DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center –
WO66-G609
Silver Spring, MD 20993-0002

November 14, 2013

Ms. Isabella R. Abati, MS
Vice President, Regulatory Affairs
NeuroPace, Inc.
1375 Shorebird Way
Mountain View, California 94043

Re: P100026
RNS® System
Filed: November 9, 2010
Amended: August 12, November 9 and December 23, 2010, March 25, April 1, October 4, December 5 and December 9, 2011; March 28, April 23, June 15, August 3, August 9, September 27, October 5, and December 19, 2012; and January 25, March 22, April 1, June 14, August 6, and October 31, 2013
Procode: PFN

Dear Ms. Abati:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the RNS® System. This device is indicated as follows:

> "…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."

We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the

device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at 9 months from the date the battery is attached for the RNS® Neurostimulator and at 3-years from the date of sterile packaging for all other sterile products including the Connector Cover Kit, Craniectomy Template Kit, Ferrule Kit, Cranial Prosthesis Kit, Cortical and Depth Leads and Lead Accessory Kits.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you must provide the following data in post-approval study reports (PAS). Two (2) copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below.

1. *Continued Follow-up PAS 1 - Long Term Treatment (LTT) Study:* This study must be conducted as per protocol (IDE G030126). The objectives of this study are to describe the long-term safety and effectiveness associated with use of the NeuroPace device through 7 years.

   Safety will be evaluated using adverse event rates (serious and non-serious) and sudden unexplained death in epilepsy (SUDEP) rate through 7 years.

   Effectiveness will be measured as the average decrease across 7 years in disabling seizure frequency from pre-implant baseline, responder rates, and quality of life. Responder rates will be the proportion of subjects with a sustained ≥50% reduction in total disabling seizures compared to pre-implant baseline. Quality of life will be measured using QOLIE-89.

The surviving patients in the premarket Long-term Treatment Investigation Study will be followed annually up to 7 years.

2. *New Enrollment PAS 2 – All Comers:* The study will be a prospective observational study of newly-enrolled patients treated with the RNS® System.

   The primary safety objective is to characterize the annual serious adverse event (SAE) rate over 5 years. SAEs include adverse events related to intra-cranial hemorrhages, adverse events related to seizure-associated injuries requiring medical attention, and all-cause mortality (including adjudicated SUDEP and suicidality).

   The secondary safety objective is to demonstrate that there is not a worsening in seizures over time in patients treated with the RNS® System beginning at 6 to 12 months post-implant and extending to 3 years. This will be to demonstrate that there is not a 20% increase in disabling seizures at 3 years compared to 6 to 12 months post-implant. The secondary safety endpoints will include seizure frequency, new seizure types (disabling and non-disabling), and seizure foci and lead location.

   The primary effectiveness objective will be to estimate the median percent reduction in seizures from baseline (3 months pre-implant) to 3 years in the PAS, and evaluate if this reduction is comparable to the median percent reduction in seizures from baseline to 3 years in the controlled clinical study (51.3%).

   The secondary objective will be to characterize observed battery longevity overall and in relation to total stimulation time and stimulation programming at 5 years. Longevity will be defined as the time to replacement and/or end of service, whichever is first.

   Additional objectives will be to describe the demographic and clinical characteristics of treated patients, additional procedures including explants and re-implants (reasons, associated complications, and resolution), responder rate, antiepileptic drug (AED) use, discontinuations, and autopsy data.

   Patients will be followed out to 5 years post implant. Based on a linear regression t-test of the slope with a one-sided alpha of 0.05 (standard deviation=0.25), and 20% overall attrition, 300 enrolled patients will provide over 80% power for the ability to detect a 20% cumulative increase in seizures over the period from 6 months to 3 years. Data will also be collected on seizure frequency from >3 to 5 years and descriptive statistics will be provided. Approximately 30 sites are to enroll no more than 15 patients per site. NeuroPace will access the National Death Index annually and search for patients who have withdrawn, are lost to follow-up, or have died.

3. *New Enrollment PAS 3 – Performance & Programming:* This will be a sub-study of the *PAS 2 – All Comers* study detailed above. This is a two-part observational study of patients who are treated with the RNS® System at NeuroPace qualified Comprehensive

Epilepsy Centers. Part 1 will study the overall performance of the device and Part 2 will assess the impact of physician and center experience and programming configuration on device performance.

Part 1: Performance

The primary safety objective is to characterize the annual serious adverse event (SAE) rate over 5 years. The primary safety endpoint of SAEs include adverse events related to intra-cranial hemorrhages, adverse events related to seizure-associated injuries requiring medical attention, and all-cause mortality (including adjudicated SUDEP and suicidality).

The secondary safety objective is to demonstrate that there is not a worsening in seizures over time in patients treated with the RNS® System beginning at 6 to 12 months post-implant and extending to 3 years. This will be to demonstrate that there is not a 20% increase in disabling seizures at 3 years compared to 6 to 12 months post-implant. The secondary safety endpoints will include seizure frequency, new seizure types (disabling and non-disabling), and seizure foci and lead location.

The primary effectiveness objective will be to estimate the median percent reduction in seizures from baseline (3 months pre-implant) to 3 years in the PAS, and evaluate if this reduction is comparable to the median percent reduction in seizures from baseline to 3 years in the controlled clinical study (51.3%).

Additional objectives will be to describe the demographic and clinical characteristics of treated patients, additional procedures including explants and revisions (reasons, associated complications, and resolution), responder rate, AED use, battery life and replacement, discontinuations, and autopsy data.

The study endpoints will be examined overall, by electrode location (mesial temporal vs. neocortical by lobe), and within patients with explanted leads.

Part 2: Programming

The primary safety objective is to demonstrate that there is no difference in safety 1 year post-implant based on the experience of NeuroPace qualified and trained treating physicians and Comprehensive Epilepsy Centers. The safety endpoints examined will include intra-cranial hemorrhages, seizure-associated injuries requiring medical attention, and all-cause mortality (including adjudicated SUDEP and suicidality).

The primary safety objective will be evaluated by examining all serious and non-serious adverse events in the perioperative period (implant through 6 weeks after implant) by neurosurgeon experience with the RNS® System, and all serious adverse events at 1 year by the experience of the Comprehensive Epilepsy Centers. Descriptive data will be provided for SAEs for each subsequent year.

The secondary safety objective is to characterize the effects of various baseline stimulation programming parameters on the overall 5-year rate of SAEs and product-related adverse events. SAEs include adverse events related to intra-cranial hemorrhages, adverse events related to seizure-associated injuries requiring medical attention, and all-cause mortality (including adjudicated SUDEP and suicidality).

The primary effectiveness objective is to demonstrate that the stimulation programming classes have similar effects on the overall seizure frequency. Stimulation programming parameters include stimulation frequency, current, total charge delivered, electrode charge density, and total stimulation time per 24 hours.

All study endpoints will be analyzed by stimulation frequency classes (75 Hz < frequency ≤ 133 Hz and 133 Hz < frequency ≤ 250 Hz), and for tertiles of current, considering epochs of at least 70 days in which stimulation settings are held constant.

Additional objectives will be to characterize observed battery longevity overall and in relation to total stimulation time and stimulation programming at 5 years. Longevity will be defined as the time to replacement and/or end of service, whichever is first.

Based on a linear regression t-test of the slope with a one-sided alpha of 0.05 (standard deviation=0.25), and 20% overall attrition, a minimum of 250 enrolled patients will provide over 80% power for the ability to detect a 20% cumulative increase in seizures over the period from 6 months to 3 years. Approximately 30 sites are to enroll no more than 15 patients each. NeuroPace will access the National Death Index annually and search for patients who have withdrawn, are lost to follow-up, or have died.

4. *PAS 4: Lead Extraction Study* – This will be a prospective, non-randomized, controlled registry study of patients with chronic extraction of RNS® system leads.

   The primary safety objective is to characterize serious and non-serious adverse events related to the surgical procedures related to the implant, explant, or revision of the RNS® neurostimulator and leads. The primary safety endpoints will also include reason for explantation, resolutions of complications, and analysis of devices returned to NeuroPace (i.e. no anomalies found, conductor wire damage, etc.).

   Additional data to be collected will be patient study identifier information, type and location of lead(s), and date of initial implant, explanation, and reimplantation.

   The NeuroPace customer service and product monitoring systems will:

   - Collect product registration data (implanted, explanted and revised)
   - Review data on field events
   - Document and evaluate product related complaints
   - Perform inspection and functional analysis of all returned products

- Determine reportable events, including device malfunction and adverse device effects
- Perform tracking and trending complaints and reportable events

Explant data will be collected and compiled from the PAS and LTT studies and from the NeuroPace customer service for study subjects and commercial patients, respectively. Of note, PAS and LTT study subjects will remain as active participants for 6 weeks following explant. Data for a minimum of 20 extraction attempts of the leads will be collected. There is no study hypothesis and data analysis will be descriptive.

5. *PAS 5: Autopsy Study* –The study will be a non-randomized, open-label, observational study of all patients implanted with the RNS® System who die and in whom it is possible to obtain an autopsy.

   The primary objective is to characterize autopsy data for deaths which have occurred in patients treated with the RNS® System. Each investigator will be asked to make a diligent attempt to have an autopsy performed to include complete removal of the NeuroPace RNS® System with the leads still implanted (explants), and, if possible, remove and preserve the contralateral tissue for histological analysis. Tissue extracted from the areas abutting the lead implant location and contralateral tissue should be subjected to standard pathological and histopathological examinations and the findings from these reports should be provided.

   The secondary objective is to describe 1) demographics and characteristics, including length of implant and lead type and location; 2) date and cause of death (including relatedness as Related, Not Related, or Unknown); and 3) device condition.

   Additional data collection will include date of original NeuroPace RNS® System implant, date of last evaluation/clinic visit and whether or not the device was still functioning, NeuroPace RNS® System Programming history for the past 6 to 12 months, and copies of recent laboratory reports of findings considered relevant to the cause or presumed cause of death.

   The autopsies can be conducted on any patients implanted with the RNS® system regardless of participation in a PAS. Of note, patients in the Newly-enrolled PAS and the Commercial Study will be followed out to 5-years post implant and patients in the LTT study will be followed 7-years post-implant. A minimum of 15 autopsies must be conducted. There is no study hypothesis and data analysis will be descriptive.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA.

Within 30 days of your receipt of this letter, you must submit separate PMA supplements for each study that include the complete protocols of your post-approval studies, for FDA review and formal approval. Your PMA supplements should be clearly labeled as a "Post-Approval Study Protocol" and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing.

FDA would like to remind you that you are required to submit separate PAS Progress Reports every six months during the first two years and annually thereafter. The reports should clearly be identified as Post-Approval Study Report. Two copies, identified as "PMA Post-Approval Study Report" and bearing the applicable PMA reference number, should be submitted to the address below. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device

which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.
CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Mail Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Kristen A. Bowsher, Ph.D. at Kristen.Bowsher@fda.hhs.gov or (301) 796-6448.

Sincerely yours,

Christy L. Foreman -S

Christy Foreman
Director
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration