Preventing episodic migraine with caloric vestibular stimulation: a randomized controlled trial

Wilkinson, David, Ph.D. [1]; Ade, Kristen K., Ph.D. [2]; Rogers, Lesco L., M.D. [2]; Attix Deborah K., Ph.D. [3]; Kuchibhatla, Maragatha, Ph.D. [4]; Slade, Martin D., M.P.H. [5]; Smith, Lanty L., LL.B. [2]; Poynter, Kathryn P. R.N.[2]; Laskowitz, Daniel T., M.D. [3]; Freeman, Marshall C., M.D.[6]; Hoffer, Michael E., M.D.[7]; Saper, Joel R., M.D.[8]; Scott, Dianne L., M.D.[9]; Sakel, Mohamed, M.D.[10]; Calhoun, Anne H., M.D.[11]; Black, Robert D., Ph.D. [2]

[1] University of Kent, School of Psychology, Canterbury, Kent CT2 7NP, UK.

[2] Scion NeuroStim, LLC, Raleigh, NC 27613, USA.

[3] Duke University Medical Center, Department of Neurology, Durham, NC 27710, USA.

[4] Duke University Medical Center, Department of Biostatistics and Bioinformatics, Durham, NC 27710 USA.

[5] Yale University, School of Public Health, New Haven, CT 06510, USA.

[6]Headache Wellness Center, Greensboro, NC 27405, USA.

[7]University of Miami Miller School of Medicine, Department of Otolaryngology, Miami, FL 33136, USA.

[8]Michigan Headache & Neurological Institute, Ann Arbor, MI 48104.

[9]Duke University Medical Center, Department of Anesthesiology, Durham, NC 27710.

[10]East Kent Neuro-Rehabilitation Service, East Kent Hospitals University NHS Foundation Trust, Canterbury, Kent CT2 7NP, UK.

[11]Carolina Headache Institute, Chapel Hill, NC 27516, USA

Conflict of Interest:

D. Wilkinson, D.K. Attix, D.T. Laskowitz, M. E. Hoffer, and D.L. Scott report no disclosures. K.K. Ade and K. Poynter report receiving compensation and ownership interests and L.L. Rogers and R.D. Black report management positions and ownership interests in Scion NeuroStim. M.C. M. Kuchibhatla and M.D. Slade were contracted through Scion NeuroStim for statistical services. M.C. Freeman reports supports/grants/contracts from Alder, Allergan, Amgen, Dr. Reddy's Laboratories, Eli Lilly, Scion NeuroStim, and Teva. J.R. Saper reports supports/grants/contracts/consulting fees from Achelios, Alder, Allergan, Amgen, Asellas, Autonomic Technologies, Daiichi Sankyo, Dr. Reddy's Laboratories, Eli Lilly, Gavis, GlaxoSmithKline, Labrys Biologics, Merck, Migraine Research Foundation, Pfizer, Scion NeuroStim, Supurnus, Teva, Tian, Tonix and Zecuity. M. Sakel reports speaker fee/ honoraria from Allergan, Merz, IPSEN, Pfizer, REX Bionics, Eisai. A.H. Calhoun reports support/honoraria/consulting fees from Allergan, Autonomic Technologies, Depomed, ElectroCore Medical, Merck, Scion NeuroStim and Teva.

Statistical analysis was performed by Maragatha Kuchibhatla.

Key Words: 1) episodic migraine, 2) prophylactic, 3) caloric vestibular stimulation, 4) non-invasive neuromodulation, 5) brainstem

Study Funding: This study was funded by Scion NeuroStim, LLC USA.

Study Registration: clinicaltrials.gov: NCT01899040

Abbreviations: Caloric Vestibular Stimulation (CVS), Thermoneuromodulation™ (TNM™), per-protocol (PP), intention-to-treat (ITT), nonsignificant risk (NSR), Beck Depression Inventory-II (BDI), Beck Anxiety Inventory (BAI), Everyday Cognition rating scale - 20 (ECOG-20).

Acknowledgements

The authors thank Lanty Smith (Scion NeuroStim) for his financial support, Amy Pruitt, Karen Fisher, Karen Grace, Jessica Carlson, Shawn Szalay, Anita Severance, Sara Murphy, Karen Bartku, Beth Fenton, Grant Meisenholder, Sean Wise, Maria Gallagher, Phil Ulrich, Rezina Sakel, Katie Smith, Shavonna Haamid, Stacey Gibson and the National Migraine Center (London,United Kingdom) for their assistance with completing the clinical trial, Global Patent Graphics (Charlotte, NC) for providing drafting services and the subjects who generously agreed to participate in the study.

Preventing episodic migraine with caloric vestibular stimulation: a randomized controlled trial

Abstract.

Objective: To evaluate the safety and efficacy of a novel solid-state, caloric vestibular stimulation (CVS) device to provide adjuvant therapy for the prevention of episodic migraine in adult migraineurs.

Background: Migraine causes significant disability in ~12% of the world population. No current migraine preventive treatment provides full clinical relief, and many exhibit high rates of discontinuation due to adverse events. Thus, new therapeutic options are needed. CVS may be an effective and safe adjuvant-therapy for the prevention of episodic migraine.

Methods: In a multicenter, parallel-arm, block-randomized, placebo-controlled clinical trial (clinicaltrials.gov: NCT01899040), subjects completed a 3-month treatment with the TNM™ device for CVS (refer to Figure 2 for patient enrollment and allocation). The primary endpoint was the change in monthly migraine days from baseline to the third treatment month. Secondary endpoints were 50% responder rates, change in prescription analgesic usage and difference in total subjective headache-related pain scores. Device safety assessments included evaluation of any impact on mood, cognition or balance.

Results: Per-protocol, active-arm subjects showed immediate and steady declines in migraine frequency over the treatment period. After three months of treatment, active-arm subjects exhibited significantly fewer migraine days (-3.8 ± 0.5 from a baseline burden of 7.7 ± 0.5 migraine days). These improvements were significantly greater than those observed in control subjects (-1.1 ± 0.6 from a baseline burden = 6.9 ± 0.7 migraine days) and represented a therapeutic gain of -2.7 migraine days, CI = -0.9 to -4.7, $p = 0.012$. Active arm subjects also reported greater reductions in acute medication usage and monthly pain scores compared to controls. No adverse effects on mood, cognition or balance were reported. Subjects completed the trial with an average rate of 90% treatment adherence. No serious or unexpected adverse events were recorded. The rate of expected adverse events was similar across the active and the placebo groups, and evaluation confirmed that subject blinding remained intact.

Conclusion: The TNM™ device for CVS appears to provide a clinically efficacious and highly tolerable

adjuvant therapy for the prevention of episodic migraine.

I. INTRODUCTION

Migraine is a common and disabling disorder afflicting approximately 12% of the population worldwide[1]. Migraine attacks often result in significant impairment and loss of ability to function. They create enormous financial burden with approximately one billion dollars spent in healthcare utilization as well as thirteen billion dollars lost in productivity annually in the United States alone[2]. Despite widespread use of medical intervention for the acute treatment of migraine attacks (approximately 98% of patients report using an over-the-counter medication, prescribed medication, or a combination thereof)[3], patients are largely resistant to the use of prophylactic treatments. Indeed, of the estimated 38% of migraineurs likely to benefit, only 13% currently use migraine prophylactics[4]. Reasons for limited use of prophylactics include unpleasant side effects, cost, and perceived low efficacy of the currently available medications and other therapies[5, 6]. Thus, a significant need for new, efficacious and more tolerable therapies exists.

Here we sought to establish the safety and efficacy of caloric vestibular stimulation (CVS) treatment using a novel, solid-state device (TNM™, Scion Neurostim, LLC) for the prevention of episodic migraine. CVS is a widespread clinical tool used both to diagnose balance disorders and to confirm the absence of brainstem function. Historically, water or air irrigators have been used to warm or cool the external auditory canal. Both warming and cooling temperature changes create convection currents in the endolymphatic fluid of the horizontal semicircular canal. These currents cause cupular deflection which alters the tonic firing rate of the vestibular nerves and, in turn, elicits broad autonomic responses, including the vestibular-ocular reflex. While CVS has a long history of clinical safety, exploration into its

therapeutic potential has been hindered by the unpleasant side-effects, thermal imprecision, lack of dose control and administration complexity of standard water and air irrigation methods[7], impediments that were overcome with the development of a solid-state device for delivering CVS[8]. The potential for CVS to provide effective prophylaxis for episodic migraine is supported by several findings.

First, while the precise pathology underlying migraine remains largely unknown and the neural circuits involved are wide-spread, results from a number of neuroimaging studies consistently suggest that migraine is a neurological disorder involving brainstem dysfunction[9-11]. This hypothesis is relevant because the brainstem is among the many neural regions activated by CVS[12, 13], a set of strong pathways corroborated by the well-established diagnostic sensitivity of CVS to brainstem dysfunction. Although neuroimaging data evaluating the precise patterns of brainstem activation by CVS have been limited due to the difficulty of achieving anatomic resolution with these techniques, anatomical tracing studies have demonstrated dense and often reciprocal connections between the vestibular nuclei, located within the pons and medulla, and other brainstem regions implicated in migraine -- including the periaqueductal gray, the parabrachial nucleus, the locus coeruleus, the reticular formation, the dorsal spinal and mesencephalic trigeminal nuclei and the dorsal raphe nuclei[14-16] (depicted in Figure 1C). Furthermore, recent transcranial Doppler sonography data demonstrate that CVS treatment with the device elicits changes in cerebrovascular dynamics that point to brainstem neuromodulation[8]. Second, irrigation calorics have been shown, albeit in small, uncontrolled samples, to acutely mitigate pain, including pain experienced during migraine attacks[17-19].

Based on the above findings, we gathered preliminary clinical evidence for CVS-mediated prevention of episodic migraine by conducting a three-subject pilot study that assessed the feasibility and safety of longitudinal CVS treatment in the home setting. All three episodic migraineurs demonstrated reduced headache frequency after six weeks of CVS therapy[8]. Notably, all subjects demonstrated excellent treatment adherence, and no adverse events were reported. To further assess the efficacy and safety of the caloric vestibular stimulation device[8] developed by Scion NeuroStim, LLC, for the prevention of episodic

migraine, we then conducted a prospectively powered, randomized, placebo-controlled clinical trial (NCT01899040; www.clinicaltrials.gov). The results are described herein.

II. METHODS

A multicenter, parallel-arm, block-randomized, double-blinded, placebo-controlled clinical trial was conducted to determine the superiority of CVS therapy over placebo treatment. Subjects were randomized in a 1: 1 ratio. Both per- protocol (PP) and intention-to-treat (ITT) data were analyzed. The study was conducted across five centers in the United States and one in the United Kingdom (see Supplemental Table 1).

Standard protocol approval and informed consent. In 2013, the device was designated by the U.S. Food and Drug Administration as nonsignificant risk (NSR) for a study of episodic migraine. This study was approved by the appropriate institutional review board for each participating center. The research coordinator for each study site evaluated eligibility, obtained informed consent and enrolled the participants in the study. Written informed consent was obtained from all participants.

Subjects and medication usage. Subjects fulfilling the following criteria were included in the study: 18-65 years old, a diagnosis of episodic migraine without aura according to the International Headache Classification of Headache Disorders-II guidelines[20, 21] at least six months prior to entering the study, a stable history of 4-14 migraine headache days per month for the three months preceding the study, and no evidence of a balance disorder according to a Berg Balance Scale assessment[22]. Exclusion criteria were failure to respond to more than two classes of properly administered migraine prophylactic pharmaceutical therapies, an inability to reliably use the device or to complete the daily headache diary, pregnancy, night shift work, history of cardiovascular disease, prior diagnosis of vestibular migraine[21], exclusive menstrual

migraine[21] or post-traumatic migraine, history of unstable mood or anxiety disorders, use of hearing aids or cochlear implants, chronic tinnitus, temporomandibular joint disease, history of traumatic brain injury, comorbidity with another neurological disease other than headaches, a diagnosis of vestibular dysfunction, abuse of drugs or alcohol, current experience with medication overuse headaches, eye surgery within three months or ear surgery within six months of the study, active ear infections or perforated tympanic membrane, participation in another clinical trial within 30 days of the trial and use of Botox treatments for migraines. Additionally, subjects who were taking migraine prophylactics were originally excluded from the study. However, because prophylactic treatment is consistent with standards of practice in headache clinics, the protocol was later modified to include these subjects. See Supplemental Appendix 2 for details relating to these changes. Subjects were allowed to use abortive medications for the symptomatic relief of migraine as well as pharmaceutical prophylactics provided there were no changes (type or dosage) during the course of the study or the three months immediately preceding. Subjects were withdrawn from the study if they exhibited more than 14 headache days during the one-month baseline (BL) period, withdrew consent, demonstrated significant non-adherence (investigator-determined) or met the exclusion criteria any time during the study.

Study design, subject randomization and blinding. Eligible subjects entered a 28-day pre-treatment baseline period during which they completed electronic daily headache diaries recording headache occurrence. If a headache occurred, subjects also logged (i) headache duration, (ii) severity on a 11-point visual analog scale (with 0 indicating no pain and 10 indicating worst possible pain)[23], (iii) whether they considered the headache to be a migraine, (iv) any migraine-associated symptoms experienced (including nausea and/or vomiting, dizziness and sensitivities to light, sound and smells) (v) qualities related to headache pain (i.e., unilaterality, pulsating quality, and prevention and/or worsening with physical activity) as well as (vi) the dose / type of abortive medication taken. The form used for the daily headache diary can be found in the complete study protocol provided in Supplemental Appendix 1. The scores from (ii) were

summed to provide a total monthly headache pain score. In accordance with the standard of care for most headache clinics in the United States which encourages appropriate use of migraine abortive medication, a migraine day was defined as any day when the subject considered his/her headache to be a migraine. All patients received training for filling out the daily headache diaries. Electronic diary entries were collected using validated REDCap electronic data capture tools hosted at Duke University[24].

Diary compliant subjects who satisfied the inclusion/exclusion criteria were randomized into active or placebo groups. Block randomization was followed to ensure that patients and investigators were blinded to treatment allocation. Each site received packets of four well-shuffled envelopes containing two active and two placebo cards. Sealed envelopes were opened by the unblinded coordinator who then inserted the appropriate SD card (either active or placebo) and logged the coded treatment arm for each subject, thereby protecting against inadvertent or inappropriate access to treatment assignment. The unblinded study site coordinator was the only individual on-site with access to the allocation information. Information about treatment arm allocation was not shared with the subjects, investigators, data technicians or the statisticians. Sites were instructed to complete a packet before opening a new packet. In the informed consent, subjects were made aware of the existence of a placebo arm, but the topic was not further discussed. Subjects were not told that CVS was the active therapy. In the Informed Consent the device was described as a brainstem neuromodulator.

On treatment day one, subjects returned to the clinic where they completed a battery of tests to assess baseline mood and cognition. These tests included the Beck Depression Inventory-II (BDI-II)[25], a subjective rating scale of depression, the Beck Anxiety Inventory (BAI)[26], a subjective rating scale of anxiety, the Digit-Symbol coding test[27] to assess sequence processing speed, the Everyday Cognition rating scale - 20[28] to assess perceived cognition in daily life, Trail Making Tests A to assess speed processing and Trail Making Test B to asses complex sequencing with set-shifting[29], the Controlled Oral Word Association test[30] to assess verbal fluency and a short term memory test[31].

The unblinded study site coordinator then administered the first treatment and trained subjects to self-

administer treatments.

CVS treatments. Subjects self-administered treatments twice daily for three months (84 days) and were instructed to separate daily treatments by at least one hour. The CVS device provided patient-lockouts which limited subjects to two prescribed treatments per day. To maximize the thermoconvective effect of CVS[32], subjects were instructed to lie supine on a ~22° wedge pillow for treatments (Figure 1A). Placebo and active CVS treatments were delivered via a headset, fashioned like music earphones, with two independently-controlled thermoelectric devices attached to aluminum earpieces which fit inside the ear canal and abut but do not enter the bony canal[8].

For active treatment, a time-varying saw-tooth waveform (shown in Figure 1B) was delivered. After each two-day period, the ears receiving the warm and cold waveforms were switched in order to mitigate the hypothetical risk of unintentionally creating a baseline vestibular asymmetry after the treatment period. There were two placebo conditions during the course of this study. The first placebo was designed to bring both earpieces to 37° C and maintain that constant temperature for approximately four minutes. However, due to the thermistor sensitivity (+/- 2° C), there was a slight divergence between the intended and actual temperature of the earpieces (i.e., an overshoot followed by small oscillations as the temperature tracking settled at the set point of 37° C). While we expected these small fluctuations to be negligible, three of 20 subjects in this placebo condition exhibited slight dizziness and/or nausea that was likely to be due to active treatment, as determined by the blinded clinicians (see Table 3). Further concern over the validity of the initial placebo was raised by a published report demonstrating that temperature differences as little as 1° C away from body temperature are sufficient to evoke vestibular responses[33]. Therefore, to minimize vestibular stimulation of unknown magnitude in the placebo condition, the study was paused, and the following changes were made to create a new inactive placebo condition: 1) earpieces remained unpowered (though the headset fans continued to function), and 2) an ethylene-vinyl copolymer cap was added to the earpieces to minimize the cooling effect of the bare aluminum during the initial headset placement. Changes were approved by all internal review boards, and the U.S. Food and Drug Administration was

notified of the protocol and design changes. See Supplemental Figure 1 for actual temperatures recorded by the thermistors during the two placebo conditions and Supplemental Appendix 3 for complete details relating to the change in the placebo condition. There were no changes to the active arm protocol during the course of the study. As such, the measures of efficacy from all active arm subjects were combined and compared to the new inactive placebo condition (referred to hereafter as "the placebo"). Although data from the first partially active placebo condition were not included in the primary analysis of efficacy, data from these subjects were still evaluated to assess device safety and usability; and evaluation of the primary endpoint including the data from these subjects is provided in Supplemental Figure 2 This group will be referred to hereafter as "the partially active placebo" group. There was no interim analysis of efficacy during the course of the study.

Treatment times and dates were recorded by the device control unit and were analyzed to assess treatment adherence. Subjects returned to the clinic after two weeks of home treatments and at the end of the three-month treatment period. At these times, balance was re-assessed using the Berg balance scale, and subjects completed questionnaires about the usability of the device. Additionally, subjects were assessed for changes in mood and cognition using the same battery of tests used at the first treatment visit. To assess potential effects on long-term memory, at the final visit subjects were asked to identify faces they had seen previously (during their first short-term memory exam).

Every two weeks during either clinic visits or phone calls with site coordinators and daily in their headache diaries, subjects were asked whether they experienced any adverse events (AEs).

Outcome measures. The change in the average number of monthly migraine days between the baseline period and the third treatment month served as the primary efficacy endpoint. Secondary efficacy measures were also analyzed and included: 1) the percentage of subjects having at least 50% reduction of monthly migraine days between the baseline and the third treatment month, 2) the change in the total monthly headache pain scores (a novel measure designed for this study) and 3) the change in monthly acute abortive

prescribed migraine medication taken. Changes in mood/cognition were intended to be a secondary endpoint; however, due to a lack of baseline dysfunction across randomized subjects, they were instead assessed to establish device safety. To assess blinding efficacy, on their final visit subjects were asked to guess their treatment allocation and provide the reasons for their guess. Inclusion in the PP analysis of headache-related endpoints required treatment adherence ≥ 50% for each treatment month and headache diary adherence for at least 25 days during the baseline and the third treatment month (28 days each). Diary adherence for at least 25 the 28 day period was required to accurately assess efficacy from our primary and secondary endpoints. Inclusion in the ITT analysis of efficacy in this study only required headache diary adherence. Subjects that did not meet the criterion for diary adherence were not included in the analysis for efficacy but were included in the measures of safety and treatment adherence. Because diary adherence was not essential to accurately assess mood and cognitive effects of CVS treatment, treatment adherence was the only requirement for inclusion in the PP analysis of mood and cognition.

Statistical analysis. Trial cohort size was chosen based on the need to demonstrate safety and by considering the designs of previous device studies[34, 35]. Given the lack of *a priori* outcome data from which to perform a power estimate for the primary endpoint, a power analysis was conducted on a binary outcome of the 50% responder rate (a secondary endpoint) for a range of assumed efficacy values. Based on previous studies, it was estimated that 15% of placebo arm subjects would exhibit a ≥ 50% response rate[34, 35]. On that basis, 80 subjects would provide ≥ 80% power to detect a significant difference in this measure (alpha < 0.05), assuming a 50% response rate in 45% of active arm subjects, and would sufficiently demonstrate device safety.

Change scores described in this study are differences in measures between the baseline and the third treatment month unless otherwise specified. Distributions of the primary and secondary endpoints were examined for normality to determine the appropriate statistical tests to use in the analysis. Statistical significance for the primary outcome was determined using Mann-Whitney U-tests. The changes in monthly migraine days between the baseline month and the third treatment month within each group were

evaluated using Wilcoxon matched-pairs signed rank tests. Statistical significance for the differences in the number of subjects demonstrating ≥ 50% response rate, the ratio of male versus female subjects and the accuracy of the allocation guesses were evaluated using two-sided chi-square tests. The percent-change in migraine days was also evaluated as an ordinal variable using a Mann-Whitney U test. The changes in total monthly headache pain scores and monthly acute anti-migraine prescription medication taken (secondary endpoints), as well as the differences in baseline demographics of age, education, and disease duration were compared using unpaired student's t-tests. Within-group changes for the secondary outcome measures were evaluated using paired student's t-tests. Only subjects with current prescriptions for acute anti-migraine medications were included in the secondary endpoint analysis evaluating medication usage. Statistical significance for all assessments of mood and cognition were evaluated using paired student's t-tests for within group effects and unpaired student's t-tests for between group effects. Secondary endpoints were assessed without adjustment for multiple tests. No stratification variables were used in the analysis. Decisions to conduct sub-analyses with respect to the change in migraine days within the PP group that guessed active allocation and within the PP group that did not comment on treatment-related sensory experience as reason for their allocation guess were made upon examination of the allocation guessing chi-square results. Likewise, the decision to evaluate the percentage reduction as a continuous variable was made after evaluating the chi-square analysis of the ≥ 50% responder rate. Outcomes of repeated measures were analyzed using linear mixed models. The linear mixed models were fit to examine the change in migraine days over the treatment period. The models included time, treatment group and treatment group by time interaction. The association among repeated measures was assumed to follow a compound symmetry variance-covariance structure. No data transformations were required to fit the models. Significance of each of the variables in the model was assessed at alpha = 0.05. Data are presented as mean ± standard error of the mean unless otherwise noted. Analysis was performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) and Prism 6 (GraphPad, La Jolla, CA) software packages.

III. RESULTS

The trial was initiated in September 2013 and was completed in February 2016. The breakdown of PP and ITT subjects by treatment arm and treatment center can be found in Supplemental Table 1. 164 subjects were screened for eligibility, and 100 subjects were randomized. 19 subjects withdrew consent or were withdrawn during the course of the study including two subjects who were randomized in error. 81 subjects completed the study. 4 subjects violated the exclusion criteria during the study, 5 subjects did not demonstrate a level of headache diary adherence sufficient to be included in the efficacy analysis and 16 subjects received the partially active placebo condition (and thus were only assessed for safety). Of the subjects that completed, 49 were included in the PP analysis for efficacy, and 57 were included in the ITT analysis for efficacy (Figure 2). Within the PP and the ITT groups, three and six subjects, respectively, exhibited more than 14 headache days during at least one treatment month. We believe that some of these subjects were likely chronic migraineurs that went undetected during the baseline screening period[20, 21]. In support of this hypothesis, a significant portion of subjects (15.2%) who entered the baseline screening process with a diagnosis of episodic migraine exhibited 15 or more monthly headaches during the baseline screening month. Yet, as the possibility that CVS treatment may increase migraine frequency could not be ruled out *a priori,* these 6 subjects are included in the primary analysis to establish efficacy for the prevention of episodic migraine. However, a sub-analysis that excludes these 6 subjects is provided as supplementary data.

There were no significant differences in demographics or concomitant medication usage between the active and placebo groups (Table 1).

Primary efficacy endpoints. The reduction in monthly migraine days during the third treatment month relative to the pre-treatment baseline month served as the primary efficacy endpoint for the study and is detailed in Table 2, Figure 3 and Supplemental Table 2. Statistically significant reductions in the number of migraine days in the PP active group were observed as early as the first treatment month (PP: -1.5 ± 0.8 days, $p = 0.0396$; ITT: -1.3 ± 0.7, $p = 0.0362$), and monthly migraine days continued to steadily decrease

over the treatment period with a final reduction during the third treatment month of -3.8 ± 0.6 days ($p <$ 0.0001) and -3.5 ± 0.6 days ($p < 0.0001$) in the PP and ITT groups, respectively. The placebo group exhibited a small but statistically significant reduction in migraine days during the third treatment month (-1.1± 0.6 days, $p = 0.048$). Notably, the primary endpoint evaluation revealed a therapeutic gain of 2.8 fewer monthly migraine days in active arm subjects relative to placebo arm subjects after three months of CVS therapy ($p = 0.012$). No effects of age, sex, race or concomitant medications were observed in the univariate analysis (Supplemental Figure 3).

Secondary efficacy endpoints. Secondary efficacy endpoints are detailed in Table 2, Figure 3 and Supplemental Table 2. A trend for increased 50% responder rates in the active arm relative to the placebo arm existed in both the PP and the ITT analysis. The lack of statistical significance for this effect was likely due to insufficient sampling for this binary statistical test given that the 50% responder rates in the placebo condition (31.6%) were significantly higher than originally anticipated (15%). However, comparison of the percent-change in migraine days across the two PP groups (Table 2, Figure 3B) revealed that the response rate was significantly greater in active arm subjects (-47.1% ± 7.0%) than in placebo arm subjects (-14.9% ± 13.5%, $p = 0.029$).

In addition to the reduction in migraine frequency, the efficacy of CVS treatment was also assessed by evaluating the reduction in subject-reported total monthly headache pain scores and the number of migraine abortive prescription medications taken. Subjects in both the active arm and the placebo arm showed reductions in total monthly headache pain burden between the baseline and the third treatment month. However, group-wise comparison of the PP groups revealed that this effect size was significantly larger in the active arm subjects than in placebo arm subjects (therapeutic gain of -19.9%). Similarly, subjects in both treatment arms took fewer migraine abortive prescription medications during the third treatment month compared to the pre-treatment baseline. While placebo arm subjects also demonstrated a statistically significant reduction in this secondary endpoint, group-wise comparison of the reduction in migraine abortive prescription medications taken revealed that the effect was significantly larger in the

active arm than in the placebo arm in both the PP and the ITT cohorts (therapeutic gain of -23.4% and -20.0%, respectively).

Safety endpoints. No serious or unexpected adverse events were reported during the trial in either the active or placebo groups. Table 3 details all adverse events possibly related to device treatment reported during the study and the likelihood that each adverse event was related to treatment, as determined by the blinded clinicians.

The side effects from the device were expected to be significantly attenuated in prevalence and severity compared to those reported from water and air irrigation[8]. In line with this prediction, the cases of dizziness and/or nausea (also common symptoms in migraineurs) were limited (4 active, 2 placebo and 3 partially active placebo cases, see Table 4). All cases were transient, and only two subjects listed dizziness/nausea as a reason for withdrawing consent; these consisted of one active subject and one placebo subject.

Some ear discomfort from the device headset was also expected. However, this adverse event was reported in less than 5% of study subjects (Table 3). Furthermore, at the end of the three-month treatment period, 96.3% of subjects reported that the headset was comfortable enough to continue with treatment (Table 5). One subject with pre-existing tinnitus felt that CVS treatment was potentially increasing tinnitus symptoms and withdrew consent. However, that subject was diagnosed with a sinus infection eight days later, and symptoms returned to normal within 11 days of early termination.

Although there are no reports in the literature or evidence from previous pilot studies using the device to suggest that CVS may disrupt normal vestibular function, the safety profile of longitudinal therapy using the device was further established by evaluating whether there was any deterioration in balance over the course of the study. Balance was assessed using the Berg balance scale on treatment day one, the two-week follow-up visit and the final visit. The Berg balance scale is a well-established diagnostic assessment for vestibular dysfunction and consists of 14 balance-related tasks. No changes in balance were observed in any of the treatment groups over the course of the study (Table 4).

We also sought to establish whether CVS treatment had any effect on mood or cognition. A battery of standardized mood and cognitive tests was performed on treatment day one, the two-week follow-up visit and on the final visit. Assessment of the baseline scores for the BDI-II and BAI revealed that very few subjects in our study exhibited baseline mood dysfunction. Additionally, the baseline scores for all cognitive tests fell within expected ranges. The performance-based cognitive tests showed significant changes within group over time, as would be expected due to practice effects; however, there was no compelling evidence of gains across measures by group, as seen by comparison of change scores in active versus placebo conditions. Yet, while the study was inadequately powered to evaluate whether CVS treatment was efficacious in treating mood or cognitive dysfunction, neither active nor placebo treatment negatively impacted any measure of the mood or cognitive (Table 5) well-being, further demonstrating the safety of the device.

Treatment adherence and device usability. Treatment times and durations were recorded by the device. Evaluation of these measures revealed that treatment adherence over the three months of treatment was excellent in both groups (86.3% ± 2.2%, n = 39 for active and 93.1% ± 1.1%, n = 37 for placebo). Three subjects were withdrawn from the study due to poor treatment/diary adherence. 31% of active arm subjects indicated that the treatment regimen was challenging to maintain, yet this subgroup still maintained an adherence rate of 79.7% ± 3.4%. The remaining 69% of active arm subjects indicated that the time spent treating each day was either enjoyable or acceptable (Table 5).

Critical elements for adherence of any device prevention therapy are the ease of use and the subjective experience of using the device. When surveyed, 90% (73/81) of subjects that completed the study reported that the device was easy to use at home, and 78% (63/81) indicated they had an overall positive experience with the device (Table 5).

Blinding. To assess whether subject blinding remained intact over the course of study, at the end of the three-month treatment period subjects were asked to guess their treatment allocation. The results are

summarized in Figure 4. In the placebo arm, 12 of 21 (57.1%) guessed that they received the placebo treatment, a rate of correct guessing that was no better than chance (compared to a hypothesized correct guessing rate of 50%, $p = 0.639$). These results indicate that subjects in the placebo arm were adequately blinded to their allocation. 71.4% of active arm subjects did correctly guess their treatment allocation, a rate of correct guessing that was significantly better than chance (compared to a hypothesized correct guessing rate of 50%, $p = 0.044$). While these results might suggest that active arm subjects were not adequately blinded, analysis of subject-provided reasons revealed that subjects based their allocation guesses primarily on perceived clinical efficacy rather than on palpable sensory experiences. When asked for the reason behind their guess, 18 of 32 (56.3%) of subjects in the active arm who guessed active arm allocation specifically stated a clinical improvement as the reason for their guess. Likewise, seven of ten (70.0%) of the active arm subjects who guessed that they had been allocated to the placebo arm provided a lack of clinical efficacy as a reason for their guess. Eight of thirty-two (25.0%) active arm subjects who guessed active allocation and three of ten (30.0%) active arm subjects who guessed placebo arm allocation did not provide a reason for their guess. Of the active arm subjects who did not provide a rationale for their guess, 6/8 (75.0%) of those who guessed active arm allocation did experience a significant reduction in monthly migraine days (-70.2% ± 10.0%) during the third treatment month relative to the pre-treatment baseline. Of the other two subjects, one had no change in monthly migraine days and the other was diary non-compliant (and thus efficacy could not be accurately assessed). Notably, only three subjects mentioned sensory experiences (i.e., warming and cooling of the ears) as a reason for guessing active allocation. Of these three subjects, two also discussed clinical efficacy as a reason for their guess.

To further explore whether the migraine prophylaxis from CVS therapy might be mediated by a placebo-effect, we performed a secondary analysis of the change in migraine days over the course of the study, specifically focusing on PP subjects who guessed they had received active treatment. If therapeutic gains in the number of monthly migraine days were indeed mediated by a placebo effect, a similar rate of clinical improvements would be expected for all subjects who guessed that they had received active treatment

regardless of their treatment allocation. However, within PP subjects who guessed that they had been allocated to the active arm, subjects who had received active treatment showed significantly greater reductions in monthly migraine days compared to those subjects who had received a placebo treatment (either inactive placebo or partially active placebo; Figure 4, main effect of treatment: : $F_{(1,11)} = 12.43$; $p = 0.005$, and treatment by time interaction: $F_{(3,33)} = 2.01$; $p = 0.131$. Finally, to rule out the possibility that sensory stimuli may have biased subjects by eliciting preconceived notions, we performed a final analysis of the PP data which excluded all subjects who mentioned any kind of sensory experience as a reason for their allocation guess (e.g., temperature change in the ears, the visual display on the touch screen, the lack of experience of expected side-effects). In this analysis which excluded two active arm and three placebo arm PP subjects, active treatment still provided significant therapeutic gains over placebo treatment (Supplemental Figure 4, main effect of treatment: $F_{(1,14)} = 7.94$; $p = 0.014$, and treatment by time interaction: $F_{(3,42)} = 2.08$; $p = 0.117$, linear mixed model).

IV. Discussion

This randomized, double-blinded, placebo-controlled trial demonstrates that treatment with the solid-state CVS device provides an efficacious and well-tolerated adjuvant prophylactic therapy for episodic migraine. Active arm subjects, who were already receiving standard-of-care therapies, exhibited significantly fewer monthly migraine days as early as the first treatment month, and the number of monthly migraine days decreased steadily over the course of treatment with a final reduction of -3.8 migraine days during the final treatment month, representing a therapeutic gain of -2.7 monthly migraine days. Furthermore, the lack of asymptote in the percent change of monthly migraine days over time (Figure 3A, C) suggests the possibility that patients may continue to improve further over longer treatment periods. To reproduce the reported findings described herein and assess the therapeutic potential for longer treatment periods, a second research clinical trial (clinicaltrials.gov: NCT02991430) has been initiated. This replication study will also seek to establish whether CVS therapy provides durable migraine prophylaxis.

In the current study, three months of active CVS treatment significantly reduced the total monthly headache pain scores in patients already receiving standard-of-care therapies by 48.1% and the acute anti-migraine prescription medication intake by 51.3% in the PP group. While the placebo group also exhibited statistically significant reductions within these domains, active treatment provided therapeutic gains ≥ 20% for both secondary outcome measures, indicating that CVS is likely to significantly improve the health economics of treating episodic migraine. Although there was not a statistically significant difference in the 50% responder rate between the active and placebo groups, an effect likely due to insufficient sampling, a response rate ≥ 50% was observed in a substantial percentage of active arm subjects (57% of PP and 53% of ITT subjects). Additionally, group-wise comparisons of the PP groups revealed that active arm subjects had greater percent-change in monthly migraine days after three months of treatment than placebo arm subjects (therapeutic gain of -32.2%). Notably, the efficacy of CVS for reducing migraine burden was not affected by concomitant drug use (Supplemental Figure 3D), indicating that CVS can be successfully used as an adjuvant therapy and may provide migraine prophylaxis through a parallel mechanism of action.

Side effects for CVS treatment were expected to be similar to those associated with irrigation-based diagnostic calorics (i.e., dizziness/nausea) though less severe owing to the reduced slew rate and less extreme temperature dynamic range provided by the programmed device[8]. Indeed, temporary dizziness/nausea occurred in only four active-arm subjects (8.1%), for whom the effects were considered to be mild in three and moderate in one. Notably, in only one subject were these effects considered to be of probable relation to the device (Table 3).

The lack of change in balance scores or falls for any treatment groups over the course of the study (Table 4) confirmed that longitudinal CVS treatment over three months has no negative sequela on vestibular function and further validated the safety of CVS therapy. Our inclusion criteria mandated that subjects exhibit no evidence of pre-existing balance disorders. As such, it is unclear whether patients with comorbid vestibular dysfunction would experience similar rates of migraine prevention efficacy, safety and tolerability, as those observed in this trial.

The lack of negative outcomes on measures of mood and cognition further highlight the safety of CVS therapy. Although mood and cognitive measures were originally intended to serve as a secondary efficacy endpoint, evaluation of baseline data indicated that there was little mood or cognitive dysfunction in our randomized study cohort. Though migraine does exhibit significant comorbidity with psychiatric disorders[14], our exclusion of subjects with histories of either unstable mood or anxiety disorders or diagnoses of neurological disorders besides migraine as well as our focus on episodic rather than chronic migraineurs likely limited the number of subjects with whom the therapeutic potential of CVS for mood and/or cognitive dysfunction could be assessed[36]. Yet, notably, the lack of negative effects of CVS treatment on any measure of mood or cognition as well as the absence of any AEs relating to fatigue and/or somnolence further exemplify the safety and tolerability of CVS therapy.

The active CVS group demonstrated an excellent overall rate of treatment adherence (86.3% ± 2.2%). This finding is especially noteworthy when one considers that CVS therapy requires subjects to suspend mobile activities and lie supine for the duration of treatment (totaling, in this study, 36 minutes per day). Future studies will be required to determine whether high CVS treatment adherence may relate to either an immediate reduction in migraine frequency or to a positive subjective experience with using the device, both of which were frequently reported in this study (Table 5). Furthermore, the ability of the CVS device to record treatments provides a unique opportunity to evaluate whether and how clinical efficacy relates to treatment adherence. In addition to using standard methods of evaluating treatment efficacy across PP and ITT groups, inferential analysis will be performed in the next research clinical trial to determine whether the rate of clinical improvement relates to treatment adherence.

The use of inactive treatment control arms in randomized controlled trials is viewed as being fundamental to establishing clinical efficacy of both drugs and devices. Whereas active and placebo pills can be made to look identical, non-invasive neuromodulation devices are likely to generate palpable sensory stimuli in active mode and thus often present significant challenges for maintaining treatment blinding in active arm subjects. While the rate of correct allocation guesses in the active treatment arm in our study (71.4%)

might appear to indicate that active arm subjects had become aware of their treatment allocation, a careful analysis of subject-provided reasons for their allocation guesses revealed that subjects primarily based their guesses on their perceived rate of clinical improvement (Figure 4). Indeed, only 3 of the 49 active arm subjects mentioned experiencing the warming/cooling sensations as reason for their allocation guess (i.e., the sensory experience that could have un-blinded them to their treatment condition). These results suggest that subjects did not attribute temperature changes in the ear canal as being a mechanism for neurostimulation, an observation that is unsurprising given the public focus on electrical stimulation for medical therapies, the absence of CVS within current treatment practice and the limited exposure to caloric vestibular stimulation that subjects with normal vestibular function are likely to have experienced prior to study participation.

Ideally, placebo devices should deliver a sub-therapeutic stimulus so as to directly mimic the active device[37, 38]. However, this approach presumes that a sub-threshold stimulus is well characterized, which may not be the case for a new experimental device. The initial placebo waveform in this study was designed to provide a subthreshold stimulus by taking both ear pieces from room temperature to 37° C and maintaining that temperature for the remainder of treatment. However, the presence of dizziness/nausea related to device treatment in three subjects provided clear evidence that the waveform produced substantive caloric vestibular stimulation. As such, the placebo condition was modified so that no power was delivered to the heating and cooling components in the headset. To ensure the integrity of results, both placebo conditions in this study produced a similar range of sensory experiences so as to produce an effective blind. Both active and placebo subjects went through the same choreography for treatment (i.e., starting the protocol using the touchscreen and lying back on a wedge pillow for treatment, cleaning and storing the device), felt pressure in the ear canals as well as an initial cooling sensation from initial headset placement and heard both the faint whirring noise produced by the cooling fans and the tones produced at the start and stop of treatment. Notably, a sub-analysis of PP subjects excluding all subjects that mentioned any kind of sensory experience during treatment as reason for their allocation guess (Supplemental Figure

4) showed clear separation between placebo and active arms, suggesting that differences in palpable sensory stimuli between the two treatment conditions were unlikely to account for prevention of episodic migraine. Furthermore, if the inactive placebo was insufficient to produce a believable blind, one might expect treatment adherence to be significantly attenuated within this treatment group. However, inactive placebo subjects demonstrated excellent overall treatment adherence (93.1% ± 1.1%). Together, these data indicate that subjects remained effectively blinded to treatment allocation over the course of the study.

To further explore whether efficacy of CVS therapy may have been driven by a placebo effect, we examined the change in monthly migraine days specifically in subjects that guessed that they had received active allocation (Figure 4) and found clear separation between the active and placebo arm subjects. The results from this sub-analysis may underestimate the therapeutic gain, particularly in the third treatment month for two reasons. First, the placebo group in this analysis combined data from the partially active placebo and the inactive placebo groups. Given the evidence for some vestibular stimulation in the partially active placebo condition, there may have been a substantive degree of vestibular stimulation which could have provided partial efficacy for migraine prevention. Second, the timing of the allocation guess during the final assessment and the finding that subjects primarily based their allocation guesses on perceived clinical efficacy may bias this sub-analysis towards subjects that experienced stochastic reductions in monthly migraine days during the third treatment month. The active group in this sub-analysis showed a relatively stable reduction in migraine days during treatment months two and three, but the placebo group demonstrated additional reductions during the third treatment month suggesting that this biasing effect may be more likely to affect the placebo group. Yet, despite these confounding factors which are likely to reduce therapeutic effect size, the reduction in monthly migraine days for subjects guessing active arm allocation was significantly greater in subjects receiving active treatment compared to the placebo, thus strongly suggesting that device efficacy was derived from vestibular stimulation rather than from placebo-effect mediated phenomenon.

While the mechanism of action for CVS-mediated migraine prevention remains unknown, we hypothesize that our effects are mediated by neuromodulation of relevant brainstem centers. While migraine is often associated with vascular flow abnormalities, neuroimaging studies provide evidence that migraine is a neurological disorder involving brainstem dysfunction[9-11]. The time-varying CVS waveforms used in this study (Figure 1B) provide substantive vestibular stimulation and induce oscillations in cerebrovascular dynamics that are consistent with brainstem neuromodulation[8]. Additionally, vestibular nuclei innervate numerous brainstem regions implicated in migraine[14-16] (see Figure 2C). Future studies using neuroimaging approaches may help elucidate mechanism by identifying both the neural circuits and temporal dynamics of activation elicited by this CVS protocol.

The primary limitation of this study arose from the change in the placebo protocol during the course of this study. Once subjects presented with dizziness/nausea in association with the initial placebo condition, it became apparent that the supposedly inactive waveform elicited substantive vestibular stimulation and thus was unlikely to provide a good null stimulation comparator for the active arm subjects. The revised protocol was approved by all IRBs, and the FDA was made aware of the protocol change; and this modification split the "placebo" condition into two distinct groups. The decrease in the placebo sample size reduced statistical power for observing statistically significant primary and secondary endpoints. Yet, importantly, the primary endpoint for both the PP and ITT groups was still statistically significant even with the change in protocol. Furthermore, when the two placebo conditions are pooled, active treatment still shows statistically significant therapeutic gains over the combined placebo conditions (-2.3 and -2.0 monthly migraine days for the PP and ITT groups, respectively; see Supplemental Figure 2). Finally, the primary and secondary outcome measures in our study depended on adherence to daily headache diaries throughout the course of the study. Thus, as with all diary-based studies, the study was also limited in so far as it was not able to assess efficacy in subjects that withdrew from the study or demonstrated significant non-adherence to the daily electronic headache diary. Rather than imputing data for these subjects, use of a

modified ITT group in this study provides accurate results clarifying the expected rates of efficacy across of spectrum of treatment adherence.

This pivotal study evaluated safety and efficacy in a relatively homogenous sample (episodic migraineurs between the ages of 18-65), however, CVS therapy may also provide a much-needed therapeutic option for adolescent migraineurs. Parents often resist the idea of their children taking daily medication given the side-effect profiles and marginal therapeutic gains of the available prophylactics[39]. However, preventative strategies not only improve quality of life, but may also decrease the longitudinal progression to chronic disease states in pediatric migraineurs[40, 41]. Although migraine symptoms differ slightly between adolescent and adult populations[42], the underlying migraine pathophysiology is presumed to be the same[43]. The long history demonstrating the safety of irrigation-based CVS in pediatric populations[44, 45] suggest that pediatric migraineurs would experience a similar safety/tolerability profile as reported herein. Furthermore, the early maturation of the vestibular system and brainstem structures suggests that pediatric migraineurs may experience similar rates of efficacy. Another natural extension of this work would be to evaluate efficacy for preventing chronic migraines and will be the focus of future studies. Furthermore, owing to the non-chemical mechanisms of action for therapy, the therapeutic potential for CVS therapy to help wean subjects with medication overuse headache off acute abortive medications could also be explored in future studies.

V. Conclusion

The results from this randomized, double-blinded, placebo-controlled trial demonstrate that CVS treatment with a novel solid-state device significantly reduces the number of migraine days per month as well as the subjective headache pain scores and the need for migraine abortive prescription medications. Treatment can be administered in the home-setting with no technical expertise and modest training. Subjects demonstrated high rates of treatment adherence and also reported subjectively positive

experiences with using the device. Together, these results indicate that CVS therapy addresses the existing need for new prophylactic therapies for episodic migraine. This approach appears to be both efficacious and very well tolerated, and further clinical testing is warranted. A second, expanded study is now underway.

REFERENCES

1. Estemalik E, Tepper S. Preventive treatment in migraine and the new US guidelines. *Neuropsychiatric disease and treatment*. 2013;9:709-720.

2. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. *Archives of internal medicine*. 1999;159:813-818.

3. Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. *Headache*. 2007;47:355-363.

4. Lipton RB, Bigal ME, Diamond M*, et al.* Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68:343-349.

5. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev*. 2013:CD010610.

6. Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: an updated Cochrane review. *Cephalalgia*. 2015;35:51-62.

7. Karlsen EA, Mikhail HH, Norris CW, Hassanein RS. Comparison of responses to air, water, and closed-loop caloric irrigators. *Journal of speech and hearing research*. 1992;35:186-191.

8. Black RD, Rogers LL, Ade KK, Nicoletto HA, Adkins HD, Laskowitz DT. Non-Invasive Neuromodulation using Time-Varying Caloric Vestibular Stimulation. *IEEE Journal of Translational Engineering in Heath and Medicine*. 2016;4:10.

9. Aurora SK, Barrodale PM, Tipton RL, Khodavirdi A. Brainstem dysfunction in chronic migraine as evidenced by neurophysiological and positron emission tomography studies. *Headache*. 2007;47:996-1003; discussion 1004-1007.

10. Goadsby PJ. Can we develop neurally acting drugs for the treatment of migraine? *Nature reviews Drug discovery*. 2005;4:741-750.

11. Chong CD, Plasencia JD, Frakes DH, Schwedt TJ. Structural alterations of the brainstem in migraine. *Neuroimage Clin*. 2017;13:223-227.

12. Dieterich M, Brandt T. Functional brain imaging of peripheral and central vestibular disorders. *Brain*. 2008;131:2538-2552.

13. Marcelli V, Esposito F, Aragri A*, et al.* Spatio-temporal pattern of vestibular information processing after brief caloric stimulation. *Eur J Radiol*. 2009;70:312-316.

14. Balaban CD, Jacob RG, Furman JM. Neurologic bases for comorbidity of balance disorders, anxiety disorders and migraine: neurotherapeutic implications. *Expert Rev Neurother*. 2011;11:379-394.

15. Brown JE, Card JP, Yates BJ. Polysynaptic pathways from the vestibular nuclei to the lateral mammillary nucleus of the rat: substrates for vestibular input to head direction cells. *Experimental brain research Experimentelle Hirnforschung Experimentation cerebrale*. 2005;161:47-61.

16. Horowitz SS, Blanchard J, Morin LP. Medial vestibular connections with the hypocretin (orexin) system. *The Journal of comparative neurology*. 2005;487:127-146.

17. Kolev O. How caloric vestibular irritation influences migraine attacks. *Cephalalgia*. 1990;10:167-169.

18. McGeoch PD, Williams LE, Lee RR, Ramachandran VS. Behavioural evidence for vestibular stimulation as a treatment for central post-stroke pain. *J Neurol Neurosurg Psychiatry*. 2008;79:1298-1301.

19. Ramachandran VS, McGeoch PD, Williams L, Arcilla G. Rapid relief of thalamic pain syndrome induced by vestibular caloric stimulation. *Neurocase*. 2007;13:185-188.

20. Headache Classification Subcommittee of the International Headache S. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24 Suppl 1:9-160.

21. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.

22. Berg K, Wood-Dauphinee S, Williams JI. The Balance Scale: reliability assessment with elderly residents and patients with an acute stroke. *Scandinavian journal of rehabilitation medicine*. 1995;27:27-36.

23. Kwong WJ, Pathak DS. Validation of the eleven-point pain scale in the measurement of migraine headache pain. *Cephalalgia*. 2007;27:336-342.

24. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics*. 2009;42:377-381.

25. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of general psychiatry*. 1961;4:561-571.

26. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *Journal of consulting and clinical psychology*. 1988;56:893-897.

27. Davis AS, Pierson EE. The relationship between the WAIS-III digit symbol Coding and executive functioning. *Applied neuropsychology Adult*. 2012;19:192-197.

28. Farias ST, Mungas D, Reed BR*, et al.* The measurement of everyday cognition (ECog): scale development and psychometric properties. *Neuropsychology*. 2008;22:531-544.

29. Reitan RM. Trail Making Test: Manual for Administration and Scoring. *Tuscon, AZ: Reitan Neuropsychological Laboratory*. 1992.

30. Benton ALH, K.D. . Multilingual aphasia examination. *Iowa City: University of Iowa*. 1976.

31. D. W. Wechsler Memory Scale–Third Edition manual. 1997.

32. Della Santina CC, Potyagaylo V, Migliaccio AA, Minor LB, Carey JP. Orientation of human semicircular canals measured by three-dimensional multiplanar CT reconstruction. *J Assoc Res Otolaryngol*. 2005;6:191-206.

33. Peitersen E. Vestibulospinal reflexes. X. Theoretical and clinical aspects of the stepping test. *Arch Otolaryngol*. 1967;85:192-198.

34. Freeman JA, Trentman TL. Clinical utility of implantable neurostimulation devices in the treatment of chronic migraine. *Medical devices*. 2013;6:195-201.

35. Schoenen J, Vandersmissen B, Jeangette S*, et al.* Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology*. 2013;80:697-704.

36. Ferrari A, Leone S, Vergoni AV*, et al.* Similarities and differences between chronic migraine and episodic migraine. *Headache*. 2007;47:65-72.

37. Asano E, Goadsby PJ. How do we fashion better trials for neurostimulator studies in migraine? *Neurology*. 2013;80:694.

38. Rakel B, Cooper N, Adams HJ*, et al.* A new transient sham TENS device allows for investigator blinding while delivering a true placebo treatment. *J Pain*. 2010;11:230-238.

39. El-Chammas K, Keyes J, Thompson N, Vijayakumar J, Becher D, Jackson JL. Pharmacologic treatment of pediatric headaches: a meta-analysis. *JAMA Pediatr*. 2013;167:250-258.

40. Bigal ME, Lipton RB. Migraine chronification. *Curr Neurol Neurosci Rep*. 2011;11:139-148.

41. Charles JA, Peterlin BL, Rapoport AM, Linder SL, Kabbouche MA, Sheftell FD. Favorable outcome of early treatment of new onset child and adolescent migraine-implications for disease modification. *J Headache Pain*. 2009;10:227-233.

42. Hershey AD, Winner P, Kabbouche MA*, et al.* Use of the ICHD-II criteria in the diagnosis of pediatric migraine. *Headache*. 2005;45:1288-1297.

43. Blume HK. Pediatric headache: a review. *Pediatr Rev*. 2012;33:562-576.

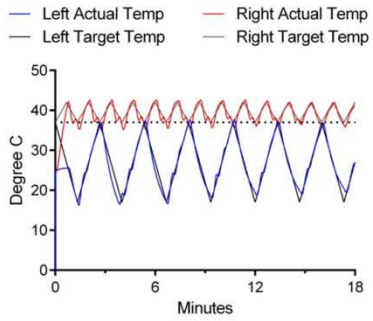
44. Andrieu-Guitrancourt J, Peron JM, Dehesdin D, Aubet J, Courtin P. Normal vestibular responses to air caloric tests in children. *Int J Pediatr Otorhinolaryngol*. 1981;3:245-250.

45. Melagrana A, D'Agostino R, Ravera B, Taborelli G. Comparison between air and water caloric tests in children. *Int J Pediatr Otorhinolaryngol*. 1999;51:139-143.

A


TMN™

B


Left Actual Temp
Left Target Temp
Right Actual Temp
Right Target Temp
Degree C
50
40
30
20
10
0
0
6
12
18
Minutes

C

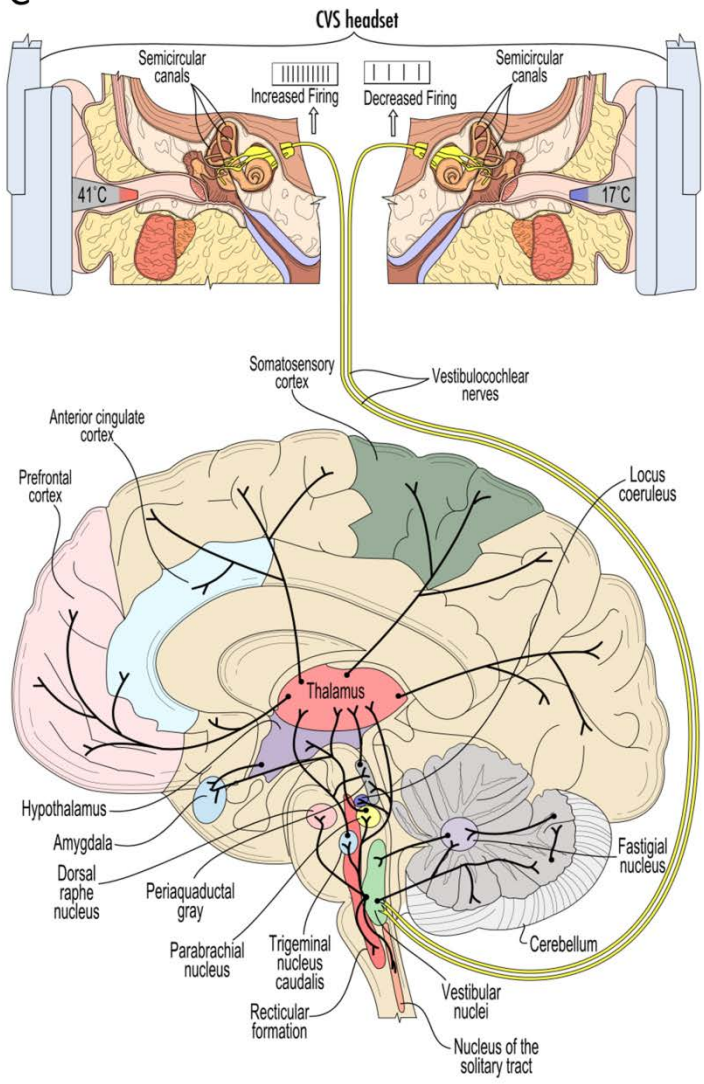

CVS headset
Semicircular canals
Increased Firing
Decreased Firing
Semicircular canals
41˚C
17˚C
Somatosensory cortex
Vestibulocochlear nerves
Anterior cingulate cortex
Prefrontal cortex
Locus coeruleus
Thalamus
Hypothalamus
Amygdala
Dorsal raphe nucleus
Periaquaductal gray
Parabrachial nucleus
Trigeminal nucleus caudalis
Rectricular formation
Fastigial nucleus
Cerebellum
Vestibular nuclei
Nucleus of the solitary tract

Figure 1. CVS treatment. (A) Schematic of a patient undergoing treatment while wearing the CVS headset and lying on an incline wedge pillow. (B) Example of target and actual thermal profiles of the saw-tooth time-varying thermal waveform used for active arm subjects in this study. (C) The mechanism of action of CVS and projections of the vestibular nuclei to brain regions implicated in migraine. The action potential firing rates of the vestibulochoclear nerves are increased by the warming of the left ear and decreased by cooling of the right ear. These nerves innervate the vestibular nuclei in the brainstem which send both direct and indirect excitatory afferents to a number of brainstem nuclei implicated in migraine pathology. The vestibular nuclei also show extensive polysynaptic connectivity with numerous structures in the midbrain and forebrain affected in migraine pathology. Orientation of the brain has been turned 90° to show connectivity in a sagittal cross-section.

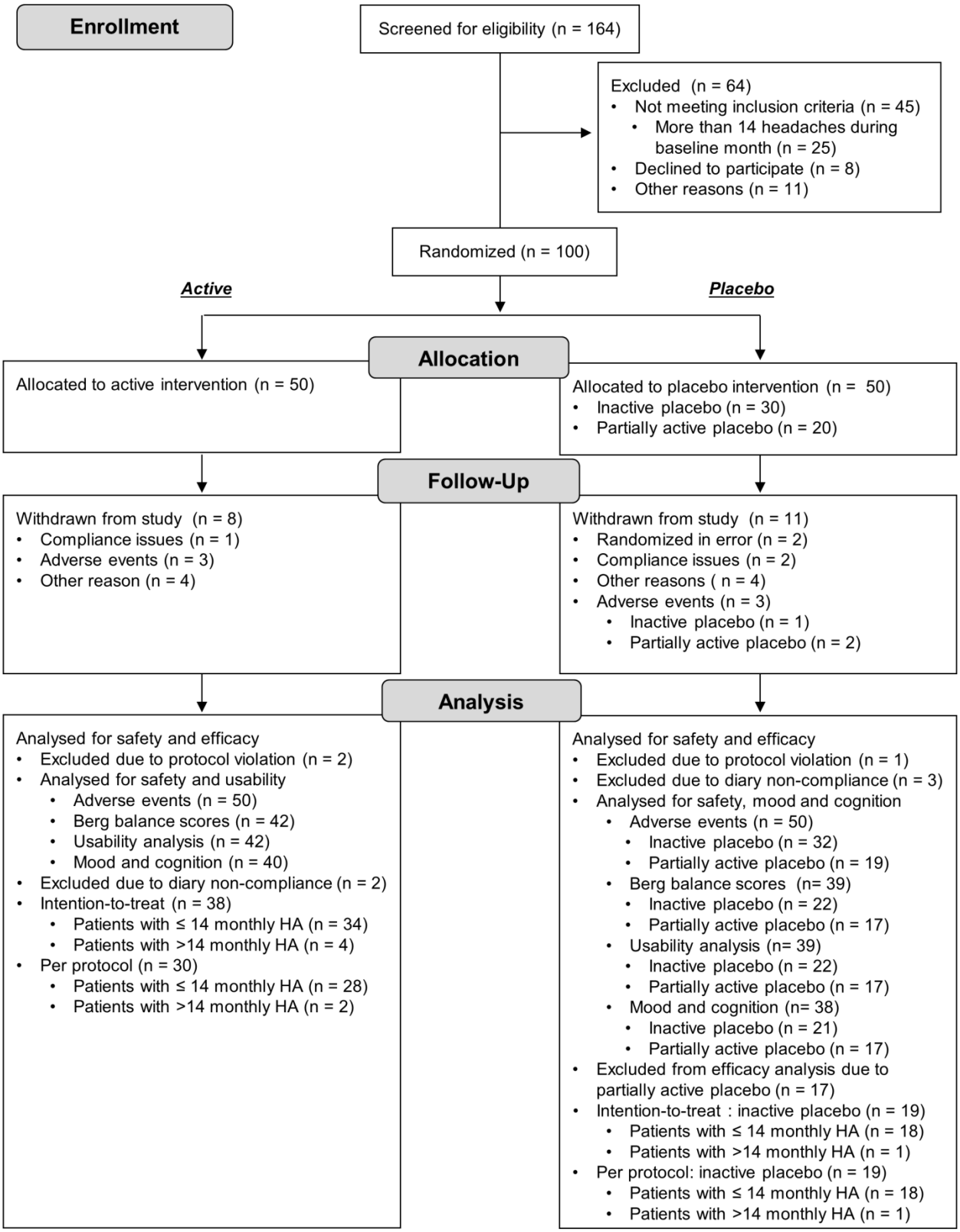


Figure 2. Study design.

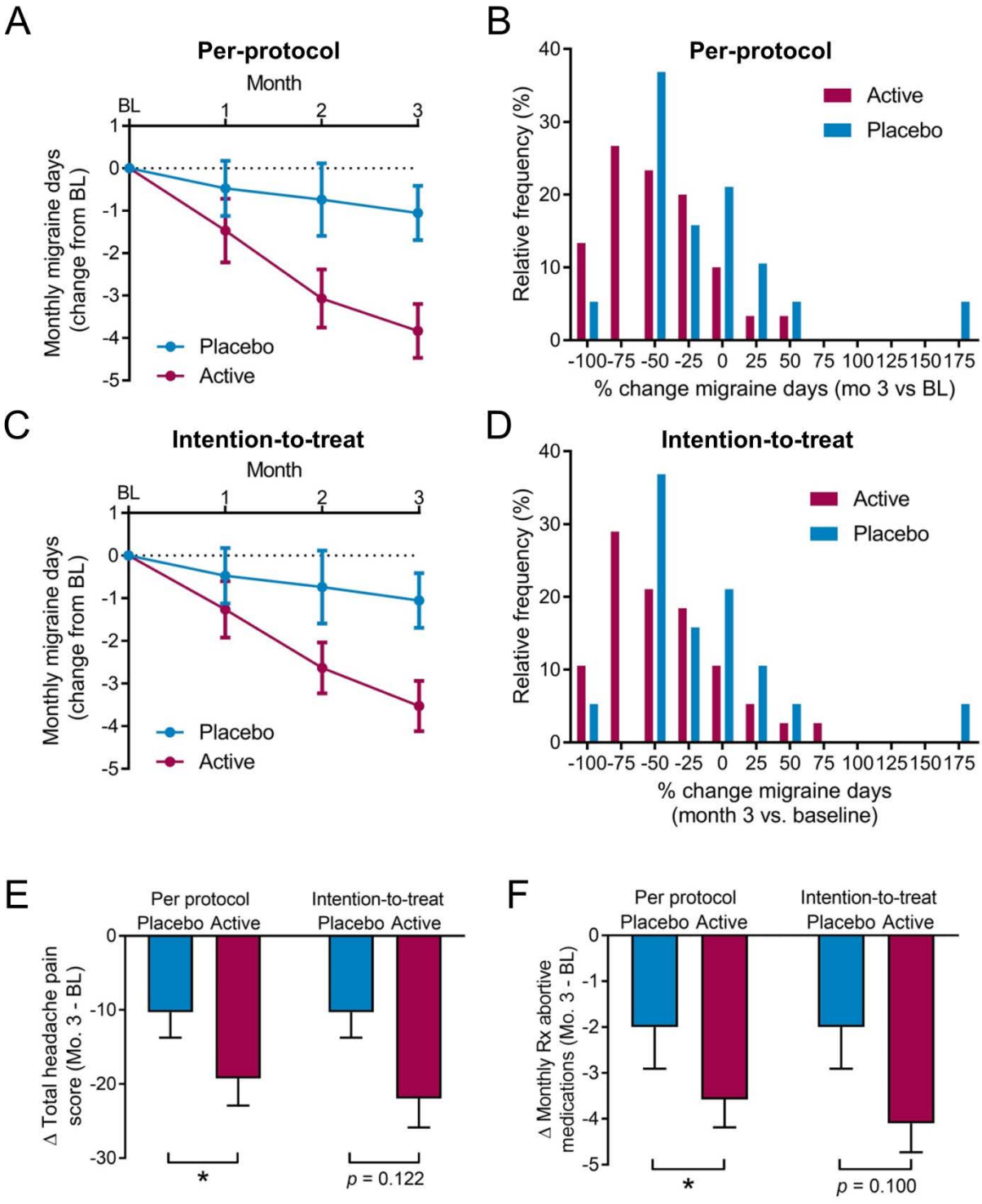


Figure 3. Prophylactic efficacy of CVS for episodic migraine. (A) Change in migraine days over the course of treatment relative to baseline (BL) in the per-protocol groups. Active versus

placebo: main effect of treatment: $F_{(1,18)} = 12.10$; $p = 0.003$, and treatment by time interaction: $F_{(3,54)} = 5.21$; $p = 0.003$, linear mixed model. (B) Distribution of the percent-change in monthly migraine days between the third treatment month (Mo. 3) and BL for the per-protocol analysis. (C) Change in migraine days over the course of treatment relative to baseline (BL) in the intention-to-treat (ITT) groups. Active versus placebo, main effect of treatment: $F_{(1,18)} = 10.62$; $p = 0.004$, and treatment by time interaction: $F_{(3,54)} = 3.81$; $p = 0.015$, linear mixed model. (D) Distribution summary for the percent-change in monthly migraine days between Mo. 3 and BL for the ITT analysis. Summaries of the change scores for (E) the total monthly headache pain and (F) the monthly use of prescription (Rx) migraine abortive drugs between Mo.3 and BL. Data for all panels are presented as the mean ± standard error of the mean. * $p < 0.05$.

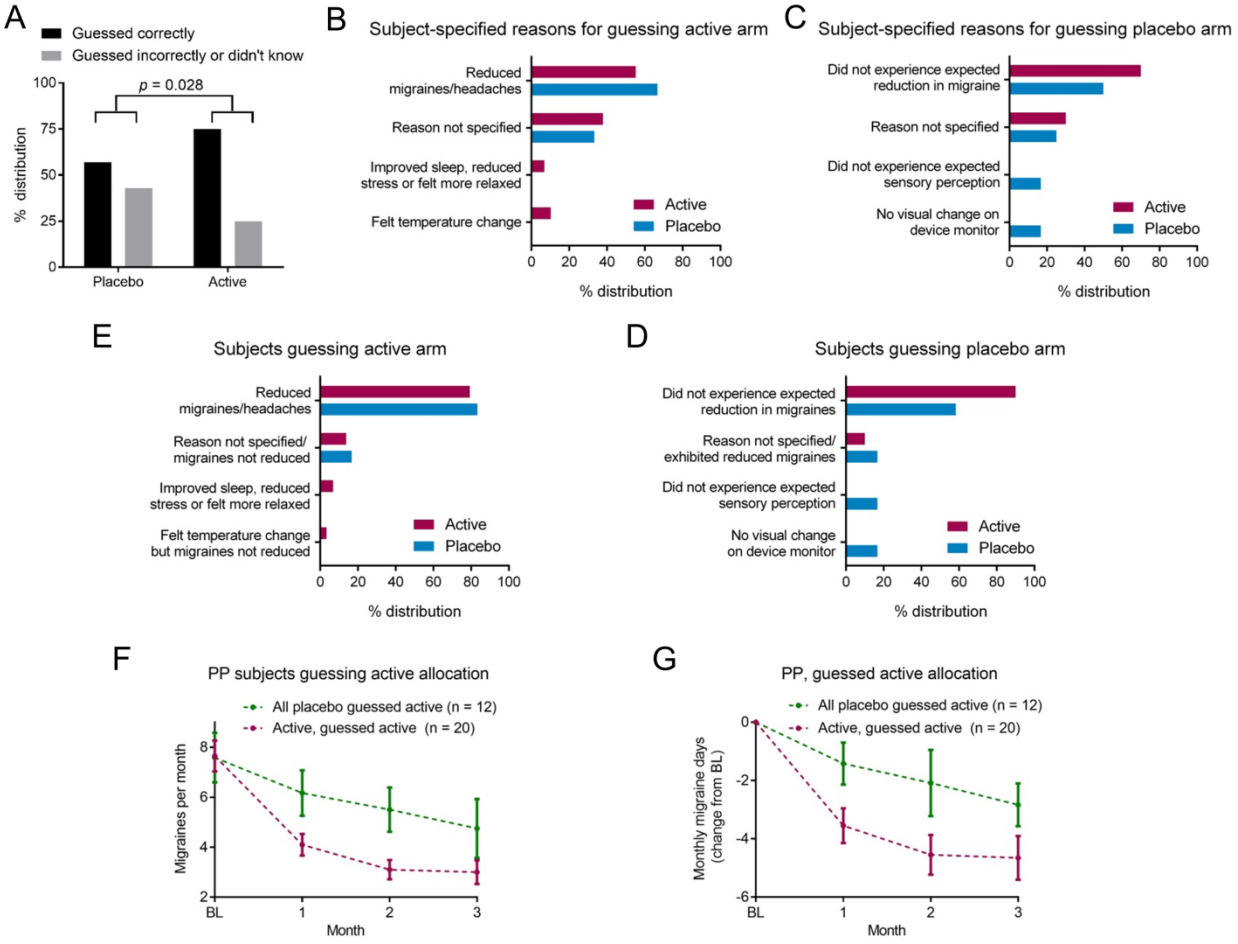


Figure 4. Assessment of treatment blinding. (A) Summary showing the distribution of subjects correctly guessing treatment allocation at the end of the study. Summaries of the subject-provided reasons for guessing (B) active arm allocation or (C) placebo arm allocation gathered from hand-written answers provided by subjects on an end-of study questionnaire. Summaries showing the distribution of subject-specified reasons and inferred reasons based on the change in migraine days between the third treatment month pre-treatment baseline and for guessing (D) active arm allocation and (E) placebo arm allocation. (F) Migraine days over the course of treatment in the per-protocol (PP) groups for subjects that guessed active allocation. (G) Change in migraine days over the course of treatment relative to baseline (BL) in the per-protocol (PP) groups for subjects that guessed active allocation. Active versus placebo $F_{(1,11)} = 12.43$; $p = 0.005$, and treatment by time interaction: $F_{(3,33)} = 2.01$; $p = 0.131$, linear mixed model.

Table 1. Patient demographics.

	Per protocol (all)		Intention-to-treat (all)	
	Active	**Placebo**	**Active**	**Placebo**
n	30	18	39	19
Age (years)	45.4 ± 1.9	39.3 ± 3.2	44.4 ± 1.7	39.6 ± 3.1
Disease duration (years)	25.7 ± 2.4	20.6 ± 2.8	25.5 ± 2.0	21.2 ± 2.7
Sex				
Male, n (%)	4 (13.3%)	2 (11.1%)	5 (12.8%)	2 (10.5%)
Female, n (%)	26 (86.7%)	16 (88.9%)	34 (87.2%)	17 (89.5%)
Education (years)	16.1 ± 0.5	15.5 ± 0.6	15.5 ± 0.6	15.5 ± 0.6
Migraine with occasional aura, n (%)	7 (23.3%)	8 (44.4%)	8 (20.5 %)	8 (42.1%)
Exclusively migraine without aura, n (%)	23 (76.7%)	10 (55.6%)	21 (79.5%)	11 (57.9%)
Concomittant medications				
Antiepileptics (AEDs)	5 (17.9%)	2 (11.1%)	6 (15.4%)	2 (10.5%)
Antihistamines	7 (25.0%)	6 (33.3%)	7 (17.9%)	7 (36.8%)
Antinausea medications	3 (10.7%)	1 (5.6%)	4 (10.3%)	1 (5.3%)
β blockers/antihypertensives	4 (14.3%)	6 (33.3%)	5 (12.8%)	7 (36.8%)
NA or DA drugs	8 (28.6%)	4 (22.2%)	9 (23.1%)	4 (21.1%)
SERT inhibitors	8 (28.6%)	6 (33.3%)	9 (23.1%)	7 (36.8%)
Hormones (birth control, etc.)	8 (28.6%)	6 (33.3%)	8 (20.5%)	7 (36.8%)

Data are presented as n (%) or mean ± standard error of the mean.

Table 2. Primary and secondary outcomes.

	Per protocol		Intention-to-treat	
	Active	**Placebo**	**Active**	**Placebo**
n	30	19	38	19
Migraine days (baseline compared to third month of treatment)				
Migraine days (baseline)	7.7 ± 0.5	6.9 ± 0.7	7.7 ± 0.4	6.9 ± 0.7
Migraine days (third treatment month)	3.8 ± 0.5	5.8 ± 0.9	4.2 ± 0.5	5.8 ± 0.9
Change in migraine days	-3.8 ± 0.6	-1.1 ± 0.6	-3.5 ± 0.6	-1.1 ± 0.6
95% confidence interval	-5.1 to -2.5	-2.4 to 0.3	-4.7 to -2.3	-2.4 to 0.3
p	< 0.0001 *	0.048 *	< 0.0001 *	0.048 *
Difference between groups (migraine days)	-2.8		-2.5	
95% confidence interval	-0.9 to -4.7		-0.6 to -4.4	
Comparison between groups, *p*	0.0119 *		0.0205 *	
Percentage of responders (reduction in monthly migraine days from baseline to third treatment month)				
Responders (≥50% reduction)	17 (56.7.1%)	6 (31.6%)	20 (52.6%)	6 (31.6%)
Comparison between the 2 groups, *p*	0.0864		0.1325	
% reduction (baseline vs. third month of treatment)	-47.1% ± 7.0%	-14.9% ± 13.5%	-42.1% ± 7.0%	-14.9% ± 13.5%
Comparison between the 2 groups, *p*	0.0288 *		0.0534	
Total monthly headache pain scores (baseline compared to third treatment month)				
Total pain baseline month	45.7 ± 3.5	36.4 ± 3.9	44.7 ± 3.1	36.4 ± 3.9
Total pain third treatment month	23.7 ± 2.8	26.1 ± 3.3	25.4 ± 2.5	26.1 ± 3.3
Change in total pain	-22.0 ± 3.9	-10.3 ± 3.4	-19.3 ± 3.6	-10.3 ± 3.4
95% confidence interval	-30.0 to -14.0	-17.5 to -3.1	-26.4 to -11.9	-17.5 to -3.1
p	< 0.0001 *	0.0073 *	< 0.0001 *	0.0073 *
Difference between groups (change in total pain)	-11.7		-9.0	
95% confidence interval	-23.0 to -0.3		-20.4 to 2.5	
Comparison between groups, *p*	0.0437 *		0.1218	
Acute anti-migraine prescription drug intake (baseline compared to third treatment month)				
n (subjects with current antimigraine prescriptions)	26	17	33	17
Acute anti-migraine drugs intake (baseline)	7.6 ± 0.8	6.1 ± 1.6	7.3 ± 0.7	6.1 ± 1.6
Acute anti-migraine drug intake third month	3.7 ± 0.6	4.4 ± 1.4	3.8 ± 0.6	4.4 ± 1.4
Change in anti-migraine drug intake	-3.9 ± 0.6	-1.7 ± 0.8	-3.5 ± 0.6	-1.8 ± 0.8
Change (third month - baseline), *p*	< 0.0001 *	0.0450 *	< 0.0001 *	0.0450 *
Difference between groups (anti-migraine drugs)	-2.2		-1.7	
95% confidence interval	-4.2 to -0.1		-3.8 to 0.3	
Comparison between groups, *p*	0.0375*		0.1001	

* $p < 0.05$.

Table 3. Adverse Events with possible relationship to device use.

	Active	Placebo	Partially active placebo
Randomized subjects	49	31	20
Serious adverse events	0	0	0
Unexpected adverse events	0	0	0
Nausea and/or dizziness	5	2	3
Device relationship	PoR (4), PrR (1)	UR (1), PoR (1)	R (2), PrR (1)
Ear discomfort, itch, irritation, pruritus	2	1	1
Device relationship	PoR (1), PrR (1)	PoR (1)	R (1)
Tinnitus/buzzing	2	2	0
Device relationship	PoR (1), PrR (1)	PoR (2)	
Neck pain exacerbation	2	0	0
Device relationship	UR (1), PoR (1)		
Increased migraines/headaches	3	0	1
Device relationship	UR (2), PrR (1)		PoR (1)
Blood pressure change during treatment	2	0	0
Device relationship	UR (1), PoR (1)		
Eye twitching	0	1	0
Device relationship		PoR (1)	
Blurred vision	0	0	1
Device relationship			UR (1)

Abbreviations: UR (unlikely related), PoR (possibly related), PrR (probably related), R (related)

Additionally, 1 patient (placebo) experienced the following adverse events deemed unlikely to be related to use of the device: ache in cheek, bad taste on tongue, blurred vision, itchy skin, jaw slipped out of alignment, menopausal symptoms, optical flashing and tingling left arm/wrist as well as right leg.

1 subject (partially active placebo) experienced short-term memory loss deemed unlikely related.

1 subject (partially active placebo) experienced vivid dreams deemed unlikely related.

Table 4. Safety measures

	Per-protocol			Intention-to-treat		
	Active	**Placebo**	**Partially active placebo**	**Active**	**Placebo**	**Partially active placebo**
n	34	20	14	40	22	17
Mood and cognition assessment measures						
Beck Depression Index						
Baseline score	3.6 ± 1.1	4.2 ± 1.4	5.6 ± 1.4	4.0 ± 1.2	4.0 ± 1.3	5.5 ± 1.2
Change from baseline to third month	-0.5 ± 0.4	-1.0 ± 0.7	-1.1 ± 1.7	-0.7 ± 0.4	-0.9 ± 0.7	-0.9 ± 1.4
p,(baseline vs. third month of treatment)	0.205	0.180	0.513	0.101	0.018	0.509
p, change scores (active vs. placebo)		0.499	0.583		0.467	0.766
Beck Anxiety Index						
Baseline score	3.9 ± 0.9	4.8 ± 1.3	5.2 ± 0.9	4.1 ± 0.7	4.6 ± 1.2	5.2 ± 0.9
Change from baseline to third month	-0.3 ± 0.5	-1.5 ± 0.7	-0.6± 0.9	-0.4 ± 0.5	-1.4 ± 0.7	-0.8 ± 0.7
p,(baseline vs. third month of treatment)	0.521	0.057	0.516	0.467	0.058	0.278
p, change scores (active vs. placebo)		0.179	0.796		0.383	0.318
Digit Symbol Coding						
Baseline score	71.8 ± 3.5	74.0 ± 3.8	77.2 ± 4.4	71.0 ± 3.2	73.5 ± 3.7	78.7 ± 3.8
Change from baseline to third month	7.2 ± 2.3	5.0 ± 1.9	7.9 ± 3.5	7.1 ± 1.9	5.0 ± 1.9	7.4 ± 2.9
p,(baseline vs. third month of treatment)	0.003 *	0.018 *	0.042 *	0.001 *	0.014 *	0.022 *
p, change scores (active vs. placebo)		0.606	0.679		0.353	0.998
Trail Making Test A (seconds to comple)						
Baseline score	28.7 ± 1.7	27.4 ± 1.7	26.1 ± 1.9	28.7 ± 1.5	27.3 ± 1.6	24.7 ± 1.8
Change from baseline to third month	-6.5 ± 1.3	-5.9 ± 1.1	-3.6 ± 1.7	-6.3 ± 1.2	-5.7 ± 1.1	-2.9 ± 1.5
p,(baseline vs. third month of treatment)	< 0.0001 *	< 0.0001 *	0.060	< 0.0001 *	< 0.0001 *	0.068
p, change scores (active vs. placebo)		0.264	0.826		0.352	0.328
Trail Making Test B (seconds to complete)						
Baseline score	73.5 ± 10.1	56.4 ± 4.2	55.2 ± 5.2	75.9 ± 9.1	56.3 ± 4.0	51.5 ± 4.8
Change from baseline to third month	-24.0 ± 7.0	-10.1± 3.5	-5.3± 5.4	-24.1 ± 6.2	-9.5 ± 3.4	-1 ± 5.5
p,(baseline vs. third month of treatment)	0.002 *	0.010 *	0.343	0.0004 *	0.011 *	0.8591
p, change scores (active vs. placebo)		0.738	0.333		0.211	0.150
Controlled Oral Word Association						
Baseline score	40.2 ± 2.0	35.6 ± 2.5	37.4 ± 3.4	40.4 ± 1.8	35.1 ± 2.5	38.3± 2.9
Change from baseline to third month	7.1 ± 1.5	4.2 ± 1.4	5.9 ± 2.4	6.2 ± 1.4	4.3 ± 1.4	4.7 ± 2.0
p,(baseline vs. third month of treatment)	< 0.0001 *	0.009 *	0.027 *	0.0001 *	0.005 *	0.036 *
p, change scores (active vs. placebo)		0.167	0.161		0.329	0.039*
Everyday Cognition - 20						
Baseline score	5.7 ± 1.1	8.1 ± 1.9	12.9 ± 2.7	5.6 ± 1.0	7.8 ± 1.9	12.0 ± 2.3
Change from baseline to third month	-0.2 ± 0.8	0.1 ± 1.7	-3.1 ± 1.5	0.7 ± 0.8	0.1 ± 1.6	-2.5 ± 1.3
p,(baseline vs. third month of treatment)	0.817	0.954	0.056	0.390	0.977	0.069
p, change scores (active vs. placebo)		0.866	0.057		0.307	0.112

Short term memory test (faces)						
Baseline score	48.9 ± 1.0	48.5 ± 1.2	47.9 ± 1.6	48.1 ± 1.0	48.5 ± 1.1	48.7 ± 1.5
Change from baseline to third month	-1.5 ± 1.0	-1.6 ± 1.6	1.3 ± 1.6	-1.0 ± 1.0	-1.9 ± 1.5	1.0 ± 1.5
p,(baseline vs. third month of treatment)	0.203	0.436	0.515	0.311	0.241	0.520
p, change scores (active vs. placebo)		0.977	0.135		0.603	0.681
Long term memory test (faces)						
Baseline score	39.1 ± 0.9	38.6 ± 1.1	41.1 ± 1.4	38.9 ± 0.8	39.1 ± 1.2	40.7 ± 1.2
p, (active vs. placebo)		0.753	0.213		0.867	0.218

	Active	**Placebo**	**Partially active placebo**
Berg Balance scores			
n	42	22	17
Baseline score	55.9 ± 0.1	56.0 ± 0.0	55.4 ± 0.4
Change from baseline to third month	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 0.4
p,(baseline vs. third month of treatment) *	0.500	1.000	0.750

Berg balance scores of 41-56 indicate low risk of fall, 21-40 indicate medium risk of fall and 0-20 indicate high risk of fall. * $p < 0.05$.

Table 5. Device usability survey responses at the end of 3 month treatment period.

	Active	Placebo	Partially active placebo
n	42	22	17
Did you find the headset to be comfortable enough to continue with your treatments?			
Yes	42 (100.0%)	20 (90.1%)	16 (94.1 %)
No	0 (0.0%)	2 (9.1%)	1 (5.9%)
Did you find that the device is easy to use at home? †			
Yes	37 (88.1 %)	21 (95.5%)	15 (88.%)
No opinion	0 (0.0%)	1 (4.5%)	0 (0.0%)
It was not easy, but I kept doing it.	5 (11.9%)	0 (0.0%)	2 (11.8%)
No	0 (0.0%)	0 (0.0%)	0 (0.0%)
Was the amount of time you spent treating per day			
Enjoyable	8 (19.0%)	7 (31.8%)	3 (17.6%)
Acceptable	19 (45.2%)	14 (63.6%)	12 (70.6%)
Circled both Enjoyable and Acceptable	2 (4.8%)	0 (0.0%)	1 (5.9%)
No opinion	0 (0.0%)	0 (0.0%)	0 (0.0%)
Challenging to maintain	13 (31.0%)	1 (4.5%)	1 (5.9%)
Impossible to maintain	0 (0.0%)	0 (0.0%)	0 (0.0%)
How would you rate your overall exeperience?			
Very positive	18 (42.8%)	9 (40.9%)	8 (47.0%)
Somewhat positive	14 (33.3%)	10 (45.5%)	4 (23.5%)
No opinion	6 (14.3%)	1 (4.5%)	4 (23.5%)
Somewhat negative	4 (9.5%)	2 (9.1%)	1 (5.9%)
Very negative	0 (0.0%)	0 (0.0%)	0 (0.0%)

† Of the 7 patients that indicated that the device was not easy to use at home, 4 active arm patients and 1 partially active placebo arm patient also indicated the time spent treating per day was challenging to maintain.

Data are presented as n (%).

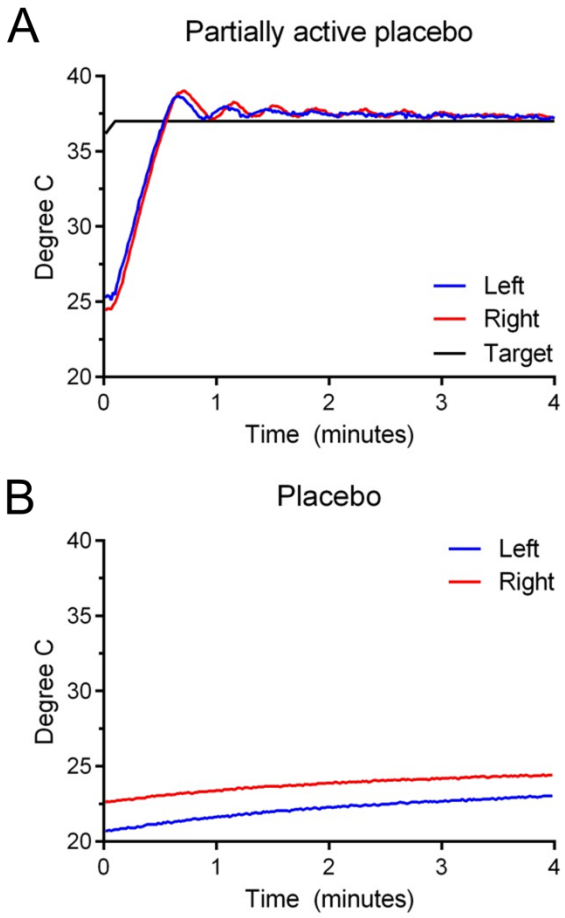
Supplemental Table 1. Patient distributions.

Clinic Location	Active	Inactive placebo	Partially active placebo	
(1) Naval Medical Center	2 (2)	0 (0)	2 (4)	PP
San Diego, CA. USA.	2 (2)	0 (0)	2 (4)	ITT
	3	0	1	w.d.
(2) Duke Pain Medicine	1 (1)	1 (1)	1 (1)	PP
Durham, NC. USA.	2 (2)	1 (1)	1 (1)	ITT
	0	0	1	w.d.
(3) The National Migraine Centre	7 (7)	3 (3)	5 (5)	PP
London, England	7 (7)	3 (3)	6 (6)	ITT
	2	1	0	w.d.
(4) Michigan Head Pain & Neurological Institute	6 (6)	4 (4)	2 (2)	PP
Ann Arbor, MI. USA.	8 (9)	4 (4)	3 (3)	ITT
	2	1	1	w.d.
(5) Carolina Headache Institute	6 (8)	6 (7)	2 (2)	PP
Chapel Hill, NC. USA.	7 (9)	6 (7)	2 (2)	ITT
	1	2	0	w.d.
(6) Headache Wellness Center	6 (6)	4 (4)	0 (0)	PP
Greensboro, NC. USA.	8 (9)	4 (4)	0 (0)	ITT
	0	4	0	w.d.
Total	28 (30)	18 (19)	12 (14)	PP
	34 (39)	18 (19)	14 (16)	ITT
	8	8	3	w.d.

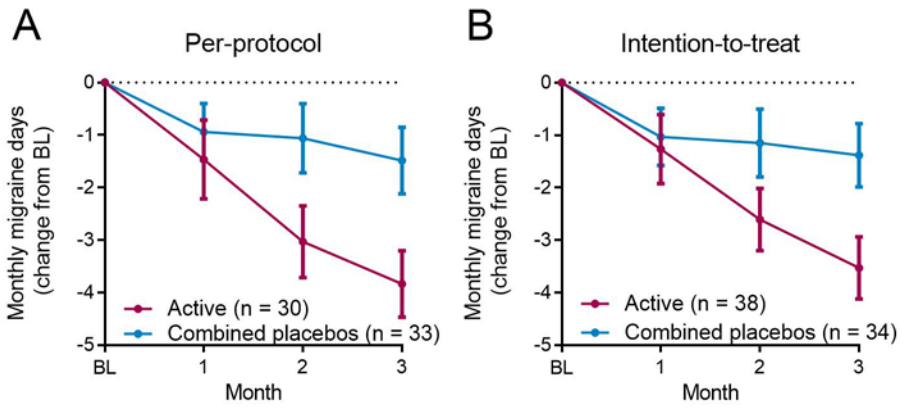
Abbreviations: Per protocol (PP), Intention-to-treat (ITT), withdrew consent during treatment period (w.d.)

† For PP and ITT n values: patients never exceeding 14 headache days during treatment months (all patients).

†† One patient (randomized in error) was withdrawn from the study during the treatment period by the site coordinator.



Supplemental Figure 1. Thermal profiles of the placebo conditions. Time course shows the target temperature *(black)* as well as the actual temperatures recorded by the thermistors located in the left ear piece *(blue)* and the right ear piece *(red)* in representative examples of (A) the partially active placebo protocol and (B) the inactive placebo protocol.

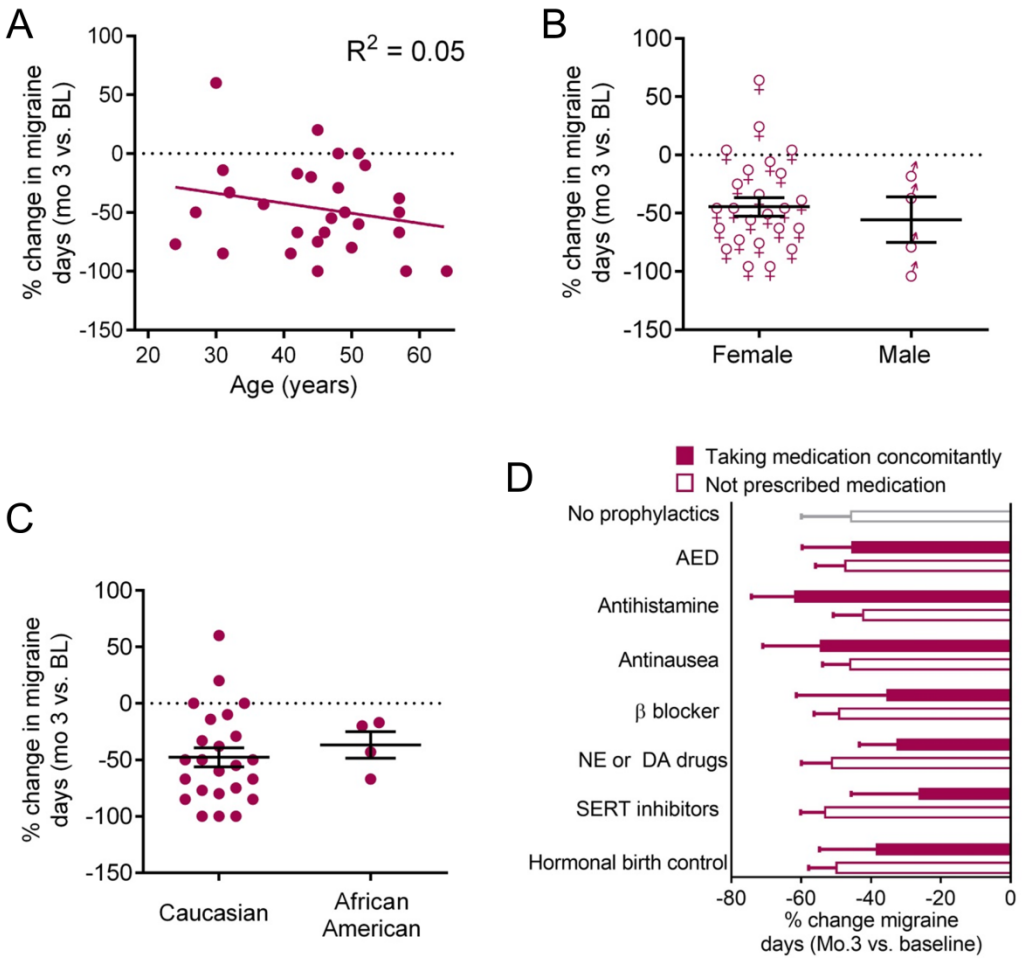


Supplemental Figure 2. Prophylactic efficacy of CVS for episodic migraine comparing active treatment to all placebo conditions combined. Change in migraine days over the course of treatment relative to the baseline (BL) period comparing subjects in the active arm to subjects in both the inactive placebo and the partially active placebo arms combined in (A) the per-protocol analysis and (B) the intention-to-treat analysis. The change in monthly migraine days during the third treatment in the per-protocol group was -3.8 ± 0.6 days for active arm subjects and -1.5 ± 0.6 days for placebo arm subjects, representing a therapeutic gain of -2.3 days, $p = 0.0287$ (Mann Whitney U-test). The change in monthly migraine days during the third treatment in the intention-to-treat group was -3.5 ± 0.6 days for active arm subjects and -1.5 ± 0.6 days for placebo arm subjects representing a therapeutic gain of -2.2 days, $p = 0.0251$ (Mann Whitney U-test). Data are presented as mean ± standard error of the mean.

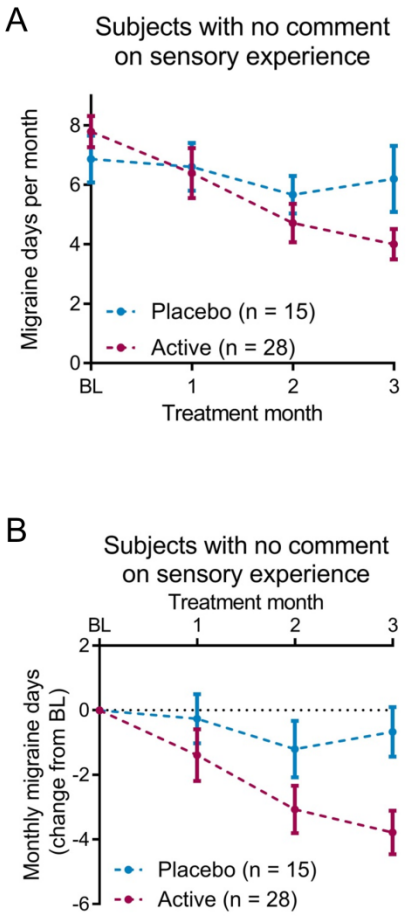
Supplemental Table 2. Primary and secondary outcomes excluding subjects > 15 monthly headaches.

	Per protocol		Intention-to-treat	
	Active	**Placebo**	**Active**	**Placebo**
n	28	18	34	18
Migraine days (baseline compared to third month of treatment)				
Migraine days (baseline)	7.4 ± 0.5	6.7 ± 0.7	7.4 ± 0.4	6.7 ± 0.7
Migraine days (third month)	3.8 ± 0.5	5.8 ± 1.0	4.1 ± 0.5	5.8 ± 1.0
Change in migraine days (third month - baseline)	-3.6 ± 0.7	-0.9 ± 0.7	-3.3 ± 0.6	-0.9 ± 0.7
95% confidence interval	-5.0 to -2.3	-2.3 to 0.5	-4.6 to -1.7	-2.3 to 0.5
Change (third month - baseline), *p*	< 0.0001 *	0.0786	< 0.0001 *	0.0786
Difference between groups (migraine days)	2.8		-2.4	
95% confidence interval	-0.8 to 4.7		-0.4 to 4.3	
Comparison between groups, *p*	0.0142 *		0.0246 *	
Percentage of responders (reduction in monthly migraine days from baseline to third treatment month)				
Responders (≥50% reduction)	16 (57.1%)	6 (33.3%)	18 (52.9%)	6 (33.3%)
Comparison between the 2 groups, *p*	0.1146		0.1772	
% reduction (baseline vs. third month of treatment)	-46.1% ± 7.3%	-13.5% ± 14.2%	-40.8% ± 7.6%	-13.5% ± 14.2%
Comparison between the 2 groups, *p*	0.0336 *		0.0677	
Total monthly headache pain scores (baseline compared to third month of treatment)				
Total pain baseline month	45.8 ± 3.7	35.7 ± 4.1	7.4 ± 0.5	7.4 ± 0.5
Total pain third month	24.5 ± 2.9	26.7 ± 3.5	7.4 ± 0.5	7.4 ± 0.5
p	< 0.0001 *	0.015 *	< 0.0001 *	0.015 *
Change from baseline to third month	-21.3 ± 4.1	-8.9 ± 3.3	-18.7 ± 3.8	-8.9 ± 3.3
95% confidence interval	-29.7 to -12.9	-15.9 to -1.9	-29.0 to -6.0	-15.9 to -1.9
Comparison between the 2 groups, *p*	0.0382 *		0.0966	
Acute anti-migraine prescription drug intake (baseline compared to third month of treatment)				
n (subjects that took antimigraine prescription drugs)	24	16	29	16
Acute anti-migraine drugs intake (baseline)	7.3 ± 0.9	5.5 ± 1.6	7.3 ± 0.7	5.5 ± 1.6
Acute anti-migraine drug intake third month	3.6 ± 0.6	4.1 ± 1.5	3.9 ± 0.6	4.1 ± 1.5
p	< 0.0001 *	0.0747	< 0.0001 *	0.0747
Change from run-in to third month	-3.7 ± 0.7	-1.4 ± 0.8	-3.4 ± 0.6	-1.3 ± 0.8
95% confidence interval	-5.1 to -2.4	-3.0 to -0.2	-5.1 to -2.4	-5.1 to -2.4
p	0.0195 *		0.0464 *	

* $p < 0.05$.



Supplemental Figure 3. Treatment efficacy is not affected by age, sex, race or concomitant medications. (A) The normalized percent-change in migraine days between baseline (BL) and the third month of treatment (mo. 3) plotted as a function of the age in years for each patient (p = 0.253). Scatter plots showing similar distributions of the percent-change in migraine days between baseline and the third month of treatment **(B)** for female and male and **(C)** for Caucasian and African American subjects. **(D)** Summary data showing treatment efficacy is not affected by concomitant medications. Taking no prophylactics (n = 7), taking antiepileptic drugs (AED, n = 8), not taking AED (n = 22), taking antihistamines (n = 7); not taking antihistamines (n = 23), taking anti-nausea medication (n = 3), not taking anti-nausea medication (n = 27), taking β blocker antihypertensive medication (n = 5), not taking β blocker antihypertensive medication (n = 25), taking drugs affecting the norepinephrine (NE) and/or dopamine (DA) systems (n = 7), not taking drugs affecting the NE and/or DA systems (n = 23), taking a drug that blocks the plasma membrane serotonin transporter (SERT inhibitors, n = 7), not taking a SERT inhibitor (n = 23), taking hormonal birth control (n = 8), not taking hormonal birth control (n = 22). All data for panels **A-D** were derived from the active arm per-protocol cohort. Data in panels **B-D** are presented as the mean ± standard error of the mean.



Supplemental Figure 4. Treatment efficacy excluding all subjects who discussed sensory experiences related to device treatment as reason for allocation guess. (A) Migraine days and **(B)** the change in migraine days over the course of treatment relative to the baseline month in the per-protocol groups excluding subjects that mentioned sensory experiences during device treatment as reason for their allocation guess. For panel B, active versus placebo main effect of treatment: $F_{(1,14)} = 7.94$; $p = 0.014$, and treatment by time interaction: $F_{(3,42)} = 2.08$; $p = 0.117$, linear mixed model

\