the Baseline Period through the post-implant periods for both the Treatment and Sham-stimulation groups for each of the summary score outcomes and domains listed therein. Changes both within and across therapy allocation groups are described.

Data through completion of the Blinded Evaluation Period for all subjects and available data from the Open Label Evaluation Period are included in the secondary and long-term safety analyses.

10.6.7.3.2.1 Rate of Occurrence of Any Adverse Event (Secondary Endpoint)

The secondary safety analysis considers the rate of occurrence of any adverse event (AE) observed during each of the post-implant periods: The Post-Operative Stabilization Period, the Stimulation Optimization Period, the Blinded Evaluation Period and the Open Label Evaluation Period. For the secondary safety analysis, the objective is to separately present the rate through the end of the Blinded Evaluation Period for both study groups (Treatment and Sham) and to compare the rates.

All adverse events (AEs) are recorded on case report forms. The frequency and rate of occurrence of each type of AE are presented in Tabular form, on both a per-subject and a per-event basis, separately for Treatment and Sham-stimulation subjects. Fisher's exact test was used to statistically compare event rates between groups.

10.6.7.3.2.2 Change in Affective Status (Secondary Endpoint)

Affective status is measured by summary scores from the Beck Depression Inventory, the Profile of Moods State, and the CES-D surveys. For both Treatment and Sham-stimulation subject groups, descriptive statistics were calculated for each summary score. The expected result is that any change in affective status relative to the Baseline Period will not differ across the Treatment and Sham groups at the end of the Blinded Evaluation Period. Changes in results between the Baseline Period and the Blinded Evaluation Period were compared using the 2-sample t-test.

10.6.7.3.2.3 Change in Neuropsychological Functioning (Secondary Endpoint)

Neuropsychological functioning is assessed by testing with validated, standardized inventories at pre-implant (within 28 days of implant), 20 weeks, 56 weeks, and 104 weeks post-implantation. The testing assesses a variety of domains that include visual and verbal memory, verbal fluency and naming, cognitive flexibility, learning and concentration. The expected result is that any change in neuropsychological functioning of subjects will not differ across the Treatment and Sham groups at the end of the Blinded Evaluation Period.

Descriptive statistics were calculated for all 9 domains assessed during the Baseline Period and at 20 weeks post-implantation, and average results between treatment groups were compared using either a 2-sample t-test.

10.6.7.3.3 PIVOTAL – LONG-TERM (OPEN LABEL) SAFETY ANALYSES AND STATISTICAL METHODS

The objective of the long-term safety analyses is to describe the continued safety of the RNS™ System throughout subject participation up through 104 weeks (2 years) post-implant. Data through completion of the Blinded Evaluation Period for all subjects and available data from the Open Label Evaluation Period are included in the long-term safety analyses.

The Open Label Evaluation Period of the trial begins at 5 months (20 weeks) post-implant and continues to 2 years post-implant. At the time of the data cutoff for this report (October 16, 2009) 56 subjects had completed the Open Label Evaluation Period. Therefore all analyses of the Open Label Evaluation Period are preliminary; a final analysis will be conducted after the Pivotal study has been completed (subjects through 2 years post-implant).

Rate of occurrence of any adverse event, change in affective status, and change in neuropsychological functioning continue to be monitored through the end of the pivotal investigation (2 years post-implant) and were analyzed as described for the secondary safety endpoints in the previous section (**Section 10.6.7.3.2**). Deaths that occur during the study also continue to be monitored; each is reviewed by the SUDEP Committee. In addition, the SUDEP rate is estimated. Deaths reported during the 2-year Pivotal investigation are combined with those reported during the 2-year RNS™ System Feasibility Clinical Investigation and the 5-year RNS™ System Long-Term Treatment Clinical Investigation to ultimately collect approximately 1500 patient years of data about the rate of Sudden Unexplained Death in Epilepsy (SUDEP). A detailed summary of all deaths that occurred in the three RNS™ System clinical investigations in epilepsy combined, and an estimate of the rate of SUDEP, is provided in **Section 10.8.5** of this PMA application.

The following long-term analyses were specified for the Open Label Evaluation Period in the investigational plan:

10.6.7.3.3.1 Rate of Occurrence of Any Adverse Event (Open Label)

As described for the secondary safety analysis, this analysis will present the rate of occurrence of any adverse event (AE) observed during each of the post-implant periods: The Post-Operative Stabilization Period, the Stimulation Optimization Period, the Blinded Evaluation Period and the Open Label Evaluation Period. For the long-term analyses, the objective is

to separately present the rate during the Open Label Evaluation Period for both study groups (Treatment and Sham) and to compare the rates. (Note that both study groups receive responsive stimulation during the Open Label Evaluation Period.) The expected result is that there would be no differences in AE rates between the groups.

10.6.7.3.3.2 Change in Affective Status (Open Label)

Affective status is measured as described for the secondary safety analysis. Changes relative to Baseline Period described within and across study groups (Treatment and Sham) at each of the assessments conducted during the Open Label Evaluation Period (at 56, 80, and 104 weeks post-implant). The expected result is that any change in affective status relative to the Baseline Period will not differ across the Treatment and Sham groups during the Open Label Evaluation Period.

10.6.7.3.3.3 Change in Neuropsychological Functioning (Open Label)

Neuropsychological functioning is assessed as described for the secondary safety analysis. Changes relative to Baseline Period (the baseline evaluation took place after qualification for implant) are described within and across study groups (Treatment and Sham) at each of the assessments conducted during the Open Label Evaluation Period (at 56 and 104 weeks post-implant). The expected result is that there will be no difference in the change in neuropsychological functioning between the Treatment and Sham groups during the Open Label Evaluation Period.

10.6.7.3.3.4 SUDEP Rate Estimate (Open Label)

Deaths reported during the 2-year Pivotal investigation will be combined with those reported during the 2-year RNS™ System Feasibility Clinical Investigation and the 5-year RNS™ System Long-Term Treatment Clinical Investigation to ultimately collect approximately 1500 patient years of data about the rate of Sudden Unexplained Death in Epilepsy (SUDEP). The analysis of the combined current data is presented in **Section 10.8.5** of this PMA application. The outcome variable is death classified as possible, probable or definite SUDEP by the SUDEP Analysis Committee occurring in patients having a Neurostimulator programmed to provide stimulation at the time of the event.

Patients participating in the NeuroPace RNS™ System clinical investigations have medically refractory partial epilepsy and fall into the category of persons with the highest risk for SUDEP. The risk is comparable to the 9.3/1000 person-years rate in patients followed in an epilepsy surgery program (Dasheiff, 1991).

The SUDEP rate is calculated as the number of possible, probable or definite SUDEP events (as classified by the SUDEP Analysis Committee) in subjects whose Neurostimulators were programmed to provide stimulation divided by the total number of patient stimulation years, with 95% confidence interval calculated by applying the normal approximation to the logarithmic transformed rate and then back transforming the result (Miller, 1981; Esteve et al., 1994). Note, as pre-specified, all deaths reported during all RNS™ System clinical investigations (Pivotal, Feasibility, and Long-Term Treatment) are included in this calculation.

In addition, although not pre-specified, a rate for all possible, probable or definite SUDEP events in subjects implanted with the Neurostimulator and Leads (whether programmed to deliver responsive stimulation or not) divided by the total number of patient implant years was calculated with the 95% confidence interval calculated according to patient implant years of follow-up.

Upon completion of the Pivotal and Long-Term Treatment studies, a final estimation of the SUDEP rate will be calculated based on all data available from the RNS™ System clinical investigations.

10.6.7.4 Pivotal – Changes in Planned Analyses

Modifications to the primary effectiveness endpoint analysis methods were required to allow results to be appropriately interpreted and accurate conclusions to be drawn.

Results of the pre-specified and modified primary effectiveness endpoints are provided in **Section 10.6.8.8.1** of this PMA application. A detailed discussion of the model modifications and rationale are provided in Appendix 15.1.1 of the *Pivotal clinical study report*, and additional statistical considerations for the primary effectiveness endpoint analysis are provided in Appendix 15.1.2 of the *Pivotal clinical study report* provided in **Appendix 10.14.3.2** of this PMA application.

Results of secondary, subset, and long-term effectiveness analyses as pre-specified in the investigational plan are provided in **Sections 10.6.8.8.2, 10.6.8.8.3** and **10.6.8.8.5**, respectively. Additional analyses requested by the FDA (not pre-specified) are summarized in **Section 10.6.8.8.4** (Blinded Evaluation Period) and **Section 10.6.8.8.6** (long-term), and are provided in detail in Appendix 15.1.4 of the *Pivotal clinical study report*. Other pre-specified exploratory analyses are provided in Appendix 15.1.3 of the *Pivotal clinical study report* provided in **Appendix 10.14.3.2** of this PMA application. The results of effectiveness analyses that were pre-specified in the investigational plan are identified as such.

The results for the safety analyses as pre-specified in the investigational plan are presented in **Section 10.6.8.9** of this PMA application. There were no modifications to the pre-specified statistical analysis methods for safety.

An interim analysis after 90 subjects had completed the Blinded Evaluation Period was proposed in the initial submission of the Pivotal study investigational plan, but was removed in Amendment 5 (as described in **Appendix 10.14.3.1**). This analysis was intended to determine whether the primary effectiveness endpoint had been met early. However, it was always intended that the trial would complete enrollment (180 subjects completing the Blinded Evaluation Period) in order to gather safety data. The timing and rate of enrollment in the trial was such that an interim analysis would not be completed before the 180th subject was implanted. Therefore, the interim analysis did not offer a significant advantage over performing the effectiveness analysis on the complete data set. Given the favorable safety experience in the trial, the Data Monitoring Committee (DMC) did not feel that there was a reason to perform the interim analysis in order to assess risk versus benefit.

As a result of the timing of enrollment, NeuroPace and the DMC made the determination that the interim analysis provided no added benefit and would not affect the conduct of the trial. Therefore the investigational plan was amended to remove reference to the interim analysis.