FINAL August 9, 2016

SCION NEUROSTIM, LLC:

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

Background

This study is a multi-center, triple-blinded, placebo-controlled, randomized clinical trial for adjunctive prophylactic treatment of episodic migraine headache (with or without aura) using a caloric vestibular stimulation (CVS) device developed by Scion NeuroStim, LLC (SNS). The investigational use of the CVS device for episodic migraine headache has been reviewed by the FDA and is classified as NSR (non-significant risk).

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 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, for example in ENT practices to assess balance and in the ED to assess brain function. The device is 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 CVS device, prophylactic neuromodulation therapy for migraines can become an inexpensive and early, rather than an expensive and belated, therapeutic option.

A pivotal RCT study of episodic migraine headache using the device has been completed (NCT01899040). The primary endpoint was met. Active arm subjects showed immediate and steady declines in migraine days over the treatment period and exhibited significantly fewer migraines during the third treatment month (-3.6 ± 0.7 days, -46.1% ± 7.3%), than placebo arm subjects (-0.9 ± 0.7 days, 13.5% ± -14.1%, $p = 0.014$). The study described herein is designed to further the evaluation of CVS neuromodulation, addressing the following aims:

1. To gather additional safety and efficacy data and reaffirm that using the CVS device leads to a significant reduction in migraine headache days relative to a placebo.
2. To extend the treatment period from 3-months to 6-months, with all subjects (including placebo) receiving active treatment in the second 3-month period.
3. To test the efficacy of once-per-day active treatments versus twice-per-day active

treatments.

4. To evaluate the durability of gains realized after the end of the treatment period through an additional 3-month long headache diary period.

All participants will be subjects whose response to prior therapies has been partially successful, but limited. As defined in detail below, under International Headache Society (IHS) guidelines all of these subjects will be classified as "episodic" or acute. None will be classified as "chronic." In assessing the effectiveness of the CVS device, the study will consider both (1) a subject's number of headaches as well as (2) the severity of each and of all of those headaches. The primary endpoint is based on outcomes data collected during the treatment period vs. the pre-treatment baseline period, focusing on the comparative number of migraine headache days.

Description of the Treatment Paradigm and Study

1) Intended Use/Indication for Use

- **Intended Use:** The CVS device is intended to stimulate the vestibular system via external ear canals using controlled thermal waveforms.
- **Indication for Use:** The CVS device is indicated for use in the prevention of episodic migraine headache.

2) Subject Selection Criteria Pre-Treatment Data

In working with and through their respective designated assistant(s)/coordinator(s), the principal investigators will identify and screen potential participants, all of whom will have previously been diagnosed as episodic migraine headache subjects. The investigators will review the subjects' medical records to select those individuals who 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 principal investigator or designee, documents that she/he meets all elements of the following:
    - The subject 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 (ICHD-II and ICHD-III beta) guidelines.
    - The subject must have a history of at least three consecutive months of stable migraine headaches prior to entering the study. The subjects will not have had changes in medication usage (prescription medications for migraine headache) for the three months leading up to the study, nor will they introduce new medications during the study period. (The primary focus is on prescription medications for migraine headache. However, medications that are prescribed for co-morbid conditions which also have

demonstrated efficacy for migraine prevention should not be altered in this time period.)

- Subjects 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, as judged by the subject.
- The subject must not have failed on more than two classes of properly administered prophylactic pharmaceutical therapies for migraine headache. The subject may be on a single migraine prophylactic drug 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 subject's ability to reliably use the CVS device and promptly complete the electronic daily headache diary forms. The daily headache diary will be completed from the beginning of the pre-treatment baseline period through the end of the study. The diary is described more fully below and in the definitions section at the end of this document.

- **Exclusion Criteria**: Individuals who:
  - have previously participated in a clinical trial using the CVS Device
  - are pregnant
  - using more than one concurrent prophylactic pharmaceutical therapy for migraine headache
  - have a history of cardiovascular disease
  - work night shifts
  - have been diagnosed with vestibular migraine
  - have menstrual migraine exclusively
  - have been diagnosed with post-traumatic migraine
  - have a history of unstable mood disorder or unstable anxiety disorder. Specifically, a BDI-II score of 20 or greater and/or a BAI score of 16 or greater will disqualify a patient from randomizing into the treatment portion of the study.
  - 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 and/or balance dysfunction
- have a history of abusing alcohol or other drugs
- are experiencing medication overuse headaches (individuals with respect to whom the principal 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 Botulinum toxin-based treatments for migraines or for facial cosmetic reasons.
- are taking anti-emetics chronically (more than 2 times per week, consistently)
- Though not excluded, subjects taking anti-histamines will be encouraged not to take such medications within four hours prior to a CVS treatment. The investigator should review other medications taken by the subject 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 treatment.

- **Withdrawal Criteria**
  - Subjects must be withdrawn from the clinical trial if any of the following events occur:
    - Surgery during the study period.
    - A subject does not continue to meet inclusion/exclusion criteria.
    - A subject is significantly non-compliant with the requirements of the protocol (principle investigator & sponsor decision).
    - The subject does not complete at least 25 of 28 daily diary entries in her/his headache diary during the baseline period. (That is, the subject must be compliant with maintaining the headache diary.)
    - 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 withdraws his/her consent.
    - The principal 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 principal investigator must make every effort to perform all evaluations for the final visit and document the reasons for discontinuation. If a subject withdraws due to an adverse event, the study coordinator will follow up with regular phone calls to document the resolution of the event.

Though a subject will not be withdrawn from the study if she/he exceeds 14 headache days in any of the treatment months, such subjects will be grouped separately during the final study analysis. The rationale for this grouping is that a large percentage of subjects in the first CVS migraine RCT were excluded from randomization because they exceeded 14 headache days, thus calling into question their stable episodic status. If a subject has a "good month" during baseline, but is potentially unstable, she/he might be recruited into the study in violation of the aim of enrolling stable EM subjects. No evidence that the CVS device increased headache burden was seen in the first RCT. However, we will continue to follow subjects who exceed 14 headache days in a month during the treatment period so as to gather more data on this sub-population.

- **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 migraine headache is one for which a subject has taken an acute abortive medication (prescription medication, not OTC).
  - The subject may be on a single migraine prophylactic drug 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 subject 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 principal 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 one hundred and twenty (120) subjects who will successfully follow through to completion of their participation in at least the first treatment portion of the study (first 3-month treatment period). The subjects will be randomly assigned to: twice-per-day active, once-per-day active or twice-per-day placebo in a 1:1:1 ratio.

The results of the first migraine RCT did not show evidence of stratification based on gender or clinical site or baseline headache frequency. Envelopes containing

randomization assignments will be grouped in batches of six, each batch containing two of each of the three assignment arms. The batches of envelopes will be randomly shuffled by an agent not involved with the study. A given batch will be completed before the next batch is opened. This procedure results in 20 possible different arrangements, for six subjects, of the ordering of treatment and placebo assignments. The unblinded coordinator will record the subject's designation but will not share the assignment with the subject, principal investigator, or statistician. Each study site will be individually randomized (no central randomization).

The assessment of the primary endpoint will be completed by a blinded, central statistician. The subjects will be told, within the informed consent document, of the existence of a placebo arm. Subjects will be told that the device stimulates the brain stem. Subjects will be told that they will receive at least 3-months of active treatment during the 6-month treatment period. In fact, subjects in the placebo arm in the first 3-month period will be switched to active in the second 3-month period. Subjects will be asked to guess (and provide reasons) about their treatment assignment at the end of the first 3-month treatment period and at the end of the second 3-month treatment period. Subjects will also be asked, after their very first treatment in the clinic, a series of questions designed to assess the quality of blinding (to provide evidence that the placebo device is an effective sham).

4) Study Schedule; Subject Enrollment and Activities

The study period will last 280 days (plus additional visit window days, as needed), beginning with a pre-treatment baseline period of one month (28 days), at the end of which the principal investigator will reconfirm the appropriateness of the subject's participation in the study, followed by a first treatment period of three months (84 days), followed by a second treatment period of three months (84 days), followed by a post-treatment diary period of three months (84 days).

As noted, subjects will be advised that during the 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.

The study will be segmented with the following aims:

1. Baseline period and the first 3-month treatment period: **This portion of the study will be viewed as a complete RCT in-and-of itself and will be analyzed while the remainder of the study is still underway. The primary endpoint applies to this portion of the study.** Subjects will use an electronic data capture system that records headache pain level, duration and associated symptoms, acute medication use, and whether the headache was a migraine headache. Also, subjects will record any occurrence of an adverse event (AE).
2. Months 5-7 (from the start of the baseline period): All subjects will be assigned to the active device. Subjects will treat with the same frequency as they did in the first 3-month treatment period (e.g., BID in the first period means BID in the second period). Subjects will record the occurrence of a headache and whether

the headache was a migraine headache. Subjects will report any adverse events to the unblinded site coordinator.

3. Months 8-10 (from the start of the baseline period): Subjects will no longer be treating with the CVS device. Subjects will record the occurrence of a headache and whether the headache was a migraine headache. Subjects will report any adverse events to the unblinded site coordinator.

The phases and activities of the 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 study, the subject will then complete a screening visit. The study coordinator will complete a headache history questionnaire for the subject. If the subject is recommended for continuation in the study after the screening visit and tentatively approved by a principal investigator, she/he will start a daily headache diary and continue to make entries for twenty-eight consecutive days. Subjects will be given Scion email accounts to be used for submitting headache diary entries. Sites will assist subjects with syncing their Scion email accounts with their smartphones or tablets, and will ensure that subjects can competently take a photo of the ediary form, upload and send according to procedure. If the subject does not complete at least 25 of 28 daily headache diary entries during the baseline period, she or he will be withdrawn and will not proceed to randomization.

(ii) **Clinic Training Visit**: 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 study, the subject will come to the clinic for an appointment(s) for training on the use of the CVS device. During the clinic visit, the subject will complete a quality of life (QOL) assessment. The assessment will consist of the HIT-6, BAI, BDI-II and Pittsburgh Sleep Quality Assessment questionnaires. The BAI and BDI-II scores will be tallied with the following outcomes:

a. Subjects who score 20 or higher on the BDI-II or answer affirmative to questions 9 on the BDI-form will not proceed to randomization and will be withdrawn from the study.
b. Subjects who score 16 or higher on the Beck Anxiety Index will not proceed to randomization and will be withdrawn from the study.

(iii) Also, women of childbearing age will complete a urine-based pregnancy test to reconfirm that they are not pregnant. The unblinded coordinator will open, at random, an envelope assigning the subject to one of the three study arms. The clinic period is described below. During the first visit, the subject will complete a training session based on a set training module. The subject will complete a proficiency evaluation and the study coordinator will certify the subject's proficiency in the use of the CVS device. The study coordinator will

complete a visit assessment form. At the end of training, a first usability questionnaire will be completed by the subject.

(iv) **First Treatment Period:** The eighty-four days (3 months) following the pre-treatment baseline period constitute the first treatment period. This is the test period, the results from which will be measured against the pre-treatment baseline period data in assessing the study endpoints. Specifically, data from the last month of the first treatment period will be compared with the one-month-long pre-treatment baseline period. As close as possible (as scheduling permits) to two weeks after the start of treatment, a clinical visit will occur and another visit assessment form will be completed. A second usability questionnaire will be completed. The subject will be asked to bring the CVS device to the clinic to perform a treatment in front of the unblinded study coordinator to reaffirm proficiency in using the device. Any issues related to balance or other safety concerns will promptly be referred to the site principal investigator, who can terminate the subject's further participation in the study if necessary.

(v) **End of First Treatment Period – Start of Second Treatment Period:** At the end of the first treatment period the subject will be asked to return to the clinic and will be asked to complete the QOL questionnaires and a third usability questionnaire. All subjects will receive new SD cards for the second treatment period and the old SD cards will be retained so that treatment compliance logs can be extracted. All subjects will receive active treatment cards with the following assignments (first treatment period -> second treatment period):

- BID placebo -> BID active
- BID active -> BID active
- QD active -> QD active

Subjects will perform a treatment in front of the unblinded coordinator to re-confirm their ability to properly use the device.

Note: The treatment delivery data (recorded on the SD cards) from the CVS device consists of temperature waveform files that contain actual measured temperature values that were delivered to the earpieces during treatments. This data is an independent record of the expected device performance and is used for confirmation purposes only. The SD card data files also record treatment times and subject compliance, which will be used to calculate the level of treatment compliance. Subjects will *not* be informed that the device monitors treatment compliance.

- **End of Second Treatment Period – Start of Observation Period**: At the end of the second treatment period, all subjects will return their devices to the clinics. The SD cards will be collected. Subjects will be asked to complete the QOL questionnaires again and will be asked to complete a final usability questionnaire.

Subjects will then be asked to continue to make recordings in their headache diaries for an additional 12 weeks.

- **End of Observation Period/End of Study**: Subjects will return to the clinics one final time. They will be asked to complete the QOL questionnaires.

5) Active Treatment Parameters; Placebo Treatments

The following parameters will be set for active treatments using the CVS device:

- A standardized CVS time-varying waveform lasting approximately 19 minutes will be used for all active treatment subjects at all study sites. Treatments will be administered once or twice daily, based upon a subject's randomization assignment. The two daily treatments should ideally be separated by at least one hour.
- The waveform schedule for active treatment subjects 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 waveform lasting approximately 19 minutes will be used for all placebo treatment subjects at all study sites. Treatments will be administered twice daily.
- The waveform schedule for placebo treatment subjects will consist of turning on the cooling fans and leaving the earpieces unpowered.

The placebo device will look identical to the Treatment Device and *will* show, on its screen, the identical progress plot shown on the active device. The y-axis of the plot will be labeled "stimulation intensity" and will not list temperature values. A subject 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 (the metal earpieces will feel cold initially). Placebo subjects 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 subject and no reference to caloric stimulation will be made. The device will be referred to as a brainstem neuromodulation device and the specific mechanism of action,

that is the use of temperature changes, will not be disclosed to subjects. Overt focus on the CVS phenomenon would create an intractable issue with successful blinding.

All subjects 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 6-month treatment period at which a change may be noticed is unknown and may vary from subject-to-subject – i.e., the treatment duration necessary for a potential reduction in pain is unknown for any particular individual. All subjects 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, or noise from the device. At the conclusion of each of the two treatment periods, subjects will be asked to identify which arm they believe they entered (active treatment or placebo) and why. Coordinators will encourage patients to provide an answer, emphasizing that there are no right or wrong answers. After the very first device treatment (in the clinic), all subjects will be asked a series of questions designed to assess the quality of blinding (to provide evidence that the placebo device is an effective sham).

6) Safety

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 serious adverse events or significant negative side effects associated with diagnostic CVS. In the first RCT, no SAE's and no unexpected AE's were reported. No reductions in balance ability, as measured with the Berg balance test, were recorded. No negative changes in mood or cognition were recorded based on the mood and cognition assessment battery in that study.

CVS 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 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.

Use of the study device may cause some, all or none of the transient adverse events listed below:

More likely:

- Dizziness
- Drowsiness
- Vertigo (whirling or spinning sensation)
- Discomfort

Less likely:

- Nausea/vomiting

- Headache
- Coughing

All of these side effects are expected to resolve once use of the device is stopped.

7) Study Endpoints

- **Primary Efficacy Endpoint for the Study**

  For the twice-per-day active-treatment subjects: During the third month of the first 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. Also, this reduction in migraine headache days will exceed that observed in the twice-per-day placebo group.

- **Secondary Endpoints**:
  - The normalized percent-reduction in migraine headache days (during the third treatment month relative to the pre-treatment baseline) in the BID active-treatment subjects will be compared to that of the BID placebo-treatment subjects. Groups will be compared on the basis of percent-change (continuous variable) as well as the "50% responder rates" (discrete variable).
  - The reduction in acute (prescribed) medication taken (during the third treatment month relative to the pre-treatment baseline) in the BID active-treatment subjects will be compared to that of the BID placebo-treatment subjects.
  - The reduction in subject-perceived headache pain scores (during the third treatment month relative to the pre-treatment baseline) in the BID active-treatment subjects will be compared to that of the BID placebo-treatment subjects.
  - To assess whether active treatment results in improved quality of life (related to the reduction in migraine), HIT-6 change scores (end of the first treatment period versus baseline) will be compared across BID active-treatment subjects and BID placebo-treatment subjects.
  - To assess whether active treatment results in improvements in depression or anxiety, BDI and BAI scores (end of the first treatment period versus baseline) will be compared across BID active-treatment subjects and BID placebo-treatment subjects.
  - To assess whether active treatment results in improved sleep quality, Pittsburgh Sleep Quality Assessment change scores (end of the first treatment period versus baseline) will be compared across BID active-treatment subjects and BID placebo-treatment subjects. Correlational analysis will be performed to determine whether a relationship exists between improved sleep and reduced migraine frequency.

- To assess whether BID active treatment provides therapeutic gains over QD active treatment, the reductions in migraine headaches, the reduction in the number of acute (prescribed) medication taken, the reduction in subject-perceived headache pain scores, the normalized percent-change in monthly headache days, and the 50% responder rates in the BID active-treatment subjects and QD active-treatment subjects during the following periods will be compared: the first treatment month, the third treatment month, the sixth treatment month and the final month of the post-treatment period. Additionally, change scores for the QOL measures (HIT-6, BDI, BAI and the Pittsburgh Sleep Quality Assessment) at the end of the first and second treatment periods and the post-treatment observation period will also be assessed. The response kinetics for each of these parameters will be evaluated by comparing time courses for each of the three treatment arms. All change scores will be calculated relative to baseline measures.
- To assess whether six months of active treatment provides improved levels of migraine prevention relative to three months of active treatment, comparisons of the reductions in migraine headache days, the reduction in the number of acute (prescribed) medication taken, the reduction in subject-perceived headache pain scores, the normalized percent-change in monthly headache days, and the 50% responder rates during the third treatment month and the sixth treatment month (relative to baseline) for the QD active and the BID active groups will be performed. Change scores for the QOL measures (HIT-6, BDI, BAI and the Pittsburgh Sleep Quality Assessment) for the QD active and the BID active groups at the end of the first and second treatment periods (relative to baseline) will also be compared. Additionally, these measures will also be compared between the BID active and BID placebo groups during the sixth treatment month. All change scores will be calculated relative to baseline measures.
- To assess whether CVS therapy provides durable migraine prevention after therapy has ceased, the number of migraine days, the reduction in subject-perceived headache pain scores, the number of acute (prescribed) medication taken, during each month in the post-Tx observation period will be compared to both baseline and the final treatment month in all 3 treatment groups. The normalized percent-change in monthly headache days and the 50% responder rates (relative to baseline) will also be assessed. Additionally, the QOL measurements (HIT-6, BDI, BAI and Pittsburgh Sleep Quality Assessment scores) at the final visit will be compared to both the baseline and the 6 month scores.

- Measures of body mass index for each subject will be calculated at baseline, after three and six months of treatment and after the post-treatment observation period and compared across the three treatment

arms.

- Measures of depression (Beck Depression Inventory) and anxiety (Beck Anxiety Inventory) for each subject will be calculated at baseline, after three and six months of treatment and after the post-treatment observation period and compared across the three treatment arms.

- To assess whether the reduction in migraine days relates to the number of active CVS treatments performed, correlational analyses will be performed to assess whether the change in the total number of headache days during defined study periods (first treatment period, second treatment period and post-treatment observational period) is a function of the cumulative CVS treatments performed. Additionally, approaches such as the GLIMMIX procedure for generalized linear mixed models will also be performed to determine the probability of a headache on any given day is predicted by the cumulative number of active treatments performed.

As noted above, the baseline period and the first 3-month treatment period will constitute a complete RCT. Those data will be analyzed when the targeted number of subjects (120) complete the first treatment period. Subjects will continue on to the second 3-month treatment period without interruption, as they progress through the study period. For additional clarity, the stated primary endpoint will be evaluated for the baseline period + first 3-month treatment period.

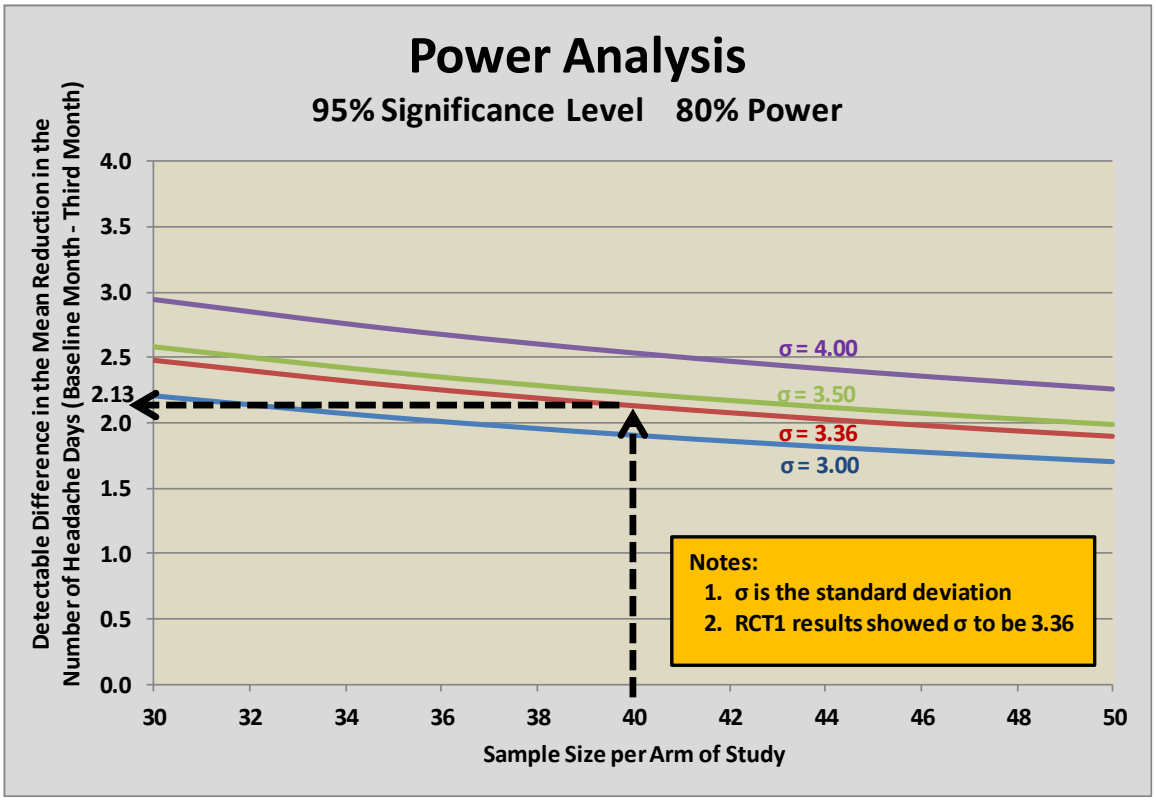
8) Statistical Analysis and Study Size

An experienced, independent and blinded Statistician will analyze and summarize the daily headache diaries for all subjects and evaluate the primary endpoint and observational aims. A blinded reviewer will analyze and summarize the quality of life data.

The primary aim of this trial is to determine if subjects randomized to the twice-daily active group, have a greater reduction in the number of headache days than those assigned to the twice-daily placebo group. For this study, the reduction in headache days (primary endpoint) is calculated as the number of headache days during the baseline month minus the number of headache days during treatment month three. An intent-to-treat methodology will be employed for the primary aim; however, per protocol analyses will also be conducted for comparison. Analysis of the primary endpoint and the secondary headache-related endpoints assessed in the daily diary will be performed for all subjects that complete at least 25 diary entries or more during the relevant 28-day treatment month. Treatment compliance is defined as completion of at least 50% during

each treatment months (for the per protocol evaluation). Subjects with treatment compliance below 50% during any treatment month will be assigned to the intent-to-treat group only. As accurate assessment of some of the secondary endpoints assessed during study period do not depend on daily headache diary compliance, treatment compliance will be the only criteria for inclusion in the per protocol analysis of those secondary outcomes. Statistical significance will be defined with a Type I error of 5% (α=0.05). Wilcoxon rank-sum tests (for non-normal data) or a paired student's t-tests (for normal data) will be used to establish whether the reductions in headache days between the baseline and third treatment month in each treatment arm are statistically significant. Mann-Whitney U tests (for non-normal data) or unpaired student's t-tests (for normal data) will be used to determine whether the reduction in migraine headaches in the twice daily active treatment arm subjects is significantly greater than that observed in the twice daily placebo treatment arm subjects. No interim analyses of efficacy are planned.

The study is powered for the primary aim. Given a sample size of 40 subjects per arm and a standard deviation in the reduction of headache days of σ=3.36, a mean difference for the reduction in the number of headache days between the twice-daily active arm and the twice daily placebo arm of 2.13 days will be detectable at the 95% significance level (a=0.05) with 80% power. The figure below shows the sensitivity of the detectable differences relative to the value of the standard deviation and the sample size.



The study is intentionally overpowered for the primary endpoint (based on the mean reduction of 2.73 headache days in the first RCT), however, a sample size of 40 subjects per arm should allow for sufficient power to assess the majority of secondary endpoints at

the end of the sixth treatment month and at the end of the post-treatment observation period given the expected dropout rate of 5 subjects per group during each 3 month period. Notably, while the 50% responder rate (a secondary outcome) will be evaluated as a discrete variable, it is unlikely to yield statistical significance due to insufficient sampling. Therefore, the similar measure of percent-change in migraine days will also be compared as a continuous variable across groups.

An analysis will be conducted to determine if blinding was successful using descriptive statistics.

9) Quality Assurance Monitor

A quality assurance monitor will be used to audit study sites. Following written procedures, the monitor will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements. Investigational site(s) will provide direct access to all trial related sites, source data/documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by regulatory authorities.

10) Procedures for adverse events:

- **Documentation and assessment**
  - Following the informed consent process, clinical study subjects will be routinely questioned about adverse events at study visits and telephone contacts by the clinical research sites. All adverse events, regardless of treatment group, or suspected causal relationship to the investigational device, will be recorded in the subjects' case report forms in their study binder.
  - For all adverse events, sufficient information will be obtained as to 1) determine the outcome of the event (i.e., whether the event should be classified as "*serious"*) and; 2) assess the casual relationship between the adverse event and the investigational device.
  - Adverse events felt to be associated with the investigational device will be followed until the event (or its sequelae) resolves or stabilizes at a level acceptable to the investigator and sponsor.

- **Causality and severity assessment**
  - The investigator will promptly review documented adverse events to determine 1) if there is a reasonable possibility that the adverse event was caused by the investigational device or other study treatments and 2) if the adverse event meets the criteria for "*serious."*
  - If the Principal Investigator (PI) is not a physician, a sub-investigator who is licensed to recognize, diagnose, and treat adverse events (e.g., MD) must review this report. The PI, must confirm that an MD sub-investigator has reviewed and acknowledges the contents of the report form.

- If the investigator's final determination of causality is "of questionable relationship to the investigational device or other study treatments," the adverse effect will be classified as *associated with the use of the investigational device or other study treatments* for reporting purposes. If the investigator's final determination of causality is "*not related* to the investigational device or other study treatments," this determination and the rationale for the determination will be documented in the respective subject's case Report form in their study binder.

- **Reporting adverse events to the responsible IRB**
  - Investigators are required to submit a report of a Unanticipated Adverse Device Effect (UADE) to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150(a)(1)). However, if the UADE involves a death, it must be reported within **24 hours** of discovery.

- **Reporting adverse events to the FDA**
  - The sponsor must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the event (21 CFR 812.46(b), 812.150(b)(1)).
  - The UADE must meet all three of the definitions: 1) Adverse Device Effect; 2) Serious; and 3) Unanticipated.
  - For any adverse event that is determined to be a UADE, the sponsor will submit an expedited safety report to the FDA's Center for Devices and Radiological Health. The expedited safety report will consist of:
    - a completed Form FDA 3500A
    - a cover letter analyzing the significance of the event
  - A copy of this safety report and the results of such report will be provided to all participating study investigators and reviewing IRBs.
  - The completed Form FDA 3500A and cover letter will be submitted to the FDA as soon as possible and, in no event, later than 10 working days after the sponsor first receives notice of the UADE.
  - If, following receipt and investigation of follow-up information regarding an adverse event that was previously determined not to be a UADE, the sponsor-investigator determines that the event does meet the requirements for expedited reporting, the sponsor-investigator will submit a completed Form FDA 3500A and cover letter as soon as possible, but in no event later than 10 working days, after the determination is made.
  - Subsequent to the initial submission of a completed FDA Form 3500A, the sponsor will submit additional information concerning the reported adverse event as requested by the FDA.

- **Procedure in the event of a mood abnormality post-randomization:** BDI-II scores above 20 or BAI scores above 16 after treatment has commenced should be referred to the PI for consultation. If the subject answers in the affirmative to question 9 of the BDI-II form, he/she should be referred for mental health counseling on that same clinic visit.

- **Withdrawal of consent due to AE**
  - If a subject withdraws consent due to an AE or if the PI determines the subject should be withdrawn due to an AE deemed to be possibly related to use of the device, the details of that event should be noted on the subject disposition form. Additional, study sites should follow up with the subject so as to document the resolution of the AE.

11) References:

ICDH-2: (2004). "The International Classification of Headache Disorders: 2nd edition." Cephalalgia **24 Suppl 1**: 9-160.

ICDH-3 beta: (2013). "The International Classification of Headache Disorders, 3rd edition (beta version)." Cephalalgia **33**(9): 629-808.

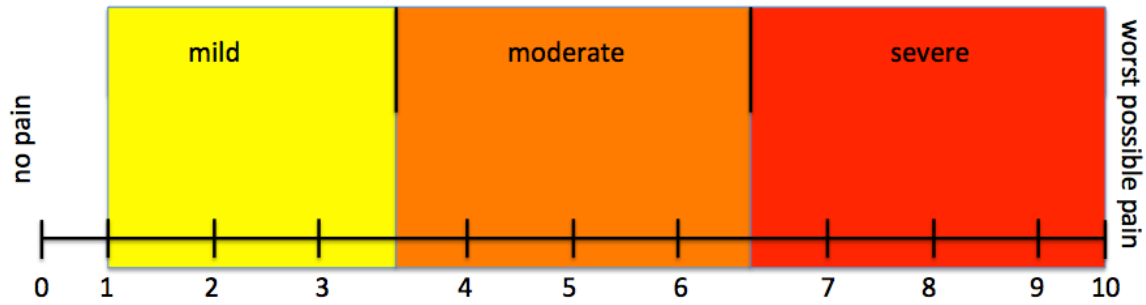
Sedjawidada, R., D. Mangape, et al. (1995). "Minimum amount of calories needed to elicit the vestibulo-ocular reflex in normal human subjects." Acta Otolaryngol Suppl **519**: 17-20.

Tfelt-Hansen, P., J. Pascual, et al. (2012). "Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators." Cephalalgia **32**(1): 6-38.

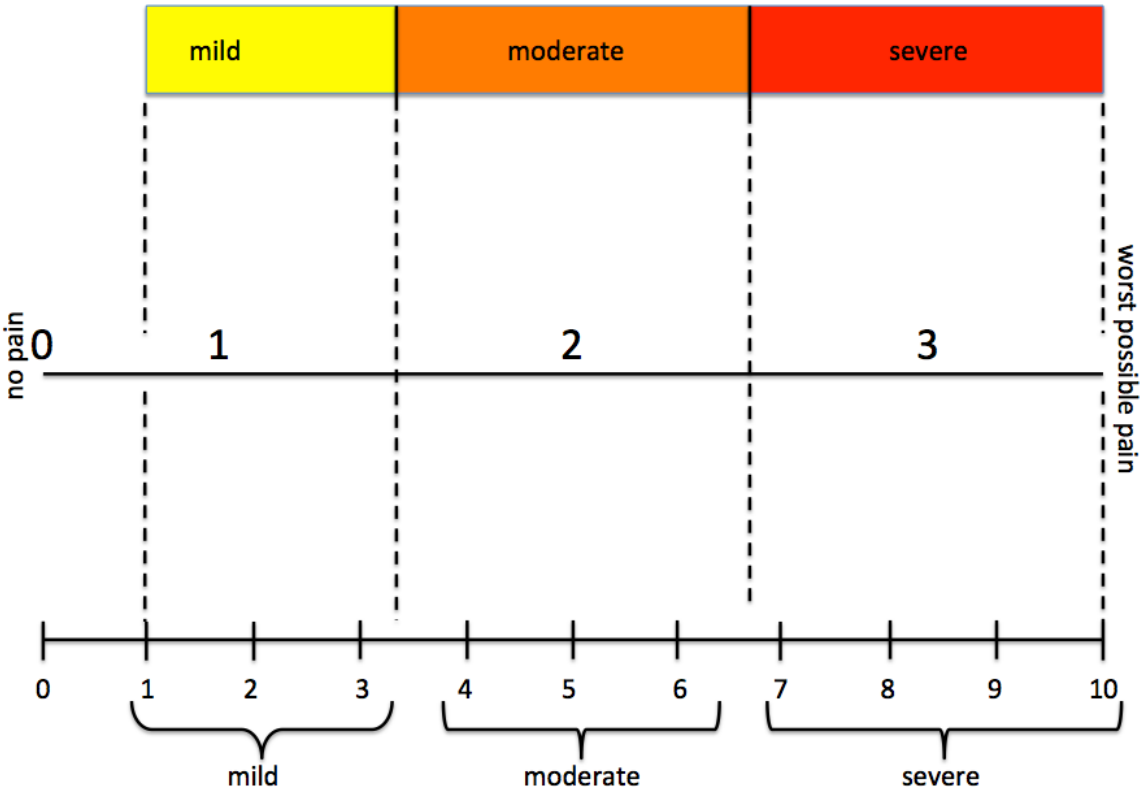
Vesterhauge, S., S. Holm-Jensen, et al. (1984). "Caloric testing with small temperature gradients. Caloric zero." ORL J Otorhinolaryngol Relat Spec **46**(2): 105-110.

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.
- **Adverse Event (AE)** shall mean any untoward medical occurrence in a subject that may or may not be related to the investigational product or have a causal relationship with the investigational treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the investigational product.
- **Adverse Device Effect (ADE)** shall mean any device related adverse event.
- **CVS** means caloric vestibular stimulation.
- **CVS device** shall mean the Scion NeuroStim, solid-state CVS treatment unit (for Investigational Use Only).
- **Daily Headache Diary** shall mean recordings of relevant headache and other study information by each subject on a daily basis using the specified procedure. Each day, subjects will complete a form documenting whether they experienced a headache, whether they thought their headache was a migraine, what their maximum headache pain score has been, the headache duration, associated symptoms, medications taken and occurrence of any side effects. Subjects will submit electronic images of these forms using their Scion associated emails. The daily headache diary will be the principal instrument for assessing the primary endpoint.
- **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 subject 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 study in the context of other prophylactic pain studies. Subjects will be trained on the scale shown below in order to rank their pain on the 11-point scale:



Pain scores can be mapped a 4-point scale as well (0-3), with which some subjects may be more familiar, where the transformation shall be achieved in accord with the graph below:



- **Investigators:** Sites and Investigators are listed on a separate roster.

- **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 subject's own judgment. Subjects will receive instructions on how to differentiate a migraine headache from a non-migrainous headache. Treated headaches using acute (prescribed) abortive medications will be considered to be migraine headaches.

- **Migraine Headache Day** shall mean any calendar day during which a subject 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.
- **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).
- **Study** shall mean this SNS-sponsored, multi-site, randomized, triple-blinded, placebo-controlled, episodic migraine clinical study.
- **Pre-Treatment Baseline Period** shall mean, with respect to each study participant, the first month (i.e., twenty-eight days) of the study period.
- **Pre-Treatment History:** the established migraine headache history of that participant.
- **Quality of Life Assessments** will consist of:
    - *HIT-6*: a common QOL measure used in migraine prevention studies.
    - *BAI*: the Beck Anxiety Index. The following ranges are established:
        - *0*-7 minimal
        - *8*-15 mild
        - *16*-25 moderate
        - *26*-63 severe
    - *BDI*-II: the Beck Depression Index. The following ranges are established:
        - *0*-13 minimal
        - *14*-19 mild
        - *20*-28 moderate
        - *29*-63 severe
    - *Pittsburg Sleep Quality Assessment*: An established test protocol to assess sleep latency and quality.
- **Serious Adverse Event (SAE)**: an adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: 1) Death; 2) a life-threatening adverse event; 3) inpatient hospitalization or prolongation of existing hospitalization; 4) a

persistent or significant incapacity or disability; 5) or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- **SNS:** Scion NeuroStim, LLC, the study sponsor.
- **Treated Headache:** A migraine headache lasting at least 30 minutes for which a subject takes an acute abortive migraine medication (prescription medication, not OTC).
- **Unanticipated**: Not previously identified in nature, severity, or degree of incidence in the investigational plan (protocol) or Investigational Brochure/Device Manual.
- **Unanticipated Adverse Device Effect (UADE)**: any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan (protocol), or is not listed at the specificity or severity that has been observed; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

BDI®-II

Date:

Patient ID

Sex: _____

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, **including** today. Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle the highest number for that group. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) or Item 18 (Changes in Appetite).

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my future is hopeless and will only get worse.

3. Past Failure

0 I do not feel like a failure.
I have failed more than I should have.
2 As I look back, I see a lot of failures.
3 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty all of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.
I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

0 I don't have any thoughts of killing myself.
I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying

0 I don't cry any more than I used to.
I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

_____ Subtotal Page 1

Continued on Back

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11. Agitation

0 I am no more restless or wound up than usual.
1 I feel more restless or wound up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than I used to.
3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.
1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.
2b I sleep a lot less than usual.

3a I sleep most of the day.
3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1a My appetite is somewhat less than usual.
1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.
2b My appetite is much greater than usual.

3a I have no appetite at all.
3b I crave food all the time.

19. Concentration Difficulty

0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0 I have not noticed any recent change in my interest in sex.
I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

_____ Subtotal Page 2

_____ Subtotal Page I

patient ID _____ DATE _____

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by each symptom during the PAST WEEK, INCLUDING TODAY, by placing an X in the corresponding space in the column next to each symptom.

	NOT AT ALL	MILDLY It did not bother me much.	MODERATELY It was very unpleasant, but I could stand it.	SEVERELY I could barely stand it.
1. Numbness or tingling.				
2. Feeling hot.				
3. Wobbliness in legs.				
4. Unable to relax.				
5. Fear of the worst happening.				
6. Dizzy or lightheaded.				
7. Heart pounding or racing.				
8. Unsteady.				
9. Terrified.				
10. Nervous.				
11. Feelings of choking.				
12. Hands trembling.				
13. Shaky.				
14. Fear of losing control.				
15. Difficulty breathing.				
16. Fear of dying.				
17. Scared.				
18. Indigestion or discomfort in abdomen.				
19. Faint.				
20. Face flushed.				
21. Sweating (not due to heat).				

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Name:_____Date:_____

HEADACHE IMPACT TEST™

Please circle the response that best describes how you feel and calculate the totals below.

1. **When you have headaches, how often is the pain severe?**

A) Never B) Rarely C) Sometimes D) Very Often E) Always

2. **How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?**

A) Never B) Rarely C) Sometimes D) Very Often E) Always

3. **When your have a headache, how often do you wish you could lie down?**

A) Never B) Rarely C) Sometimes D) Very Often E) Always

4. **In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?**

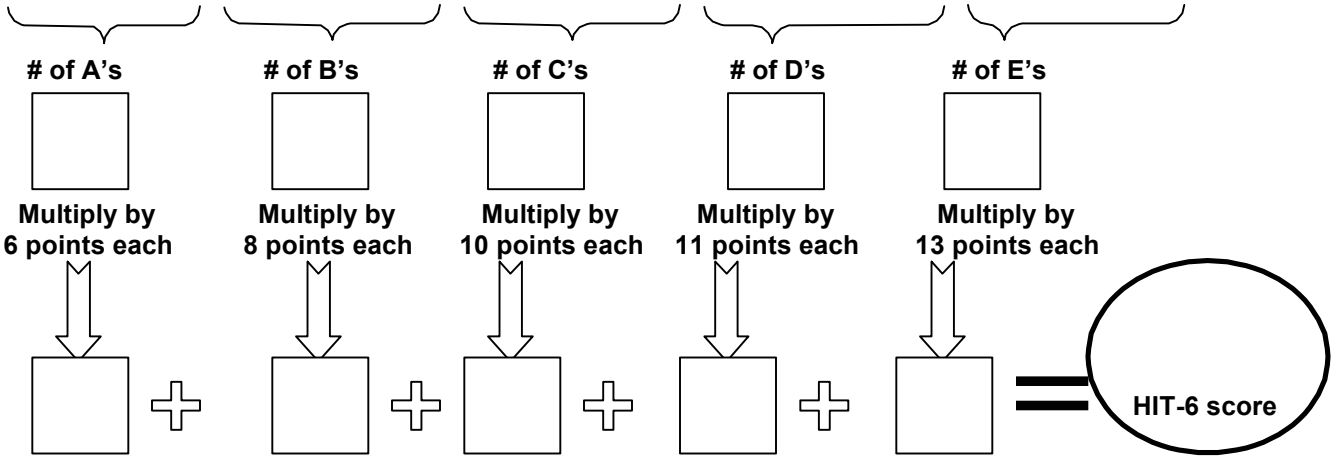
A) Never B) Rarely C) Sometimes D) Very Often E) Always

5. **In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?**

A) Never B) Rarely C) Sometimes D) Very Often E) Always

6. **In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?**

A) Never B) Rarely C) Sometimes D) Very Often E) Always



Bonus Questions

On a scale of 0-10, with "10" being the worst discomfort imaginable above the shoulders, and a "0" is no pain at all (you feel fabulous), how many mornings per week do you wake with a "0", that is, *you feel fabulous?*_____

On those mornings that you wake "with a number", what's the average number that you have? _____

HEADACHE IMPACT TEST™

What Does Your Score Mean?

If You Scored 60 or More

Your headaches are having a very severe impact on your life. You may be experiencing disabling pain and other symptoms that are more severe than those of other headache sufferers. Don't let your headaches stop you from enjoying the important things in your life, like family, work, school or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 56 – 59

Your headaches are having a substantial impact on your life. As a result you may be experiencing severe pain and other symptoms, causing you to miss some time from family, work, school, or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 50 – 55

Your headaches seem to be having some impact on your life. Your headaches should not make you miss time from family, work, school, or social activities.

Make sure you discuss your HIT-6 results and your headaches at your next appointment with your doctor.

If You Scored 49 or Less

Your headaches seem to be having little to no impact on your life at this time. We encourage you to take HIT-6 monthly to continue to track how your headaches affect your life.

If Your Score on HIT-6 is 50 or Higher

You should share the results with your doctor. Headaches that are disrupting your life could be migraine.

Take HIT-6 with you when you visit your doctor because research shows that when doctors understand exactly how badly headaches affect the lives of their patients, they are much more likely to provide a successful treatment program, which may include medication.

HIT is also available on the Internet at www.headachetest.com.

The Internet version allows you to print out a personal report of your results as well as a special detailed version for your doctor.

Don't forget to take HIT-6 again or try the Internet version to continue to monitor your progress.

About HIT

The Headache Impact Test (HIT) is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36→* health assessment tool.

HIT is not intended to offer medical advice regarding medical diagnosis or treatment. You should talk to your healthcare provider for advice specific to your situation.

HIT-6 Scoring Interpretation English Version 1.1

Name_____ Date_____

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates "poor" from "good" sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. A. How many hours of actual sleep did you get at night? _____
   B. How many hours were you in bed? _____

5. During the past month, how often have you had trouble sleeping because you	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				
J. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)

Scoring

Component 1	#9 Score	C1 _____
Component 2	#2 Score (<15min (0), 16-30min (1), 31-60 min (2), >60min (3)) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2 _____
Component 3	#4 Score (>7(0), 6-7 (1), 5-6 (2), <5 (3)	C3 _____
Component 4	(total # of hours asleep) / (total # of hours in bed) x 100 >85%=0, 75%-84%=!, 65%-74%=2, <65%=3	C4 _____
Component 5	# sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5 _____
Component 6	#6 Score	C6 _____
Component 7	#7 Score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7 _____

Add the seven component scores together _____ ***Global PSQI*** _____

A total score of "5" or greater is indicative of poor sleep quality.
If you scored "5" or more it is suggested that you discuss your sleep habits with a healthcare provider

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

SCREENING VIST (Visit 1)

Informed Consent Process	**Yes**	**No**
1. Is the subject able to read and understand the informed consent form?		
2. Has a thorough review and discussion of the study been conducted with the subject?		
3. Has the subject had an opportunity to ask questions and have those questions answered?		
4. Did the subject sign/date the informed consent prior to any study procedures being done?		
5. Has a copy of the signed consent been given to the subject?		
ICF Version/Date:		

Signature (of person obtaining informed consent):_____ **Date:**_____

Inclusion Criteria: Each participant must have a pre-treatment history that, when initially screened by a principal investigator or designee, documents that she/he meets all elements of the following:

	Yes	**No**
• 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, as judged by the patient.		
• 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 drug 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 device and promptly complete the electronic daily headache diary forms. The daily headache diary will be completed from the beginning of the pre-treatment baseline period through the end of the study. The diary is described more fully below and in the definitions section at the end of this document.		

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Exclusion Criteria Individuals who:	**Yes**	**No**
• have previously participated in a clinical trial using the TNM Device		
• are pregnant		
• have a history of cardiovascular disease		
• work night shifts		
• have been diagnosed with vestibular migraine		
• 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 principal 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 Botulinum toxin-based treatments for migraines		
• are taking anti-emetics chronically		

Please Note: Though not excluded, patients taking anti-histamines will be encouraged not to take such medications within four (4) hours prior to a CVS 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 (4) hours prior to a CVS treatment.

Demographics:	**Complete or Circle**	
Date of Birth: (dd/mmm/yyyy)	_____/_____/_____	
Gender:	Male	Female

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Headache History Questionnaire

	Complete or Circle		
Date of Diagnosis (Episodic migraine): dd/mmm/yyyy	____/____/____		
Monthly Total of **all** Headache Days (including migraines):			
Of those, Monthly Total of Migraine Days (only migraines):			
Did you have an accident or injury that may have started your headaches?	YES	NO	
Are your headaches attributed to another disorder?	YES	NO	
Do you have any warnings/symptoms of a headache for a period of time before the headache begins?	YES	NO	
Please describe the severity of your headaches:	Mild	Moderate	Severe

When you have a headache:	**Yes**	**No**
Activity/Exercise makes it worse		
Bright lights bother you		
Loud sounds bother you		
Like to stay in a quiet, dark room and try to fall asleep		
Have nausea and/or vomiting		
Feel lightheaded or dizzy		
Certain odors bother you		

My headaches are often brought on by:	**Yes**	**No**
Fatigue		
Lying down		
Chewing		
Talking		
Certain Foods		
Stress/Tension		
Stooping		
Certain Medications		
Menstruation		
Alcohol		
Oversleeping		
Washing face		
Coughing		
Shaving		

SUBJECT ID:_____ SITE #:_____

DATE: _____ PROTOCOL NUMBER:_____

Family History (blood relatives that have severe headaches): Check all that apply

___Mother_____Father____Sister_____Brother__None_____Unknown

Maternal (Mother's side):____Aunt_____Uncle_____Grandparent__Cousin

Paternal (Father's side):_____Aunt_____Uncle_____Grandparent_Cousin

Social History:	**Yes**	**No**	
Do you smoke?			If so, how much?_____How often? _____
Do you drink alcohol?			If so, how much?_____How often? _____
Do you use caffeine?			If so, how much?_____How often? _____

Prophylactic Migraine Medications: What medications do you take currently (**"C"**) or have you taken in the past (**"P"**) for your headaches? Chose all that apply

Amitriptyline (Elavil)		Nortriptyline		Propranolol (Inderal)	
SOMA		Flexeril		Topamax	
Timolol		Corgard (Nadolol)		Lamictal	
Neurontin		Depakote		Remeron	
Lyrica		Serzone		Lexapro	
Zoloft		Celexa		Wellbutrin	
Cymbalta		Paxil		Zyprexa	
Clonidine		Effexor		Prednisone	
Seroquel		Zanaflex			
Lithium		Doxepin			

Allergic Reactions to Food/Drugs: (Please list)

_____

_____

_____

_____

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 migraine headache is one for which a subject has taken an acute abortive medication (prescription medication, not OTC). The subject may be on a single migraine prophylactic drug 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 subject 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 principal investigator's discretion, if the subject is taking a stable dose for at least three months prior to screening and continues throughout the study.

SUBJECT ID:__________________ SITE #:______________________________

DATE: _______________________ PROTOCOL NUMBER:________________

Concomitant Medications: (Rx and OTC)

Medication	Dose	Route	Frequency	Start Date	Stop Date	Indication	Was med taken for AE?

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Medical History Form

Medical History	**Onset Date**	**Resolution Date** (or Ongoing)
Episodic Migraines		

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Ear Exam: Observations and check for presence of cerumen (recommend cleaning procedure as needed).____

Physician Signature (for ear exam):_____**Date:**_____

Screening Results:	**Yes**	**No**
Did the subject satisfy all study entry criteria at Screening Visit?		
If **No**, please complete Subject Disposition Form. Subject is a Screen Failure.		

- Dispense Daily Headache Diary to subject.
- Train subject on completing the Daily Headache Diary.
- Assign gmail account to subject with their Subject ID.
- Train subject on how to use the gmail account to upload Daily Headache Diary.

Study Coordinator: *I have verified that the subject has shown competence in filling out the Daily Headache Diary and using the gmail account to upload the Daily Headache Diary. I have confirmed with the subject that he/she will contact me regarding any future questions about proper diary recordation methods, should they arise.*

_____ _____
Study Coordinator Signature Date

I have reviewed the data from this visit and found the information to be complete and accurate. I verify that all of the tasks have been performed.

_____ _____
Principal Investigator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Treatment Day 1 (Visit 2)

Baseline Daily Headache Diary:	**Yes**	**No**
Does the subject have 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, as judged by the subject.		
If **Yes**, please proceed with Treatment Day 1 Visit procedures. If **No**, please conclude the visit, and complete the Subject Disposition Form. Subject is a Screen Failure.		

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Vital Signs:

Height:	_____ cm / inches (circle one)
Weight:	_____ kg / lbs (circle one)

Urine Pregnancy Test Results:			**Positive**	**Negative**	**N/A**
Name:	Lot #:	Exp. Date:			

Ear Exam: Observations and check for presence of cerumen (recommend cleaning procedure as needed).____

Physician Signature (for ear exam):_____ **Date:**_____

Quality of Life Assessments:	**Yes**	**No**	**Scores**
Hit-6 Questionnaire (completed)			
Pittsburgh Sleep Quality Assessment (completed)			
BDI-II (completed)			
BAI (completed)			
A **BDI-II** score of 20 or greater and/or a **BAI** score of 16 or greater will disqualify a patient from randomizing into the treatment portion of the study.			

Randomization:	**Yes**	**No**
Does the subject met all eligibility criteria for randomization?		
If **Yes**, please proceed with Device Treatment Training. If **No**, please conclude the visit, and complete the Subject Disposition Form. Subject is a Screen Failure.		

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Device Treatment at the Clinical Site:	**Yes**	**No**
Any side effects or AEs reported after device treatment?		
Was the device treatment aborted?		
Any complaints from subject?		
Any concerns about the subject?		
If **Yes,** to any questions above, please provide comment:		

- Dispense TNM Device to subject.
- Review device compliance and proper operation of the device and delivery of treatments.
- Administer Usability Questionnaire after completion of device training.
- Review Daily Headache Diary completion and upload to gmail account each day.

Study Coordinator: *I verify that the subject has received training and has shown competence in using the TNM Device. I believe that the subject will be able to complete device treatments in the home setting. I have confirmed with the subject that he/she will contact me regarding any future questions regarding safe use of the TNM device, should they arise.*

_____ _____
Study Coordinator Signature Date

I have reviewed the data from this visit and found the information to be complete and accurate. I verify that all of the tasks have been performed.

_____ _____
Principal Investigator Signature Date

SUBJECT ID:_____ SITE #:_____

DATE: _____ PROTOCOL NUMBER:_____

Clinic Visit Day 14 (Visit 3)

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Ear Exam: Observations and check for presence of cerumen (recommend cleaning procedure as needed)._____

_____

_____

Physician Signature (for ear exam):_____ **Date:**_____

Vital Signs:

Height:	_____ cm / inches
Weight:	_____ kg / lbs

Device Treatment at the Clinical Site:	**Yes**	**No**
Any side effects or AEs reported after device treatment?		
Was the device treatment aborted?		
Any complaints from subject?		
Any concerns about the subject?		
If **Yes,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Administer Usability Questionnaire after completion of device training.
- Review Daily Headache Diary completion and upload to gmail account each day.

I have reviewed the data from this visit and found the information to be complete and accurate. I verify that all of the tasks have been performed.

_____ _____

Principal Investigator Signature Date

SUBJECT ID:_____ SITE #:_____

DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 9)

A phone call to the subject is required every 2 weeks after Clinic Visit Day 14

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with daily device treatments?		
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/____/____.

_____ _____

Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 11)

A phone call to the subject is required every 2 weeks after Clinic Visit Day 14

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with daily device treatments?		
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/____/____.

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____

DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 13)

A phone call to the subject is required every 2 weeks after Clinic Visit Day 14

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with daily device treatments?		
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/____/____.

_____ _____

Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE:_____ PROTOCOL NUMBER:_____

Phone Contact (Week 15)

A phone call to the subject is required every 2 weeks after Clinic Visit Day 14

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with daily device treatments?		
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the **Final Visit for Initial Treatment Period** scheduled on_____/____/____ at end of week 16. This visit will also be the **Initiation of 2nd Treatment Period.**

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Final Visit for Initial Treatment Period; Initiation of 2nd Treatment Period (Visit 4-End of Week 16)

Study Continuation:	**Yes**	**No**
Is the subject continuing in the study (2nd Treatment Period)?		
If **Yes**, please proceed with Visit procedures. If **No**, please proceed with Early Termination Visit, and complete the Subject Disposition Form.		

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Vital Signs:

Height:	_____ cm / inches (circle one)
Weight:	_____ kg / lbs (circle one)

Urine Pregnancy Test Results:			**Positive**	**Negative**	**N/A**
Name:	Lot #:	Exp. Date:			

Ear Exam: Observations and check for presence of cerumen (recommend cleaning procedure as needed).____

_____

_____

Physician Signature (for ear exam):_____ **Date:**_____

Quality of Life Assessments:	**Yes**	**No**	**Scores**
Hit-6 Questionnaire (completed)			
Pittsburgh Sleep Quality Assessment (completed)			
BDI-II (completed)			
BAI (completed)			
BDI-II scores above 20 or **BAI** scores above 16 after treatment has commenced should be referred to the PI for consultation with Dr. Attix. If the subject answers in the affirmative to question 9 of the BDI-II form, he/she should be referred for mental health counseling on that same clinic visit.			

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Device Treatment at the Clinical Site with new Treatment Card:	**Yes**	**No**
Was a new Treatment Card (SD card) inserted into the device before treatment?		
Any side effects or AEs reported after device treatment?		
Was the device treatment aborted?		
Any complaints from subject?		
Any concerns about the subject?		
If **Yes,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Administer Usability Questionnaire after completion of device training.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Collect and return old Treatment card (SD card) from the device to Scion NeuroStim (SNS).

I have reviewed the data from this visit and found the information to be complete and accurate. I verify that all of the tasks have been performed.

_____ _____
Principal Investigator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 18)

A phone call to the subject is required every 2 weeks after Initiation of 2nd Treatment Period

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with daily device treatments?		
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/____/____.

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 20)

A phone call to the subject is required every 2 weeks after Initiation of 2nd Treatment Period

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with daily device treatments?		
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/____/____.

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 22)

A phone call to the subject is required every 2 weeks after Initiation of 2nd Treatment Period

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with daily device treatments?		
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/____/____.

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 24)

A phone call to the subject is required every 2 weeks after Initiation of 2nd Treatment Period

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with daily device treatments?		
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/____/____.

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 26)

A phone call to the subject is required every 2 weeks after Initiation of 2nd Treatment Period

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with daily device treatments?		
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to any questions above, please provide comment:		

- Review device compliance and proper operation of the device and delivery of treatments.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the **Final Visit for 2nd Treatment Period** (end of Week 28) and **Start of Observation Period** scheduled on_____/_____/_____.

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Final Visit for 2nd Treatment Period; Start of Observation Period (Visit 5-End of Week 28)

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Ear Exam: Observations and check for presence of cerumen (recommend cleaning procedure as needed)._____

_____

_____

Physician Signature (for ear exam):_____ **Date:**_____

Vital Signs:

Height:	_____ cm / inches (circle one)
Weight:	_____ kg / lbs (circle one)

Quality of Life Assessments:	**Yes**	**No**	**Scores**
Hit-6 Questionnaire (completed)			
Pittsburgh Sleep Quality Assessment (completed)			
BDI-II (completed)			
BAI (completed)			
BDI-II scores above 20 or **BAI** scores above 16 after treatment has commenced should be referred to the PI for consultation with Dr. Attix. If the subject answers in the affirmative to question 9 of the BDI-II form, he/she should be referred for mental health counseling on that same clinic visit.			

- Subject returns device to study coordinator.
- Administer Usability Questionnaire.
- Review Daily Headache Diary completion and upload to gmail account each day.
- Collect and return Treatment card (SD card) from the device to Scion NeuroStim (SNS).

I have reviewed the data from this visit and found the information to be complete and accurate. I verify that all of the tasks have been performed.

_____ _____
Principal Investigator Signature Date

SUBJECT ID:_____ SITE #:_____

DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 30)

A phone call to the subject is required every 2 weeks after Start of Observation Period

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to the question above, please provide comment:		

- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/_____/_____.

_____ _____

Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 32)

A phone call to the subject is required every 2 weeks after Start of Observation Period

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to the question above, please provide comment:		

- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/_____/_____.

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 34)

A phone call to the subject is required every 2 weeks after Start of Observation Period

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to the question above, please provide comment:		

- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/____/____.

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 36)

A phone call to the subject is required every 2 weeks after Start of Observation Period

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to the question above, please provide comment:		

- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the next phone contact in 2 weeks, scheduled on_____/_____/_____.

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Phone Contact (Week 38)

A phone call to the subject is required every 2 weeks after Start of Observation Period

Date of this phone contact	_____/_____/_____

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Subject Compliance:	**Yes**	**No**
Is the subject compliant with Daily Headache Diary and uploads?		
If **No,** to the question above, please provide comment:		

- Review Daily Headache Diary completion and upload to gmail account each day.
- Remind subject of the **Final Study Visit** (end of Week 40) scheduled on_____/____/____.

_____ _____
Study Coordinator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Final Study Visit
(Visit 6-End of Week 40)

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Vital Signs:

Height:	_____ cm / inches (circle one)
Weight:	_____ kg / lbs (circle one)

Ear Exam: Observations and check for presence of cerumen (recommend cleaning procedure as needed).____

_____

_____

Physician Signature (for ear exam):_____ **Date:**_____

Quality of Life Assessments:	**Yes**	**No**	**Scores**
Hit-6 Questionnaire (completed)			
Pittsburgh Sleep Quality Assessment (completed)			
BDI-II (completed)			
BAI (completed)			
BDI-II scores above 20 or **BAI** scores above 16 after treatment has commenced should be referred to the PI for consultation with Dr. Attix. If the subject answers in the affirmative to question 9 of the BDI-II form, he/she should be referred for mental health counseling on that same clinic visit.			

- Complete Subject Disposition Form (Subject Status=Completed)

I have reviewed the data from this visit and found the information to be complete and accurate. I verify that all of the tasks have been performed.

_____ _____
Principal Investigator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Subject Disposition Form

Select the Subject's Status for the Study:

☐ **Excluded** (select reason below)

- ☐ Screen Failure
- ☐ Physician Decision

☐ **Discontinued** (select reason below)

- ☐ Adverse Event
- ☐ Protocol Violation
- ☐ Withdrawal by Subject
- ☐ Physician Decision
- ☐ Lost to Follow-up
- ☐ Lack of Efficacy
- ☐ Study Terminated by Sponsor
- ☐ Lack of Qualifying Event

☐ **Completed**

Comments:_____

_____

_____

_____

_____

_____

_____

_____

_____ _____
Study Coordinator Signature Date

_____ _____
Principal Investigator Signature Date

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Early Termination Visit

Adverse Events and Concomitant Medication Assessment:	**Yes**	**No**
Any Adverse Events (AEs) since last visit?		
If **Yes,** please complete AE form.		
Any new medications or changes in medications since last visit?		
If **Yes**, please add medication(s) to the Concomitant Medication form. Acute abortive medications and migraine prophylactic medications should not be changed during the clinical trial.		

Vital Signs:

Height:	_____ cm / inches (circle one)
Weight:	_____ kg / lbs (circle one)

Ear Exam: Observations and check for presence of cerumen (recommend cleaning procedure as needed).____

_____

_____

Physician Signature (for ear exam):_____ **Date:**_____

Quality of Life Assessments:	**Yes**	**No**	**Scores**
Hit-6 Questionnaire (completed)			
Pittsburgh Sleep Quality Assessment (completed)			
BDI-II (completed)			
BAI (completed)			
BDI-II scores above 20 or **BAI** scores above 16 after treatment has commenced should be referred to the PI for consultation with Dr. Attix. If the subject answers in the affirmative to question 9 of the BDI-II form, he/she should be referred for mental health counseling on that same clinic visit.			

- Complete Subject Disposition Form (Subject Status=Discontinued; select reason)
- Return device and study related materials, as needed.

I have reviewed the data from this visit and found the information to be complete and accurate. I verify that all of the tasks have been performed.

_____ _____
Principal Investigator Signature Date

The following questionnaires are to be completed by the study patients in accordance with establishing the acceptance criteria set forth in the usability validation plan (*PLN-04-ENG-004-SN, section 11). Questionnaires will be completed at the end of the training period, once a treatment is completed, at the 2-week clinic visit, and at the end of the first and second treatment periods. The following acceptance criteria will be addressed during the evaluation periods:

- At the completion of training:
  - Device comfort, ease of use, intuitive nature of GUI, ability to hear alarm, identification of labeling, etc.
- At the 2-week clinic visit:
  - Device comfort, ease of use, device cleaning, device storage, treatment protocol
- End of the study periods
  - Device comfort, ease of use, treatment protocol

Usability Questionnaire after Completion of Training:

Date:_____ Subject ID_____

1. Is the headset comfortable enough that you will be able to use it consistently during the study period?
    a. Yes
    b. Probably
    c. Not sure
    d. Probably not
    e. No
2. Over all, does the device seem easy to use?
    a. Yes
    b. Not sure
    c. No
3. Is the touchscreen easy to use?
    a. Yes
    b. No opinion
    c. No
4. Are you able to hear the tones from the control unit?
    a. Always
    b. Not all the time
    c. Not sure
    d. Never

5. Is the labeling on the control unit and headset clear and understandable?
    a. Yes
    b. Not in all cases
    c. No opinion
    d. No
6. Is the device easy to unpack and assemble?
    a. Yes
    b. I have some trouble with it
    c. No opinion
    d. No
7. Are you comfortable with the entire treatment procedure, including use of the wedge pillow and lying down with your head facing up until the end of treatment chime sounds?
    a. Yes
    b. I have some trouble with it
    c. No opinion
    d. No
8. Do you have any other observations or comments you would like to make at this time?

User experience questionnaire after first treatment session:

"Remember we said in the Informed Consent that we are testing a brainstem neuromodulator. Now that you have used the device for the first time, we want to ask you some questions."

1. What sounds, if any, did you hear?
2. Did you feel any pressure from the earpieces in your ear canals?
3. Did you detect a very slight sensation in your head or ears, such as a weak electrical current might have made?
4. Did you notice any change in the clarity of your vision during the treatment?
5. At any point, did you notice any changes in temperature in your ear canals?
6. Did you experience any dizziness or nausea?
7. Could you tell from the control unit screen when the stimulus period started and ended?
8. Did you feel relaxed during the treatment?
9. Any other comments you'd like to make?

Subject ID: _____ Site #: _____
Date: _____ Protocol #: _____

Answers to Subject Questions after first use of TNM Device:

"Remember we said in the Informed Consent that we are testing a brainstem neuromodulator. Now that you have used the device for the first time, we want to ask you some questions."

1. What sounds, if any, did you hear?

_____

2. Did you feel any pressure from the earpieces in your ear canals?

_____

_____

3. Did you detect a very slight sensation in your head or ears, such as a weak electrical current might have made?

_____

_____

4. Did you notice any change in the clarity of your vision during the treatment?

_____

_____

5. At any point, did you notice any changes in temperature in your ear canals?

_____

_____

6. Did you experience any dizziness or nausea?

_____

_____

7. Could you tell from the control unit screen when the stimulus period started and ended?

_____

_____

8. Did you feel relaxed during the treatment?

_____

_____

9. Any other comments you'd like to make?

Questionnaire for the 2-week Clinic visit:

Date:_____ Subject ID_____

1. Do you find the headset to be comfortable enough to continue with your treatments?
    a. Yes
    b. Not sure
    c. No
2. Do you find that the device is easy to use at home?
    a. Yes
    b. No opinion
    c. It is not easy, but I can keep doing it
    d. No
3. Is the amount of time you spend treating per day:
    a. Enjoyable
    b. Acceptable
    c. No opinion
    d. Challenging to maintain
    e. Impossible to maintain
4. Is the device easy to clean at home?
    a. Yes
    b. No

5. Storing the device between uses:
    a. I have no problem storing the Device safely
    b. It is challenging to store the Device safely
    c. I cannot store the Device safely
6. Are you able to complete treatments without interruption?
    a. Yes
    b. Most of the time
    c. Not all of the time
    d. No
7. Have you dropped the device or has it been damaged as far as you know?
    a. Yes (if yes, do you feel that you created a hazard for yourself or others?)
    b. No
8. Do you have any other comments or observations at this time?

Questionnaire for the End of the first 3-month treatment period:

Date:_____ Subject ID_____

1. Did you find the headset to be comfortable enough to continue with your treatments?
   a. Yes
   b. No
2. Did you find that the device is easy to use at home?
   a. Yes
   b. No opinion
   c. It was not easy, but I kept doing it
   d. No
3. Was the amount of time you spent treating per day:
   a. Enjoyable
   b. Acceptable
   c. No opinion
   d. Challenging to maintain
   e. Impossible to maintain
4. Storing the device between uses:
   a. I had no problem storing the Device safely
   b. It was challenging to store the Device safely
   c. I could not store the Device safely

5. Were you able to complete treatments without interruption?
    a. Yes
    b. Most of the time
    c. Not all of the time
    d. No
6. Have you dropped the device or has it been damaged as far as you know?
    a. Yes (if yes, do you feel that you created a hazard for yourself or others?)
    b. No
7. How would you rate your overall experience with the device?
    a. Very positive
    b. Somewhat positive
    c. No opinion
    d. Somewhat negative
    e. Very negative
    f. What are some reasons for your opinion?
8. Do you think that you were in the active treatment group or the placebo group?
    a. Active
    b. Placebo
9. Please provide the reason(s) for your answer to question #8.

10. Do you have any final comments to share?

Questionnaire for the End of the second 3-month treatment period:

Date:_____ Subject ID_____

1. Did you find the headset to be comfortable enough to continue with your treatments?
    a. Yes
    b. No
2. Did you find that the device is easy to use at home?
    a. Yes
    b. No opinion
    c. It was not easy, but I kept doing it
    d. No
3. Was the amount of time you spent treating per day:
    a. Enjoyable
    b. Acceptable
    c. No opinion
    d. Challenging to maintain
    e. Impossible to maintain
4. Storing the device between uses:
    a. I had no problem storing the Device safely
    b. It was challenging to store the Device safely
    c. I could not store the Device safely

5. Were you able to complete treatments without interruption?
    a. Yes
    b. Most of the time
    c. Not all of the time
    d. No
6. Have you dropped the device or has it been damaged as far as you know?
    a. Yes (if yes, do you feel that you created a hazard for yourself or others?)
    b. No
7. How would you rate your overall experience with the device?
    a. Very positive
    b. Somewhat positive
    c. No opinion
    d. Somewhat negative
    e. Very negative
    f. What are some reasons for your opinion?
8. Do you think that you were in the active treatment group or the placebo group?
    a. Active
    b. Placebo
9. Please provide the reason(s) for your answer to question #8.

10. Do you have any final comments to share?

Scion NeuroStim Daily Headache Diary – Baseline Period

- This form is for which calendar date? _____(day, month, year)
- Did you have a headache today? ☐ Yes ☐ No
- Do you feel that your headache was a migraine headache? ☐ Yes ☐ No
- Maximum Pain Level (0-10 scale) on this date: _____
- Duration of any headache (0-24 hours): _____
- Check the box next to any symptoms associated with your headache:

  ☐ Nausea and/or vomiting?
  ☐ Dizziness?
  ☐ Sensitivity to light?
  ☐ Sensitivity to sound?
  ☐ Sensitivity to smells?
  ☐ None of the above

Regarding your headache pain, did it:

☐ Mostly occur on one side of your head?
☐ Have a pulsating quality?
☐ Prevent you from undertaking routine physical activity (e.g., walking, climbing stairs)?
☐ Become worse during physical activity?
☐ None of the above

- Check the box if you took any medications to treat your headache? (If you took medications, list types and dosages below): ☐ Yes Please list types and dosages below:

1)

2)

3)

Do you have any side effects to record in the space below? ☐ Yes ☐ No

Please report to your study doctor, as soon as possible, any side effect that you consider to be serious or severe.

Side Effect 1:

Start Date 1: Stop Date 1:

List any additional side effects below

Scion NeuroStim Daily Headache Diary – Treatment Period 1

- This form is for which calendar date? _____ (day, month, year)
- Did you have a headache today? ☐ Yes ☐ No
- Do you feel that your headache was a migraine headache? ☐ Yes ☐ No
- Maximum Pain Level (0-10 scale) on this date: _____
- Duration of any headache (0-24 hours): _____
- Check the box next to any symptoms associated with your headache:

  ☐ Nausea and/or vomiting?
  ☐ Dizziness?
  ☐ Sensitivity to light?
  ☐ Sensitivity to sound?
  ☐ Sensitivity to smells?
  ☐ None of the above

Regarding your headache pain, did it:

☐ Mostly occur on one side of your head?
☐ Have a pulsating quality?
☐ Prevent you from undertaking routine physical activity (e.g., walking, climbing stairs)?
☐ Become worse during physical activity?
☐ None of the above

- Check the box if you took any medications to treat your headache? (If you took medications, list types and dosages below): ☐ Yes Please list types and dosages below:

1)

2)

3)

Do you have any side effects to record in the space below? ☐ Yes ☐ No

Please report to your study doctor, as soon as possible, any side effect that you consider to be serious or severe.

Side Effect 1:

Start Date 1: Stop Date 1:

List any additional side effects below

Scion NeuroStim Daily Headache Diary – Treatment Period 2

- This form is for which calendar date? _____ (day, month, year)
- Did you have a headache today? ☐ Yes ☐ No
- Do you feel that your headache was a migraine headache? ☐ Yes ☐ No
- Maximum Pain Level (0-10 scale) on this date: _____
- Duration of any headache (0-24 hours): _____
- Check the box next to any symptoms associated with your headache:

  ☐ Nausea and/or vomiting?
  ☐ Dizziness?
  ☐ Sensitivity to light?
  ☐ Sensitivity to sound?
  ☐ Sensitivity to smells?
  ☐ None of the above

Regarding your headache pain, did it:

☐ Mostly occur on one side of your head?
☐ Have a pulsating quality?
☐ Prevent you from undertaking routine physical activity (e.g., walking, climbing stairs)?
☐ Become worse during physical activity?
☐ None of the above

- Check the box if you took any medications to treat your headache? (If you took medications, list types and dosages below): ☐ Yes Please list types and dosages below:

1)

2)

3)

Do you have any side effects to record in the space below? ☐ Yes ☐ No

Please report to your study doctor, as soon as possible, any side effect that you consider to be serious or severe.

Side Effect 1:

Start Date 1: Stop Date 1:

List any additional side effects below

Scion NeuroStim Daily Headache Diary – Observation period

- This form is for which calendar date? _____ (day, month, year)
- Did you have a headache today? ☐ Yes ☐ No
- Do you feel that your headache was a migraine headache? ☐ Yes ☐ No
- Maximum Pain Level (0-10 scale) on this date: _____
- Duration of any headache (0-24 hours): _____
- Check the box next to any symptoms associated with your headache:

☐ Nausea and/or vomiting?
☐ Dizziness?
☐ Sensitivity to light?
☐ Sensitivity to sound?
☐ Sensitivity to smells?
☐ None of the above

Regarding your headache pain, did it:

☐ Mostly occur on one side of your head?
☐ Have a pulsating quality?
☐ Prevent you from undertaking routine physical activity (e.g., walking, climbing stairs)?
☐ Become worse during physical activity?
☐ None of the above

- Check the box if you took any medications to treat your headache? (If you took medications, list types and dosages below): ☐ Yes Please list types and dosages below:

1)

2)

3)

Do you have any side effects to record in the space below? ☐ Yes ☐ No

Please report to your study doctor, as soon as possible, any side effect that you consider to be serious or severe.

Side Effect 1:

Start Date 1: Stop Date 1:

List any additional side effects below

Adverse Events/Adverse Device Effects

SUBJECT ID:_____ SITE #:_____

PROTOCOL NUMBER:_____

☐ Please check the box, if the subject **did not** experience any AEs/Adverse Device Effects (ADEs) during the study._____(Initial/Date)

Adverse Event	**Date of Onset** dd/mmm/yyyy	**Outcome** **1**=Resolved **2**=Resolved w/Sequelae **3**=Ongoing **4**=Unknown	**Date of Resolution** dd/mmm/yyyy (If <24 hrs, please indicate Hrs/Mins)	**Intensity** **1**=Mild **2**=Moderate **3**=Severe	**Action taken w/Study Device Tx** **1**=None **2**=Reduced **3**=Interrupted **4**=Discontinued	**Relationship to Study Device** **1**=Not Related **2**=Unlikely Related **3**=Possibly Related **4**=Probably Related **5**=Related	**Serious AE?** **1**=No **2**=Yes (If Yes, Complete SAE/UADE Form)	**Unanticipated AE?** **1**=No **2**=Yes

PI Signature (at end of clinical trial): _____ **Date:** _____

Adverse Events/Adverse Device Effects

SUBJECT ID:_____ SITE #:_____

PROTOCOL NUMBER:_____

☐ Please check the box, if the subject **did not** experience any AEs/Adverse Device Effects (ADEs) during the study._____(Initial/Date)

Adverse Event	**Date of Onset** dd/mmm/yyyy	**Outcome** **1**=Resolved **2**=Resolved w/Sequelae **3**=Ongoing **4**=Unknown	**Date of Resolution** dd/mmm/yyyy (If <24 hrs, please indicate Hrs/Mins)	**Intensity** **1**=Mild **2**=Moderate **3**=Severe	**Action taken w/Study Device Tx** **1**=None **2**=Reduced **3**=Interrupted **4**=Discontinued	**Relationship to Study Device** **1**=Not Related **2**=Unlikely Related **3**=Possibly Related **4**=Probably Related **5**=Related	**Serious AE?** **1**=No **2**=Yes (If Yes, Complete SAE/UADE Form)	**Unanticipated AE?** **1**=No **2**=Yes

PI Signature (at end of clinical trial): _____ **Date:** _____

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Serious Adverse Event (SAE)/ Unanticipated Adverse Device Effect (UADE)

Adverse Event (AE) Term:	
Event Start Date _____/_____/_____ (dd/mmm/yyyy)	**Event End Date** _____/_____/_____ (dd/mmm/yyyy)
Is the event still ongoing? ☐Yes ☐No	
Type of Report: ☐Initial ☐Follow up ☐Final	

Demographics with no personal identifiers:

Date of Birth:_____/_____/_____ ☐Male ☐Female

Serious Criteria: (check all that apply)

☐Inpatient hospitalization or prolongation of hospitalization
Date of Hospitalization_____/_____/_____
Date of Discharge_____/_____/_____

☐Immediately Life Threatening (immediate risk of death)

☐Persistent or significant disability/incapacity

☐Congenital anomaly/Birth defect

☐Other important medical event which required an intervention to prevent permanent impairment

☐Death
Date of Death_____/_____/_____

	Yes	**No**
Was the AE unanticipated (unexpected)?		
Was the AE caused by, or associated with the investigational device?		
Did the event improve or disappear after stopping device treatment?		
Is there a relationship of the event to any other suspect cause?		

SUBJECT ID:_____ SITE #:_____
DATE: _____ PROTOCOL NUMBER:_____

Serious Adverse Event (SAE)/ Unanticipated Adverse Device Effect (UADE)

Briefly describe the presentation and clinical course, including medical treatment, of the event: (attach additional pages, if needed)

Please Note: For device clinical trials, investigators are required to submit a report of SAE/UADE to the sponsor and reviewing IRB as soon as possible, but no later than **10 working days** after the investigator first learns of the event (21 CRF 812.150(a)(1)). However, if the SAE/UADE involves a death it must be reported within **24 hours** of discovery. Any follow-up information will be submitted to the sponsor and IRB as soon as the relevant information is available.

Signature/Date of person completing form:_____

Signature/Date of Principal Investigator:_____

Connecting your new Scion Trials email account to a smartphone or tablet

This guide is in two sections. The first section covers Apple iPhones and iPads, and the second section covers Android smartphones and tablets.

Section 1: Apple iPhones and iPads

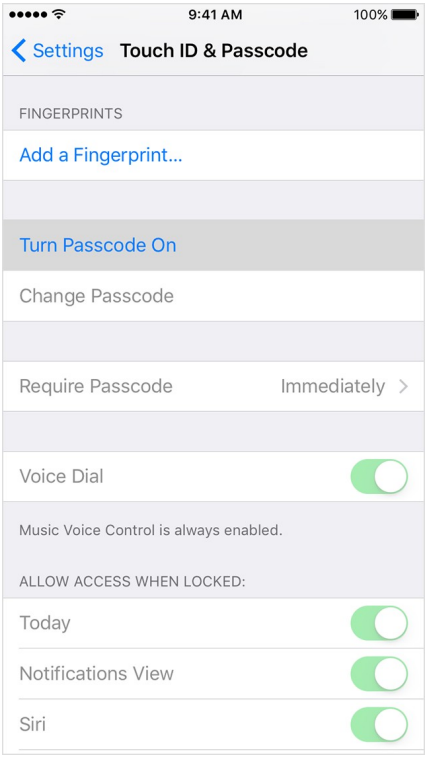
Adding security to your iPhone or iPad

We ask that you set a passcode on the iPhone or iPad that you plan to use which, once set, will need to be entered when you turn on the iPhone or iPad. It is possible that you already have a passcode set. If you do not, follow these steps to add one:

1. Go to the main screen of the iPhone or iPad that shows all of your icons and tap on the Settings icon.

2. Go down to Touch ID & Passcode and tap on it, or it might just say Passcode depending on the model of iPhone or iPad that you have.

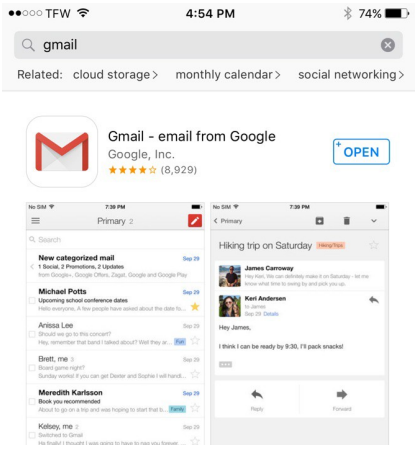
3. Tap turn passcode on.



4. Enter a passcode and re-enter it to confirm when prompted to do so. Remember what you set as the passcode, because you will need to enter it each time you want to use your device.

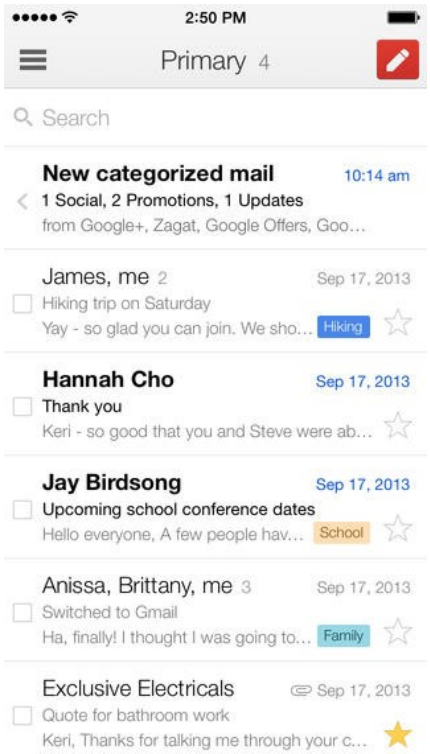
Connecting your iPhone or iPad to your new Scion Trials email account

1. Go to the App Store and search for the Gmail app. If you locate it correctly, the title of the app show as “Gmail – email from Google” as shown below. Tap GET to download it and enter the password for your Apple ID if prompted to complete the download. If you see the word OPEN next to the app listing then you already have the Gmail app on your device.

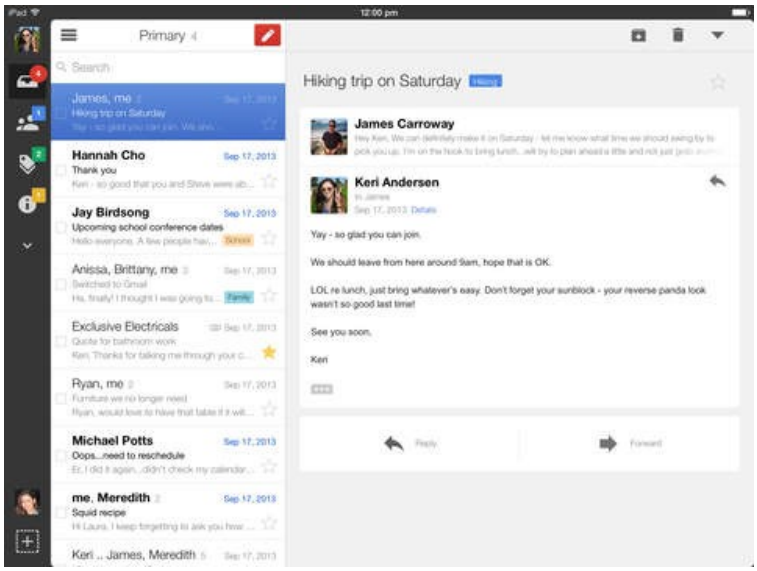


2. Open the app and enter your new Scion Trials email address when prompted. The app should bring you to the inbox for the email account.

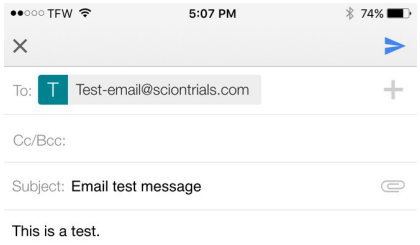
3a. To write a new email on the **iPhone** version of the app, tap on the red box icon that has a pencil inside it at the top right corner of the inbox.

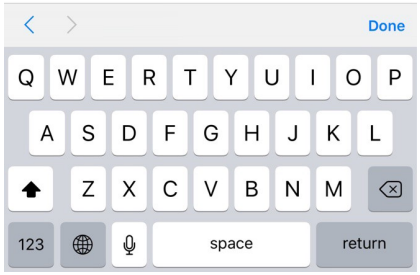


3b. To write a new email on the **iPad** version of the app, tap on the red box icon that has a pencil inside it above the inbox.



4. When you have finished writing the email, tap on the blue arrow at the top right corner to send the message:





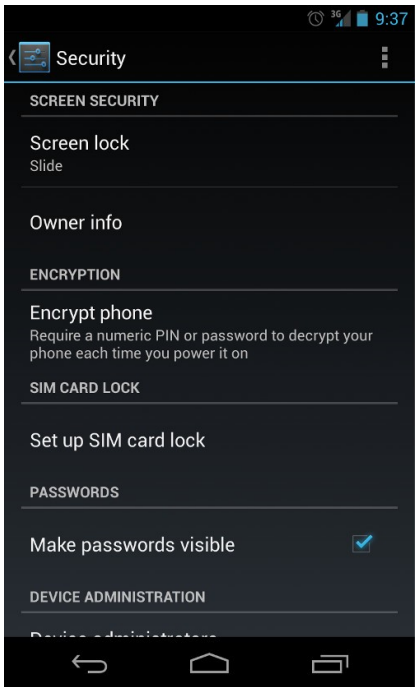
Section 2: Android smartphones and tablets

Since there are so many different types of Android smartphones and tablets, this guide will describe the general steps involved. It is possible that this guide may exactly reflect the screens you see, but if not you should see general similarities on your screens.

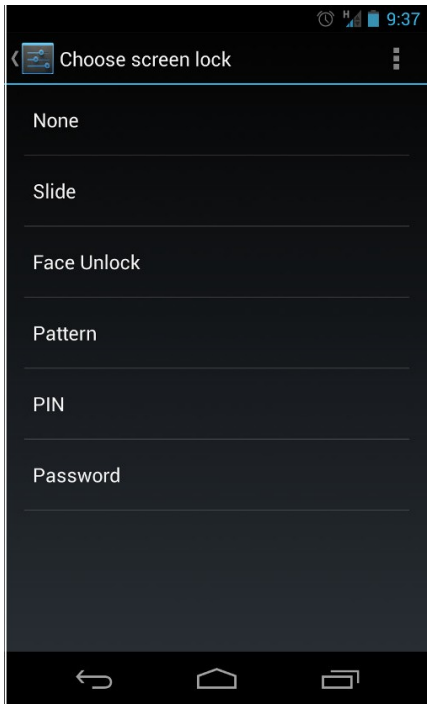
Adding security to your Android smartphone or tablet

We ask that you set a passcode on the Android smartphone or tablet that you plan to use which, once set, will need to be entered when you turn on the smartphone or tablet in the future. It is possible that you already have a passcode set. If you do not, follow these steps to add one:

1. Go to the settings on your Android smartphone or tablet and tap on Security. Then tap on Screen lock.



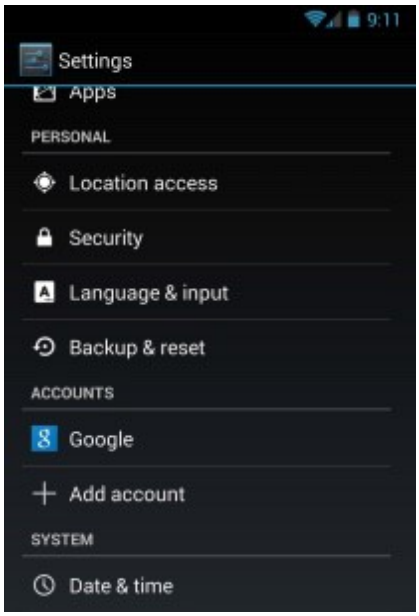
2. Tap on PIN to make a numeric code.



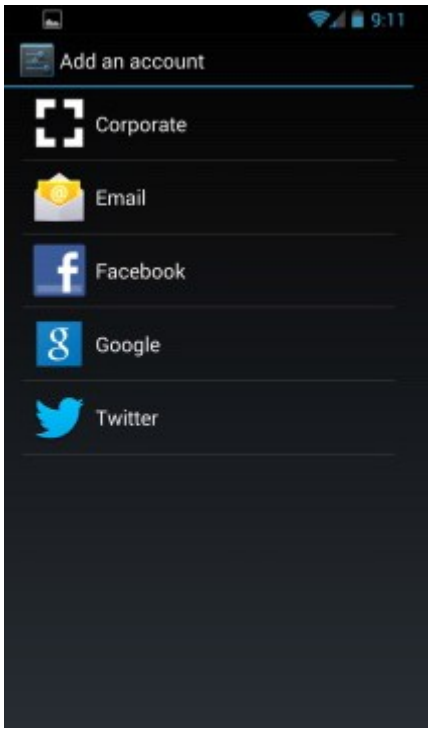
3. Enter the PIN code that you want to use and re-enter it if prompted to do so. Remember what you set as your PIN because you will need it in the future when you turn on your device.

Connecting your Android smartphone or tablet to your new Scion Trials email account

1. Go to the settings on your Android smartphone or table and tap on the Add Account setting.

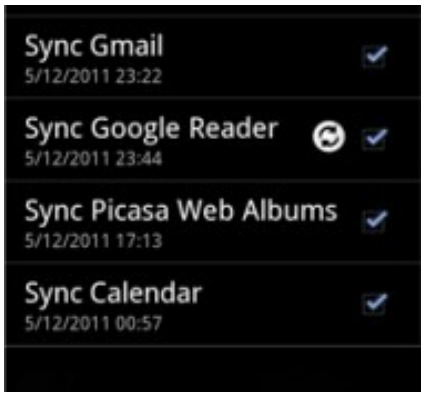


2. In the next screen tap on Google.



3. In the next Add a Google Account screen if you are asked whether you want to create a new account or use an existing account, tap Existing. Then type your Scion Trials email address and password when prompted to do so.

4. If you then see a screen asking you what you want to sync for this email account, only put a check mark next to Gmail. Clear the other check marks.



That's it! If you have any questions, please contact us at administration@sciontrials.com.

Sponsor: Scion NeuroStim, LLC (SNS)

Schedule of Visits and Procedures

Procedures	Screening Visit	Baseline Period (28 days; weeks 1-4)	Treatment Day 1 Week 5	Clinic Visit Day (week 7; check on treatment experience)	Phone Contact Week 9	Phone Contact Week 11	Phone Contact Week 13	Phone Contact Week 15
Informed Consent	X							
Inclusion/Exclusion criteria	X							
Headache History Questionnaire	X							
Medical History	X							
Medication Usage (Concomitant Medication)	X		X	X	X	X	X	X
Ear Exam (presence of cerumen)	X		X	X				
Vital Signs (height & weight)	X		X	X				
Device Treatment Training			X	X				
Device Treatment at Research Site			X	X				
Usability Questionnaire			X	X				
Train/Review Daily Headache Diary	X	X	X	X	X	X	X	X
Quality of Life Questionnaires (HIT-6, Pittsburg Sleep, BDI-II, BAI)			X					
Urine Pregnancy Test			X					
Randomization			X					
Dispense CVS Device			X					
Collect Treatment Data from CVS-M Device								
Return CVS Device								
Adverse Event Reporting	X	X	X	X	X	X	X	X

Sponsor: Scion NeuroStim, LLC (SNS)

Schedule of Visits and Procedures

Procedures	Final Visit for Initial Tx Period (end of week 16); Also Initiation of 2nd Tx period	Phone Contact Week 18	Phone Contact Week 20	Phone Contact Week 22	Phone Contact Week 24	Phone Contact Week 26	Final Visit for 2nd Tx Period; end of Tx (end of week 28); Start of Observation Period
Informed Consent							
Inclusion/Exclusion Criteria							
Headache History Questionnaire							
Medical History							
Medication Usage (Concomitant Medicaton)	X	X	X	X	X	X	X
Ear Exam (presence of cerumen)	X						X
Vital Signs (height & weight)	X						X
Device Treatment Training							
Device Treatment at Research Site	X						
Usability Questionnaire	X						X
Train/Review Daily Headache Diary	X	X	X	X	X	X	X
Quality of Life Questionnaires	X						X
Urine Pregnancy Test	X						
Randomization							
Dispense CVS-M Device	New treatment cards for all subjects						
Collect Treatment Data from CVS-M Device	X						X
Return CVS Device							X
Adverse Event Reporting	X	X	X	X	X	X	X

Schedule of Visits and Procedures

Procedures	Phone Contact Week 30	Phone Contact Week 32	Phone Contact Week 34	Phone Contact Week 36	Phone Contact Week 38	Final Study visit (end of week 40) Or Early Termination Visit
Informed Consent						
Inclusion/Exclusion Criteria						
Headache History Questionnaire						
Medical History						
Medication Usage(Concomitant Medicatio	X	X	X	X	X	X
Ear Exam (presence of cerumen)						X
Vital Signs (height & weight)						X
Device Treatment Training						
Device Treatment at Research Site						
Usability Questionnaire						
Train/Review Daily Headache Diary	X	X	X	X	X	
Quality of Life Questionnaires						X
Urine Pregnancy Test						
Randomization						
Dispense CVS-M Device						
Collect Treatment Data from CVS-M Device						
Return CVS Device						
Adverse Event Reporting	X	X	X	X	X	X