RNS® System Clinical Summary

Information for Prescribers

This Manual is intended to be read in conjunction with the RNS® System manuals. Refer to the physician manual for device description, package contents, device specifications and instructions for use.

℞ Only

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Contents

Introduction

The clinical use of the NeuroPace® RNS® System for epilepsy is supported by the NeuroPace clinical studies presented in this clinical summary manual.

Contacting NeuroPace®

All questions or concerns regarding the NeuroPace® RNS® System should be forwarded to:

NeuroPace, Inc.
455 N. Bernardo Ave.
Mountain View, CA 94043

Customer Support: 866-726-3876 (Toll Free in the United States)

Website: www.NeuroPace.com

About this Manual

This manual is intended to provide information about the Clinical Studies conducted on the NeuroPace® RNS® System.

This Manual is intended to be read in conjunction with the RNS® System user manual. Please read the entire user manual for complete directions, warnings, and precautions as well as a description of the RNS® System and its components. The user manual is available online at www.NeuroPace.com. For a paper copy, contact NeuroPace.

NeuroPace® RNS® System

The NeuroPace® RNS® System includes a cranially implantable programmable RNS® Neurostimulator that senses and records brain electrical activity. The Neurostimulator detects previously identified electrical patterns in the brain and then delivers electrical stimulation to the brain to interrupt those patterns before the patient experiences clinical seizures. The implantable device consists of a responsive Neurostimulator and one or two Leads that connect to the Neurostimulator. The non-implantable RNS® System products include the RNS® Tablet, NeuroPace® Remote Monitor, PDMS (Patient Data Management System) and Wand. **The NeuroPace® RNS® System is not a seizure detection device.**

Note: For purposes of this document the NeuroPace® RNS® System will be referred to as the RNS® System. The term "programmer" as used in this manual is a generic term that refers to either the RNS® Tablet or the NeuroPace® Programmer (laptop computer).

Indications for Use

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

Contraindications

The RNS® System is contraindicated for:

- Patients at high risk for surgical complications such as active systemic infection, coagulation disorders (such as the use of anti-thrombotic therapies) or platelet count below 50,000.
- Patients who have medical devices implanted that deliver electrical energy to the brain.
- Patients who are unable, or do not have the necessary assistance, to properly operate the NeuroPace® Remote Monitor or magnet.

The following medical procedures are contraindicated for patients with an implanted RNS® System. Energy from these procedures can be sent through the implanted brain stimulation system and cause permanent brain damage which may cause severe injury, coma, or death. Brain damage can occur from any of the listed procedures even if the RNS® Neurostimulator is turned off or if the leads are not connected to the neurostimulator, and can occur even if the neurostimulator has been removed and any leads (or any part of a lead) or the cranial prosthesis remain.

- Diathermy procedures are contraindicated in patients implanted with an RNS® Neurostimulator and associated leads. (Diathermy is any treatment that uses high-frequency electromagnetic radiation, electric currents, or ultrasonic waves to produce heat in body tissues.) Patients absolutely CANNOT be treated with any type of shortwave, microwave, or therapeutic ultrasound diathermy device whether or not it is used to produce heat. These treatments should not be applied anywhere on the body.
- Electroconvulsive Therapy (ECT) is contraindicated for patients with an implanted RNS® System.
- Transcranial Magnetic Stimulation (TMS) is contraindicated for patients with an implanted RNS® System.

Warnings and Cautions

WARNINGS

Clinical Use

WARNING: Physician and Center Access to the RNS® System

The RNS® System should only be implanted by neurosurgeons with adequate experience in the implantation of subdural and stereotactic implantation of intraparenchymal electrodes and in the surgical treatment of intractable epilepsy. The RNS® System should only be used by neurologists or neurosurgeons with adequate experience in the management of intractable epilepsy and in the localization of epileptic foci, including the use of scalp and intracranial electrodes.

Neurologists and neurosurgeons using the RNS® System must have completed the NeuroPace® RNS® System training program. To qualify to manage patients with the RNS® System, physicians must demonstrate specific expertise related to epilepsy, video-EEG monitoring, interpretation of electrocorticograms (ECoGs), the pharmacology of antiepileptic medications and selection of patients for epilepsy surgery. Implantation of the RNS® System should be performed only by qualified neurosurgeons at centers capable of providing comprehensive epilepsy care, i.e. “Comprehensive Epilepsy Centers”. These centers should have the expertise to provide diagnostic services that include video-EEG monitoring with scalp and intracranial electrodes and neuroimaging, and are experts in the treatment of epilepsy with antiepileptic medications, epilepsy surgery, and devices.

WARNING: Management of patients with the RNS® System by physicians at centers that do not provide the services provided at comprehensive epilepsy centers

In some instances, post-implant programming may be conducted by neurologists meeting the experience and certification requirements for neurologists at Comprehensive Epilepsy Centers, but who are not practicing in such centers. This situation might occur if the patient is not able to travel to a Comprehensive Epilepsy Center for regular follow-up (e.g. because of distance from the Center or limited access to transportation). These neurologists will be qualified by NeuroPace to provide post-implant programming. After NeuroPace® RNS® System training is complete, the qualified programming neurologist may receive external NeuroPace products (programmer, remote monitor).

Surgical

WARNING: Compatibility with Similar Implantable Products

The RNS® Neurostimulator, NeuroPace® Cortical Strip Lead, and NeuroPace® Depth Lead are not compatible with non-NeuroPace leads and/or pulse generators. Incompatible configurations may cause damage to the products and may result in unsafe current densities delivered to the patient.

WARNING: Cortical strip lead explantation

Explanting a chronically implanted cortical strip lead may cause tissue damage.

WARNING: Infection

Infection, including bacterial meningitis, may occur as a result of the RNS® System implant procedures and/or the RNS® System materials. Standard surgical infection prevention measures (antibiotics etc.) should be taken both pre- and post-implantation.

WARNING: Intracranial Hemorrhage

Intracranial hemorrhage may occur when implanting the RNS® System. Placing the leads, ferrule, and/or neurostimulator in an area where excess pressure may occur to the underlying blood vessels may cause intracranial hemorrhage. Patients with underlying risk factors for intracranial hemorrhage, such as patients with previous head trauma, anticoagulant use, or who experience head injury with seizures should be taken into specific consideration.

WARNING: Surgical Procedure Side Effects

Surgical procedure risks may include, but are not limited to, temporary pain at the implant site, CSF leakage and although rare, epidural hemorrhage, seroma, subdural or epidural hematoma, and paralysis.

RNS® System and Therapy

WARNING: Adverse Tissue Reaction

Allergic reaction to the implanted RNS® System materials and/or leads is possible.

WARNING: Chronic Tissue Stimulation

The effects of long-term brain stimulation are not completely known and may present some risks to the patient.

WARNING: Skin Erosion

Skin erosion may occur on and/or around the neurostimulator and/or lead implant site, particularly in the case of protrusion of the implanted RNS® System products above the surface of the skull.

WARNING: Lead Migration

The implanted lead(s) may migrate from their desired implant location. Lead migration can result in changes in detections and stimulation effectiveness, and may require additional surgical procedures to modify the lead location.

WARNING: Pregnant Women

The safety and effectiveness of the RNS® System has not been studied in pregnant women.

WARNING: RNS® System Failure

As with any electronic device, the RNS® System may malfunction (not work). Potential causes include battery malfunction, electrical short, open circuit, lead fracture, lead insulation failure, or damage as a result of head trauma. These malfunctions are unpredictable, and may result in too little stimulation or no stimulation. A lead failure may result in the lead needing to be removed or repositioned, which would require surgery. A malfunctioning neurostimulator may need to be replaced, which would require surgery. Although the neurostimulator is designed to turn off if overstimulation or excess current occurs, there is a possibility that product failure could result in brain tissue damage.

WARNING: Patient Data Collection

The patient must be willing to collect data daily from their neurostimulator and send the data to the PDMS database at least once a week.

WARNING: Case Damage

If the neurostimulator case is ruptured or pierced due to outside forces, severe brain tissue damage could result from exposure to the battery chemicals.

WARNING: ElectroMagnetic Interference (EMI)

Electromagnetic interference is a field of energy generated by equipment found in the home, work, medical, or public environments that is strong enough to interfere with neurostimulator function. Sources of strong electromagnetic interference can result in the following effects:

- Serious patient injury or death - It is possible for the interference sources to couple enough energy into a neurostimulator system to damage brain tissue.
- System damage - resulting in a loss or change in symptom control and requiring reoperation.
- Operational changes to the neurostimulator - causing stimulation to turn on or off, or resetting or reprogramming the neurostimulator resulting in a return of symptoms.
- Unexpected changes in stimulation - causing a momentary increase in stimulation which may be felt by the patient.

Patients should exercise caution to avoid devices which generate a strong electric or magnetic field. Refer to the Electromagnetic Emissions and Immunity section in the Physician Manual for more information.

WARNING: Radio Frequency Identification (RFID) Interference

Sources of RFID can result in signals that appear as ECoG activity to the neurostimulator. Signals that appear as ECoG activity could also result in delivering the programmed stimulation to the patient (per the device detection programming). The physician should be aware of possible sensing artifacts when assessing ECoG recordings. Potential sources of RFID may occur in a health care environment, retail stores, public libraries, airports and business environments.

Refer to the Electromagnetic Emissions and Immunity section in the Physician Manual for more information.

WARNING: Security and Electronic Tracking Systems

Security screening devices (such as theft detectors, security tag deactivators, and airport security screening devices) can result in signals that appear as ECoG activity to the neurostimulator. Signals that appear as ECoG activity could also result in delivering the programmed stimulation to the patient (per the device detection programming). Such devices may be found at retail stores, public libraries and airports. The physician should be aware of possible sensing artifacts when assessing the ECoG recordings. Patients should be instructed to walk through the center of such security screening units without stopping, when possible, and exit the area of the screening device as soon as possible.

Refer to the Electromagnetic Emissions and Immunity section in the Physician Manual for more information.

WARNING: Interaction with Implanted Cardiac Devices

Possible effects of implanted device interaction with an implanted cardiac device (such as a pacemaker or defibrillator) include the following:

- Defibrillation therapy from an implanted defibrillator may damage the neurostimulator.
- The electrical pulses from the neurostimulation system may interact with the sensing operation from a cardiac device and could result in an inappropriate response of the cardiac device and vice versa.

Programmer

WARNING: Potential Shock

Submerging any part of the programmer, or operating the programmer in or near a wet environment, may result in an electrical shock.

The programmer must be disconnected from the electrical outlet prior to cleaning to avoid the potential of electrical shock.

Electrical shock may occur if the programmer AC adapter and power cord are not properly connected to a grounded power source.

Medical Environment

WARNING: MRI Safety Information

RNS® Neurostimulator model RNS-320: An MRI scan may be safely performed on patients with the RNS® System (with RNS Neurostimulator model RNS-320) only under the specific conditions of safe use detailed in the MRI Guidelines for the RNS® System. Scanning under different conditions may result in device damage or malfunction and serious patient risks including permanent brain damage which may cause severe injury, coma, or death. All NeuroPace® manuals are available at www.NeuroPace.com or by contacting NeuroPace, Inc.

RNS® Neurostimulator model RNS-300M of the RNS® System is MR Unsafe. Having an MRI scan with a model RNS-300M neurostimulator implanted may result in serious injury or possible death.

RNS® System External Components: All external components and accessories such as the Magnet, RNS® Tablet, NeuroPace® Programmer, NeuroPace® Remote Monitor, and Wand are MR Unsafe and can pose a projectile hazard in the MR environment, and therefore, must be kept out of the MRI scanner room.

WARNING: Lithotripsy

The effects of extracorporeal shock wave lithotripsy on the RNS® System have not been studied. Exposure to high-output ultrasonic frequencies may damage the RNS® System. This could result in loss of therapy, and additional surgery to remove or replace components of the RNS® System. Prior to any administration of lithotripsy, the administering physician should consult with the physician prescribing the RNS® System.

WARNING: Radiation

The effects of high radiation sources (such as cobalt 60 or gamma radiation used in cancer therapy) on the RNS® System have not been studied. Exposure to high levels of radiation may damage the RNS® System. This could result in loss of therapy, and additional surgery to remove or replace components of the RNS® System. Prior to any course of radiation therapy, the radiation oncologist should consult with the physician prescribing the RNS® System.

WARNING: Electrolysis

The effects of electrolysis on the RNS® System have not been studied. Electrolysis on the head or neck should be avoided.

WARNING: Computerized Tomography (CT) Scans

For CT procedures on a patient with an implanted RNS® Neurostimulator, the operator should:

- Ask the patient to have the neurostimulator temporarily shut off with a programmer while the scan is performed, if possible.
- Minimize x-ray exposure to the implanted electronic medical device by:
  - Using the lowest possible x-ray tube current consistent with obtaining the required image quality.
  - Making sure that the x-ray beam does not dwell over the device for more than a few seconds.

Important:

For CT procedures that require scanning over the medical device continuously for more than a few seconds, as with CT perfusion or interventional exams, attending staff should be ready to take emergency measures to treat adverse reactions if they occur.

After CT scanning, the operator should:

- Ask the patient to have the neurostimulator turned back on with a programmer if it had been turned off prior to scanning.
- Advise the patient to contact their healthcare provider as soon as possible if they have questions or suspect their device is not functioning properly after any medical procedure.

CAUTIONS

Surgical

Caution: Connector Plug

A vacant port in the connector cover must be filled with a connector plug (provided in the connector cover kit). There is an increased risk of neurostimulator failure if a connector cover port is vacant.

Caution: Epidural Lead Placement

Leads placed epidurally may cause pain during electrical stimulation.

Caution: Lead Damage

Bending, kinking, and stretching of the lead may cause lead damage. Handle the lead with care.

Caution: Sub-Galeal Lead Placement

Wrapping the lead(s) on/around the neurostimulator, or placing excess lead near the neurostimulator, may result in lead damage during subsequent surgical procedures.

Caution: Suture Sleeves

Suture sleeves are provided for use if sutures are used to stabilize the lead. Suturing directly on the lead may cause lead body damage and malfunction.

RNS® System and Therapy

Caution: Afterdischarge Activity

If evidence of afterdischarge activity resulting from stimulation is seen either on stored ECoGs or during test stimulation delivery, stimulation parameters should be adjusted to prevent such occurrence.

Caution: Battery Depletion

For continued operation, the neurostimulator needs to be surgically replaced when the battery is depleted.

Caution: Neurostimulator Longevity

High and frequent levels of stimulation reduce neurostimulator battery longevity.

Caution: Draining the Neurostimulator Battery

Testing the wand placement over the RNS® Neurostimulator for more than 10 minutes per day may drain the neurostimulator battery prematurely.

Caution: Frequency of Remote Monitoring

The patient should interrogate the RNS® Neurostimulator with the remote monitor and wand daily and synchronize the remote monitor with the PDMS at least once a week.

Caution: Explantation and EMI Considerations

If any system components (neurostimulator, leads, lead fragments, or cranial prosthesis) remain implanted in the patient after a partial system explant, the patient is still susceptible to possible adverse effects from strong sources of EMI. It is possible for the interference sources to couple enough energy into a neurostimulator system to damage brain tissue, resulting in serious patient injury or death. Patients who have system components implanted should exercise caution in avoidance of devices which generate a strong electric or magnetic field.

Refer to the Electromagnetic Emissions and Immunity section in the Physician Manual for more information.

Caution: Lead replacement and abandoned leads

The long-term safety associated with leads left in place without use, replacement of leads, and lead removal is unknown.

Programmer

Caution: Programmer Failure

As with any electronic device, the programmer may be damaged or malfunction if the programmer AC adapter and power cord are not properly connected to a grounded power source.

Caution: Telemetry Artifact

Telemetry may produce an electrographic artifact. If responsive therapy is enabled with a sensitive detection set, detection of the electrographic artifact may occur, resulting in therapy delivery. The physician should be aware of possible sensing artifacts when assessing the ECoG recordings.

Medical Environment

Caution: Medical procedures

Patients should always inform any healthcare personnel that they have an implanted RNS® System (and show their medical implant identification card) before any procedure is performed.

Advise the patient to contact their healthcare provider as soon as possible if they have questions or suspect their device is not functioning properly after any medical procedure.

Caution: Electrosurgery

The use of electrosurgery can affect the operation of neurostimulators. The RNS® System has been designed to prevent or minimize the effects of electrosurgery, however the energy levels used in electrosurgery can temporarily interfere with or cause permanent damage to device operation.

Electrosurgery applied near the RNS® Neurostimulator may cause it to temporarily stop sensing, delivering therapy, or may reset the neurostimulator. Under these conditions the neurostimulator may require interrogation and possible reprogramming.

Electrosurgery applied directly to the neurostimulator or leads may couple enough energy into a neurostimulator system to damage brain tissue.

If electrosurgery is necessary, the following recommendations may be effective in minimizing potential complications.

Before the procedure:

- If possible, temporarily disable stimulation using a programmer.

During the procedure:

- Use of bipolar electrosurgery is recommended and should be considered, whenever possible.
- Keep the electrosurgery tip more than 2 cm (approximately one inch) from the implanted device.
- The selected output power of the electrosurgery unit should be as low as possible for the relevant application and not used for greater than 10 seconds in any one burst.

After the procedure:

- If stimulation was temporarily disabled before the procedure, re-enable stimulation with the programmer and synchronize the programmer with the PDMS.
- Advise the patient to contact their healthcare provider as soon as possible if they have questions or suspect their device is not functioning properly after any medical procedure.

Caution: Dental Therapy and Procedures

Dental therapy and procedures that do not involve any of the procedures in the *Contraindications* on page 2 or *Warnings* on page 3 and following should be performed with caution. The dentist or dental technician should be informed that the patient is implanted with the RNS® System.

The following medical procedures may be performed without affecting the RNS® System:

- Diagnostic x-rays
- Diagnostic ultrasound

Advise the patient to contact their healthcare provider as soon as possible if they have questions or suspect their device is not functioning properly after any medical procedure.

Caution: Other Active Implanted Medical Devices

RNS® System interactions with other active implantable medical devices (such as pacemakers, defibrillators, implanted spinal cord and peripheral nerve stimulators, cochlear implants, and vagus nerve stimulators) are not known. Exercise caution when other implanted devices are operating concurrently with the RNS® System. Possible effects include sensing problems and inappropriate device responses.

Caution: Incompatibility of Programmer with Other Medical Devices

The effects of using the programmer to interrogate other electronic, programmable devices such as pacemakers, defibrillators, cochlear implants, and other neurostimulators or CPAP machines are unknown. It could result in reprogramming of the other device and therefore, the physicians familiar with each device should check the programmed parameters of each device before the patient is discharged and after each programming session of either device.

Caution: Electronic Interference

Communications between the programmer and the implanted neurostimulator may be interrupted by emissions from nearby electronic devices. Examples of sources of EMI are lithotripsy, computer monitors, cellular telephones, motorized wheel chairs, x-ray equipment, and other monitoring equipment. Interruption of telemetry can result in incomplete communication. If EMI disrupts programming, move the programmer away from the likely source of EMI. Refer to the Troubleshooting section of the Physician Manual for more information.

Caution: Placement of the Programmer Power Cord

Make sure nothing rests on the programmer power cord and that the cord is not located where it can be tripped over or stepped on.

Caution: Heating

The programmer's AC adapter may become hot during normal operation. Use care when handling during or immediately after operation.

Home or Occupational

Caution: Keep magnets at least 4 inches away from the implanted RNS® Neurostimulator

Magnets that are contained in such products as stereo speakers, AM/FM radios, power tools, cellular, cordless and conventional phones, as well as magnets used therapeutically or worn on the body, should be kept at least 4 inches away from the neurostimulator. The neurostimulator may not deliver stimulation while these magnets are closer than 4 inches. Most headsets and earphones available in stores do not interfere with the RNS® System, but not all have been tested.

Caution: Magnet

Use care when handling the magnet as it may break if dropped and the broken pieces may have sharp edges.

Caution: Scuba Diving or Hyperbaric Chambers

Patients should not dive below 10 meters (33 feet) of water or enter hyperbaric chambers above 2.0 atmospheres absolute (ATA). Such pressures could damage the RNS® System.

Caution: Population for which safety and efficacy have not been established

The safety and effectiveness of the RNS® System has not been established for:

- People with generalized epilepsy
- People with a seizure focus that cannot be adequately localized
- Pregnant women
- Nursing mothers
- People under the age of 18
- People with simple partial sensory seizures only
- People with less than three seizures a month on average
- People who have more than two epileptic foci
- People who have not failed two antiepileptic drugs

Caution: Safety and Effectiveness Beyond 24 Months

The safety and effectiveness of the RNS® System beyond 24 months is unknown.

Glossary

Adverse Event

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. All adverse events are classified as serious or non-serious, and device-related or not device-related.

AED

Antiepileptic Drug (or antiseizure medication)

Baseline Period

The period of the Pivotal study beginning with enrollment and ending on the day of implant.

Battery

The battery is the power source for the RNS® Neurostimulator.

Blinded Evaluation Period

The Blinded Evaluation Period was the 3-month period beginning 8 weeks post- implant and ending at 20 weeks post-implant. During this period, subjects in the Treatment group received responsive stimulation while subjects in the Sham group did not. Subjects and the Assessment Protocol investigators were blinded to the therapy allocation assignment during the Stimulation Optimization and Blinded Evaluation Periods, and remained so until the end of the clinical investigation. The primary and secondary effectiveness analyses, as well as secondary safety analyses, used data collected within this period.

Burr Hole

Hole made in the skull used for the insertion and securing of implanted cortical and/or depth leads.

Complex partial seizure

A clinically evident seizure that arises in a focus or region of the brain. The seizure, by definition, is associated with loss of awareness but does not include generalized tonic, clonic, myoclonic or tonic-clonic movements. The patient may display 'automatic' behaviors (automatisms) such as lip smacking, chewing, vocalization, picking or aimless wandering. The patient will not recall events occurring during the seizure.

Cortical Strip Lead

The NeuroPace® Cortical Strip Lead lies on the surface of the brain (cortex) and can detect the electrical activity of the brain and deliver stimulation.

DBS

Deep Brain Stimulation

Depth Lead

The NeuroPace® Depth Lead is implanted into the brain and can detect the electrical activity of the brain and deliver stimulation.

Device-related adverse event

An adverse event definitively or potentially related to a NeuroPace investigational device.

Diathermy

Diathermy is a treatment that uses high-frequency electromagnetic radiation, electric currents, or ultrasonic waves to produce heat in body tissues.

Disabling seizures

Motor simple partial seizures or complex partial seizures with or without secondarily generalized seizures. (Also referred to within this report as “total disabling seizures.”)

DTS

Due to seizure

ECoG

Electrocorticogram. Electrical activity derived directly from the cerebral cortex. Also used to describe the neurostimulator or programmer stored record of this activity (e.g. “ECoG record”).

EEG

Electroencephalogram

EMC

Electromagnetic compatibility

EMI

Electromagnetic interference

Epilepsy

Epilepsy is a common neurological disorder that produces seizures.

Eval

Evaluation

Feasibility study

RNS® System Feasibility Clinical Investigation in epilepsy

GEE

Generalized Estimating Equations

Intent-to-Treat

Primary and secondary analyses presented in this report were performed on an intent-to-treat basis. The intent-to-treat population for the safety analyses included all subjects who were implanted with the RNS® Neurostimulator and Leads, and the intent-to-treat population for effectiveness analyses included all subjects who were randomized in the Pivotal study.

LTT Study

RNS® System Long-term Treatment Clinical Investigation in epilepsy

MedDRA

Medical Dictionary for Regulatory Activities (MedDRA®)

MRI

Magnetic Resonance Imaging

Neurostimulator

The RNS® Neurostimulator is an implantable, battery powered, microprocessor controlled device that can amplify and analyze the patient's electrocorticographic activity, detect activity from intracranial electrodes and deliver a short train of current pulses to the brain to attempt to interrupt the detected activity.

Non-serious adverse event

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

Open

Open Label Evaluation Period (Pivotal study)

Open Label Evaluation Period

The Open Label Evaluation Period began following completion of the Blinded Evaluation Period at the Week 20 post-implant visit and continued until the subject completed the clinical investigation (Week 104 post-implant). During this period, all subjects received responsive stimulation, independent of their therapy allocation during the Stimulation Optimization and Blinded Evaluation Periods.

Patient Data Management System (PDMS)

The NeuroPace® Patient Data Management System is a secure database that provides a means for a clinician to review information that has been transmitted by the programmer and the remote monitor.

Pivotal study

RNS® System Pivotal Clinical Investigation in epilepsy

Post-Op

Post-Operative Stabilization Period (Pivotal study)

Post-Operative Stabilization Period

The period of the Pivotal study that began immediately following implantation of all implantable components of the RNS® System and the first 28 days following the implant procedure.

Pre-Implant Period

Three months (12 weeks) of the Baseline Period during which subjects met key inclusion criteria for RNS® System implant. The Pre-Implant Period was used for effectiveness and secondary safety endpoints.

Programmer

The programmer provides the clinician with a user interface to select and download operating parameters to the neurostimulator for detection and responsive stimulation settings, to view live ECoG signals, to test the RNS® System integrity, and to upload data and diagnostic information from the neurostimulator for viewing.

Programming

Using the programmer to program settings into the neurostimulator.

PSF study

Prospective Seizure Frequency Clinical Investigation

PT

MedDRA Preferred Term

P-Value

Probability of obtaining a test statistic at least as extreme as the one that was observed, assuming null hypothesis is true.

QOLIE

Quality Of Life in Epilepsy inventory

Remote Monitor

The NeuroPace® Remote Monitor is a home-use monitoring device used to collect data from the RNS® Neurostimulator and to upload these data using telephone lines to the Internet by way of a secure connection to the PDMS. The uploaded data are accessible for review by physicians by way of a secure connection to the PDMS. This offers a convenient option for remotely monitoring the RNS® Neurostimulator between patient visits to the clinic.

Responsive Stimulation

Electrical stimulation output to cortical tissue by the RNS® Neurostimulator in response to a detection.

SAE

Serious Adverse Event

SD

Standard Deviation

Secondarily generalized seizures

Partial seizures that evolve into generalized seizures most often with tonic-clonic convulsions.

Seizure

Seizures are a disturbance in the normal electrical activity of the brain resulting in abnormal behavioral activity.

Seizure focus

See seizure onset zone.

Seizure onset zone

The area of the brain (cerebral cortex) that contains the abnormal, epileptogenic tissue that causes seizures. (Also referred to as seizure focus.)

Serious adverse event

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.

Sham group

Refers to the group of subjects that were randomized to receive sham-stimulation (i.e. responsive stimulation disabled) during the Blinded Evaluation Period (Months 3 – 5 post-implant). (Also referred to as “Therapy OFF” and “Sham-stimulation”.)

Simple partial motor seizure

A seizure beginning in a focal or regional area of the brain that causes transient neurological motor symptoms. By definition, the patient retains full awareness during this type of seizure.

Simple partial sensory seizure

A seizure beginning in a focal or regional area of the brain that causes transient neurological sensory symptoms. By definition, the patient retains full awareness during this type of seizure.

Status epilepticus

Continuous seizure lasting longer than 30 minutes or a cluster of seizures longer than 30 minutes during which the subject does not regain baseline awareness.

Stim Opt

Stimulation Optimization Period (Pivotal study)

Stimulation Optimization Period

The second month after implant in the Pivotal study. Randomization occurred at the beginning of the Stimulation Optimization Period. During this period, subjects randomized to the Treatment group received responsive stimulation and stimulation parameters were adjusted weekly as needed; subjects randomized to the Sham group did not receive responsive stimulation, but were also seen weekly for mock stimulation programming to maintain the treatment blind.

SUDEP

Sudden Unexplained Death in Epilepsy

Tonic-clonic seizures

Seizures that involve bilateral involuntary movements of the arms and legs that begin with stiffening (extension, tonic) and are followed by a series of bending movements (flexion, clonic). Consciousness is lost during generalized tonic-clonic seizures although some patients with frontal lobe onset tonic-clonic seizures will retain awareness.

Treatment group

Refers to the group of subjects that were randomized to receive responsive stimulation during the Blinded Evaluation Period (Months 3 – 5 post-implant). Stimulation was enabled during the Stimulation Optimization Period (second month post-implant) and continued throughout the subject's participation in the study. (Also referred to as “Therapy ON”.)

Unanticipated adverse event

A device-related adverse event not noted in the Investigation Plan as potentially caused or contributed to by the investigational device.

VNS

Vagus Nerve Stimulator

Summary of Clinical Studies

Epilepsy is a common neurological disorder that affects as many as 1 in 100 people. Epilepsy is characterized by recurrent clinical seizures, which result from disturbances in the normal electrical activity of the brain. Partial onset seizures, the most common type of seizures in adults, are the kinds of seizures that start in one part of the brain. Even though these seizures start in one part of the brain, the seizures may spread to involve most of the brain. Symptoms of a seizure may include altered awareness, extreme confusion, odd feelings, déjà vu, staring into space, altered vision, speech difficulties, sudden shaking, passing out, and/or convulsions.

The NeuroPace® RNS® System is designed to monitor brain electrical activity and to deliver stimulation to the seizure focus (the part of the brain where the seizures start) when abnormal electrical activity (as defined by the physician) occurs.

NeuroPace has conducted the following studies to support the use of the RNS® System for the treatment of partial onset seizures that are refractory to antiepileptic medications:

RNS® System Feasibility Clinical Investigation (completed) see *Feasibility Study* on page 17

This multi-center prospective clinical study conducted in the United States was designed to demonstrate adequate safety and evidence of effectiveness for the RNS® System to support the commencement of the Pivotal Clinical Investigation. The baseline (pre-implant) data for the Feasibility study was provided by the nonsignificant risk Prospective Seizure Frequency (PSF) study. For ease of understanding, the combined data are simply presented as Feasibility study data throughout this document.

The safety results of the Feasibility study are presented within the combined safety analysis, see *Safety Results* on page 35 The effectiveness data in this primarily open label study were used only in the analyses to provide evidence of sufficient effectiveness to support commencement of the Pivotal study and to assess the integrity of the Blind.

RNS® System Pivotal Clinical Investigation (completed) see *Pivotal Study* on page 18

This multi-center prospective randomized, double-blinded, sham-stimulation controlled clinical study conducted in the United States was designed 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 effectiveness results are presented in *Effectiveness Results* on page 27. The safety results of the study are presented within the combined safety analysis, see *Safety Results* on page 35.

RNS® System Long-term Treatment Clinical Investigation (LTT) (ongoing) see *Long-term Treatment Study* on page 19

This multi-center prospective open label clinical study conducted in the United States was designed to assess the ongoing safety and to evaluate the long-term effectiveness of the RNS® System. Subjects having completed the Feasibility or Pivotal Clinical Investigation were potential candidates for the LTT study.

The safety data collected during this ongoing study are presented within the combined safety analysis, see *Safety Results* on page 35. The effectiveness endpoint analyses for this ongoing study have not been completed.

Study Designs and Methods

Study Designs and Timelines

Feasibility Study

The Feasibility study was a multi-center clinical investigation of individuals with medically intractable epilepsy. Sixty-five subjects were implanted with the RNS® Neurostimulator and leads in the Feasibility study.

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

The first four subjects implanted with the RNS® Neurostimulator and leads at a clinical site participated in an open label protocol (all subjects received responsive stimulation), and subsequent subjects at that site participated in a randomized, double-blind, concurrent sham stimulation control protocol in which the Treatment group received stimulation and Sham group did not. Forty-two (42) subjects were in the open label protocol and 23 were in the blinded protocol. Following completion of the 16 week Evaluation Period, subjects transitioned to an Open Label Period, and all subjects were able to receive responsive stimulation. Subjects continued in the Open label Period through the end of study participation, which was 2 years post-implantation (*Figure 1* on page 18). The Feasibility Study was designed to evaluate preliminary safety and effectiveness. The results were used to inform the design of the Pivotal Study and to assess the integrity of the blind.

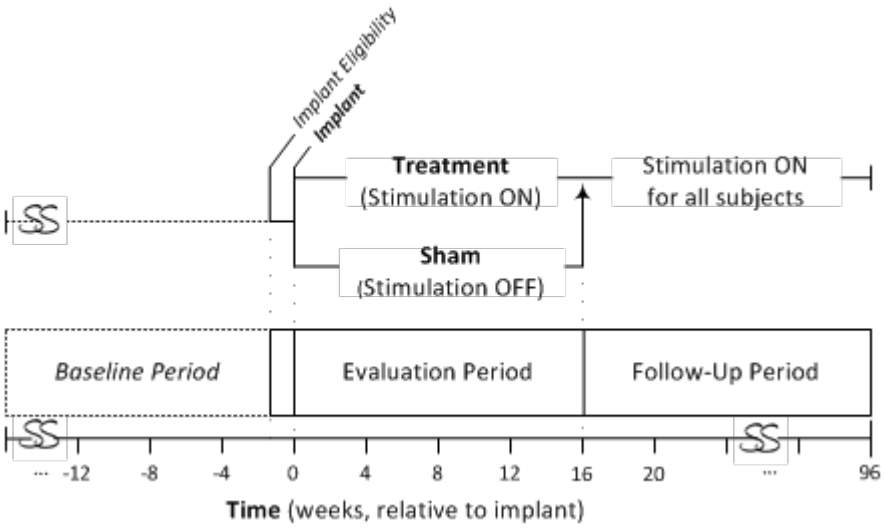

Figure 1: RNS® System Feasibility Clinical Investigation – Trial Flow and Periods

Pivotal Study

The RNS® System Pivotal Clinical Investigation was a randomized, double-blinded, multi-center, sham-controlled clinical investigation. In total, 191 subjects were implanted with the RNS® Neurostimulator and leads in the Pivotal study.

Eligible subjects were 18-70 years of age with medically intractable partial onset seizures and an average of three or more disabling seizures per month over the three most recent months, with no month with less than two seizures. Subjects were required to be on a stable antiepileptic medication regimen and must have previously undergone diagnostic testing that localized seizures to no more than one or two epileptogenic region(s). Subjects with psychogenic or non-epileptic seizures, status epilepticus, active psychosis, severe depression, or suicidal ideation within the preceding year were excluded.

The investigation had five periods: the Baseline Period, Post-Operative Stabilization Period, Stimulation Optimization Period, Blinded Evaluation Period, and Open Label Period.

To qualify for implantation with the RNS® Neurostimulator and Leads, the subjects were required to remain on a stable AED regimen while having an average of three or more disabling seizures (motor partial seizures, complex partial seizures and/ or secondarily generalized seizures) per month over three consecutive months during the Baseline Period, with no month with less than two seizures.

Subjects were implanted with the RNS® Neurostimulator and leads within 28 days following the date of qualification for implantation of the RNS® Neurostimulator and leads. Subjects were randomized 1:1 at the end of the Post-Operative Stabilization Period (4 weeks post-implant). Subjects randomized to the Treatment group received responsive stimulation during the Stimulation Optimization and Blinded Evaluation Periods; subjects randomized to the Sham group did not receive responsive stimulation during these periods. Following completion of the Blinded Evaluation Period (20 weeks post-implant), subjects transitioned to the Open Label Evaluation Period and both Treatment and Sham group subjects received responsive stimulation.

A schematic of the study timeline is provided in *Figure 2* on page 19. The primary effectiveness analysis compares changes in seizure frequency in the Treatment group and in the Sham group during the 12-week Blinded Evaluation Period relative to the 12-week Pre-Implant Period. The Pre-Implant Period (not shown in the figure) is defined as the 12 weeks in the Baseline Period leading up to and including the date of qualification for implantation. Primary safety analyses include adverse event data over the first 12 weeks post-implantation. Secondary safety and effectiveness analyses include data from all periods of the study.

Information regarding daily seizure counts, subject safety and subject well-being was collected by a physician investigator who was blinded to the subject's randomization status and a second non-blinded physician investigator was responsible for neurostimulator programming.

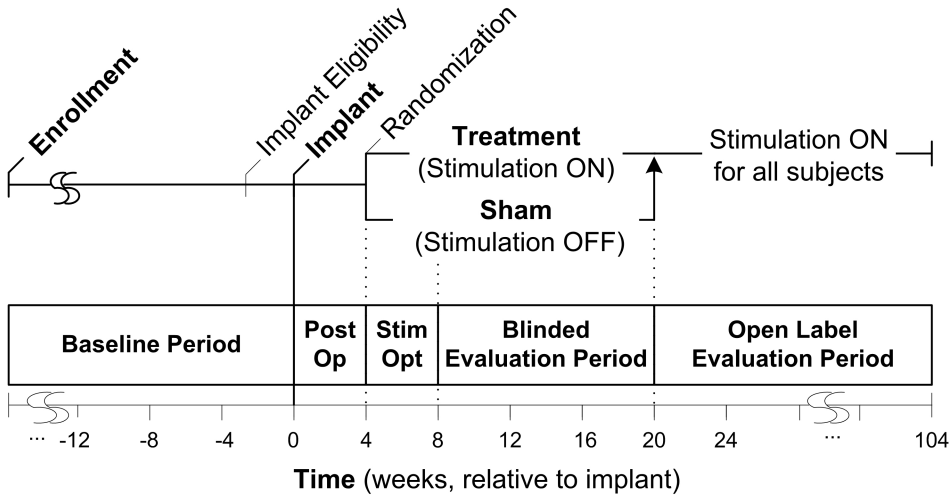

Figure 2: RNS® System Pivotal Clinical Investigation – Trial Flow and Periods

Long-term Treatment Study

The RNS® System Long-term Treatment Clinical Investigation (LTT) is an ongoing open label, multi-center, prospective clinical investigation of individuals with medically intractable, partial onset epilepsy. Subjects could enroll in the LTT study once they completed the RNS® System Feasibility or Pivotal Clinical Investigations; 230 subjects did so. During the LTT study, subjects can continue to receive responsive stimulation. Each subject participates for a maximum of 7 years. Adverse event and seizure data are collected at 6-month intervals, and data regarding quality of life are collected at yearly intervals. Antiepileptic drug adjustments are permitted as needed.

Randomization

In the Pivotal Study subjects implanted with the RNS® System neurostimulator and leads were randomized 1:1 to Treatment or Sham stimulation. To ensure equal representation in the two therapy groups, an adaptive randomization approach (minimization) 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); and
4. Previous resection (whether the subject had previously undergone a therapeutic epilepsy surgery).

Sample Size

The Pivotal Study was designed to have 80% power with an over-all 2-sided Type 1 error of 0.05, assuming 50% responder rates in the Treatment group and Sham groups of 40% and 20%, respectively. 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.

Effectiveness (Pivotal Study Only)

The primary effectiveness objective for the Pivotal Study was 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.

Seizure frequency was modeled using the generalized estimating equations (GEE) method, which accounts for within subject correlations and variability across subject populations. The pre-specified primary efficacy endpoint variable was the group-by-time interaction term in the generalized estimating equation (GEE) model using a Poisson distribution, where “group” refers to the therapy allocation (Treatment group or Sham group) and “time” refers to the trial period (Pre-Implant Period or Blinded Evaluation Period). The dependent variable was each subject’s daily seizure frequency during the Pre-Implant and Blinded Evaluation Periods.

While the pre-specified GEE analysis assumed that daily seizure count data would follow a Poisson distribution; the variability observed in the study exceeded the variability anticipated by the Poisson distribution as a result of a large variability in day to day seizure counts in most subjects, as well as a large variability between subjects. The lack of a good fit of this model to the data was indicated by a large over-dispersion parameter and a discrepancy between model based and empirical standard errors. Therefore, the following post hoc modifications were made to the pre-specified primary endpoint GEE analysis (referred to as the post hoc GEE model):

1. Using monthly rather than daily seizure count data
2. Modeling data with a negative binomial distribution rather than a Poisson distribution
3. Including the following clinical covariates used in the adaptive randomization:
    a. Seizure onset zone location (subjects with seizure onsets exclusively in the mesial temporal lobe versus any other region(s) of the cortex)
    b. Number of seizure foci (unifocal versus bifocal)
    c. Prior therapeutic epilepsy surgery (resection, subpial transection and/or corpus callosotomy, versus no such surgery)

The post-hoc GEE analysis was used to demonstrate efficacy.

The secondary efficacy endpoints were as follows:

- Comparison of the Treatment group responder rate to the Sham group rate over the 84-day Blinded Evaluation Period of the investigation. (Responder rate is defined as the proportion of subjects who experience a 50% or greater reduction in mean disabling seizure frequency compared to the Pre-Implant Period.)
- Change in average frequency of disabling seizures during the Blinded Evaluation Period versus the Pre-Implant Period for the Treatment group compared to the Sham group.
- Proportion of seizure-free days during the Blinded Evaluation Period versus the Pre-Implant Period for the Treatment group compared to the Sham-stimulation group.

- Change in seizure severity, as determined by the Liverpool Seizure Severity Scale during the Blinded Evaluation Period versus the Pre-Implant Period for the Treatment group compared to the Sham group.

Safety (Combined RNS® System Studies)

The primary safety endpoint variables for the Feasibility and Pivotal studies were the serious adverse event (SAE) rates during the Acute Period (initial implant procedure and the following month) and the Short-Term Chronic Period (initial implant procedure and the following three months). The SAE rate is defined as the proportion of subjects having a serious adverse event. The SAE rate includes all SAEs whether reported as device-related or not.

Other safety analyses (for combined RNS® System studies) considered the rate of occurrence of any adverse event during any period of the study. Rates of adverse events are described by the percentage of subjects experiencing one or more serious or non-serious adverse events.

An additional safety objective (for combined RNS® System studies) was to collect data on the frequency of Sudden Unexplained Death in Epilepsy (SUDEP) and upon completion of the clinical investigation estimate the SUDEP rate as a ratio of the number of events in subjects programmed to receive stimulation/total number of patient stimulation years, with a 95% confidence interval calculated according to patient stimulation years.

Description of Subject Population

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the Feasibility and Pivotal studies were similar (the key inclusion and exclusion criteria for the studies are presented in *Table 1* on page 22 and *Table 2* on page 23). The key differences between studies were:

- The Feasibility study included simple partial sensory seizures as a qualifying seizure type, whereas the Pivotal study did not include simple partial sensory seizures as a qualifying seizure type.
- The Feasibility study required a minimum of 4 seizures per month (including simple partial sensory seizures), whereas the Pivotal study required an average of 3 seizures per month (excluding simple partial sensory seizures).
- The Feasibility study included individuals between ages 18 and 65 and the Pivotal study included individuals between ages 18 and 70.

Table 1: Key Inclusion Criteria

Inclusion Criteria	Feasibility Study	Pivotal Study
Subject has simple partial motor seizures, complex partial seizures and/or secondarily generalized seizures	Yes[1]	Yes
Seizure counts per month	4 or more [2]	average of 3 or more[3]
Age	18 - 65 years	18 - 70 years
Subject has seizures that are severe enough to cause injuries or significantly impair functional ability in domains including employment, psychosocial, education and mobility.	Yes	Yes
Subject has seizures that are distinct, stereotypical events that can be reliably counted	Yes	Yes
Subject failed treatment with a minimum of two antiepileptic medications (used in appropriate doses) with adequate monitoring of compliance and the effects of treatment.	Yes	Yes
Subject has remained on the same antiepileptic medication(s) over the preceding three (3) months	Yes	Yes
Subject has undergone diagnostic testing that has established the epileptiform activity onset region(s)	Yes	Yes, with no more than 2 epileptogenic regions

[1] The Feasibility study also included simple partial sensory seizures.
[2] Subject has a minimum of four (4) or more countable seizures every month over the last three (3) months.
[3] Subject has an average of three or more disabling simple partial seizures, complex partial seizures, or secondarily generalized seizures per month (28 days) over the three most recent months, with no month with less than two seizures.

Table 2: Key Exclusion Criteria

Exclusion Criteria	Feasibility Study	Pivotal Study
Subject has been diagnosed with psychogenic or non-epileptic seizures in the preceding year.	Yes	Yes
Subject has been diagnosed with primarily generalized seizures.	Yes	Yes
Subject has experienced unprovoked status epilepticus in the preceding year.	Yes	Yes
Subject has a clinically significant or unstable medical condition or a progressive central nervous system disease.	Yes	Yes
Subject is taking anticoagulants.	Yes	Yes
Subject has been diagnosed with active psychosis, severe depression or suicidal ideation in the preceding year.	Yes	Yes
Subject has an implanted Vagus Nerve Stimulator (VNS).	Yes[1]	Yes[2]
Subject has had therapeutic surgery to treat epilepsy	in the preceding year	in the preceding 6 months
Subject is implanted with an electronic medical device that delivers electrical energy to the head.	Yes	Yes
Subject requires repeat MRIs	Yes	in which the head is exposed to the radio frequency field
Subject's epileptogenic region(s) is/are located caudal to the level of the thalamus.	Yes	Yes
Subject is pregnant.	Yes	Yes

[1] A subject with an inactive VNS could be enrolled so long as the VNS was explanted prior to or at the same time as the RNS® System implant.

[2] A subject could be enrolled if the subject is willing to have the VNS explanted (excluding leads) prior to or at the time of the RNS® System implant. (Subjects with VNS devices must have had VNS therapy discontinued for at least three months prior to enrollment.)

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

Subject Accountability and Analysis Population

Subject participation in the Feasibility, Pivotal and LTT studies is presented in *Figure 3* on page 24 as of May 12, 2011. Of the 256 implanted subjects, 22 subjects discontinued the Feasibility or Pivotal studies and 21 discontinued the LTT study. Reasons for discontinuations include adverse events which resulted in explant (8), subject preference (20) and physician preference (1), lost to follow-up (3), death (9) and reasons unknown (2). The adverse events included 7 due to infection and one as a result of a cerebral hemorrhage.

Analysis Populations

The safety and effectiveness analysis populations for the Pivotal study included all 191 subjects implanted and randomized; this is the intent-to-treat population. The combined safety analysis population includes the

intent-to-treat safety population from the RNS® System Feasibility, Pivotal and Long-term Treatment (LTT) Clinical Investigations combined. This includes all 256 subjects implanted with the RNS® Neurostimulator and leads.

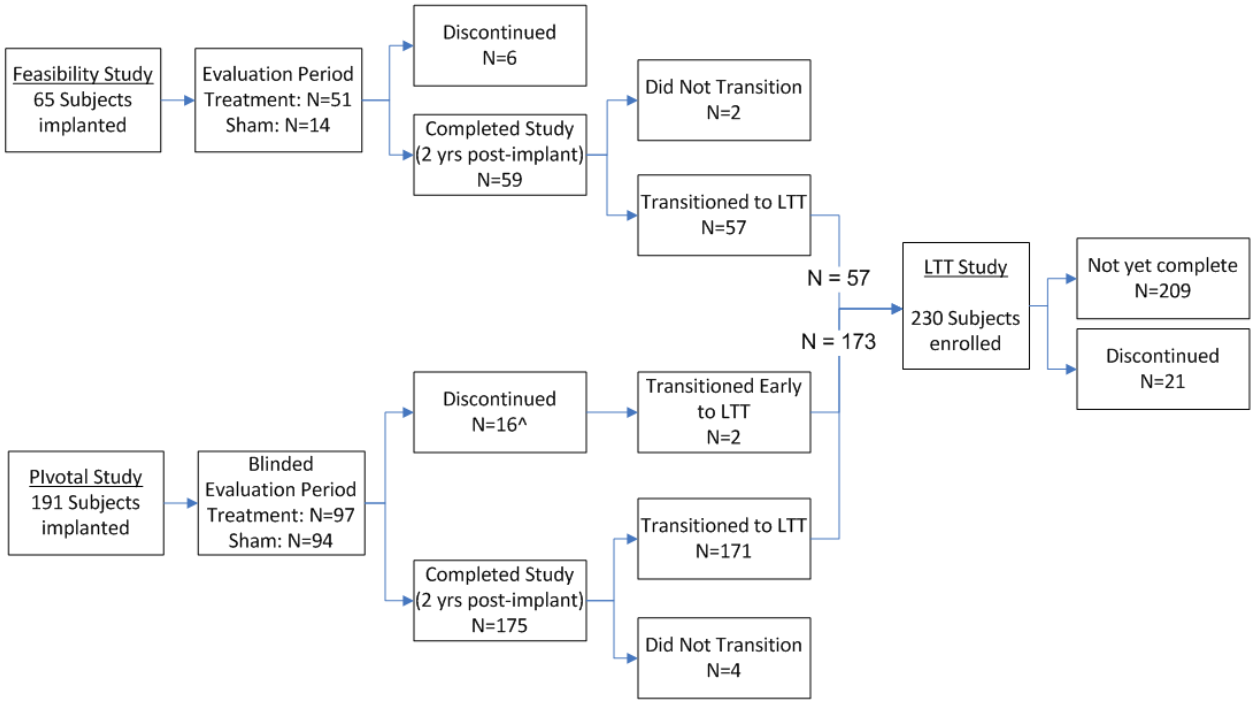

Figure 3: Patient Flow Diagram

^ Two subjects withdrew early (discontinued) from the Pivotal study to undergo resective epilepsy surgery. Waivers were granted to allow enrollment into the LTT study so that the subjects could continue to receive responsive stimulation to treat seizures arising from the non-resected seizure focus.

Demographics and Baseline Characteristics

Demographic information for subjects implanted in the Feasibility and Pivotal studies is presented in *Table 3* on page 25. All subjects participating in the LTT study originally enrolled in the Feasibility or Pivotal study. *Table 4* on page 26 provides information on epilepsy clinical characteristics and prior treatment for epilepsy, by randomization group. *Table 5* on page 26 provides information on the number and types of leads implanted.

Table 3: Demographics

Characteristic	All (N = 256)	By Study	
		Feasibility (N = 65)	Pivotal (N = 191)
Gender (percent female)	49% (125/256)	52% (34/65)	48% (91/191)
Age in years[1] (average, SD, range)	34.0 ± 11.4 (18 - 66)	30.9 ± 10.3 (18 - 56)	34.9 ± 11.6 (18 - 66)
Years with epilepsy (average, SD, range)	19.6 ± 11.4 (2 - 57)	17.0 ± 10.1 (2 - 42)	20.5 ± 11.6 (2 - 57)
Number of AEDs (average, SD, range)	2.9 ± 1.1 (0 - 8)	2.9 ± 1.0 (1 - 6)	2.8 ± 1.2 (0 - 8)
Seizures per month (average, SD, range, median)	50.7 ± 177.4 (0 – 2320) median = 10.2	99.2 ± 332.8 (0 – 2320) median = 11.3	34.2 ± 61.9 (3 – 338) median = 9.7

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

Table 4: Subset Populations of Interest (Implanted Subjects)

Characteristic	All Implanted (N = 191)	By Randomization Group		
		Treatment (N = 97)	Sham (N = 94)	p-value[1]
Seizure onset location - Mesial Temporal Lobe Only (v. other)[2]	50% (95/191)	49% (48/97)	50% (47/94)	0.943
Number of seizure foci - Bifocal (v. unifocal)[2]	55% (106/191)	49% (48/97)	62% (58/94)	0.089
Prior therapeutic surgery for epilepsy[2]	32% (62/191)	35% (34/97)	30% (28/94)	0.437
Prior EEG monitoring with intracranial electrodes	59% (113/191)	65% (63/97)	53% (50/94)	0.098
Prior VNS	34% (64/191)	31% (30/97)	36% (34/94)	0.443
Anatomical brain abnormality (by neuroimaging)	67% (128/191)	68% (66/97)	66% (62/94)	0.759
Benzodiazepine use (acute)[3]	36% (69/191)	31% (30/97)	41% (39/94)	0.129

[1] p-value per chi-square.
[2] Characteristics used as strata in adaptive randomization algorithm.
[3] Subjects who used acute benzodiazepines as rescue medications for seizures at any time during the Pre-Implant Period up until the implantation procedure. Does not include daily use of benzodiazepines.

Table 5: Leads Implanted at Time of Initial Neurostimulator Implantation (Treatment and Sham)

	Subject Population		
	Implanted (N = 191)	Treatment (N = 97)	Sham (N = 94)
Number of Leads	**% (n/N) of subjects**		
1	0% (0/191)	0% (0/97)	0% (0/94)
2	58% (110/191)	57% (55/97)	59% (55/94)
3	14% (26/191)	14% (14/97)	13% (12/94)
4	29% (55/191)	29% (28/97)	29% (27/94)
Types of Leads			
Cortical Strip Leads Only	31% (59/191)	31% (30/97)	31% (29/94)
Depth Leads Only	39% (74/191)	37% (36/97)	40% (38/94)
Cortical Strip and Depth Leads	30% (58/191)	32% (31/97)	29% (27/94)

Results – Effectiveness and Safety

Effectiveness Results

Effectiveness of the RNS® System was established by the post-hoc primary effectiveness analysis of the Pivotal study which demonstrated that the Treatment group (receiving responsive stimulation) experienced a statistically significant greater reduction in total disabling seizures compared to the Sham group (not receiving stimulation) during the Blinded Evaluation Period compared to the Pre-Implant Period of the investigation. None of the secondary endpoints were statistically significant. During the Open Label Period of the Pivotal study, there was a reduction in the frequency of disabling seizures. Another measure of effectiveness was quality of life. A clinically important improvement is defined as a 5-point improvement. There was no difference between the Treatment and Sham group subjects in the percent of subjects who achieved a clinically important improvement in QOL (36.6% and 39.1% respectively) at the end of the Blinded Evaluation Period. At 1 and 2 years post-implant, 38% and 44% of subjects (respectively) experienced a significant clinical improvement on the QOLIE assessment.

Primary Effectiveness Endpoint

Observed Data

Group Level Response

A total of 97 and 94 patients entered the Pre-Implant Period in the Treatment and Sham groups, respectively. The mean pre-implant seizure frequency per month in the Treatment group was 33.5 (with a range of 3 – 295) and 34.9 (with a range of 3 – 338) in the Sham group. Over the entire Blinded Evaluation Period, the mean seizure frequency per month in the Treatment group was 22.4 (with a range of 0 – 227) and was 29.9 (with a range of 0 – 447) in the Sham group. *Table 6* on page 28 presents the mean percent change, median percent change, mean, median and range of seizure frequencies for the Treatment and Sham groups for the Pre-Implant and Blinded Evaluation Period overall and by individual month.

Table 6: Pivotal Effectiveness – Seizure Frequency per Month Pre-Implant and Blinded Evaluation Periods

		Treatment				Sham			
		N	% Change		Mean, Median (Min - Max)	N	% Change		Mean, Median (Min - Max)
			Mean	Median			Mean	Median	
Pre-Implant Months	0 - 1	97			34.5, 9.3 (2.0 - 305.0)	94			28.7, 10.0 (1.0 - 283.0)
	1 - 2	97			34.3, 9.0 (2.0 - 294.0)	94			34.5, 12.0 (2.0 - 342.0)
	2 - 3	97			31.7, 9.0 (0.0 - 350.0)	94			41.5, 11.5 (2.0 - 634.0)
Pre-Implant Period		97			33.5, 8.7 (3.0 - 294.7)	94			34.9, 11.6 (3.0 - 338.0)
Post-Op Months	0 - 1	96	-24.7%	-33.3%	23.8, 6.0 (0.0 – 258.1)	94	-19.8%	-30.2%	24.2, 7.0 (0.0 – 286.0)
	1 - 2	96	-25.3%	-28.4%	25.0, 6.4 (0.0 – 247.0)	93	-13.5%	-21.9%	27.5, 9.0 (0.0 – 323.0)
Blinded Evaluation Period Months	2 - 3	96	-19.9%	-27.2%	22.9, 6.5 (0.0 - 226.0)	93	-19.5%	-31.9%	27.1, 8.3 (0.0 - 369.4)
	3 - 4	95	-30.8%	-36.4%	22.8, 6.0 (0.0 - 266.0)	90	-14.1%	-25.0%	28.9, 8.3 (0.0 - 336.0)
	4 - 5	95	-28.0%	-34.0%	21.4, 6.0 (0.0 - 226.0)	91	-13.7%	-18.9%	35.4, 7.0 (0.0 - 799.0)
Blinded Evaluation Period		96	-24.1%	-28.0%	22.4, 5.8 (0.0 - 226.8)	93	-17.3%	-19.2%	29.9, 7.6 (0.3 - 446.6)

Figure 4 on page 29 depicts the mean seizure frequency per month for Treatment and Sham groups. Following implantation of the RNS® Neurostimulator and leads and prior to enabling stimulation in either the Treatment or Sham group, both groups experienced a mean percent reduction in the observed number of seizures (25% Treatment and 20% Sham) and a median percent reduction in the observed number of seizures (33% Treatment and 30% Sham). Whether this is an effect of the surgical procedure and/or anesthesia, an effect of lead implantation, regression to the mean or placebo effect is not known.

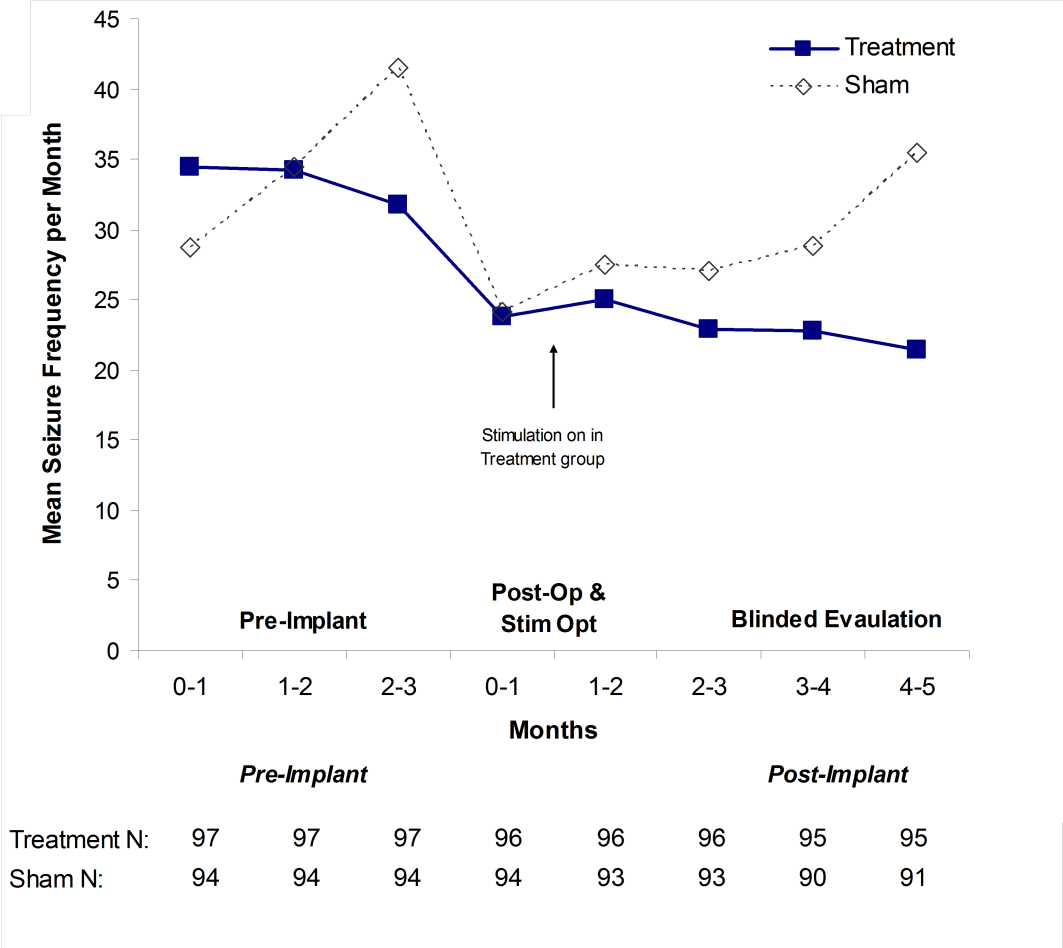

Figure 4: Mean Seizure Frequency per Month (Pre-Implant through Blinded Evaluation Period)

Primary Effectiveness Endpoint Analysis

The pre-specified GEE analysis (see *Effectiveness (Pivotal Study Only)* on page 20) was based on daily seizure counts during the Pre-Implant and Blinded Evaluation Periods. There are two standard error estimation methods for the pre-specified analysis, the empirical and model-based method. In this case, these two methods yielded distinctly different p-values (empirical p=0.15 vs. model-based p<0.0001). The large difference between these p-values was indicative of a poor fit of the model to the data. As a result, a post hoc alternative analysis model was used to demonstrate effectiveness.

The pre-specified GEE model assumed that daily seizure count data would follow a Poisson distribution; however, the variability observed in the study exceeded the variability of the Poisson distribution due to large variability in day to day seizure counts in most subjects, as well as a large variability between subjects. A model that fits the data well has similar model based and empirical standard errors and has an over-dispersion parameter (Φ) that is close to one. This was not the case, which indicated that the pre-specified model did not fit the data.

The post hoc analysis of the data using monthly seizure counts, the negative binomial distribution and adjusting for the clinical covariates achieved statistical significance with both of the standard errors (model-based p=0.0056; empirical p=0.012) demonstrating that the reduction in seizure frequency of subjects randomized to receive responsive stimulation during the Blinded Evaluation Period (Treatment group) was significantly greater than that experienced by subjects randomized to receive sham stimulation (Sham group). Please note that there was no correction for multiplicity. Over the entire Blinded Evaluation Period, the Treatment group had a reduction in seizure frequency of 37.9% (95% confidence interval (CI): -46.7%,

-27.7%) compared to a 17.3% (95% CI: -29.9%, -2.3%) reduction in the Sham group. See *Table 7* on page 30.

Table 7: Estimates of seizure frequency percent change from the modified GEE model over the entire Blinded Evaluation Period

	Parameter Estimate (log scale)[1]	Ratio of Seizure Frequency (Blinded Evaluation Period vs. Pre-Implant Period)[2]	Percent Change from Pre-Implant Period[3] [95% confidence interval]
Treatment	-0.4771	0.621	-37.9% [-46.7%, -27.7%]
Sham	-0.1898	0.827	-17.3% [-29.9%, -2.3%]

[1] The parameter estimate (β) for the Sham group is the coefficient for Time (β1). The parameter estimate for the Treatment group is the coefficient for Time + the coefficient for Group-by-Time (β1 + β2).
[2] The ratio of seizure frequency (natural scale) is given by e β.
[3] The percent change is given by (eβ -1)*100%.

To put the model-predicted percent change from baseline into perspective, the mean number of seizures the model predicts for a subject in the Treatment group with 30 seizures at baseline, would be a reduction of 11 seizures per month in the Blinded Evaluation Period and the mean number of seizures the model predicts for a subject in the Sham group with 30 seizures at baseline, would equate to a reduction of 5 seizures per month in the Blinded Evaluation Period. The difference between treatment and sham as predicted by the model is 6 seizures per month in the Blinded Evaluation Period.

The Forest Plot in *Figure 5* on page 31 shows models that explore combinations of the 3 modifications: distribution, covariate inclusion, and time. The pre-specified model is the last model while the modified post-hoc model is the first model in *Figure 5* on page 31. Ninety-five percent (95%) confidence intervals are presented for model-based (solid) and empirical (dashed) horizontal lines. The scale parameter is denoted as Φ. A model that fits the data well has similar model-based and empirical confidence intervals and has a scale parameter that is close to 1, which is not the case for the pre-specified or many of the additional exploratory post-hoc models. The relative risk reduction corresponds to the additional reduction in seizure frequency attributable to active stimulation relative to Sham stimulation; a value of 1 would suggest there is no additional benefit from active stimulation, while a value less than 1 or greater than 1 would indicate that active stimulation reduces or increases seizures relative to Sham stimulation.

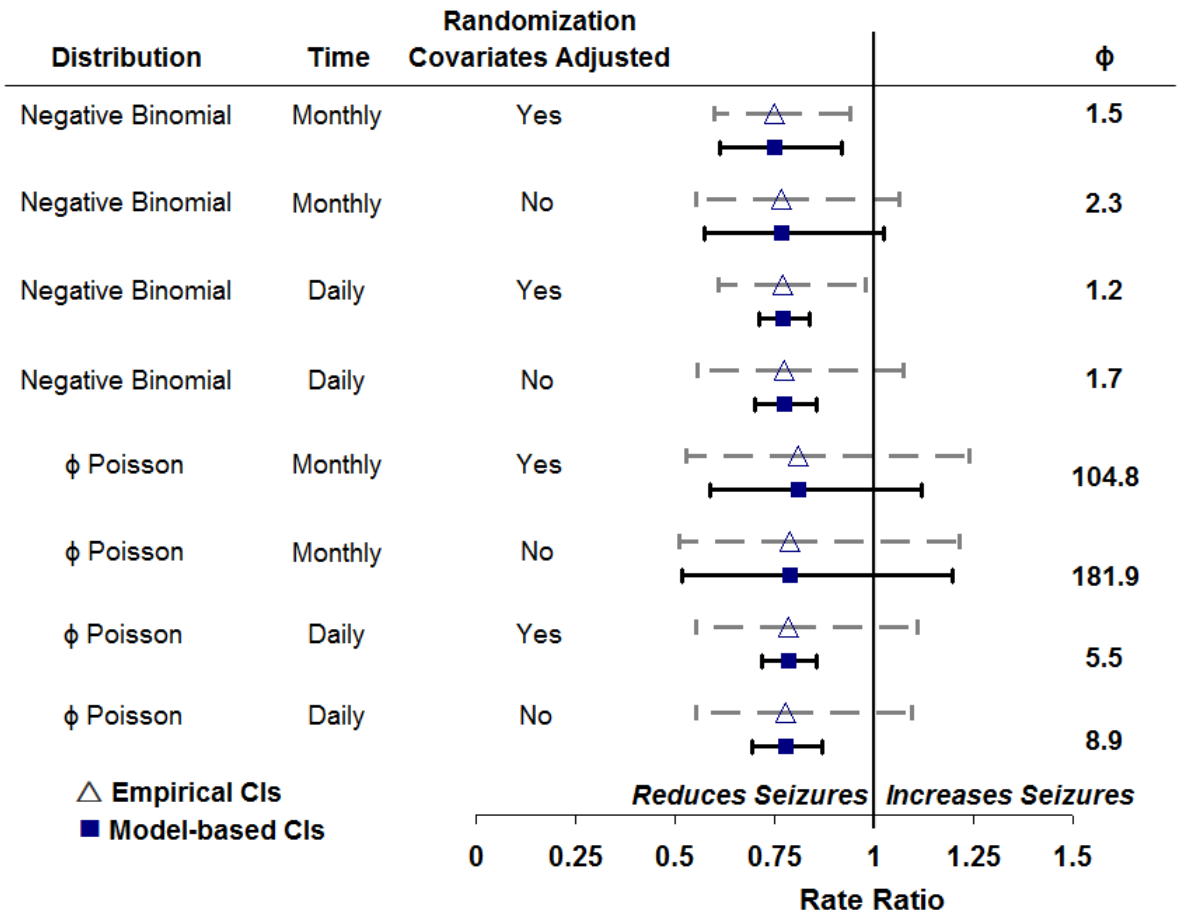

Figure 5: "Forest plot" Comparison of Alternative GEE Models

Individual Subject Success

Seventy-six percent (76%) of subjects in the Treatment group and 70% in the Sham group reported a decrease in seizures during the Blinded Evaluation Period. *Figure 6* on page 32 depicts the distribution of subject results.

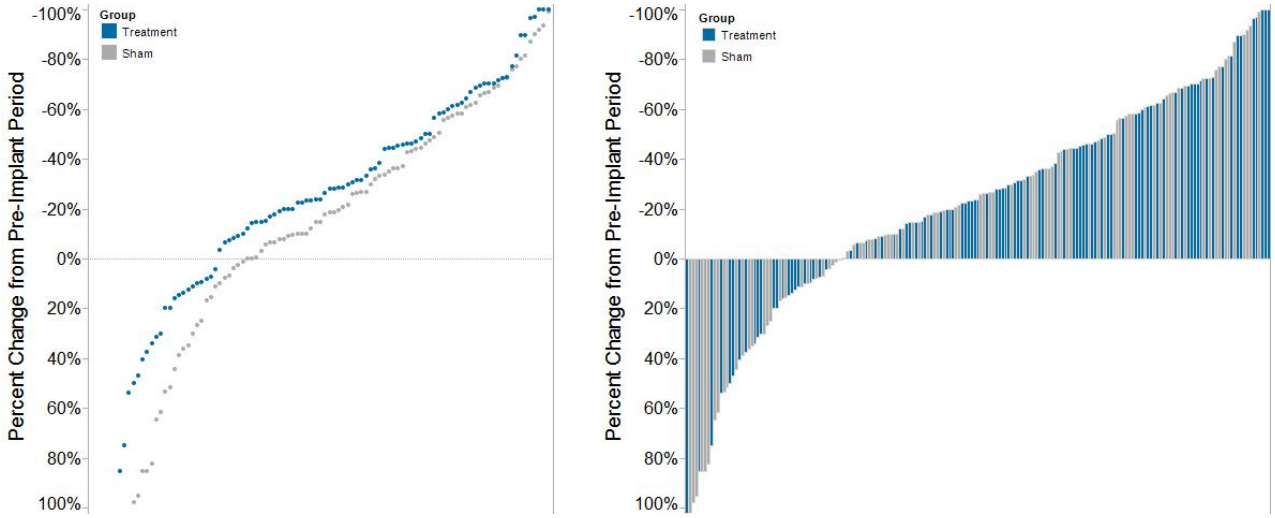

Figure 6: Percent change* in seizure frequency in Blinded Evaluation Period compared to pre-implant baseline (Treatment and Sham)

* Two patients had an increase > 100%; Sham (n=1, 115%); Treatment (n=1, 281%)

Secondary Effectiveness Endpoints

The secondary effectiveness analyses were intended to support the primary effectiveness endpoint. Pre-specified secondary effectiveness endpoints were the responder rate, change in mean seizure frequency, proportion of seizure-free days, and self-reported seizure severity according to the Liverpool Seizure Severity Scale inventory. The results of the four secondary effectiveness analyses are presented in *Table 8* on page 32. None of the secondary endpoints achieved statistical significance. Note that with the exception of the responder rate comparison, which was used to determine the trial's sample size, the protocol did not evaluate the trial's power to detect a statistically significant difference for the secondary outcomes.

Table 8: Pivotal Study – Secondary Effectiveness Endpoints over the Entire Blinded Evaluation Period

Effectiveness Endpoint	Treatment	Sham	p-value[1]
50% Responder Rate[2]	29%	27%	0.727[3]
Change in Mean Seizure Frequency	-11.4	-5.3	0.238[4]
% Change in Days with Seizures	-19%	-18%	0.9[5]
Liverpool Seizure Severity Change	-4.7	-5.9	0.574[4]

1 p-values represent across group evaluations.
2 used to power sample size.
3 z-statistic
4 two-sample t-test.
5 paired t-test.

Open Label Period

Subjects entered the open label phase of the study at 5 months (20 weeks) post-implant. At the 20-Week visit, subjects in the Sham group were able to receive responsive stimulation for the first time. When subjects in the Sham group first received responsive stimulation in the Open Label Period, there was an immediate reduction in seizure frequency. The mean change in seizures in the Sham group compared to the pre-implant baseline and compared to the Blinded Evaluation Period is presented in *Table 9* on page 33.

Table 9: Mean Change in Seizure Frequency in Sham Group

Time Period	Seizure Frequency[1] (mean ± SD, seizures/month)	
	Open Label to Pre-Implant Comparison (N = 91)	Open Label to Blinded Evaluation Comparison (N=91)
Pre-Implant	35.725 ± 68.037	--
Blinded Evaluation (Months 2-5)	--	30.442 ± 67.082
Open Label (Months 6-9)	27.964 ± 2.014	27.964 ± 62.014
Change	-7.763 ± 35.498	-2.478 ± 27.33

[1] Calculations include those subjects who were randomized to the Sham group for the Blinded Evaluation Period.

Open Label Data

The following considerations should be taken into account when interpreting the Open Label data for the RNS® System Studies:

- All subjects were aware that they were receiving stimulation.
- Sixteen of the 191 subjects did not complete the full two years (8.4%).
- Changes in antiepileptic medications were permitted in the Open Label Period.
  - 47.5% of subjects had no change in AEDs.
  - 24.6% had both an increase and decrease in AEDs.
  - 21.9% increased their AEDs.
  - 6% decreased their AEDs.

The responder rate was a pre-specified effectiveness analysis for the Open Label Period. As a group, there was a sustained long-term reduction in seizures in subjects treated with responsive stimulation as measured by the responder rate. The responder rates for the subjects randomized to the Treatment and Sham groups during the Blinded Evaluation Period and for all subjects over the Open Label Evaluation Period are presented in *Table 10* on page 34. During Months 6-8, subjects in the Treatment group had already been receiving responsive stimulation for 4 months, whereas Sham group subjects had just begun. The responder rate for both groups was 43.6% for all subjects combined at 1 year after implant and reached 54.6% at 2 years. The responder rate uses a last observation carried forward analysis which considers the most recent 3 months of data provided in the Open Label Period of the Pivotal study.

For those subjects who reached 2 years post-implant, 55% of the subjects experienced a 50% or greater reduction in seizures.

Table 10: Pivotal Study – Responder rates: Open Label Period (All Subjects Receiving Stimulation)

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

[1] All randomized subjects with seizure data during the specified 3-month period.

Table 11 on page 34 provides the mean change in disabling seizures per month for implanted subjects over periods of the Pivotal Study compared to those subjects' pre-implant seizure frequency. Means and standard deviations are provided.

Table 11: Change in Mean Frequency of Total Disabling Seizures, Blinded Evaluation Period Through Open Label

Analysis Population	Frequency of Total Disabling Seizures (mean ± SD, seizures/month)							
	Blinded Evaluation Period	Open Label Evaluation Period (All Subjects Receiving Stimulation)						
	Months 2-5	Months 5-8	Months 8-11	Months 11-14	Months 14-17	Months 17-20	Months 20-23	Months 23-26
Treatment Group								
N[1]	96	95	93	92	90	89	88	87
Pre-Implant Period	33.8 ± 57.0	34.1 ± 57.2	32.1 ± 56.1	31.9 ± 56.4	31.1 ± 56.7	31.1 ± 57.0	31.0 ± 57.3	31.6 ± 57.5
Post-implant Period	22.4 ± 39.5	18.6 ± 32.3	16.0 ± 25.0	13.7 ± 23.5	11.6 ± 17.7	13.5 ± 25.7	11.5 ± 17.4	11.0 ± 16.5
Change	-11.4 ± 32.1	-15.5 ± 42.1	-16.1 ± 44.5	-18.2 ± 47.8	-19.5 ± 49.8	-17.6 ± 45.2	-19.5 ± 47.5	-20.6 ± 48.7
Sham Group								
N[1]	93	91	90	89	89	89	87	87
Pre-Implant Period	35.2 ± 67.4	35.7 ± 68.0	35.6 ± 68.4	35.9 ± 68.7	35.7 ± 68.8	35.7 ± 68.8	35.9 ± 69.5	35.9 ± 69.5
Post-implant Period	29.9 ± 66.5	27.3 ± 55.7	27.9 ± 71.3	25.7 ± 66.2	26.4 ± 77.9	25.4 ± 80.7	25.5 ± 77.9	24.5 ± 79.9
Change	-5.3 ± 39.1	-8.4 ± 33.6	-7.6 ± 44.4	-10.2 ± 49.5	-9.3 ± 56.9	-10.3 ± 63.0	-10.3 ± 59.5	-11.3 ± 61.7

[1] Calculations include all randomized subjects who had had the opportunity to complete the study appointment(s) associated with the specified 3-month period by 5/12/2011.

Quality of Life

Quality of Life (QOL) was an additional assessment performed in the Pivotal study. A significant clinical improvement on the QOLIE assessment is defined as an improvement of 5 points or more. 36.6% of subjects in the Treatment group and 39.1% of the subjects in the Sham group had at least a 5 point improvement at the end of the blinded phase. At 1 and 2 years post-implant, 38% and 44% of subjects (respectively) experienced a 5 point improvement.

Safety Results

The RNS® System Feasibility, Pivotal and Long-term Treatment studies evaluated the safety of the RNS® System for epilepsy in 256 implanted subjects over 903 patient years of implant experience and 819 patient years of responsive stimulation. During all study periods 165/256 (64.5%) subjects experienced a serious adverse event and 254/256 (99.2%) subjects experienced a non-serious adverse event, including common and expected illnesses. A full listing of adverse events in subjects by study period is presented in *Table 30* on page 59. There were no unanticipated device-related serious adverse events during the RNS® System studies. Acute and short term chronic adverse events compared favorably to comparable procedures as demonstrated by the primary safety endpoint. The primary safety endpoint was to compare comparable procedures to the significant adverse events for the surgical procedure and following 28 days (acute) and to compare comparable procedures to the surgical procedure and the following 84 days (short-term chronic). The primary safety endpoint was met. There was no difference between the Treatment and Sham groups in the overall percentage of subjects experiencing an adverse event, or any specific type of adverse event during the evaluation periods of the studies. The overall frequency of adverse events or of specific adverse events does not increase over time, whether or not the investigator considered the event as device-related or not device-related.

Primary Safety Endpoint

The RNS® System Feasibility and Pivotal studies met the safety endpoints pre-specified in the investigational plans. The rate of serious adverse events after implantation of the neurostimulator and leads was similar over the first 4 weeks (Acute Period) and in the first 12 weeks (Short-Term Chronic Period) compared to comparable procedures, i.e., the combined risks of implantation of intracranial electrodes for purposes of an epilepsy surgery evaluation and epilepsy surgery, and the risks of deep brain stimulation for treatment of movement disorders. The SAE rate for the Acute Period in the Pivotal study was 12% (23/191) [upper one-sided 95% CI: 16.5%], lower than the pre-specified literature-derived comparator of 15% [upper one-sided 95% CI: 20%]. The SAE rate for the Short-Term Chronic Period for the Pivotal study was 18.3% (35/191) [upper one-sided 95% CI: 23.4%]. These rates were lower than the pre-specified literature-derived comparator of 36% [upper one-sided 95% CI: 42%]. The results, presented in *Table 12* on page 36, demonstrate that the SAE rate over the first month and the first 3 months after implantation is comparable to the literature based historical controls.

Table 12: Pivotal Study – Primary safety endpoint

Period	SAE Rate [1]		Met primary safety endpoint?
	RNS System	Comparator	
	% subjects (n/N) [upper 95% CI]		
Acute: **Implant – 4 weeks** Pre-specified comparator: Intracranial electrodes + surgery	12.0% (23 /191) [16.5%]	15% [20%]	Yes, upper limit for the RNS® System is less than that of the comparator: (16.5% < 20%)
Short-Term Chronic: **Implant – 12 weeks** Pre-specified comparator: DBS for movement disorders	18.3% (35 /191) [23.4%]	36% [42%]	Yes, upper limit for the RNS® System is less than that of the comparator: (23.4% < 42%)

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

Adverse Events

Adverse events were collected for all subjects in the RNS® System studies. All data are current as of May 12, 2011. The investigator classified each adverse event as serious or non-serious and as device-related (which includes device-related and device-relation uncertain) or not device-related. Adverse events were considered serious if the event resulted in significant risks or consequences to the subject's acute or long-term health, serious injury or death, hospital admission, or if invasive medical intervention was required to alleviate the adverse event. Adverse events are presented using MedDRA Coding according to the PT = Preferred Term.

Pivotal Study: Post-operative Stabilization Period

Table 13 on page 37 presents the serious adverse events (SAEs) that occurred in 23 subjects during the Post-operative Stabilization Period. Five (5) subjects had implant site infections, one of which required explant of the leads and stimulator. Two additional subjects had serious adverse events reported as effusion or discharge at the implant site. One subject was reported to have bacterial meningitis, that was diagnosed before the RNS® Neurostimulator and NeuroPace Leads were implanted. The infection was a chronic infection from a prior evaluation with intracranial electrodes. The investigator elected to implant the RNS® Neurostimulator and NeuroPace Leads despite the observed infection and treated the patient with antibiotics. Three subjects had intracranial hemorrhages; there were no neurological consequences. Additional information regarding all hemorrhages is provided in section *Intracranial Hemorrhage* on page 46. Adverse events that occurred in ≥ 2.5% of subjects are presented in *Table 14* on page 38. A full listing of adverse events during the Post-operative Stabilization Period is presented in *Table 29* on page 55.

Table 13: Pivotal Study – Serious Adverse Events during the Post-operative Stabilization Period [1]

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

[1] All SAEs resolved.
[2] Subject was diagnosed with bacterial meningitis before implant.

Table 14: Pivotal Study – Adverse Events occurring in ≥ 2.5% of subjects during the Post-operative Stabilization Period

MedDRA Preferred Term	% (#) Subjects with events (N=191)
Implant site pain	28.3% (54)
Procedural headache	27.2% (52)
Procedural nausea	4.7% (9)
Implant site swelling	4.2% (8)
Dizziness	3.7% (7)
Postoperative constipation	3.7% (7)
Swelling face	3.7% (7)
Postoperative fever	3.1% (6)
Therapeutic agent toxicity	3.1% (6)
Adverse drug reaction	2.6% (5)
Implant site infection	2.6% (5)

Pivotal Study: Stimulation Optimization Period

Table 15 on page 39 presents the serious adverse events (SAEs) that occurred in 12 subjects (6 in the Treatment group and 6 in the Sham group) during the Stimulation Optimization Period. Serious adverse events of particular interest include implant site infection and subdural hematoma (due to a seizure). Adverse events that occurred in ≥ 2.5% of subjects are presented in *Table 16* on page 39.

Table 15: Pivotal Study – Serious Adverse Events During the Stimulation Optimization Period (Treatment and Sham)

MedDRA Preferred Term	Treatment (N=97)	Sham (N=94)
	% (#) Subjects with events	% (#) Subjects with events
Summary of All SAEs in this Period	**6.2% (6)**	**6.4% (6)**
Device lead revision	1.0% (1)	1.1% (1)
Medical device removal (VNS)	1.0% (1)	1.1% (1)
Adverse drug reaction	1.0% (1)	--
Arthritis	--	1.1% (1)
Central venous catheterisation	1.0% (1)	--
Death	--	1.1% (1)
EEG monitoring	--	1.1% (1)
Implant site infection (dts)	1.0% (1)	--
Meningioma benign	1.0% (1)	--
Non-cardiac chest pain	--	1.1% (1)
Psychotic disorder	--	1.1% (1)
Skin laceration (dts)	1.0% (1)	--
Subdural hematoma (dts)	1.0% (1)	--
Syncope	1.0% (1)	--

Table 16: Pivotal Safety – Adverse Events in ≥ 2.5% of Subjects During the Stimulation Optimization Period (Treatment and Sham)

MedDRA Preferred Term	Treatment (N=97)	Sham (N=94)	p-value[1]
	% (#) Subjects with events	% (#) Subjects with events	
Headache	4.1% (4)	8.5% (8)	0.245
Nasopharyngitis	5.2% (5)	3.2% (3)	0.721
Depression	3.1% (3)	3.2% (3)	1.000
Implant site pain	2.1% (2)	3.2% (3)	0.679

[1] Comparison of percentage of subjects with events in Treatment vs. Sham groups per Fisher's exact test.

Pivotal Study: Adverse Events during the Blinded Evaluation Period

The total number of subjects that experienced any serious or non-serious adverse event during the Blinded Evaluation Period was 90/97 (92.8%) for the Treatment group and 88/94 (93.6%) for the Sham group. There was no difference in the frequency of serious adverse events between the Treatment and Sham stimulation groups. Only one type of adverse event was significantly different between the Treatment and Sham stimulation groups. Therapeutic agent toxicity, which refers to side effects of antiepileptic medications, was more common in the Sham group (5 subjects, all non-serious events) than the Treatment group (none). There were no other differences in adverse events between the Treatment group and Sham group.

Table 17 on page 40 presents the serious adverse events that occurred in 9 subjects (4 in the Treatment group and 5 in the Sham group) during the Blinded Evaluation Period. *Table 18* on page 41 presents

adverse events reported in 2.5% or more of the subjects in either the Treatment or the Sham groups who entered the 12 week Blinded Evaluation Period of the Pivotal Study. This includes all adverse events whether device-related or not.

Table 17: Pivotal Safety – Serious Adverse Events During the Blinded Evaluation Period (Treatment and Sham)

MedDRA Preferred Term	Treatment (N=96)	Sham (N=93)
	% (#) Subjects with events	% (#) Subjects with events
Complex partial seizures increased	1.0% (1)	1.1% (1)
Alcohol poisoning	1.0% (1)	--
Hernia	--	1.1% (1)
Implant site infection (dts)	--	1.1% (1)
Jaw fracture (dts)	--	1.1% (1)
Myocardial infarction	1.0% (1)	--
Nephrolithiasis	--	1.1% (1)
Pneumonia	1.0% (1)	--
Simple partial seizures (sensory)	--	1.1% (1)
Simple partial seizures increased (sensory)	--	1.1% (1)
Summary of All SAEs in Period	**4.2% (4)**	**5.4% (5)**

Differences between the percentage of subjects in the Treatment group reporting the events and that in the Sham group were not significant (all p-values > 0.05 by Fisher's exact test).

Table 18: Pivotal Study – Adverse Events in ≥ 2.5% of Subjects in Either Group During the Blinded Evaluation Period (Treatment vs. Sham)

MedDRA Preferred Term	Treatment (N=96)	Sham (N=93)	p-value[1]
	% (#) subjects with events	% (#) subjects with events	
Nasopharyngitis	6.3% (6)	8.6% (8)	0.588
Headache	5.2% (5)	7.5% (7)	0.563
Contusion (dts)	7.3% (7)	2.2% (2)	0.170
Skin laceration (dts)	6.3% (6)	3.2% (3)	0.498
Complex partial seizures increased	4.2% (4)	3.2% (3)	1.000
Depression	5.2% (5)	2.2% (2)	0.445
Dysesthesia	2.1% (2)	5.4% (5)	0.273
Influenza	4.2% (4)	3.2% (3)	1.000
Vomiting	3.1% (3)	3.2% (3)	1.000
Adverse drug reaction	3.1% (3)	2.2% (2)	0.445
Therapeutic agent toxicity	--	5.4% (5)	0.027
Upper respiratory tract infection	1.0% (1)	4.3% (4)	0.206
Pain of skin	4.2% (4)	--	0.121
Pharyngitis	1.0% (1)	3.2% (3)	0.363
Abdominal pain	3.1% (3)	--	0.246
Balance disorder	--	3.2% (3)	0.117
Head injury	--	3.2% (3)	0.117

[1] Fisher's exact test

Pivotal Study: Adverse Events during All Study Periods through Two Years Post-Implant

All device-related adverse events (serious and non-serious) occurring during the Pivotal study through 2 years post-implant in 2.5% or more of the subjects are presented by study period in *Table 19* on page 42. This represents 379 patient implant years and 328 patient stimulation years. A full listing of adverse events during the Pivotal Study is presented in *Table 30* on page 59.

Table 19: Pivotal Study – Device-Related Adverse Events in ≥ 2.5% of Subjects by Study Period through 2 Years

	Post Op (Implant - Week 4)	Stim Opt (Weeks 4 - 8)	Blinded Eval (Weeks 8 - 20)	Open Label Period		All Study Periods[1]
				(Weeks 20 - 52)	(Weeks 52 - Completion)	
# of subjects entering interval / implant years within interval	**191 / 14.7**	**191 / 14.6**	**189 / 43.2**	**187 / 113.4**	**182 / 193.4**	**191 / 379.2**
Preferred Term	% subjects (# subjects)[2]					
Implant site pain	9.9% (19)	2.1% (4)	0.5% (1)	3.7% (7)	4.4% (8)	18.3% (35)
Procedural headache	11.5% (22)	--	--	0.5% (1)	0.5% (1)	12.6% (24)
Device interaction	1.6% (3)	0.5% (1)	1.1% (2)	1.6% (3)	0.5% (1)	5.2% (10)
Implant site infection	2.6% (5)	--	--	1.1% (2)	1.6% (3)	4.7% (9)
Implant site swelling	3.7% (7)	0.5% (1)	--	--	0.5% (1)	4.7% (9)
Device Lead damage	--	--	--	2.7% (5)	0.5% (1)	2.6% (5)
Implant site paresthesia	--	0.5% (1)	1.1% (2)	--	1.1% (2)	2.6% (5)
Incision site infection	--	--	1.1% (2)	0.5% (1)	1.6% (3)	2.6% (5)

[1] Row totals may not sum to totals in this column because some subjects may have had AEs in more than one period

[2] % subjects = # subjects with event / number of subjects entering interval

The most frequent serious adverse event during the 28 days after implant was implant site infection, occurring in 2.6% of subjects. There were 5 implant site infections; one of these subjects had the neurostimulator and leads explanted. The most common non-serious adverse events were implant site pain, procedural headache and implant site swelling and infection.

The most common serious device-related adverse events through two years post-implant were implant site infection (3.7%), device lead damage (2.6%), and device lead revision (2.1%). Device-related serious adverse events affecting 1% (2 subjects) were extradural hematoma, hydrocephalus, and premature battery depletion.

Device-related serious adverse events affecting 0.5% (1 subject) at any time over the entire Pivotal Study were cerebral hemorrhage, implant site discharge, implant site erosion, implant site pain, intracranial hypotension, medical device removal, procedural headache, subdural hematoma, and suture related complication.

Pivotal Study: Neuropsychological Testing

Neuropsychological function was a safety endpoint. The results of the neuropsychological testing are presented in the following tables. There was no difference between Treatment and Sham groups at the end of the Blinded Evaluation Period and no statistically significant deterioration in any of the 16 neuropsychological domains at the end of the Blinded Evaluation Period or at 1 and 2 years after implant.

Table 20: Pivotal Study – Neuropsychological Measures: Change in Summary Scores at End of Blinded Evaluation Period Relative to Baseline, Treatment vs Sham

Test	Treatment		Sham		p-value[1]
	N	Mean ± SD	N	Mean ± SD	
Visual Motor Speed					
Trailmaking - Part A[2]	91	0.87 ± 14.61	86	-0.37 ± 14.97	0.578
Trailmaking - Part B[2]	90	-6.02 ± 52.72	85	-6.06 ± 33.49	0.996
Motor Speed / Dexterity					
Grooved Pegboard - Dominant[2]	89	-1.24 ± 14.95	79	-2.19 ± 22.80	0.746
Grooved Pegboard - Nondominant[2]	88	-1.89 ± 18.81	76	1.32 ± 27.31	0.378
Auditory Attention					
WAIS-III Digit Span	90	-0.21 ± 1.55	86	0.09 ± 1.48	0.185
General Verbal Ability					
WAIS-III Information	91	0.11 ± 1.14	83	0.12 ± 1.17	0.952
General Visuospatial Ability					
WAIS-III Block Design	90	-0.03 ± 2.06	84	0.31 ± 1.62	0.227
Verbal Memory					
RAVLT - I-V (Sum Across Trials)	86	-1.94 ± 9.20	84	-0.21 ± 10.01	0.243
RAVLT - VII (Delayed Recall)	86	-0.10 ± 2.75	84	0.01 ± 2.33	0.766
RAVLT - Recognition Memory	86	-0.21 ± 2.69	83	0.23 ± 3.12	0.329
Visuospatial Memory					
BVMT-R - Total Recall	90	1.94 ± 6.16	85	2.00 ± 5.95	0.952
BVMT-R - Delayed Recall	87	0.24 ± 2.75	85	0.32 ± 2.26	0.832
BVMT-R - Recognition Discrimination Index	88	0.14 ± 1.42	83	-0.07 ± 1.24	0.309
Language					
BNT - Spontaneous with semantic cue	90	0.70 ± 4.37	84	1.36 ± 3.89	0.297
D-KEFS Verbal Fluency - Condition 1: Letter Fluency	83	-0.06 ± 1.69	77	0.53 ± 2.32	0.065
Design Fluency					
D-KEFS Design Fluency - Total Composite	89	0.49 ± 2.32	80	0.40 ± 2.40	0.795

[1] Statistical significance of the between-group difference in change in score (at 20 weeks relative to pre-implant) between Treatment and Sham groups per two-sample t-test.
[2] Higher values mean improved performance with the exception of the footnoted tests where lower mean values indicate improved performance.

Analysis includes subjects (N) with assessments at both Baseline and end of Blinded Evaluation Period time points.

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

Table 21: Pivotal Study – Neuropsychological Measures: Change in Summary Scores at 1 and 2 years relative to Baseline

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

[1] Statistical significance of the change from the Baseline score per the paired t-test.
[2] Higher values mean improved performance with the exception of the footnoted tests where lower mean values indicate improved performance.

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

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

Combined RNS® System Studies: Device-Related Serious Adverse Events by Year

As of the data cutoff date, device-related serious adverse events that occurred at any time after implant of the RNS® Neurostimulator and leads in subjects in the Feasibility, Pivotal and Long-term Treatment studies are presented in order of decreasing frequency in *Table 22* on page 45. Adverse events are presented by year from the first through five years post-implant. Adverse events that occurred after the fifth year are included in the total (All Study Periods). The most frequent device-related serious adverse events (occurring in ≥ 2.5% of subjects) were implant site infection (5.9%), premature battery depletion (which required a surgical procedure) (4.3%), medical device removal (3.5%), and device Lead damage (2.7%).

Table 22: Combined Studies – Device-Related Serious Adverse Events by Year

	Year 1	Year 2	Year 3	Year 4	Year 5	All Study Periods[1]
Number of Subjects Entering (N)/ Total Implant years within Interval	**256 / 249.9**	**246 / 240.1**	**235 / 188.6**	**148 / 112.2**	**85 / 60.6**	**256 / 903.4**
SOC Preferred Term	**% (#) Subjects with Event[2]**					
Premature battery depletion	1.6% (4)	2.4% (6)	0.4% (1)	--	--	4.3% (11)
Device lead damage	2.0% (5)	0.4% (1)	0.9% (2)	--	--	2.7% (7)
Device lead revision	0.4% (1)	1.2% (3)	--	--	--	1.6% (4)
Implant site erosion	0.4% (1)	0.4% (1)	--	0.7% (1)	--	1.6% (4)
Extradural hematoma	0.8% (2)	--	--	--	--	0.8% (2)
Device electrical finding[3]	--	--	--	0.7% (1)	--	0.4% (1)
Device malfunction[4]	--	--	--	0.7% (1)	--	0.4% (1)
Intracranial hypotension	--	0.4% (1)	--	--	--	0.4% (1)
Procedural headache	0.4% (1)	--	--	--	--	0.4% (1)
Subdural hematoma	0.4% (1)	--	--	--	--	0.4% (1)
Suture related complication	--	0.4% (1)	--	--	--	0.4% (1)
Cerebral hemorrhage	0.4% (1)	--	1.3% (3)	--	--	1.6% (4)
Hydrocephalus	0.8% (2)	--	--	--	--	0.8% (2)
Implant site infection	2.3% (6)	0.4% (1)	2.1% (5)	1.4% (2)	--	5.9% (15)
Stitch abscess	--	--	0.4% (1)	--	--	0.4% (1)
Medical device removal	0.4% (1)	1.2% (3)	0.9% (2)	0.7% (1)	1.2% (1)	3.5% (9)
Cranioplasty	--	--	--	0.7% (1)	--	0.4% (1)
Implant site discharge	0.4% (1)	--	--	--	--	0.4% (1)
Implant site pain	--	0.4% (1)	--	--	--	0.4% (1)

[1] Row totals may not sum to totals in this column because some subjects may have had SAEs in more than one period. Events beyond year 5 are only included in the total.
[2] % Subjects = # subjects with event / number of subjects entering interval.
[3] Device electrical finding: the battery appeared to be depleting faster than anticipated so was replaced. However, when explanted, the NeuroPace product investigation determined that the device performed as designed.
[4] Device malfunction: subject was unable to interrogate the Neurostimulator after being assaulted in the head so the Neurostimulator was replaced. Post-implant investigation showed normal Neurostimulator function.

Year 1 (implant - Week 52), Year 2 (Weeks 52 - 104), Year 3 (Weeks 104 - 156), Year 4 (Weeks 156 - 208), Year 5 (Weeks 208 - 260)

Combined RNS® System Studies: Deaths and SUDEP Analysis

As of October 24, 2012, there were eleven deaths in the RNS® System trials. One (1) occurred in the Feasibility investigation, 6 in the Pivotal investigation and 4 in the Long-term Treatment investigation. Two (2) of the deaths were suicide (1 each in the Pivotal and LTT studies), 1 was due to lymphoma, 1 was related to complications of status epilepticus and 7 were attributed to possible, probable, or definite SUDEP.

Table 23: Deaths Attributed to SUDEP

Pre-specified Comparator Rate: SUDEP in candidates for epilepsy surgery (Dasheiff, 1991)	9.3 / 1000 patient years
SUDEP in RNS® System Trials	5.9 / 1000 implant years (two-sided 95% C.I. 2.8 - 12.3 / 1000 implant years)

Combined RNS® System Studies Adverse Events of Particular Relevance

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

Intracranial Hemorrhage

Serious adverse events related to intracranial hemorrhage (all hemorrhage categories) occurred in 12 of the 256 implanted subjects (4.7%) over the 903 implant years. Hemorrhages were attributed to seizure-related head trauma in 5 of the 12 subjects. Therefore, the percentage of subjects with SAEs related to intracranial hemorrhage that were not attributed to seizure-related trauma was 2.7% (7 subjects).

Four subjects (1.6%) had a serious adverse event related to intracranial hemorrhage in the first 28 days and 3 of those were within the first 72 hours after implantation of the neurostimulator and leads. These included 2 subjects with epidural hematomas that were evacuated, one subject with a subdural hematoma that required surgical evacuation, and one subject with a small intraventricular hemorrhage identified by CT scan who was observed in the hospital for 1 day. There were no neurological consequences of these hemorrhages.

After the initial month post-implant, there were 8 serious adverse events related to hemorrhage. Two were evacuated, and 1 subject had the neurostimulator and leads explanted at the time the subject withdrew from the study (> 13 months after the event). The remaining patients required no surgical intervention.

Out of the twelve total subjects who experienced serious adverse events related to intracranial hemorrhage, nine subjects had no persistent sequelae from the intracranial hemorrhage. Three subjects had sequelae, which included 1 subject with worsening of a pre-existing memory deficit, 1 subject with a persistent right hand paresis and 1 subject who reported an ongoing headache.

Infection

Serious adverse events related to infections at the implant site occurred in 18 subjects (7.0%) over the 903 implant years. In 2 of the 18 subjects, the implant site infection was attributed to seizure-related head trauma. Therefore, the percentage of subjects with serious infection was 6.3%.

One infection was diagnosed by a positive culture prior to implantation of the neurostimulator and leads; this was believed to be an incompletely treated infection that began with implantation of intracranial electrodes for video-EEG monitoring 3 years before. All infections were treated with antibiotics with or without drainage or debridement. Eleven (4.3%) subjects had the neurostimulator and/or leads explanted because of infection. One of the subjects was re-implanted after the infection resolved. There were no infections of the brain, no sepsis and no permanent neurological consequences related to infection.

Psychiatric Adverse Events

Many subjects in these studies had a history of depression (49%) and/or suicidality (5.2%). According to responses on the Beck Depression Inventory (BDI-II) during the Baseline Period, 15.6% of subjects had moderate depression before implant and 9.2% endorsed suicidality.

In order to fully capture any adverse event that could be representative of suicidality, suicidality was broadly defined to include the MedDRA preferred terms: suicide attempt, suicidal behavior, suicidal ideation, depression suicidal, self-injurious ideation, and suicide. In the combined studies over the 903 patient years, psychiatric adverse events occurred in a total of 102 of 256 subjects (39.8%). Twenty-one of the 102 subjects had a total of 33 serious adverse events. Serious adverse events were related to depression (1 subject), suicidality (12 subjects; discussed below), acute psychosis (2 subjects, 3 events in 1 subject), chronic psychosis (3 subjects), post-ictal psychosis (1 subject) and conversion disorder (2 subjects). The remaining psychiatric serious adverse events affected 1 subject each and were emotional distress, affect lability, agitation, alcohol abuse and alcohol withdrawal, and an episode of a visual hallucination.

There were 12 subjects with serious suicidality adverse events; some subjects had more than one event. The serious adverse events were: suicide (2), suicidal depression (6), suicide attempt (6), suicidal ideation (2) and suicidal behavior (2). Eleven of the 12 subjects with serious adverse events related to suicidality had a history of suicidality and/or depression or met depression criteria at baseline per BDI-II or CES-D. Fifty-six (56) subjects reported a depression adverse event. One subject had a serious adverse event of depression and 55 had non-serious adverse events. The one serious adverse event was a brief hospitalization because of depression.

Sixteen (16) subjects had adverse events related to memory impairment, all of which were non-serious. Seven of these 16 subjects had a history of memory dysfunction and 11 of the 16 had memory deficits documented by neuropsychological testing obtained prior to implantation.

Adverse Events Related to Changes in Seizures

In the Pivotal Study over the 379 patient implant years of experience, 41 subjects had 70 adverse events related to changes in seizures that were considered serious. The majority of these adverse events were considered serious because the subject was admitted for video-EEG monitoring or hospitalized to modify antiepileptic medications. An increase in complex partial seizure frequency was seen in 6.3% of subjects, and an increase in generalized tonic-clonic seizures in 5.9% and of simple partial motor seizures in 1.6%. A serious exacerbation of complex partial seizures was seen in 2.0%, of generalized tonic-clonic seizures in 4.3% and of simple partial motor seizures in 0.4%. A serious adverse event of a new seizure type occurred in 3 subjects.

Status Epilepticus

There were 10 subjects (3.9%) with serious and non-serious adverse events of status epilepticus. There were 16 serious adverse events related to status epilepticus in 8 subjects (3.1%) implanted with the neurostimulator and leads. One additional subject had convulsive status epilepticus after the RNS® System was explanted but before the subject had withdrawn from the study; the status occurred when the patient had AEDs tapered during an EEG monitoring procedure with intracranial electrodes.

Of the subjects implanted with the neurostimulator and leads, 6 episodes were convulsive and 10 were non-convulsive (note that if the type of status was not known, it was coded as convulsive). Seven subjects had 1 episode of status epilepticus and 1 subject had 9 episodes. In addition, there was one subject with a single episode of nonconvulsive status that was considered non-serious. None of the events occurred acutely at the time responsive stimulation was enabled (all events occurred during the open period at least 1 month after enabling responsive stimulation).

Seizure-Related Injury

In the combined studies over the 903 patient implant years, there were 402 non-serious and serious events of injury related to a seizure occurring in 126 subjects (49.2%). Thirty-two serious events of injury related to a seizure occurred in 23 subjects (9.0%). Head injury due to a seizure occurred 31 times in 27 subjects (10.5%). Two of the events were considered serious. There were 4 serious intracranial hemorrhages, 3 subdural and one traumatic intracranial hemorrhage. Sixteen (16) subjects sustained skeletal bone fractures due to a seizure, 7 events were considered serious.

Device Failures and Replacements

Serious adverse events requiring replacement of the neurostimulator and/or leads included premature battery malfunction, presumed neurostimulator malfunction, lead damage, and lead revision.

Neurostimulator

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

Two subjects had their neurostimulator replaced due to presumed malfunction. One required a neurostimulator replacement after being assaulted and struck with a board on the head at the site of the neurostimulator. After the assault, the subject was unable to interrogate the neurostimulator; however post-implant investigation showed normal neurostimulator function.

The reasons for neurostimulator replacement or explant are shown in *Table 24* on page 48.

Table 24: Neurostimulator Explant or Replacement Reasons

Reason	Device Explant	Device Replacement	Total
Expected battery depletion	0	265	265
Infection or skin erosion	13	3	16
Lead revision	0	11	11
Premature battery depletion	0	11	11
Other[1]	15	6	21
Total	**28**	**296**	**324**

[1] Other includes explant for epilepsy surgery (7) or due to lack of efficacy (3) or to pursue other treatments (2), no reason provided (4), unrelated CSF leak (1), cerebral hemorrhage (1), ongoing complaints (1), not implanted (1), and presumed malfunction due to head trauma (1).

There were 28 neurostimulator explant procedures. Thirteen neurostimulators were explanted due to infection (11 subjects) or scalp erosion at the incision site (2 subjects); 2 were reimplanted at a later date. Other reasons for neurostimulator explant included epilepsy surgery (7), insufficient efficacy (3), to pursue other treatments (2), ongoing complaints (1), cerebral hemorrhage (1) and no reason provided (1).

Two hundred and sixty-five (265) of the 296 replacements were due to expected battery depletion. The Kaplan-Meier estimate of the median time to replacement due to expected battery depletion was 2.2 years. Three (3) neurostimulators were replaced due to infection or erosion. Eleven (11) neurostimulators were replaced during a procedure for lead revision. Eleven (11) neurostimulators were replaced due to premature battery depletion. Other reasons for neurostimulator replacement included a replacement after a procedure to stop an unrelated CSF leak (1), and presumed malfunction due to head trauma (1). One (1) neurostimulator was found to be non-functional immediately upon implantation (at a replacement procedure); the device was removed and replaced before the operative site was closed. No reasons were provided for 3 additional replacement procedures.

Lead Revisions

Table 25 on page 49 provides a summary of reasons for lead revisions. The most common type of lead "revision" was to change the leads that were initially connected to ones that had been previously implanted but not connected at the initial surgery.

There were 11 procedures to replace (9) or revise (2) a total of 14 damaged leads in 10 subjects. One subject's leads passed between the skull and a titanium plate and required 2 procedures to replace damaged leads; during the first procedure, 2 damaged leads required replacement, during the second procedure, 1 damaged lead required replacement. Two subjects also required 2 leads to be revised; during a routine neurostimulator replacement procedure, the 2 leads that were originally connected to the neurostimulator were inadvertently cut and the neurosurgeon connected the other 2 previously implanted

and intact leads to the neurostimulator. The remaining 7 subjects each underwent one surgical procedure to replace one damaged lead.

There were 27 procedures in which the leads were revised to change the location for sensing and stimulation. In 18 of the procedures a previously implanted lead was connected. In 9 cases, the lead revision was performed to improve lead placement over the epileptogenic region: in 5 procedures, new leads were implanted (3 were lead replacements and 2 were new lead implants), and in 4 procedures, previously implanted leads were repositioned.

There were an additional 10 lead revision procedures. These were to: implant a new lead (4), connect a lead that was already implanted to the neurostimulator (4), replace a lead due to high impedance (1), and to replace leads after a procedure to stop an unrelated cerebrospinal fluid leak (1).

There were 24 procedures in which leads were explanted or abandoned at the same time that the neurostimulator was removed; 9 were due to infection, 7 were due to epilepsy surgery, 3 were due to insufficient efficacy, 2 were done to pursue other treatments, 1 was after a cerebral hemorrhage, 1 was as a result of ongoing complaints and 1 subject had no reason provided.

Table 25: Lead Revision Reasons

Reason for Revision	Number of Procedures
Lead damage	11
Infection or skin erosion	9
Change in Lead placement or connection	27
Other - Lead implants and replacements [no reason given (8), CSF leak (1), high impedance (1)]	10
Other - Lead explants (or abandoned) [discontinuation with explant (10), reimplanted following epilepsy surgery (2), other (3)]	15

Other Neurosurgical Procedures

There were five other neurosurgical procedures during the Long-Term Treatment trial. One subject had a cranioplasty to repair a skull defect after removal of an RNS® System neurostimulator. Four subjects underwent therapeutic resective epilepsy surgeries. One of these subjects had a right amygdalo-hippocampectomy 1267 days after initial implant. The neurostimulator and a right temporal depth lead was left in place and the subject continued to be treated with responsive stimulation. A second subject had a resection of a seizure focus 1504 days after initial implant. The neurostimulator and leads were left in place and the subject continued to receive responsive stimulation. A third subject had a resection of a seizure focus in the frontal premotor cortex 1700 days after initial implant. The RNS® System was explanted prior to and re-implanted subsequent to the resection, and the subject continued to be treated with responsive stimulation. A fourth subject had a resection of a seizure focus in the left frontal lobe 2444 days after initial implant. The RNS® System was explanted prior to and re-implanted subsequent to the resection, and the subject continued to be treated with responsive stimulation.

Withdrawals and Discontinuations

As of May 12, 2011, 43 of 256 (16.8%) subjects in the combined 3 studies discontinued treatment. The Feasibility study had 6 of 65 subjects discontinue prior to full participation. The Pivotal study had 16 of 191 subjects discontinue. Two hundred twenty-eight (228) of the 234 subjects who completed the Feasibility and Pivotal studies chose to transition to the LTT study (6 subjects did not transition). In addition, 2 patients who discontinued the Pivotal study later enrolled in the LTT study for a total of 230 LTT study subjects. As of May 12, 2011, the LTT study had 21 of 230 subjects discontinue. An additional 2 subjects have died since May 12, 2011, bringing the total to 45 subjects who had discontinued treatment.

For the subjects who discontinued treatment, 7 subjects were explanted because of infection, 1 subject was explanted because of hemorrhage, 3 subjects were lost to follow-up, 9 subjects died and 23 subjects withdrew electively. The reasons for elective withdrawal included: to pursue other treatments (13), because the reduction in seizures was not sufficient (4), and because the subject did not want to have the neurostimulator replaced when the battery reached expected end of service (3). Another subject had a

seizure-related fall that caused a scalp laceration that exposed the neurostimulator: this subject chose not to have the laceration sutured and withdrew from the trial. Another subject was withdrawn because the physician felt that the subject was no longer a suitable candidate to participate because of psychiatric issues not related to treatment with the RNS® System. The reason for withdrawal for one subject was not specified.

Potential Adverse Effects of the Device on Health

Possible complications of the RNS® System include those related to the implantation procedure, those related to performance of the neurostimulator and leads and those related to long-term patient tolerance of the implant. Adverse events which may potentially occur, but were not reported in the clinical trials for the RNS® System, include:

- Allergic reaction to the implanted material
- Brain abscess

Stimulation Parameters and Detection Algorithm

The initial recommended stimulation settings were a frequency of 200 Hz, a pulse duration of 160 µs, and a 100 ms burst duration. Subsequent changes in detection and stimulation parameters were not specified by the protocol. Stimulation settings could be modified by the investigator based on subject status, subject perception of stimulation (for the Treatment group) and the presence of afterdischarges. With the exception of 1 Hz frequency and 1000 µs pulse duration, subjects used the full range of available stimulation parameters. The range of stimulation parameters that were used in the Pivotal study are provided in *Table 26* on page 50.

Table 26: Range of Stimulation Parameters used in the Pivotal Study

	Min	Max
Current Amplitude (mA)	0.5	12
Burst Duration (ms)	10	5000
Pulse Width (µs)	40	480
Frequency (Hz)	1	333.3
Stimulation Therapy Limit (per day)	1000	9000

A Line Length detector with a 75% threshold (to detect small changes in amplitude) was recommended as an initial detector in the clinical trials. However, physicians could use any of the detectors on a given channel based on the ECoG patterns that were of interest in that subject. Initial programmings were Line Length detector (52% of subjects), Bandpass detectors set to detect a wide range of frequencies (82%), and a combination of Line Length and Bandpass detectors (40%) when the intent was to detect changes in frequency and amplitude.

Initial detection settings were modified in 83% of subjects after the physician reviewed the stored ECoGs. Overall, the most common detectors used during the Pivotal study were Bandpass detectors (98% of subjects) to detect rhythmic activity of specific frequencies. The two most common Bandpass settings detected rhythmic frequencies of 0.5 – 125.0 Hz (25%) or rhythmic frequencies of 10.3 – 62.5 Hz (17%). The second most common detector was a Line Length detector (60% of subjects). The Line Length detector threshold was reduced if the physician chose to have smaller changes in amplitude detected and was increased if larger changes were to be detected. The two most common Line Length thresholds were 75% (55% of subjects) and 50% (42% of subjects). Area detectors, which detect changes in signal power, were infrequently used.

Up to four detectors could be enabled at the same time. *Table 27* on page 51 describes the number of subjects using specific combinations of detectors.

Table 27: Detection Programming Over the Pivotal Study

Detectors	Subjects programmed to these detector settings at any time in the Pivotal study[1]
Bandpass Detectors Only	121/191 (63%)
Bandpass + Line Length Detectors	115 (60%)
Line Length Detectors Only	34 (18%)
Bandpass + Area Detectors	11 (6%)
Bandpass + Line Length + Area Detectors	11 (6%)

[1] Detectors were adjusted over the course of the clinical study. Therefore, a single subject can be represented more than once

During the Pivotal study, 76% of subjects' neurostimulators were initially programmed to the default stimulation settings (frequency = 200 Hz, pulse width = 160 µs, burst duration = 100 ms). The physician varied current amplitude as necessary. Stimulation programming was changed in all but 4 subjects over the 2 post-implant years. Burst duration was adjusted in 55%, frequency in 52%, and pulse width in 21% of subjects.

Very few subjects used any of the additional responsive stimulation therapy options (see *Table 28* on page 51). These were: Pattern Specific Therapy (each detector triggers a different stimulation setting); Adaptive Therapy (the stimulation frequency adjusts with the ECoG frequency); Synchronized Stimulation (stimulation is delivered into a specific part of the ECoG waveform); and Post Episode Monitoring/Post Episode Monitoring Interval (responsive therapies are disabled for a specified period of time after detecting the end of the episode). *Table 28* on page 51 provides the number and percentage of subjects who were treated with any of the additional stimulation therapy options.

Table 28: Additional Responsive Stimulation Therapy Options

	Number and (%) of Subjects Programmed
Pattern Specific Therapy	29 (15%)
Adaptive Therapy	4 (2%)
Synchronized Stimulation	3 (2%)
Post-Episode Monitoring Interval	4 (2%)

The investigator determined which electrocorticographic records would be stored in the neurostimulator by selecting one of four possible storage categories. These included time of day, duration of detection, sustained high amplitude and when the magnet was swiped over the neurostimulator by the patient. Analysis of the electrocorticograms and the method by which they were stored was not an intent of this study.

Conclusions Drawn from the Studies

Effectiveness

The RNS® System Pivotal Investigation has demonstrated that responsive stimulation as delivered by the RNS® System reduces the frequency of disabling seizures in a population of persons with medically intractable partial seizures arising from 1 or 2 foci. Statistically significant seizure reduction was achieved in a group receiving responsive stimulation (Treatment group) compared to a group receiving no stimulation (Sham group). As estimated using a post-hoc generalized estimating equation model (GEE model), over the entire Blinded Evaluation Period, the Treatment group experienced a reduction in seizure frequency of 37.9% compared to a 17.3% reduction in the Sham group; this difference is statistically significant ($p = 0.012$). There was no significant difference between the Treatment and the Sham groups on the secondary endpoints, i.e. responder rate, change in mean seizure frequency, proportion of seizure-free days or seizure severity as assessed using the Liverpool Seizure Severity Scale.

There was a reduction in seizures over the Open Label Period. At 1 year, 44% of subjects experienced a 50% or greater reduction in seizures and at 2 years 55% of the subjects experienced a 50% or greater reduction in seizures. However, without a comparative group and with changes in AEDs the open label data are not conclusive evidence for continued effectiveness.

Safety

Safety was demonstrated in the Feasibility and Pivotal studies in a comparison with historical controls that included procedures related to epilepsy surgery (implantation of intracranial electrodes for purposes of localizing the seizure focus and the epilepsy surgery procedure) and implantation of deep brain stimulation (DBS) systems for treatment of movement disorders. During the evaluation periods, there was no difference between the Treatment and Sham groups in the overall percentage of subjects experiencing a serious adverse event, or any specific type of serious adverse event.

The total number of subjects that experienced any serious or non-serious adverse event during the Blinded Evaluation Period were 90/97 (92.8%) for the Treatment group and 88/94 (93.6%) for the Sham group. There were 55 serious adverse events (38 subjects) from the time of implant through the end of the Blinded Evaluation Period (20 weeks post-implantation). These included 7 subjects with implant site infection, 5 with intracranial hemorrhages, 3 subjects requiring the repositioning or removal of the lead, and a single subject with bacterial meningitis diagnosed before implant of the neurostimulator and leads.

Over the entire RNS® Studies experience in 256 subjects with over 903 patient years of implant experience and 819 patient years of responsive stimulation, there were no serious unanticipated device-related adverse events. The device-related serious adverse events reported with the greatest frequency were implant site infection (5.9%; 3.1% requiring explant), premature battery depletion (4.3%), and medical device removal (3.5%). The percentage of subjects with serious non-seizure related intracranial hemorrhage was 2.7%. Serious adverse events related to depression or suicidality were reported for 5.1% of subjects. Serious adverse events related to a change in seizures occurred in 16% of subjects; no subject withdrew from the study because of seizure related adverse events. Three percent of subjects had a serious adverse event related to convulsive or non-convulsive status epilepticus. Nine percent of subjects had a serious adverse event due to seizure related injury.

Over the combined RNS® System clinical studies, as of October 24, 2012, there were 11 deaths. Two deaths were by suicide, one was due to status epilepticus, one was due to lymphoma, and seven were attributed by an independent SUDEP adjudication committee to possible, probable, or definite SUDEP.

There can be no assurances that additional long-term data will not reveal new adverse information presently unknown to NeuroPace. However, two year data shows no increase or worsening of adverse events.

Risk Benefit Analysis

The clinical experience from the RNS® System Clinical Investigations demonstrates that the benefits of seizure reduction outweigh the risks. The Pivotal study data showed that treatment of medically intractable partial onset epilepsy with responsive stimulation as provided by the RNS® System reduces the frequency of disabling seizures. An analysis of safety data combined from the Feasibility, Pivotal and Long-term Treatment Clinical Investigations and a review of the related published literature suggests that the safety of the RNS® System is equivalent to comparable procedures: implantation of intracranial electrodes for localization of the seizure focus, epilepsy surgery and DBS for movement disorders. Therefore, the NeuroPace® RNS® System has demonstrated safety and effectiveness as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than 2 epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and / or secondarily generalized seizures). The RNS® System has demonstrated safety and effectiveness in patients who average 3 or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures. There can be no assurances that the efficacy of the RNS® System will not decline over time, nor can there be assurances that additional long-term data will not reveal new adverse information presently unknown to NeuroPace. However, two year data shows no increase or worsening of adverse events and for those subjects who reached 2 years post-implant, 55% of the subjects experienced a 50% or greater reduction in seizures.

Bibliography

A bibliography of animal and clinical studies is available from NeuroPace on request.

Additional Adverse Event Data

Table 29: All Adverse Events in Subjects During the Post-operative Stabilization Period

MedDRA Preferred Term	% (#) Subjects with events (N = 191)
Implant site pain	28.3% (54)
Procedural headache	27.2% (52)
Procedural nausea	4.7% (9)
Implant site swelling	4.2% (8)
Dizziness	3.7% (7)
Postoperative constipation	3.7% (7)
Swelling face	3.7% (7)
Postoperative fever	3.1% (6)
Therapeutic agent toxicity	3.1% (6)
Adverse drug reaction	2.6% (5)
Implant site infection	2.6% (5)
Decreased appetite	2.1% (4)
Device interaction	2.1% (4)
Hypoacusis	2.1% (4)
Insomnia	2.1% (4)
Neck pain	2.1% (4)
Pain in jaw	2.1% (4)
Procedural vomiting	2.1% (4)
Simple partial seizures (motor)	2.1% (4)
Skin laceration (dts)	2.1% (4)
Anxiety	1.6% (3)
Aphasia	1.6% (3)
Contusion (dts)	1.6% (3)
Extradural haematoma	1.6% (3)
Fatigue	1.6% (3)
Hydrocephalus	1.6% (3)
Impaired healing	1.6% (3)
Muscle twitching	1.6% (3)
Nasopharyngitis	1.6% (3)
Pain in extremity	1.6% (3)
Photophobia	1.6% (3)
Rash	1.6% (3)
Simple partial seizures (sensory)	1.6% (3)

MedDRA Preferred Term	% (#) Subjects with events (N = 191)
Upper respiratory tract infection	1.6% (3)
Urinary tract infection	1.6% (3)
Balance disorder	1.0% (2)
Cerebral haemorrhage	1.0% (2)
Complex partial seizures increased	1.0% (2)
Dizziness postural	1.0% (2)
Facial pain	1.0% (2)
Hiccups	1.0% (2)
Implant site discharge	1.0% (2)
Implant site paraesthesia	1.0% (2)
Memory impairment	1.0% (2)
Monoparesis	1.0% (2)
Nephrolithiasis	1.0% (2)
Paraesthesia	1.0% (2)
Postictal state	1.0% (2)
Tinnitus	1.0% (2)
Tremor	1.0% (2)
Vision blurred	1.0% (2)
Acne	0.5% (1)
Acquired epileptic aphasia	0.5% (1)
Agitation postoperative	0.5% (1)
Altered visual depth perception	0.5% (1)
Application site excoriation	0.5% (1)
Apraxia	0.5% (1)
Arthralgia	0.5% (1)
Ataxia	0.5% (1)
Atelectasis	0.5% (1)
Axillary candidiasis	0.5% (1)
Back injury (dts)	0.5% (1)
Biopsy brain	0.5% (1)
Blepharospasm	0.5% (1)
Brain oedema	0.5% (1)
Catheter site pain	0.5% (1)
Catheter site rash	0.5% (1)
Cerebellar syndrome	0.5% (1)

MedDRA Preferred Term	% (#) Subjects with events (N = 191)
Cerumen impaction	0.5% (1)
Complex partial seizures	0.5% (1)
Complex partial seizures exacerbated	0.5% (1)
Confusional state	0.5% (1)
Contusion	0.5% (1)
Coordination abnormal	0.5% (1)
Decubitus ulcer	0.5% (1)
Deep vein thrombosis	0.5% (1)
Depression	0.5% (1)
Depression suicidal	0.5% (1)
Device lead revision	0.5% (1)
Diarrhoea	0.5% (1)
Diplopia	0.5% (1)
Drug hypersensitivity	0.5% (1)
Drug withdrawal syndrome	0.5% (1)
Dysaesthesia	0.5% (1)
Dyskinesia	0.5% (1)
Dysphasia	0.5% (1)
Dysphemia	0.5% (1)
Ear discomfort	0.5% (1)
Ear infection	0.5% (1)
Eye irritation	0.5% (1)
Facial paresis	0.5% (1)
Feeling abnormal	0.5% (1)
Gait disturbance	0.5% (1)
Gastroenteritis	0.5% (1)
Generalised oedema	0.5% (1)
Head injury	0.5% (1)
Headache	0.5% (1)
Hearing impaired	0.5% (1)
Hepatic enzyme increased	0.5% (1)
Hyperhidrosis	0.5% (1)
Hypoaesthesia	0.5% (1)
Implant site effusion	0.5% (1)
Implant site pruritus	0.5% (1)

MedDRA Preferred Term	% (#) Subjects with events (N = 191)
Incision site haemorrhage (dts)	0.5% (1)
Incision site infection	0.5% (1)
Lethargy	0.5% (1)
Meningitis bacterial	0.5% (1)
Multiple injuries (dts)	0.5% (1)
Musculoskeletal pain	0.5% (1)
Musculoskeletal stiffness	0.5% (1)
Myalgia	0.5% (1)
Night sweats	0.5% (1)
Nystagmus	0.5% (1)
Oedema peripheral	0.5% (1)
Panic attack	0.5% (1)
Pneumothorax	0.5% (1)
Polyuria	0.5% (1)
Post procedural diarrhoea	0.5% (1)
Procedural dizziness	0.5% (1)
Procedural hypertension	0.5% (1)
Removal of foreign body from external ear	0.5% (1)
Retching	0.5% (1)
Sciatica	0.5% (1)
Seasonal allergy	0.5% (1)
Simple partial seizures exacerbated (sensory)	0.5% (1)
Simple partial seizures increased (sensory)	0.5% (1)
Subdural haematoma	0.5% (1)
Syncope	0.5% (1)
Tachycardia	0.5% (1)
Tooth infection	0.5% (1)
Tooth injury	0.5% (1)
Urinary retention postoperative	0.5% (1)
Visual acuity reduced	0.5% (1)
Visual acuity reduced transiently	0.5% (1)
Visual field defect	0.5% (1)
Vomiting	0.5% (1)
Wrist fracture (dts)	0.5% (1)

Table 30: Adverse Events in Subjects by Study Period through 2 Years

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
# of subjects entering interval / implant years within interval	**191 / 379.2**	**191 / 14.7**	**191 / 14.6**	**189 / 43.2**	**187 / 113.4**	**182 / 193.4**
SOC / MedDRA Preferred Term	**% subjects (# subjects)** [1]					
Summary of All AEs in Period	**100.0% (191)**	**75.9% (145)**	**51.3% (98)**	**69.8% (132)**	**87.7% (164)**	**91.2% (166)**
Nervous system disorders	**82.2% (157)**	**25.7% (49)**	**20.9% (40)**	**28.0% (53)**	**52.9% (99)**	**55.5% (101)**
Headache	25.1% (48)	0.5% (1)	6.3% (12)	6.3% (12)	12.8% (24)	8.8% (16)
Complex partial seizures increased	15.7% (30)	1.0% (2)	0.5% (1)	3.7% (7)	8.6% (16)	6.6% (12)
Dizziness	13.1% (25)	3.7% (7)	1.6% (3)	0.5% (1)	3.2% (6)	4.9% (9)
Complex partial seizures	12.6% (24)	0.5% (1)	2.1% (4)	1.6% (3)	5.3% (10)	6.0% (11)
Dysaesthesia	12.6% (24)	0.5% (1)	2.1% (4)	3.7% (7)	5.3% (10)	3.8% (7)
Simple partial seizures (sensory)	11.0% (21)	1.6% (3)	1.6% (3)	1.1% (2)	5.3% (10)	3.3% (6)
Complex partial seizures exacerbated	9.9% (19)	0.5% (1)	--	1.6% (3)	4.8% (9)	4.4% (8)
Tonic-clonic seizures exacerbated	9.9% (19)	--	1.0% (2)	--	6.4% (12)	3.3% (6)
Tremor	9.9% (19)	1.0% (2)	1.6% (3)	0.5% (1)	4.8% (9)	3.8% (7)
Tonic-clonic seizures increased	9.4% (18)	--	0.5% (1)	0.5% (1)	5.9% (11)	4.4% (8)
Insomnia	8.4% (16)	2.1% (4)	1.6% (3)	0.5% (1)	4.3% (8)	1.6% (3)
Memory impairment	8.4% (16)	1.0% (2)	0.5% (1)	0.5% (1)	4.3% (8)	2.7% (5)
Paraesthesia	6.8% (13)	1.0% (2)	--	1.6% (3)	2.7% (5)	2.7% (5)
Photopsia	6.3% (12)	--	1.0% (2)	--	4.3% (8)	1.6% (3)
Simple partial seizures (motor)	6.3% (12)	2.1% (4)	1.0% (2)	1.6% (3)	2.1% (4)	2.2% (4)
Nystagmus	5.2% (10)	0.5% (1)	1.0% (2)	1.1% (2)	--	2.7% (5)
Confusional state	4.7% (9)	0.5% (1)	--	--	2.7% (5)	2.2% (4)
Somnolence	4.7% (9)	--	0.5% (1)	0.5% (1)	--	3.8% (7)
Balance disorder	4.2% (8)	1.0% (2)	0.5% (1)	1.6% (3)	1.6% (3)	0.5% (1)
Postictal state	4.2% (8)	1.0% (2)	1.0% (2)	--	1.6% (3)	1.1% (2)

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Migraine	3.7% (7)	--	0.5% (1)	1.1% (2)	1.1% (2)	1.1% (2)
Simple partial seizures increased (motor)	3.7% (7)	--	--	0.5% (1)	2.1% (4)	1.1% (2)
Aphasia	3.1% (6)	1.6% (3)	0.5% (1)	--	--	1.1% (2)
Dizziness postural	3.1% (6)	1.0% (2)	--	--	1.1% (2)	1.1% (2)
Hypoaesthesia	3.1% (6)	0.5% (1)	0.5% (1)	0.5% (1)	0.5% (1)	1.1% (2)
Simple partial seizures exacerbated (motor)	3.1% (6)	--	--	0.5% (1)	1.6% (3)	1.1% (2)
Simple partial seizures increased (sensory)	3.1% (6)	0.5% (1)	--	0.5% (1)	1.6% (3)	0.5% (1)
Dyskinesia	2.6% (5)	0.5% (1)	--	--	1.6% (3)	0.5% (1)
Monoparesis	2.6% (5)	1.0% (2)	--	--	1.1% (2)	0.5% (1)
Sciatica	2.6% (5)	0.5% (1)	--	1.1% (2)	0.5% (1)	0.5% (1)
Simple partial seizures exacerbated (sensory)	2.6% (5)	0.5% (1)	0.5% (1)	--	1.1% (2)	1.6% (3)
Syncope	2.6% (5)	0.5% (1)	0.5% (1)	--	--	1.6% (3)
Ataxia	2.1% (4)	0.5% (1)	0.5% (1)	--	--	1.1% (2)
Cerebellar syndrome	2.1% (4)	0.5% (1)	--	1.1% (2)	0.5% (1)	--
Dysarthria	2.1% (4)	--	--	--	1.1% (2)	1.1% (2)
Peripheral nerve injury	2.1% (4)	--	0.5% (1)	1.6% (3)	--	0.5% (1)
Visual field defect	2.1% (4)	0.5% (1)	0.5% (1)	--	0.5% (1)	0.5% (1)
Atonic seizures increased	1.6% (3)	--	--	--	--	1.6% (3)
Coordination abnormal	1.6% (3)	0.5% (1)	0.5% (1)	--	--	0.5% (1)
Disturbance in attention	1.6% (3)	--	0.5% (1)	--	0.5% (1)	0.5% (1)
Hydrocephalus	1.6% (3)	1.6% (3)	--	--	--	--
Lethargy	1.6% (3)	0.5% (1)	--	--	0.5% (1)	0.5% (1)
Photophobia	1.6% (3)	1.6% (3)	--	--	--	--
Tonic-clonic seizures	1.6% (3)	--	--	--	1.1% (2)	0.5% (1)
Acquired epileptic aphasia	1.0% (2)	0.5% (1)	--	--	0.5% (1)	--
Atonic seizures	1.0% (2)	--	--	1.1% (2)	--	--
Atonic seizures exacerbated	1.0% (2)	--	--	--	--	1.1% (2)

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Blindness transient	1.0% (2)	--	--	0.5% (1)	0.5% (1)	--
Cerebral haemorrhage	1.0% (2)	1.0% (2)	--	--	--	--
Convulsive status epilepticus	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Dysgeusia	1.0% (2)	--	--	--	1.1% (2)	--
Dysphasia	1.0% (2)	0.5% (1)	--	0.5% (1)	--	--
Nonconvulsive status epilepticus	1.0% (2)	--	--	--	1.1% (2)	--
Sleep apnea	1.0% (2)	--	--	--	1.1% (2)	--
Abnormal dreams	0.5% (1)	--	0.5% (1)	--	--	--
Alexia	0.5% (1)	--	--	0.5% (1)	0.5% (1)	--
Altered visual depth perception	0.5% (1)	0.5% (1)	--	--	--	--
Anosmia	0.5% (1)	--	--	--	0.5% (1)	--
Apraxia	0.5% (1)	0.5% (1)	--	--	--	--
Aura	0.5% (1)	--	--	--	--	0.5% (1)
Bradyphrenia	0.5% (1)	--	--	--	0.5% (1)	--
Brain oedema	0.5% (1)	0.5% (1)	--	--	--	--
Carpal tunnel syndrome	0.5% (1)	--	--	--	--	0.5% (1)
Disorientation	0.5% (1)	--	--	0.5% (1)	--	--
Dysphemia	0.5% (1)	0.5% (1)	--	--	--	--
Dystonia	0.5% (1)	--	--	--	--	0.5% (1)
Essential tremor	0.5% (1)	--	--	--	--	0.5% (1)
Eyelid ptosis	0.5% (1)	--	0.5% (1)	--	--	--
Facial paresis	0.5% (1)	0.5% (1)	--	--	--	--
Head titubation	0.5% (1)	--	--	--	--	0.5% (1)
Headache (dts)	0.5% (1)	--	--	--	--	0.5% (1)
Hemiparesis	0.5% (1)	--	--	--	0.5% (1)	--
Masked Facies	0.5% (1)	--	--	--	0.5% (1)	--
Mononeuropathy	0.5% (1)	--	--	0.5% (1)	--	--
Myoclonus	0.5% (1)	--	--	--	--	0.5% (1)
Neuropathy peripheral	0.5% (1)	--	--	--	--	0.5% (1)
Scintillating scotoma	0.5% (1)	--	--	--	--	0.5% (1)

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Tonic seizures	0.5% (1)	--	--	0.5% (1)	--	--
Tonic seizures exacerbated	0.5% (1)	--	--	0.5% (1)	0.5% (1)	--
Toxic encephalopathy	0.5% (1)	--	--	--	0.5% (1)	--
Injury, poisoning and procedural complications	**81.7% (156)**	**42.4% (81)**	**15.2% (29)**	**22.8% (43)**	**42.8% (80)**	**50.5% (92)**
Procedural headache	28.8% (55)	27.2% (52)	--	--	1.6% (3)	1.6% (3)
Therapeutic agent toxicity	22.5% (43)	3.1% (6)	0.5% (1)	2.6% (5)	8.6% (16)	11.5% (21)
Contusion (dts)	16.8% (32)	1.6% (3)	1.6% (3)	4.8% (9)	5.9% (11)	6.6% (12)
Skin laceration (dts)	16.2% (31)	2.1% (4)	2.1% (4)	4.8% (9)	5.3% (10)	9.3% (17)
Head injury (dts)	8.9% (17)	--	1.0% (2)	--	1.6% (3)	6.6% (12)
Excoriation (dts)	7.3% (14)	--	0.5% (1)	1.1% (2)	4.8% (9)	2.7% (5)
Head injury	7.3% (14)	0.5% (1)	1.0% (2)	1.6% (3)	2.1% (4)	2.7% (5)
Contusion	6.3% (12)	0.5% (1)	0.5% (1)	1.6% (3)	2.1% (4)	1.6% (3)
Joint injury (dts)	6.3% (12)	--	1.6% (3)	--	2.1% (4)	2.7% (5)
Procedural nausea	6.3% (12)	4.7% (9)	--	--	0.5% (1)	1.1% (2)
Implant site swelling	5.8% (11)	4.2% (8)	0.5% (1)	--	0.5% (1)	0.5% (1)
Joint injury	5.2% (10)	--	--	0.5% (1)	1.6% (3)	3.8% (7)
Multiple injuries (dts)	4.7% (9)	0.5% (1)	--	0.5% (1)	2.1% (4)	3.3% (6)
Skin laceration	4.7% (9)	--	0.5% (1)	1.1% (2)	1.6% (3)	1.6% (3)
Device lead revision	3.7% (7)	0.5% (1)	1.0% (2)	--	0.5% (1)	1.6% (3)
Postoperative constipation	3.7% (7)	3.7% (7)	--	--	--	--
Postoperative fever	3.7% (7)	3.1% (6)	--	--	0.5% (1)	--
Thermal burn	3.7% (7)	--	--	--	2.1% (4)	1.6% (3)
Limb injury	3.1% (6)	--	0.5% (1)	1.1% (2)	1.1% (2)	0.5% (1)
Multiple injuries	3.1% (6)	--	--	1.1% (2)	0.5% (1)	1.6% (3)
Thermal burn (dts)	3.1% (6)	--	--	0.5% (1)	1.1% (2)	1.6% (3)
Back injury	2.6% (5)	--	--	--	1.1% (2)	1.6% (3)
Back injury (dts)	2.6% (5)	0.5% (1)	--	--	1.1% (2)	1.1% (2)
Device lead damage	2.6% (5)	--	--	--	2.7% (5)	0.5% (1)
Excoriation	2.6% (5)	--	0.5% (1)	0.5% (1)	1.1% (2)	0.5% (1)

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Laceration (dts)	2.6% (5)	--	1.0% (2)	1.1% (2)	1.1% (2)	--
Limb injury (dts)	2.6% (5)	--	--	--	2.1% (4)	0.5% (1)
Procedural vomiting	2.6% (5)	2.1% (4)	--	--	--	0.5% (1)
Tongue injury (dts)	2.6% (5)	--	0.5% (1)	--	1.1% (2)	1.1% (2)
Foot fracture	2.1% (4)	--	--	--	1.1% (2)	1.1% (2)
Muscle strain	2.1% (4)	--	--	--	1.1% (2)	1.1% (2)
Road traffic accident	2.1% (4)	--	--	0.5% (1)	1.1% (2)	0.5% (1)
Extradural haematoma	1.6% (3)	1.6% (3)	--	--	--	--
Fall (dts)	1.6% (3)	--	--	0.5% (1)	1.1% (2)	--
Lower limb injury (dts)	1.6% (3)	--	--	0.5% (1)	0.5% (1)	0.5% (1)
Skeletal injury (dts)	1.6% (3)	--	--	0.5% (1)	--	1.1% (2)
Subdural haematoma (dts)	1.6% (3)	--	0.5% (1)	--	0.5% (1)	0.5% (1)
Tooth injury	1.6% (3)	0.5% (1)	0.5% (1)	--	--	0.5% (1)
Chest injury (dts)	1.0% (2)	--	--	--	1.1% (2)	--
Face injury (dts)	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Hand fracture (dts)	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Incision site haemorrhage (dts)	1.0% (2)	0.5% (1)	--	--	--	0.5% (1)
Mouth injury (dts)	1.0% (2)	--	0.5% (1)	--	--	0.5% (1)
Muscle injury (dts)	1.0% (2)	--	0.5% (1)	--	0.5% (1)	--
Post procedural diarrhoea	1.0% (2)	0.5% (1)	--	--	--	0.5% (1)
Premature battery depletion	1.0% (2)	--	--	--	1.1% (2)	--
Procedural dizziness	1.0% (2)	0.5% (1)	--	--	--	0.5% (1)
Vertebral injury (dts)	1.0% (2)	--	0.5% (1)	--	0.5% (1)	--
Wrist fracture (dts)	1.0% (2)	0.5% (1)	--	--	--	0.5% (1)
Agitation postoperative	0.5% (1)	0.5% (1)	--	--	--	--
Alcohol poisoning	0.5% (1)	--	--	0.5% (1)	--	--
Animal bite	0.5% (1)	--	--	--	--	0.5% (1)
Ankle fracture	0.5% (1)	--	--	--	--	0.5% (1)
Ankle fracture (dts)	0.5% (1)	--	--	0.5% (1)	--	--

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Application site excoriation	0.5% (1)	0.5% (1)	--	--	--	--
Arthropod bite	0.5% (1)	--	--	--	--	0.5% (1)
Barotitis media	0.5% (1)	--	--	0.5% (1)	--	--
Catheter site rash	0.5% (1)	0.5% (1)	--	--	--	--
Chest injury	0.5% (1)	--	--	--	--	0.5% (1)
Corneal abrasion	0.5% (1)	--	--	--	--	0.5% (1)
Corneal perforation (dts)	0.5% (1)	--	--	--	--	0.5% (1)
Ear canal abrasion	0.5% (1)	--	--	0.5% (1)	--	--
Ear injury (dts)	0.5% (1)	--	--	--	--	0.5% (1)
Electric shock	0.5% (1)	--	--	--	0.5% (1)	--
Facial bones fracture	0.5% (1)	--	--	--	0.5% (1)	--
Facial bones fracture (dts)	0.5% (1)	--	--	--	0.5% (1)	--
Fall	0.5% (1)	--	--	--	0.5% (1)	--
Foot fracture (dts)	0.5% (1)	--	--	--	0.5% (1)	--
Hand fracture	0.5% (1)	--	--	--	--	0.5% (1)
Hip fracture (dts)	0.5% (1)	--	--	--	--	0.5% (1)
Implant site erosion	0.5% (1)	--	--	--	--	0.5% (1)
Implant site pruritus	0.5% (1)	0.5% (1)	--	--	--	--
Intracranial hypotension	0.5% (1)	--	--	--	--	0.5% (1)
Jaw fracture (dts)	0.5% (1)	--	--	0.5% (1)	--	--
Lower limb fracture	0.5% (1)	--	--	0.5% (1)	--	--
Muscle strain (dts)	0.5% (1)	--	--	--	--	0.5% (1)
Obstetric procedure complication	0.5% (1)	--	--	--	--	0.5% (1)
Periorbital haematoma	0.5% (1)	--	--	--	0.5% (1)	--
Periorbital haematoma (dts)	0.5% (1)	--	--	0.5% (1)	--	--
Road traffic accident (dts)	0.5% (1)	--	--	--	0.5% (1)	--
Scar pain	0.5% (1)	--	--	--	0.5% (1)	--
Sinus barotrauma	0.5% (1)	--	--	--	--	0.5% (1)
Subdural haematoma	0.5% (1)	0.5% (1)	--	--	--	--

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Suture related complication	0.5% (1)	--	--	--	--	0.5% (1)
Tendon rupture	0.5% (1)	--	--	--	--	0.5% (1)
Tooth injury (dts)	0.5% (1)	--	0.5% (1)	--	--	--
Upper limb fracture	0.5% (1)	--	--	--	0.5% (1)	--
Urinary retention postoperative	0.5% (1)	0.5% (1)	--	--	--	--
Infections and infestations	**64.9% (124)**	**8.9% (17)**	**8.9% (17)**	**21.7% (41)**	**34.8% (65)**	**32.4% (59)**
Nasopharyngitis	28.3% (54)	1.6% (3)	4.2% (8)	7.4% (14)	11.2% (21)	12.6% (23)
Upper respiratory tract infection	16.2% (31)	1.6% (3)	0.5% (1)	2.6% (5)	7.5% (14)	7.7% (14)
Influenza	14.7% (28)	--	2.1% (4)	3.7% (7)	5.9% (11)	7.1% (13)
Urinary tract infection	9.4% (18)	1.6% (3)	0.5% (1)	1.1% (2)	3.2% (6)	3.3% (6)
Implant site infection	5.2% (10)	2.6% (5)	0.5% (1)	--	1.1% (2)	1.6% (3)
Sinusitis	4.2% (8)	--	0.5% (1)	1.1% (2)	1.6% (3)	1.6% (3)
Tooth infection	3.7% (7)	0.5% (1)	--	1.6% (3)	1.1% (2)	1.1% (2)
Incision site infection	3.1% (6)	0.5% (1)	--	1.1% (2)	0.5% (1)	1.6% (3)
Pharyngitis	3.1% (6)	--	--	2.1% (4)	1.1% (2)	1.1% (2)
Pneumonia	3.1% (6)	--	--	1.1% (2)	1.1% (2)	2.2% (4)
Ear infection	2.6% (5)	0.5% (1)	--	--	1.6% (3)	0.5% (1)
Skin infection	1.6% (2)	--	0.5% (1)	0.5% (1)	--	0.5% (1)
Implant site infection (dts)	1.0% (2)	--	0.5% (1)	0.5% (1)	--	--
Oral herpes	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Pharyngitis streptococcal	1.0% (2)	--	--	0.5% (1)	--	0.5% (1)
Staphylococcal infection	1.0% (2)	--	--	--	1.1% (2)	--
Vaginal infection	1.0% (2)	--	--	--	1.1% (2)	--
Appendicitis	0.5% (1)	--	--	--	0.5% (1)	--
Axillary candidiasis	0.5% (1)	0.5% (1)	--	--	--	--
Bed bug infestation	0.5% (1)	--	--	--	--	0.5% (1)
Cellulitis	0.5% (1)	--	--	--	0.5% (1)	--
Cervicitis	0.5% (1)	--	--	--	0.5% (1)	--
Hordeolum	0.5% (1)	--	--	--	0.5% (1)	--

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Infected sebaceous cyst	0.5% (1)	--	--	--	--	0.5% (1)
Infection	0.5% (1)	--	--	--	0.5% (1)	--
Meningitis bacterial	0.5% (1)	0.5% (1)	--	--	--	--
Onychomycosis	0.5% (1)	--	--	0.5% (1)	--	--
Oral candidiasis	0.5% (1)	--	--	--	--	0.5% (1)
Peritoneal infection	0.5% (1)	--	--	--	0.5% (1)	--
Prostate infection	0.5% (1)	--	--	0.5% (1)	--	--
Stitch abscess	0.5% (1)	--	--	--	0.5% (1)	--
General disorders and administration site conditions	**63.9% (122)**	**36.1% (69)**	**6.8% (13)**	**11.6% (22)**	**19.3% (36)**	**29.1% (53)**
Implant site pain	37.7% (72)	28.3% (54)	2.6% (5)	2.1% (4)	4.3% (8)	9.3% (17)
Adverse drug reaction	16.8% (32)	2.6% (5)	1.0% (2)	2.6% (5)	5.9% (11)	8.8% (16)
Fatigue	8.9% (17)	1.6% (3)	--	0.5% (1)	2.7% (5)	4.9% (9)
Device interaction	5.8% (11)	2.1% (4)	0.5% (1)	1.1% (2)	2.1% (4)	0.5% (1)
Implant site paraesthesia	4.7% (9)	1.0% (2)	1.0% (2)	1.6% (3)	--	1.1% (2)
Death	3.1% (6)	--	0.5% (1)	--	1.6% (3)	1.1% (2)
Pyrexia	2.6% (5)	--	--	0.5% (1)	1.1% (2)	1.1% (2)
Gait disturbance	2.1% (4)	0.5% (1)	--	--	1.1% (2)	0.5% (1)
Implant site scar	2.1% (4)	--	0.5% (1)	0.5% (1)	--	1.1% (2)
Non-cardiac chest pain	2.1% (4)	--	0.5% (1)	--	0.5% (1)	1.1% (2)
Impaired healing	1.6% (3)	1.6% (3)	--	--	--	--
Implant site discharge	1.6% (3)	1.0% (2)	--	0.5% (1)	0.5% (1)	--
Oedema peripheral	1.6% (3)	0.5% (1)	--	--	--	1.1% (2)
Catheter site pain	1.0% (2)	0.5% (1)	--	--	--	0.5% (1)
Chest pain	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Drug withdrawal syndrome	1.0% (2)	0.5% (1)	--	0.5% (1)	--	--
Facial pain	1.0% (2)	1.0% (2)	--	--	--	--
Generalised oedema	1.0% (2)	0.5% (1)	--	--	0.5% (1)	--
Hernia	1.0% (2)	--	--	0.5% (1)	0.5% (1)	--
Night sweats	1.0% (2)	0.5% (1)	--	--	0.5% (1)	--
Procedural pain	1.0% (2)	--	--	0.5% (1)	--	0.5% (1)

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Alcoholic hangover	0.5% (1)	--	--	0.5% (1)	--	--
Facial swelling	0.5% (1)	--	--	0.5% (1)	--	--
Feeling abnormal	0.5% (1)	0.5% (1)	--	--	--	--
Flushing	0.5% (1)	--	--	--	0.5% (1)	--
Hyperhidrosis	0.5% (1)	0.5% (1)	--	--	--	--
Implant site atrophy	0.5% (1)	--	--	--	0.5% (1)	--
Implant site effusion	0.5% (1)	0.5% (1)	--	--	--	--
Local swelling	0.5% (1)	--	--	--	--	0.5% (1)
Thirst	0.5% (1)	--	--	--	0.5% (1)	--
Musculoskeletal and connective tissue disorders	**31.9% (61)**	**8.9% (17)**	**3.7% (7)**	**6.3% (12)**	**10.7% (20)**	**15.4% (28)**
Pain in extremity	6.8% (13)	1.6% (3)	0.5% (1)	1.6% (3)	1.1% (2)	2.2% (4)
Muscle twitching	6.3% (12)	1.6% (3)	1.6% (3)	0.5% (1)	2.7% (5)	1.1% (2)
Arthralgia	5.2% (10)	0.5% (1)	--	0.5% (1)	1.6% (3)	3.8% (7)
Back pain	5.2% (10)	--	--	0.5% (1)	2.7% (5)	2.2% (4)
Pain in jaw	4.2% (8)	2.1% (4)	--	1.1% (2)	--	1.6% (3)
Neck pain	3.7% (7)	2.1% (4)	--	--	0.5% (1)	1.1% (2)
Myalgia	2.6% (5)	0.5% (1)	0.5% (1)	0.5% (1)	--	1.1% (2)
Osteoporosis	2.1% (4)	--	--	0.5% (1)	0.5% (1)	1.1% (2)
Musculoskeletal pain	1.6% (3)	0.5% (1)	0.5% (1)	--	--	0.5% (1)
Musculoskeletal stiffness	1.6% (3)	0.5% (1)	--	0.5% (1)	0.5% (1)	--
Muscle injury	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Musculoskeletal pain (dts)	1.0% (2)	--	--	--	--	1.1% (2)
Pain in extremity (dts)	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Arthritis	0.5% (1)	--	0.5% (1)	--	0.5% (1)	--
Bursitis	0.5% (1)	--	--	0.5% (1)	--	--
Intervertebral disc disorder	0.5% (1)	--	--	0.5% (1)	--	--
Intervertebral disc protrusion	0.5% (1)	--	--	--	0.5% (1)	--
Muscle spasms	0.5% (1)	--	--	--	0.5% (1)	--

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Musculoskeletal chest pain	0.5% (1)	--	--	--	--	0.5% (1)
Plantar fasciitis	0.5% (1)	--	--	--	--	0.5% (1)
Rotator cuff syndrome	0.5% (1)	--	--	--	0.5% (1)	--
Temporomandibular joint syndrome	0.5% (1)	--	--	--	--	0.5% (1)
Temporomandibular joint syndrome (dts)	0.5% (1)	--	--	--	0.5% (1)	--
Tendonitis	0.5% (1)	--	--	--	--	0.5% (1)
Psychiatric disorders	**31.4% (60)**	**3.1% (6)**	**5.8% (11)**	**6.9% (13)**	**13.9% (26)**	**13.7% (25)**
Depression	14.1% (27)	0.5% (1)	3.1% (6)	3.7% (7)	4.3% (8)	4.9% (9)
Anxiety	7.3% (14)	1.6% (3)	1.0% (2)	--	3.2% (6)	3.3% (6)
Panic attack	3.7% (7)	0.5% (1)	0.5% (1)	1.1% (2)	1.6% (3)	0.5% (1)
Depression suicidal	3.1% (6)	0.5% (1)	--	0.5% (1)	1.6% (3)	0.5% (1)
Suicidal ideation	2.1% (4)	--	0.5% (1)	--	--	1.6% (3)
Acute psychosis	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Affect lability	1.0% (2)	--	--	--	--	1.1% (2)
Aggression	1.0% (2)	--	--	1.1% (2)	--	--
Conversion disorders	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Hallucination, auditory	1.0% (2)	--	--	--	1.1% (2)	--
Hallucination, visual	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Sleep disorder	1.0% (2)	--	--	--	--	1.1% (2)
Suicide attempt	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Anger	0.5% (1)	--	--	--	0.5% (1)	--
Bipolar disorder	0.5% (1)	--	--	0.5% (1)	--	--
Dissociative disorder	0.5% (1)	--	--	--	0.5% (1)	--
Epileptic psychosis	0.5% (1)	--	--	--	--	0.5% (1)
Frustration	0.5% (1)	--	--	0.5% (1)	--	--
Paranoia	0.5% (1)	--	--	0.5% (1)	--	--
Personality change	0.5% (1)	--	--	--	0.5% (1)	--
Psychotic disorder	0.5% (1)	--	0.5% (1)	--	--	--
Self-injurious ideation	0.5% (1)	--	--	--	--	0.5% (1)
Sleep paralysis	0.5% (1)	--	--	--	0.5% (1)	--

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Social phobia	0.5% (1)	--	--	--	--	0.5% (1)
Gastrointestinal disorders	**26.7% (51)**	**2.1% (4)**	**2.1% (4)**	**5.8% (11)**	**9.1% (17)**	**13.2% (24)**
Vomiting	6.8% (13)	0.5% (1)	--	3.2% (6)	1.1% (2)	2.7% (5)
Abdominal pain	5.8% (11)	--	0.5% (1)	1.6% (3)	0.5% (1)	3.3% (6)
Diarrhoea	4.7% (9)	0.5% (1)	0.5% (1)	--	2.1% (4)	2.2% (4)
Nausea	3.7% (7)	--	0.5% (1)	0.5% (1)	1.1% (2)	1.6% (3)
Constipation	3.1% (6)	--	--	--	1.1% (2)	2.2% (4)
Gastroenteritis	2.6% (5)	0.5% (1)	--	--	1.1% (2)	1.6% (3)
Gastroesophageal reflux disease	2.1% (4)	--	--	--	1.1% (2)	1.1% (2)
Haemorrhoids	1.6% (3)	--	--	--	1.1% (2)	0.5% (1)
Toothache	1.6% (3)	--	--	--	1.6% (3)	--
Hiatal hernia	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Oral pain	1.0% (2)	--	0.5% (1)	--	0.5% (1)	--
Barretts oesophagus	0.5% (1)	--	--	--	0.5% (1)	--
Breath Odour	0.5% (1)	--	--	--	0.5% (1)	--
Gingival recession	0.5% (1)	--	--	0.5% (1)	--	--
Haematochezia	0.5% (1)	--	--	--	--	0.5% (1)
Haemorrhagic erosive gastritis	0.5% (1)	--	--	--	0.5% (1)	--
Intestinal obstruction	0.5% (1)	--	--	--	--	0.5% (1)
Irritable bowel syndrome	0.5% (1)	--	--	--	--	0.5% (1)
Loose tooth	0.5% (1)	--	--	--	0.5% (1)	--
Nausea (dts)	0.5% (1)	--	--	--	0.5% (1)	--
Oesophagitis	0.5% (1)	--	--	--	0.5% (1)	--
Retching	0.5% (1)	0.5% (1)	--	--	--	--
Stomach discomfort	0.5% (1)	--	--	0.5% (1)	--	--
Skin and subcutaneous tissue disorders	**19.9% (38)**	**6.3% (12)**	**1.6% (3)**	**5.3% (10)**	**5.9% (11)**	**5.5% (10)**
Rash	6.3% (12)	1.6% (3)	0.5% (1)	0.5% (1)	2.1% (4)	1.6% (3)
Swelling face	4.2% (8)	3.7% (7)	--	--	0.5% (1)	--
Dermal cyst	3.1% (6)	--	--	0.5% (1)	1.1% (2)	1.6% (3)

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Pain of skin	3.1% (6)	--	--	2.1% (4)	1.1% (2)	--
Acne	2.1% (4)	0.5% (1)	0.5% (1)	0.5% (1)	--	0.5% (1)
Alopecia	1.0% (2)	--	--	0.5% (1)	0.5% (1)	--
Dermatitis contact	1.0% (2)	--	--	--	--	1.1% (2)
Folliculitis	1.0% (2)	--	0.5% (1)	--	0.5% (1)	--
Pruritus	1.0% (2)	--	--	0.5% (1)	0.5% (1)	--
Skin lesion	1.0% (2)	--	--	0.5% (1)	--	0.5% (1)
Anhidrosis	0.5% (1)	--	--	--	--	0.5% (1)
Decubitus ulcer	0.5% (1)	0.5% (1)	--	--	--	--
Ingrowing nail	0.5% (1)	--	--	--	0.5% (1)	--
Subcutaneous nodule	0.5% (1)	--	--	--	0.5% (1)	--
Investigations	**17.3% (33)**	**1.0% (2)**	**2.6% (5)**	**1.6% (3)**	**3.7% (7)**	**12.1% (22)**
EEG monitoring	7.3% (14)	--	0.5% (1)	--	2.1% (4)	5.5% (10)
Anticonvulsant drug level below therapeutic	1.6% (3)	--	--	--	0.5% (1)	1.1% (2)
Angiogram cerebral	1.0% (2)	--	--	--	--	1.1% (2)
Haemoglobin decreased	1.0% (2)	--	0.5% (1)	0.5% (1)	--	--
Positive Rombergism	1.0% (2)	--	--	--	1.1% (2)	--
Weight decreased	1.0% (2)	--	--	0.5% (1)	--	0.5% (1)
Weight increased	1.0% (2)	--	0.5% (1)	--	--	0.5% (1)
Anticonvulsant drug level above therapeutic	0.5% (1)	--	--	--	--	0.5% (1)
Biopsy brain	0.5% (1)	0.5% (1)	--	--	--	--
Bronchoscopy	0.5% (1)	--	--	--	--	0.5% (1)
C-reactive protein increased	0.5% (1)	--	--	0.5% (1)	--	--
Full blood count abnormal	0.5% (1)	--	--	--	0.5% (1)	--
Heart rate increased	0.5% (1)	--	--	--	--	0.5% (1)
Hepatic enzyme increased	0.5% (1)	0.5% (1)	--	--	--	--
Liver function test abnormal	0.5% (1)	--	--	--	0.5% (1)	--
Medical observation	0.5% (1)	--	--	--	--	0.5% (1)

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Peripheral nervous system function test abnormal	**0.5% (1)**	**--**	**0.5% (1)**	**--**	**--**	**--**
Platelet count decreased	0.5% (1)	--	--	--	--	0.5% (1)
Urine analysis abnormal	0.5% (1)	--	--	--	--	0.5% (1)
Vibration test abnormal	0.5% (1)	--	0.5% (1)	--	--	--
Vitamin D abnormal	0.5% (1)	--	--	--	--	0.5% (1)
Respiratory, thoracic and mediastinal disorders	**17.3% (33)**	**2.1% (4)**	**1.6% (3)**	**2.6% (5)**	**4.8% (9)**	**9.9% (18)**
Bronchitis	6.3% (12)	--	0.5% (1)	1.1% (2)	2.7% (5)	3.8% (7)
Cough	3.1% (6)	--	0.5% (1)	0.5% (1)	0.5% (1)	1.6% (3)
Epistaxis	2.6% (5)	--	--	1.1% (2)	--	1.6% (3)
Dyspnoea	1.6% (3)	--	0.5% (1)	--	0.5% (1)	0.5% (1)
Atelectasis	1.0% (2)	0.5% (1)	--	--	--	0.5% (1)
Hiccups	1.0% (2)	1.0% (2)	--	--	--	--
Nasal congestion	1.0% (2)	--	--	--	1.1% (2)	--
Asthma	0.5% (1)	--	--	--	--	0.5% (1)
Dyspnoea (dts)	0.5% (1)	--	--	--	--	0.5% (1)
Pneumonia aspiration	0.5% (1)	--	--	--	--	0.5% (1)
Pneumothorax	0.5% (1)	0.5% (1)	--	--	--	--
Pulmonary congestion	0.5% (1)	--	--	--	--	0.5% (1)
Eye disorders	**16.8% (32)**	**3.1% (6)**	**3.7% (7)**	**2.6% (5)**	**5.3% (10)**	**3.8% (7)**
Vision blurred	4.7% (9)	1.0% (2)	1.6% (3)	0.5% (1)	--	1.6% (3)
Blepharospasm	2.6% (5)	0.5% (1)	--	--	1.1% (2)	1.1% (2)
Eye pain	2.6% (5)	--	0.5% (1)	0.5% (1)	2.1% (4)	--
Conjunctivitis	2.1% (4)	--	--	0.5% (1)	1.6% (3)	--
Diplopia	1.6% (3)	0.5% (1)	0.5% (1)	--	0.5% (1)	--
Eye irritation	1.6% (3)	0.5% (1)	--	--	--	1.1% (2)
Visual acuity reduced	1.6% (3)	0.5% (1)	0.5% (1)	0.5% (1)	--	--
Contact lens intolerance	0.5% (1)	--	--	0.5% (1)	--	--
Lacrimation increased	0.5% (1)	--	0.5% (1)	--	--	--
Visual acuity reduced transiently	0.5% (1)	0.5% (1)	--	--	--	--

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Surgical and medical procedures	**14.1% (27)**	**0.5% (1)**	**1.6% (3)**	**--**	**6.4% (12)**	**7.7% (14)**
Tooth extraction	3.7% (7)	--	--	--	2.7% (5)	1.1% (2)
Medical device removal (VNS)	1.6% (3)	--	1.0% (2)	--	0.5% (1)	--
Endodontic procedure	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Medical device removal	1.0% (2)	--	--	--	--	1.1% (2)
Removal of foreign body	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Tubal ligation	1.0% (2)	--	--	--	--	1.1% (2)
Central venous catheterisation	0.5% (1)	--	0.5% (1)	--	--	--
Contraception	0.5% (1)	--	--	--	--	0.5% (1)
Dental implantation	0.5% (1)	--	--	--	--	0.5% (1)
Lesion excision	0.5% (1)	--	--	--	0.5% (1)	--
Removal of foreign body from external ear	0.5% (1)	0.5% (1)	--	--	--	--
Scar excisions	0.5% (1)	--	--	--	--	0.5% (1)
Shoulder operation	0.5% (1)	--	--	--	0.5% (1)	--
Skin cosmetic procedure	0.5% (1)	--	--	--	--	0.5% (1)
Skin neoplasm excision	0.5% (1)	--	--	--	0.5% (1)	--
Stapes mobilisation	0.5% (1)	--	--	--	--	0.5% (1)
Tendon transfer	0.5% (1)	--	--	--	--	0.5% (1)
Vasectomy	0.5% (1)	--	--	--	0.5% (1)	--
Ear and labyrinth disorders	**11.5% (22)**	**4.7% (9)**	**2.1% (4)**	**0.5% (1)**	**3.7% (7)**	**2.2% (4)**
Hypoacusis	2.6% (5)	2.1% (4)	--	--	0.5% (1)	--
Tinnitus	2.6% (5)	1.0% (2)	0.5% (1)	--	2.1% (4)	--
Vertigo	2.6% (5)	--	0.5% (1)	--	0.5% (1)	1.6% (3)
Cerumen impaction	1.6% (3)	0.5% (1)	--	0.5% (1)	0.5% (1)	--
Ear pain	1.6% (3)	--	--	--	0.5% (1)	1.1% (2)
Ear discomfort	1.0% (2)	0.5% (1)	0.5% (1)	--	--	--
Hearing impaired	0.5% (1)	0.5% (1)	0.5% (1)	--	--	--
Immune system disorders	**10.5% (20)**	**1.0% (2)**	**1.6% (3)**	**0.5% (1)**	**3.7% (7)**	**3.8% (7)**

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Seasonal allergy	5.8% (11)	0.5% (1)	1.0% (2)	0.5% (1)	1.6% (3)	2.2% (4)
Drug hypersensitivity	4.7% (9)	0.5% (1)	0.5% (1)	--	2.7% (5)	1.1% (2)
Erythema multiforme	0.5% (1)	--	--	--	--	0.5% (1)
Renal and urinary disorders	**8.9% (17)**	**1.6% (3)**	**--**	**2.6% (5)**	**2.1% (4)**	**3.8% (7)**
Nephrolithiasis	3.1% (6)	1.0% (2)	--	0.5% (1)	0.5% (1)	1.1% (2)
Polyuria	2.6% (5)	0.5% (1)	--	0.5% (1)	0.5% (1)	1.1% (2)
Dysuria	1.0% (2)	--	--	1.1% (2)	--	--
Bladder spasm	0.5% (1)	--	--	--	--	0.5% (1)
Micturition urgency	0.5% (1)	--	--	--	--	0.5% (1)
Renal cyst	0.5% (1)	--	--	--	0.5% (1)	--
Urinary incontinence	0.5% (1)	--	--	--	0.5% (1)	--
Urinary retention	0.5% (1)	--	--	--	--	0.5% (1)
Urine flow decreased	0.5% (1)	--	--	0.5% (1)	--	--
Vascular disorders	**7.3% (14)**	**1.0% (2)**	**--**	**0.5% (1)**	**2.1% (4)**	**3.8% (7)**
Hypertension	4.2% (8)	--	--	0.5% (1)	0.5% (1)	3.3% (6)
Deep vein thrombosis	1.0% (2)	0.5% (1)	--	--	0.5% (1)	--
Hypotension	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Orthostatic hypotension	0.5% (1)	--	--	--	--	0.5% (1)
Procedural hypertension	0.5% (1)	0.5% (1)	--	--	--	--
Raynauds phenomenon	0.5% (1)	--	--	--	0.5% (1)	--
Metabolism and nutritional disorders	**6.8% (13)**	**2.1% (4)**	**1.0% (2)**	**--**	**2.1% (4)**	**1.6% (3)**
Decreased appetite	3.1% (6)	2.1% (4)	0.5% (1)	--	0.5% (1)	--
Hyponatraemia	1.6% (3)	--	--	--	0.5% (1)	1.1% (2)
Hypokalaemia	1.0% (2)	--	0.5% (1)	--	--	0.5% (1)
Hypoglycaemia	0.5% (1)	--	--	--	0.5% (1)	--
Vitamin B12 deficiency	0.5% (1)	--	--	--	0.5% (1)	--
Reproductive system and breast disorders	**6.8% (13)**	**--**	**--**	**--**	**1.6% (3)**	**6.0% (11)**
Menstrual disorder	3.1% (6)	--	--	--	1.1% (2)	2.2% (4)
Ovarian cyst	2.6% (5)	--	--	--	0.5% (1)	2.2% (4)
Uterine leiomyoma	1.0% (2)	--	--	--	--	1.1% (2)

	All Study Periods (Post-Implant)	Post-Op Stabilization Period (Week 0-4)	Stimulation Optimization Period (Weeks 4-8)	Blinded Evaluation Period (Weeks 8-20)	Open Label Period (Weeks 20-52)	Open Label Period (Week 52-Completion)
Breast cyst	0.5% (1)	--	--	--	--	0.5% (1)
Breast mass	0.5% (1)	--	--	--	--	0.5% (1)
Breast pain	0.5% (1)	--	--	--	--	0.5% (1)
Pelvic congestion syndrome	0.5% (1)	--	--	--	--	0.5% (1)
Premenstrual syndrome	0.5% (1)	--	--	--	--	0.5% (1)
Vulvovaginal pruritus	0.5% (1)	--	--	--	--	0.5% (1)
Cardiac disorders	**4.2% (8)**	**0.5% (1)**	**0.5% (1)**	**0.5% (1)**	**0.5% (1)**	**2.2% (4)**
Palpitations	2.1% (4)	--	--	--	0.5% (1)	1.6% (3)
Tachycardia	1.0% (2)	0.5% (1)	--	--	--	0.5% (1)
Cardiac flutter	0.5% (1)	--	0.5% (1)	--	--	--
Myocardial infarction	0.5% (1)	--	--	0.5% (1)	--	--
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3.1% (6)**	**--**	**1.0% (2)**	**--**	**1.1% (2)**	**1.1% (2)**
Benign breast neoplasm	1.0% (2)	--	0.5% (1)	--	--	0.5% (1)
Colon cancer	0.5% (1)	--	--	--	0.5% (1)	--
Lymphoma	0.5% (1)	--	--	--	0.5% (1)	--
Meningioma benign	0.5% (1)	--	0.5% (1)	--	--	--
Thyroid neoplasm	0.5% (1)	--	--	--	--	0.5% (1)
Blood and lymphatic system disorders	**1.6% (3)**	**--**	**--**	**--**	**1.1% (2)**	**0.5% (1)**
Anaemia	1.0% (2)	--	--	--	0.5% (1)	0.5% (1)
Lymphadenopathy	0.5% (1)	--	--	--	0.5% (1)	--
Pregnancy, puerperium and perinatal conditions	**1.0% (2)**	**--**	**--**	**--**	**--**	**1.1% (2)**
Abortion spontaneous	0.5% (1)	--	--	--	--	0.5% (1)
Live birth	0.5% (1)	--	--	--	--	0.5% (1)
Endocrine disorders	**0.5% (1)**	**--**	**--**	**--**	**0.5% (1)**	**--**
Thyroid disorder	0.5% (1)	--	--	--	0.5% (1)	--
Social circumstances	**0.5% (1)**	**--**	**--**	**--**	**0.5% (1)**	**--**
Victim of crime	0.5% (1)	--	--	--	0.5% (1)	--

[1] % Subjects = # subjects with event / number of subjects entering interval

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