July 24, 2014

SCION NEUROSTIM, LLC:

PIVOTAL MIGRAINE STUDY

Title: A Non-Invasive Neuromodulation Device for Treatment of Migraine Headache

Background

This "Pivotal Study" is a multi-center, triple-blinded, placebo-controlled, randomized Pivotal Study for adjunctive prophylactic treatment of episodic migraine headache using a caloric vestibular stimulation (CVS) Device developed by Scion NeuroStim, LLC (SNS). This Study has been reviewed by the FDA and is classified as NSR (non-significant risk).

Set forth at the end of this document is an alphabetical listing of the various capitalized definitions and terms that are used throughout the document, and attached are various forms that will be used to conduct and collect data during the Pivotal Study.

Efficacy of neuromodulation therapy for migraines is reasonably well-established. Traditionally, however, neuromodulation, especially when accomplished through an expensive, surgically implanted device, has been available only as a treatment of last resort -- to be used (and covered by health insurance) if, but only after, patients have failed all other interventions, principally pharmaceuticals. Typically, patients receive neuromodulation for migraines only after they are refractory or close to being refractory. SNS envisions changing that paradigm, providing effective early interventions and thereby improving outcomes for migraine patients. The CVS-M Device is non-invasive and utilizes the same underlying mode of neural modulation (activation of the vestibular nuclei in the brainstem) that for a century has been well-understood by the medical profession and has been used safely via caloric irrigators for diagnostic purposes -- in ENT practices to assess balance and in the ER to assess brain function. The SNS Device is relatively inexpensive and easy to operate; it can be used safely at home by a patient under the supervision of a prescribing physician. Through availability and use of the SNS CVS-M Device, prophylactic neuromodulation therapy for migraines can become an inexpensive and early, rather than an expensive and belated, therapeutic option.

Experience with pilot study patients as well as a theoretical understanding of CVS indicates that the SNS Device likely can effectively treat both episodic and chronic migraine patients, but this Pivotal Study will focus on only episodic patients. The Investigators at the Pivotal Study sites will identify, select and treat a carefully defined population of individuals who are current patients with an established history of episodic migraines and who have substantial monthly migraine days and pain, but who have not

yet become refractory to all conventional treatments. CVS-M Device treatments will be evaluated as a therapy to be used alongside the therapies that are currently being utilized by participating patients (i.e., as an adjuvant), again underscoring the potential advantages of earlier neuromodulation therapy intervention. Limiting participation to patients who meet the carefully selected qualifications will simplify how the Pivotal Study is conducted and how the results are evaluated.

All participants will be patients whose response to prior therapies has been partially successful, but limited, and whose disease state and current course represent risk for eventual refractoriness but who have not yet become fully refractory. As defined in detail below, under International Headache Society (IHS) guidelines all of these patients will be classified as "episodic" or acute. None will be classified as "chronic." In assessing the effectiveness of the SNS CVS-M Device, the Pivotal Study will consider both (1) a patient's number of Headaches as well as (2) the severity of each and of all of those Headaches. The current design path involves evaluating those two disease factors both separately and on a blended basis. The primary endpoint is based on a traditional measure with which both the FDA and the medical profession are quite familiar: outcomes data collected during the Treatment Period vs. baseline data from the Pre-Treatment Baseline Period, focusing on comparative number of Migraine Headache Days. Additionally, the concept of blending those two disease measures into one quantitative assessment will be introduced: a Total Monthly Headache Pain score. As defined below, that Monthly measure will be the cumulative maximal Headache Pain Scores for all Headache Days (days on which the patient's Headache Pain level is one or higher on an eleven-point scale) during the Month in question – thus, a quantitative indication of Total Monthly Headache Pain. Study data can (and will) also be analyzed using other metrics, as described below.

For the Pivotal Study to demonstrate efficacy from SNS CVS-M Device treatments, the therapy must provide prophylactic and/or abortive-response benefits for patients. (However, for clarity, CVS-M is viewed as providing adjunctive prophylactic therapy.) Experience from IRB-approved pilot studies indicates that beneficial preventive effects and diminished incidence and severity of Headaches are achieved through daily CVS-M treatments, but not necessarily beginning immediately upon the first treatment. For that reason, patients will be treated for three Months and only the Headache burden during the last Month will be used for comparison with baseline data.

Description of the Treatment Paradigm and Study

1) Intended Use/Indication for Use

- **Intended Use:** The SNS CVS-M Device is intended to stimulate the vestibular system via external ear canals using controlled thermal waveforms.
- **Indication for Use:** The SNS CVS-M Device is specifically indicated to treat episodic Migraine Headache pain.

2) Patient Selection Criteria Pre-Treatment Data

In working with and through their respective designated Pivotal Study assistant(s)/coordinator(s), the Investigators will identify and screen potential participants, all of whom will have previously been diagnosed as episodic migraine patients. The Investigators will review the patients' medical records to select those individuals whom they identify as meeting the inclusion criteria for participating in the Study.

- **Inclusion Criteria:** Each participant must have a Pre-Treatment History that, when initially screened by a Pivotal Study Investigator or designee, documents that she/he meets all elements of the following:
    - The patient must have been diagnosed with episodic Migraine Headache at least six months prior to entering into the Study, consistent with the International Headache Classification of Headache Disorders-II (ICHD-II) guidelines.
    - The patient must have a history of at least three consecutive months of stable Migraine Headaches prior to entering the Study. The patients will not have had changes in medication usage for the three Months leading up to the Study, nor will they introduce new medications during the Study period. Patients will satisfy these criteria: On a Monthly basis, at least four, and not more than a total of fourteen (4-14), Headache Days of which between four and fourteen (4-14) are Migraine Headache Days.
    - The patient must not have failed on more than two classes of properly administered prophylactic pharmaceutical therapies for migraine headache. The patient may be on a single migraine prophylactic as long as the dosage has not been altered within three months of starting the Study and the dosage must not be altered for the duration of the Study;
    - The Investigator must have confidence in the patient's ability to reliably use the CVS-M Device and promptly complete the Daily Headache Diary forms and promptly return them to the Study coordinator. That Daily Headache Diary will be completed from the beginning of the Pre-Treatment Baseline Period through the end of the Pivotal Study. It is described more fully below and in the Definitions section at the end of this document.

- **Exclusion Criteria**: Individuals who:
    - are pregnant
    - have a history of cardiovascular disease
    - work night shifts
    - have been diagnosed with vestibular migraine
    - have been diagnosed with migraine with aura
    - have menstrual migraine exclusively

- have been diagnosed with post-traumatic migraine
- have a history of unstable mood disorder or unstable anxiety disorder
- use a hearing aid
- have a cochlear implant
- have chronic tinnitus
- have temporomandibular joint disease
- have been diagnosed with traumatic brain injury
- have been diagnosed with neurological disease other than Headaches
- have a diagnosed vestibular dysfunction
- abuse alcohol or other drugs
- are experiencing medication overuse Headaches (individuals with respect to whom the Investigator is concerned that analgesic abuse is involved based on the ICHD-II guidelines).
- are less than 18 years old or greater than 65 years old
- have had eye surgery within the previous three months or ear surgery within the previous six months
- have active ear infections or a perforated tympanic membrane
- have participated in another clinical trial within the last 30 days or are currently enrolled in another clinical trial
- are using Botox treatments for migraines.
- Though not excluded, patients taking anti-histamines or anti-nausea drugs will be encouraged not to take such medications within four hours prior to a CVS-M treatment. The Investigator should review other medications taken by the patient with properties that mimic anti-nausea or anti-dizziness drugs as these may reduce responsiveness of the vestibular system to caloric stimulation. Such medications should also be avoided within four hours prior to a CVS-M treatment.

- **Withdrawal Criteria**
  - Subjects must be withdrawn from the clinical trial if any of the following events occur:
    - A subject does not continue to meet Inclusion/Exclusion criteria.
    - A subject is significantly non-compliant with the requirements of the protocol (Investigator decision).
    - A subject becomes pregnant during the trial as evidenced by a positive pregnancy test.
    - The subject develops an illness (Adverse Event) that would interfere with his/her continued participation.
    - The subject is unwilling to continue due to lack of efficacy.

- The subject withdraws his/her consent.
- The Investigator feels that it is the subject's best interest to be withdrawn.
- Scion Neurostim discontinues the study or has achieved the targeted enrollment.

If the subject is discontinued from the participation in the study for any reason, the Investigator must make every effort to perform all evaluations for the final visit and document the reasons for discontinuation.

- **Concomitant Medications**
  - The use of acute abortive medications for the symptomatic treatment of migraine headache will be allowed during the clinical trial. Subjects may use their usual acute abortive medications, and medications should not be changed during the clinical trial. A Treated Headache will be a Migraine Headache for which a patient has taken an acute abortive medication.
  - The patient may be on a single migraine prophylactic as long as the dosage has not been altered within three months of starting the Study and the dosage must not be altered for the duration of the Study. The patient must not have failed on more than two classes of properly administered prophylactic pharmaceutical therapies for migraine headache. Prophylactic medications used to treat other medical conditions may be used, at the Investigator's discretion, if the subject is taking a stable dose for at least three months prior to screening and continues throughout the study.

3) Pivotal Study Size; Randomization

The design size contemplates enrolling up to eighty (80) patients who will successfully follow through to completion of their participation in the Pivotal Study. Half of these patients will be assigned a Treatment Device, and half will be assigned a Placebo Device. Whether a patient is in the treatment arm or placebo arm will be decided randomly based on an assignment within a sealed envelope, which will be opened only by the Pivotal Study coordinator at the relevant Pivotal Study site. The envelopes will be randomized as described below and provided to the participating clinics. A given patient and the Investigator will remain blinded as to the arm to which the patient has been assigned. The assessment of the primary endpoints will be completed by a blinded, central Statistician. The patients will be told, within the informed consent document, of the existence of a placebo arm.

Block randomization with a block size of four (4) will be used at each site. Each site will receive sets of well-shuffled envelopes in packets of four. A given packet will be completed before the next packet is opened. Each packet of four will contain two cards specifying that a subject should be in the active treatment arm and two cards specifying the placebo arm. This procedure results in six possible different arrangements, for four patients, of the ordering of treatment and placebo assignments. The unblinded Pivotal Study coordinator will record the patient’s designation but will not share the assignment with the patient, Investigator, or Statistician.

4) Pivotal Study Schedule; Subject Enrollment and Activities; Monitoring

The Pivotal Study Period will last one hundred and twelve days, beginning with a Pre-Treatment Baseline Period of one Month (28 days), at the end of which the Investigator will reconfirm the appropriateness of the subject's participation in the Pivotal Study, followed by a Treatment Period of three Months (84 days).

As noted, subjects will be advised that during the Pivotal Study Period they may maintain patterns of usage of approved therapeutic medications that they normally use and that they should not initiate new medications, medicating patterns or other interventions. Accommodations for rescue medications will be made, using pharmaceuticals from an approved list developed by the Investigators.

Potential participants will be required to keep a Daily Headache Diary throughout the Pivotal Study Period and, *inter alia*, to document times of CVS-M treatments. They will enter the Daily Headache Diary information using a computer-based system.

The phases and activities of the Pivotal Study are listed below:

(i) **Screening & Baseline Period:** Once the subject has been established as having the appropriate Pre-Treatment History, she/he will be asked to complete a review of the informed consent. If the subject agrees to participate in the Pivotal Study, the subject will then complete a Screening Visit. If the subject is recommended for continuation in the Study after the Screening Visit and tentatively approved by an Investigator, she/he will start a Daily Headache Diary and continue to make entries for twenty-eight consecutive days. The Pivotal Study coordinator will complete a Headache History Questionnaire for the subject. The subject will undergo a Vestibular Testing Procedure to establish a baseline record. Any abnormality identified during the Vestibular Testing Procedure for a potential subject will be reported both to the relevant Investigator and to the Vestibular System Coordinator, either of whom can disqualify such potential subject from participating in the Pivotal Study.

(ii) **Clinic Period**: After enrollment, the completion of one Month of Daily Headache Diary entries, and reconfirmation by the relevant Investigator of the subject's participation in the Pivotal Study, the subject will come to the clinic for appointments for two days (within the same week) for treatments and for training with respect to use of the CVS-M Device. During the first clinic visit, the subject will complete a Quality of Life and Cognition Assessment exam. Also, women of childbearing age will complete a urine-based pregnancy test to reconfirm that they are not pregnant. The local Pivotal Study coordinator will open, at random, an envelope assigning the patient to the treatment arm or the placebo arm. The second clinic day may be skipped if the Study Coordinator feels that the patient is prepared to use the CVS-M device properly (this should be confirmed with a phone call on the second day). The clinic period is described below.

On each visit during the clinic period, the subject will receive a treatment and be instructed in how to self-administer a defined, controlled treatment using

the CVS-M Device. During the first visit, the patient will complete a training session based on a set training module. The patient will complete a proficiency evaluation and the Pivotal Study coordinator will certify the patient's proficiency in the use of the CVS-M Device. Blood pressure will be monitored every five minutes until the treatment is completed. The Pivotal Study coordinator will complete a Visit Assessment form each day. During the first clinic visit, the "2-week" visit and the final visit, the relevant Pivotal Study coordinator will collect treatment delivery data from the CVS-M Device. The treatment delivery data from the CVS-M Device consists of temperature waveform files that contain actual measured temperature values that were delivered to the earpieces during treatments. This data will be plotted in graphical form and the Pivotal Study coordinator will place the temperature data in the patient records. This data is an independent record of the expected Device performance and is used for confirmation purposes only. The data files also record treatment times and patient compliance will be verified based on those time records. At the end of training, a first Usability questionnaire will be completed by the patient.

For clarity, the treatment schedule is:

- Days 1 & 2: Completion of a set training module. A single treatment administered by the Pivotal Study coordinator with the subject following the treatment procedure closely. Both before and after the treatment the Pivotal Study coordinator will describe and demonstrate to the patient how a treatment procedure is initiated and successfully completed. At the end of the session the Pivotal Study coordinator will ask the patient to proceed as if she or he were providing a treatment to herself or himself, and the Pivotal Study coordinator will observe, monitor and instruct as advisable. If the Study Coordinator believes that the patient does not need a second day of training, a phone call interview can be conducted instead (in that case, the usability questionnaire should be completed on Day 1). If a second treatment day is used, a single treatment at the clinic administered by the subject with the Pivotal Study coordinator overseeing the treatment procedure closely and assessing the competence of the patient to self-treat is recommended. If the Pivotal Study coordinator concludes that the subject is ready, the subject will then be allowed to continue twice-daily treatments at home until the end of the Treatment Period. The patient will be instructed that if she or he has any questions or encounters any issues at home, the patient should immediately call the Pivotal Study coordinator. If the Pivotal Study coordinator concludes that the patient is not ready for self-treating at home and that additional training is needed, the patient will be instructed to return to the clinic the next day to receive such additional training. A usability questionnaire will be completed.

- Day 3-4: repeat the schema specified for Day 2 only if the subject needs additional training time.

(iii) **Treatment Period:** The eighty-four days (3 Months) following the Pre-treatment Baseline Period constitute the Treatment Period. This is the test period, the results from which will be measured against the Pre-Treatment Baseline Period data. Specifically, data from the last Month of the Treatment Period will be compared with the Monthly data from the one-month-long Pre-treatment Baseline Period. Roughly two weeks after the start of treatment, a Pivotal Study clinical visit will occur and another Visit Assessment form will be completed, treatment delivery data from the CVS-M Device will be collected, and a Quality of Life and Cognition Assessment exam will be performed. A Vestibular Testing Procedure will be completed. A second usability questionnaire will be completed. The patient will be asked to bring the CVS-M Device to the clinic to perform a treatment in front of the Pivotal Study coordinator to reaffirm proficiency in using the Device. Any issues related to balance or other safety concerns will promptly be referred to both the relevant Investigator and the Vestibular System Consultant, either of whom can terminate the patient's further participation in the Pivotal Study if necessary.

(iv) **Return of CVS-M Device & clinic visit:** At the end of the Treatment Period the patient will be asked to return the CVS-M Device and a Quality of Life and Cognition Assessment exam will be performed. A Vestibular Testing Procedure will be completed. A third usability questionnaire will be completed. All remaining treatment delivery data from the CVS-M Device will be collected.

(v) During each of the clinic visits, the relevant Pivotal Study coordinator will interview the subject, collect treatment delivery data from the CVS-M Device according to the schedule above and complete assessment forms. Collectively, data from the Daily Headache Diary, Quality of Life and Cognition Assessment and Visit Assessments will ensure assessment of safety and also coverage of all six core areas of assessment highlighted by Turk et al.: (1) pain; (2) physical functioning; (3) emotional functioning; (4) global ratings of satisfaction; (5) any negative health states and/or adverse events; and (6) subject disposition. Additionally, Visit Assessments and usability questionnaire forms will provide information to SNS with respect to satisfaction with the comfort, fit, operation, etc. of the CVS-M Device. *At all times* throughout the Study Period all subjects will have access to an Investigator or her/his designated Study coordinator by telephone, email and/or visit.

5) Active Treatment Parameters; Placebo Treatments

The following parameters will be set for active treatments using the CVS-M Device:

- A standardized CVS time-varying waveform lasting approximately 19 minutes will be used for all active treatment patients at all Pivotal Study sites. Treatments will be administered twice daily. The two daily treatments will be separated by at least one hour.
- The waveform schedule for active treatment patients will consist of a warm sawtooth delivered to one ear and a cold sawtooth delivered to the other ear. The warm sawtooth will go from body temperature to 42 °C, and the cold sawtooth will go from body temperature to 17 °C. The two waveforms will be delivered simultaneously, but will have different oscillation frequencies. After each two-day period, the warm and cold waveforms will be switched so that the opposite ears will be treated with the different caloric stimulation. Thus every two days the ear receiving the cold stimulus will be switched to the warm stimulus and vice versa.

The following parameters will be set for the placebo treatments using the CVS-M Device:

- A standardized CVS time-varying waveform lasting approximately 4 minutes will be used for all placebo treatment patients at all Pivotal Study sites. Treatments will be administered twice daily. The two daily treatments will be separated by at least one hour.
- The waveform schedule for placebo treatment patients will consist of turning on the cooling fans and leaving the earpieces unpowered for a ~4-minute period.
- The earpiece tips will be covered with EVA rubber to prevent cooling of the ear canal by the metallic earpieces.

The Placebo Device will look identical to the Treatment Device and *will* show, on its screen, a time-varying waveform similar to that for an active treatment. The y-axis of the plot will be labeled "stimulation intensity" and will not list temperature values (the same will be true for the Treatment Device). A patient receiving a placebo treatment will have the sensation of the earpieces creating some pressure in the ear canals and may feel the earpieces warm up to body temperature. Placebo patients will not undergo material caloric vestibular stimulation since no temperature gradient will be created across the horizontal semicircular canal. (The threshold for therapeutic benefit using CVS has not been established, but even small temperature changes can result in nystagmus (Sedjawidata et al. & Vesterhauge et al.).) The term "CVS" will not be used in describing the Device to any patient and no reference to caloric stimulation will be made. The Device will be referred to as a neuromodulation device and the specific mechanism of action will not be disclosed to patients.

All patients will be told that they may or may not benefit from the Device in terms of

pain reduction and that, further, the point in the 3-month treatment period at which a change may be noticed is unknown and may vary from patient-to-patient – i.e., the treatment duration necessary for a potential reduction in pain is unknown for any particular individual. Patients will be told that they may or may not sense slight pressure from the earpieces, a warming or cooling sensation, or slight nausea or dizziness, especially at the end of the treatment session. At the conclusion of the Treatment Period, patients will be asked to identify which arm they believe they entered (active treatment or placebo).

6) Safety; Vestibular System Examination and Monitoring

CVS has been used extensively and safely in the practice of medicine since its discovery more than a century ago by Dr. Robert Barany, a discovery for which he received the Nobel Prize in Physiology/Medicine in 1914. There have been no reports in the literature of adverse events or significant negative side effects associated with CVS. The side effect profile from use of the CVS-M Device is expected to be the same as that associated with diagnostic CVS procedures.

CVS-M acts on the central nervous system via the vestibular organs. This mechanism is distinctly different from most forms of neurostimulation that involve either electrical currents applied directly to a target nerve or region (implanted neurostimulators) or a diffuse current to larger areas of the cortex (TMS, CES, tDCS). CVS is non-invasive and easily employed. The SNS CVS-M Device enables its therapeutic use and utility by controlling thermal induction and providing safeguards that ensure treatments remain firmly within parameters established by the supervising physician.

The Berg Balance test (Berg et al.) is well-established and widely used in clinical settings to asses a person's static and dynamic balance abilities. *Inter alia*, the Test is used to quantify clinical improvement or deterioration in patients -- from evaluation of "normals" to assessment of individuals with a wide range of balance impediments. The long form Test consists of 14 balance- related tasks ranging from standing up from a sitting position to standing on one foot. Each task is graded from 0 – 4, and the final measure is the sum from all elements of the Test:

- 41-56 = low risk of fall
- 21-40 = medium risk of fall
- 0–20 = high risk of fall

The Berg Balance test will provide a consistent and easily administered, task-based scheme for identification and quantification of deterioration, if any, of a subject's balance that could be associated with use of the CVS-M Device. The local clinical coordinators will undergo training on administration of the Berg test prior to the Study. Abnormal findings with the Berg test may lead to a more extensive vestibular assessment evaluation. No unexpected side effects, nor any adverse events, have occurred in prior studies utilizing the CVS-M Device.

7) Pivotal Study Endpoints

- **Primary Efficacy Endpoint for the Pivotal Study**

  For active-treatment subjects as a group: During the third Month of the Treatment Period, their average total number of Monthly Migraine Headache Days will be lower than their comparable averages derived from the Pre-Treatment Baseline Period.

- **Secondary Efficacy Endpoints for the Pivotal Study**
  - The number of active-treatment subjects having a reduction of 50% or more in Migraine Headache Days during the third Month of the Treatment Period as compared with the Pre-Treatment Baseline Period will exceed the number of placebo-treatment patients having that response rate.
  - For active-treatment subjects as a group: During the third Month of the Treatment Period, their average Total Monthly Headache Pain Scores will be lower than their comparable averages derived from the Pre-Treatment Baseline Period.
  - For active-treatment subjects as a group: During the third Month of the Treatment Period, their average number of Treated Headaches will be lower than their comparable averages derived from the Pre-Treatment Baseline Period.
  - For active-treatment subjects as a group: On average, in comparison with their Pre-Treatment Baseline Period, they will have at the end of the Treatment Period, improvement in scores associated with the Quality of Life and Cognition Assessment measures.

- **Safety Endpoint for the Pivotal Study**:

  The principal safety endpoint for the Study is to verify the absence of material dizziness, with the associated risk of falls, as a consequence of using the active-treatment Device. The Berg Balance test will be used to assess any changes in balance performance as a result of Device usage. Transient nausea and minor dizziness may be experienced by patients, as is sometimes reported in the diagnostic CVS literature, and patients will be trained to verify balance stability after a treatment and before standing up. Previous pilot studies using the Device did not identify nausea or dizziness as side effects attributable to the Device, based on patient self-reporting.

8) Calculating Total Monthly Headache Pain Scores

For each subject the following Total Monthly Headache Pain calculations will be made:

a. Using the Daily Headache Diary data from the Pre-Treatment Baseline Period, the cumulative Pain Scores for all of the days on which the subject had a Headache during the Month will be calculated; and

b. For the third Month of the Treatment Period, the cumulative Pain Scores for all of

the days on which the subject had a Headache during the Month will be calculated.

At the conclusion of the Pivotal Study, Total Monthly Headache Pain score comparisons will be made for each subject: Pre-Treatment Baseline Period vs. the third Month of the Treatment Period. Additionally, such Total Monthly Headache Pain scores for the active-treatment subjects as a group will be compared with those for the placebo-treatment subjects as a group.

9) Statistical Analysis and Pivotal Study Size

As noted above, an experienced, independent and blinded Statistician will be utilized to analyze and summarize the Daily Headache Diaries for all patients. Also, as noted, a blinded Neuropsychologist will analyze and summarize the Quality of Life and Cognition Assessment data, and a Vestibular System Consultant will perform a blinded analysis and summary of the data from the Vestibular Testing Procedures.

Summary of the analytical methodology to be used for the Primary Endpoints

- **No prospective stratification**: Based on the inclusion and exclusion criteria, there is no medical reason to stratify the Pivotal Study's episodic migraine population.

- **Statistical method**: The Pearson's chi-square test will be used to evaluate the null hypothesis, which is that "There is no difference between the number of Migraine Headache Days (during the third Month of the Treatment Period as compared with the Month during the Pre-Treatment Baseline Period) when comparing subjects treated with the Treatment Device and subjects treated with Placebo Device."

  The corresponding alternative hypothesis is that: "There is a reduction in Migraine Headache Days (during the third Month of the Treatment Period as compared with the Month during the pre-Treatment Baseline Period) when comparing subjects treated with the Treatment Device and subjects treated with Placebo Device."

  We seek to power the Study so as to reject the null hypothesis and accept the corresponding alternative hypothesis. The following power calculations are based on probabilities from binomial distributions (2-sided test):
  - Assumed efficacy metric (response rate): a reduction of 50% or more in Migraine Headache Days with respect to baseline.
  - Assumed range of efficacy measured in the placebo arm: 10-15%
  - Assumed range of efficacy measured in the treatment arm: 45-55%

Treatment efficacy	Placebo efficacy	Statistical power	Total minimum cohort size
45%	15%	80%	72
50%	15%	80%	54
55%	15%	80%	44
45%	10%	80%	50
50%	10%	80%	40
55%	10%	80%	32

The ONSTIM (occipital nerve stimulator) study (Saper et al.) recorded a placebo (preset stimulation) efficacy of 6% and a responder rate (reduction of 50% or more in headache frequency) of 39%. Results from the PREMICE study (Cefaly, supraorbital transcutaneous neurostimulation) cited by Lambert listed a placebo efficacy of 12.1% and a responder rate of 37%. Both studies evaluated between 60-70 patients. Therefore, the range of 10-15% for placebo efficacy is felt to be relatively conservative as compared with other recent studies involving neuromodulation devices addressing Migraine Headache. The assumed efficacy rate range for the CVS Device is based on non-statistically significant observations in the two previous Migraine pilot studies. We therefore conclude that a total Study size of 80 patients is likely to be sufficient for the most probable outcomes, as that number exceeds the minimum in the table above for the most likely treatment and placebo efficacy cases. For comparison, Topiramate (Topamax) used as a prophylactic migraine treatment reports responder rates in the 37-54% range and a placebo response in the low 20% range. Therefore CVS-M responder rates in the 45-55% range would be clinically meaningful.

- **Cohort size**: Each of the sites will enroll subjects with an overall goal of 80 patients. Once up to 80 subjects have completed the Pivotal Study successfully, enrollment in the Pivotal Study will be stopped (at least temporarily) and the data will be analyzed and summarized. Using expected levels of efficacy for the Treatment and Placebo Devices, this cohort size will likely be more than adequate to demonstrate statistical significance and reject the null hypothesis. The cohort size is also expected to be adequate to establish the low rate of unanticipated adverse events associated with usage of the Device. The Sponsor may choose to extend the Study, with IRB approval, should it be necessary to increase the patient cohort size.

Summary of analytical methodologies to be used for additional safety assessments and for the Secondary Endpoints:

- Impact with respect to usage of abortive pain medications and co-morbid conditions such as nausea, dizziness, photophobia and phonophobia will be assessed based on the subjects' Daily Headache Diary entries and the Visit Assessments performed by the Investigators and their designates. An assessment will be made by the blinded Statistician as to whether there is evidence of acute or

sustained alterations in the listed measures and co-morbidities during the Treatment Period as separately compared with the Pre-Treatment Baseline Period.

- Data collected from the Quality of Life and Cognition Assessment questionnaires will be utilized for two purposes. Scoring and analysis will be performed by a single, highly experienced, blinded Neuropsychologist. Analysis first will involve review for safety, with protocols being reviewed for *changes* from baseline on the order of one standard deviation or greater on cognitive measures (using published data) and declines indicating clinical change on affective measures. Triggering during this review will prompt a broader review for consideration of withdrawal due to negative effects. Analysis will then secondarily involve pilot comparisons between Treatment and Placebo groups with respect to *changes* in scores across measures. While the present Study is not powered for detection of treatment effects on cognitive/affective measures, the acquired data can serve as pilot work to identify promising areas for future research.
- The following null hypothesis and alternative hypothesis will be evaluated for the Total Monthly Headache Pain secondary endpoint:
    - "There is no difference between the Total Monthly Headache Pain scores (during the third Month of the Treatment Period as compared with the Month during the Pre-Treatment Baseline Period) when comparing subjects treated with the Treatment Device and subjects treated with Placebo Device."
    - "There is a reduction in Total Monthly Pain scores (during the third Month of the Treatment Period as compared with the Month during the Pre-Treatment Baseline Period) when comparing subjects treated with the Treatment Device and subjects treated with Placebo Device."

10) Quality Assurance Monitor

An independent quality assurance monitor will be used to audit Pivotal Study Sites.

11) References:

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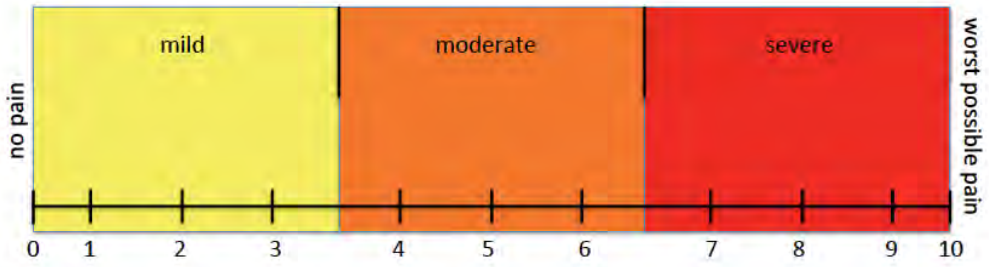
12) Test procedures, frequency and potential actions

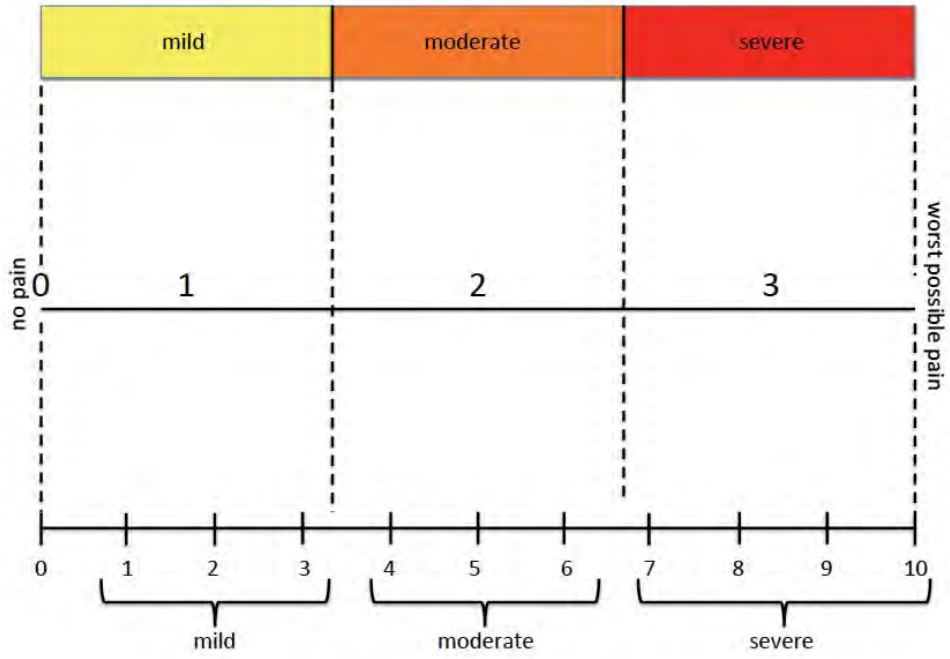
Test	Test frequency	Actions taken in case of a suspected adverse outcome
Blood pressure monitoring	At baseline, then during visits in the clinic period; measured every five minutes.	A 20% change in either direction of diastolic or systolic BP shall constitute an adverse event. Treatment will be aborted and subject's BP will be monitored until recovery.
Quality of Life and Cognition Assessment	During Treatment Day 1 (in clinic), during the during the "2-week" visit and at the conclusion of the Study	If the consulting Neuropsychologist concludes that the subject is exhibiting significant changes from baseline, the subject will be withdrawn from the treatment phase of the Pivotal Study and assessed again 3 months later.
Vestibular Testing Procedure	All patients will undergo testing at the start of the Pre-Treatment Baseline Period, during the "2-week" visit and at the conclusion of the Pivotal Study. The Berg Balance test long form will be used.	If the subject is found to have a significant vestibular abnormality not detected or disclosed in the baseline history, prior to the start of the treatment phase he/she will be withdrawn from participation. If the subject is found to have a change with respect to the baseline exam, upon completion of the Pivotal Study appropriate mitigating actions will be taken and the patient will be assessed again after 3 months.

Definitions

- Generally, International Headache Society (IHS) definitions, including the definition of Migraine Headache and episodic Migraine Headache, will be used in planning and conducting the Study. The summary in Tfelt-Hansen et al. for prophylactic migraine studies serves as the principal reference.
- **CVS** means caloric vestibular stimulation.
- **CVS-M** shall mean using CVS therapy for migraine headaches.
- **Daily Headache Diary** shall mean recordings of relevant Headache and other Pivotal Study information by each subject on a daily basis using the computer-based entry system. Each subject will be instructed to complete the Daily Headache Diary report between six p.m. and midnight each day during the Study Period. The Daily Headache Diary will ask the subject to record, for that day, what her/his maximum Headache Pain Score has been and the times at which she/he administered the treatments. The Daily Headache Diary will be the principal instrument for assessing the Primary Endpoints and Secondary Endpoints, and the Diary data will be analyzed by a qualified, blinded clinical studies Statistician.
- **Enrollment Re-Confirmation Period** shall be a few days (as few as reasonably practicable) immediately following the end of the Pre-Treatment Baseline Period, during which time the relevant Investigator will evaluate a potential Pivotal Study participant's data from the Pre-Treatment Baseline Period, assess all other factors and determine whether the individual should be enrolled and scheduled to begin treatments.
- **Headache** shall mean a pain located within the subject's head when the subject assigns to it a Pain Score between one and ten on the Headache Pain Scale.
- **Headache Day** shall mean a day during which the subject has a Headache.
- **Headache-Free Day** shall mean a day on which the subject does not have a Headache – that is, a day when the subject has a Headache Pain Score of zero.
- **Headache History Questionnaire** shall mean a listing of patient history elements relevant to the assessment of her or his migraine headache status.
- **Headache Pain Scale** shall mean an eleven-point pain measurement scale from zero (no pain) to ten (most intense pain). The pain data will also be mapped onto a four-point (0 – 3) scale and to a description based on "mild/moderate/severe" categories to facilitate placing this Pivotal Study in the context of other prophylactic pain studies. Patients will be trained on the scale shown below in order to rank their pain on the 11-point scale:



Pain scores will be summarized on a 4-point scale as well (0-3) where the transformation shall be achieved in accord with the graph below:



- **Investigators** will include**:**
  - Daniel Laskowitz, MD, Ph.D., Duke U. Medical Center, Dept. of Medicine-Neurology, Durham, NC
  - Dianne Scott, MD, Duke U. Medical Center, Dept. of Anesthesiology-Pain Division, Durham, NC
  - Michael Hoffer, MD, Naval Medical Center San Diego, Dept. of Otolaryngology, San Diego, CA
  - Dr. Mohamed Sakel, FRCP, East Kent University Foundation Hospital Trust, Director/Consultant Physician of East Kent Neurorehab Unit, Kent, UK
  - David Wilkinson, Ph.D., Dept. of Psychology, University of Kent, UK
  - Joel Saper, MD, Michigan Headache and Neurology Institute, Ann Arbor, MI
  - Anne Calhoun, MD, Carolina Headache Institute, Chapel Hill, NC

  - Marshall Freeman, MD, Headache Wellness Center, Greensboro, NC

- **Migraine Headache** In terms of *diagnosis* shall mean (following the ICDH-II guidelines) a Headache that lasts at least four hours, reaches a Pain Score of at least four on the Headache Pain Scale (moderate or severe), is not attributed to another disorder and has at least two of the following characteristics from A and at least one of the characteristics from B, respectively:
  - A: (1) unilateral location; (2) pulsating quality; (3) moderate or severe pain intensity; (4) aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs);
  - B: During Headache: (1) nausea and/or vomiting; (2) photophobia and phonophobia;

  For the purpose of the Study, headaches will be classified using the patient's own judgment. Patients will receive instructions on how to differentiate a migraine headache from a non-migrainous headache. Treated Headaches will be considered to be Migraine Headaches.

- **Migraine Headache Day** shall mean any calendar day during which a patient had a Migraine Headache of at least 30-minutes in duration.
- **Month or Monthly** shall mean or refer to a period of twenty-eight days, usually consecutive in timing.
- **Neuropsychologist** will be Deborah Attix, Ph.D., Duke U. Medical Center, Depts. of Medical Psychology and Medicine-Neurology, Durham, NC.
- **Pain Score** shall mean a maximal pain rating made by a subject for an individual Headache or for a Headache-Free Day based on using the Headache Pain Scale (zero to ten).
- **Pivotal Study** shall mean this SNS-sponsored, multi-site, randomized, triple-blinded, placebo-controlled, episodic migraine clinical study.
- **Pivotal Study Period** shall mean, with respect to each Pivotal Study participant, a period of 112 days beginning with the first day of the subject's Pre-Treatment Baseline Period and ending when she/he completes making recordings in her/his Daily Headache Diary at the end of the Treatment Diary Period (excluding the Enrollment Re-Confirmation Period and any gaps due to clinic scheduling issues). In outline, the Study Period will chronologically consist of the following:
  - Days 1-28 – Pre-Treatment Baseline Period.
  - Whatever few days are required for the Enrollment Re-Confirmation Period (it may be possible to complete this enrollment re-evaluation on the first day during the clinic

treatment week). Any time gap here is ignored in terms of listing the timeframe for the Pivotal Study.
    - One to four days during which the patient comes to the clinic for treatments.
    - Days 29 through 112 – Treatment Period (includes days of treatment in the clinic).

- **Pivotal Study Sites** will be the Duke University Medical Center, the Naval Medical Center at San Diego, East Kent University Hospital & University of Kent in England, Michigan Headache and Neurological Institute, Carolina Headache Institute, and Headache Wellness Center.
- **Placebo Device** shall mean the SNS CVS-M Device wherein the earpieces are maintained at body temperature, thus eliminating any therapeutically meaningful CVS effect from operation of the Device.
- **Pre-Treatment Baseline Period** shall mean, with respect to each Pivotal Study participant, the first month (i.e., twenty-eight days) of the Pivotal Study Period for such patient.
- **Pre-Treatment History** shall mean, with respect to each Pivotal Study participant, the established migraine headache history of that participant.
- **Quality of Life and Cognition Assessment** will consist of:
    - *General mood and cognition:* the Beck Depression Inventory® (BDI-II), Beck Anxiety Inventory® (BAI), Everyday Cognition 20 (Ecog20-PT), Digit-Symbol Subtest of the WAIS-III, Trail Making, and Controlled Oral Word Association (COWA). These tests will be administered at three time points during the Study.
    - *Long & short-term memory*: an old/new paradigm for face recognition administered during the start of the Treatment Period and again after the Treatment Period.
    - The test administration and scoring will be overseen by a qualified Neuropsychologist who is blinded as to the identity of each patient.
- **Screening Visit** – Once a candidate patient has signed the informed consent document at her/his clinical site, a screening procedure will be implemented. The screening exams will include a Vestibular Testing Procedure.
- **SNS** means Scion NeuroStim, LLC, the Pivotal Study sponsor.
- **Statistician** will be Maragatha Kuchibhatla, Ph.D, Duke University School of Medicine, Associate Professor of Biostatistics and Bioinformatics, Associate Professor of Psychiatry and Behavorial Sciences. Dr. Kuchibhatla will compile and analyze data from all sites in creating a summary report.
- **Total Monthly Headache Pain** shall mean, for a subject for any relevant monthly period, the cumulative daily Pain Scores for all

days on which the subject has a headache during such month. An example, with analysis, for a hypothetical month (twenty-eight days) is provided as follows:

Number of Days	Pain Score on Those Days
18	0
0	1
1	2
1	3
2	4
1	5
0	6
2	7
1	8
2	9
0	10

The subject's Total Monthly Headache Pain for this hypothetical month would be fifty-eight, calculated as follows: nothing for the eighteen Headache-Free Days when the subject's Pain Score was zero; then, summing 0x1 plus 1x2 plus 1x3 plus 2x4 plus 1x5 plus 0x6 plus 2x7 plus 1x8 plus 2x9 plus 0x10 = 58. During the month the subject had ten Headache Days – i.e., ten days on which the subject had a Pain Score of one or greater – of which eight were Migraine Headaches Days (Pain Score of four or greater). Thus, the patient qualifies to participate in the Study, providing she/he meets all other qualifications. (See inclusion criteria discussion.)

- **Treated Headache:** A Migraine Headache lasting at least 30 minutes for which a patient takes an acute abortive medication.
- **Treatment Device** shall mean a SNS CVS-M Device that is fully active and functioning.
- **Treatment Period** shall mean, with respect to each Pivotal Study participant, the three months following the end of the pre-Treatment Baseline Period. The third Month of the Treatment Period shall be the primary period for which efficacy of the SNS CVS-M Device treatments shall be evaluated.
- **Vestibular System Consultant** will be Carey Balaban, Ph.D., U. of Pittsburgh Medical Center, Dept. of Otolaryngology, Pittsburgh, PA.
- **Vestibular Testing Procedure** shall consist of the administration of the Berg Balance test. The test results will be reviewed by the Vestibular System Consultant (who will remain blinded).