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# RNS® System Pivotal Clinical Trial Fact Sheet

**Pivotal Clinical Trial Overview:**

NeuroPace, Inc. sponsored an investigational device study of the RNS® System, the company's responsive brain stimulation system for treating refractory epilepsy.

The RNS System Pivotal Clinical Investigation was a prospective, randomized, double-blind, sham stimulation controlled investigation that included 191 people implanted with the RNS System across 32 Comprehensive Epilepsy Centers. The trial was completed in May 2011.

**Primary Objectives:**

The purpose of pivotal trial was to assess the safety and demonstrate the effectiveness of the RNS System as an add-on (adjunctive) therapy in reducing the frequency of seizures in individuals 18-70 years of age with partial onset seizures (those that start from one or two areas of the brain) that are refractory (resistant or hard to treat) to two or more antiepileptic medications.

**Primary Endpoints:**

The primary endpoints of the trial were to assess the safety of the RNS System and to evaluate the effect of the RNS System on seizure frequency.

**Pivotal Trial Results*:**

The pivotal trial primary effectiveness endpoint was met by demonstrating a 37.9 percent reduction in seizure frequency in patients treated with responsive stimulation compared to a 17.3 percent reduction in patients who were implanted with the device but were not receiving responsive stimulation during a three month blinded period. The difference is statistically significant (p=0.012). For those subjects who reached two years post-implant, 55% of the subjects experienced a 50% or greater reduction in seizures.

The pivotal trial primary safety endpoint was met by demonstrating a serious adverse event rate comparable to similar procedures. The rate

* For Indications for Use, Contraindications, Warnings and Precautions please see Brief Statement for the RNS® System provided in this media kit. Refer to the product labeling for detailed disclosure of specific indications, contraindications, warnings, precautions and adverse events.

for the first four weeks was 12% [upper one-sided 95% CI: 16.5%], lower than the pre-specified literature-derived comparator of 15% [upper one-sided 95% CI: 20%]. The rate for the first 12 weeks was 18.3% [upper one-sided 95% CI: 23.4%], lower than the pre-specified literature-derived comparator of 36% [upper one-sided 95% CI: 42%]. There was no difference between the active and sham stimulation groups in the overall percentage of subjects experiencing an adverse event, including depression and memory impairment, or any specific type of adverse event during the evaluation periods of the studies. There were no serious unanticipated device-related adverse events reported in any of the RNS® System clinical trials. Although there can be no assurances that additional long-term data will not reveal new adverse information presently unknown to NeuroPace, two year data shows no increase or worsening of adverse events.

**Trial Design:**

After enrolling in the study, participants first completed the baseline period, which lasted a minimum of three months up to a maximum of 15 months. During this part of the study, participants were given a seizure diary to keep track of their seizures. A doctor at each clinical site reviewed the frequency and severity of seizures during monthly telephone calls or office visits. Study participants had to have an average of three or more seizures for three consecutive months with no less than two seizures in any one month to be eligible for implantation of the RNS System.

Once the eligibility criteria were met, participants were implanted with the RNS Neurostimulator and leads. The blinded evaluation period of the trial began eight weeks after implantation and lasted 12 weeks. Half the participants were randomly assigned to have responsive stimulation activated and half had responsive stimulation remain inactive. Participants and one doctor (assessment physician) at each site in the trial did not know whether stimulation was active or not. A separate doctor (treatment physician) at each site programmed the devices in order to ensure that the assessment physician remained blinded. Five months after implantation, when the double-blinded portion of the trial was completed, stimulation was activated for all participants in the trial. Each participant in the trial was evaluated for two years following implant. After completion of the pivotal trial, all patients were given the option to enroll in the RNS System Long Term Treatment Clinical Investigation designed to provide up to an additional seven years of safety and effectiveness data.

**Previous Clinical Research:**

Previous research had shown that electrical stimulation of the brain can stop seizure activity. A multi-center RNS System Feasibility Clinical Investigation demonstrated safety and provided preliminary evidence for efficacy of responsive stimulation in epilepsy sufficient to proceed to the pivotal study. The feasibility study also assessed and confirmed that the blind could be maintained. Sixty-five (65) subjects were implanted with the device in this study.

**The RNS System:** Recently, the U.S. Food and Drug Administration granted premarket approval for the NeuroPace® RNS® System, a treatment for adults with partial onset seizures that have not been controlled with two or more antiepileptic drugs. The RNS System is the first closed-loop responsive brain stimulation system.

The RNS System is a novel, implantable therapeutic device that delivers responsive neurostimulation, an advanced technology designed to continuously monitor brain electrical activity, detect abnormal electrical activity and respond by delivering imperceptible levels of electrical stimulation to normalize that activity before an individual experiences seizures. Physicians can program the detection and stimulation parameters of the implanted RNS Neurostimulator non-invasively to customize therapy for each individual.

The RNS System includes a neurostimulator and leads (tiny wires containing electrodes). The neurostimulator is placed within the skull and beneath the scalp by a surgeon. The device is then connected to one or two leads that are placed within the brain or rest on the brain surface in the area of the seizure focus.