Received: 6 March 2022 | Accepted: 23 May 2022

DOI: 10.1111/head.14350

RESEARCH SUBMISSION

Migraine treatment with external concurrent occipital and trigeminal neurostimulation—A randomized controlled trial

Stewart J. Tepper MD[1,2] | Brian Grosberg MD[3,4] | Oved Daniel MD[5] | Deena E. Kuruvilla MD, FAHS[6] | Gabriel Vainstein MD[7] | Lisa Deutsch PhD[8] | Roni Sharon MD[9,10]

[1]Geisel School of Medicine at Dartmouth, Hanover, New Hampshire, USA

[2]Dartmouth Headache Center, Lebanon, New Hampshire, USA

[3]Hartford Healthcare Headache Center, Ayer Neuroscience Institute, West Hartford, Connecticut, USA

[4]Department of Neurology, University of Connecticut School of Medicine, Farmington, Connecticut, USA

[5]Headache and Facial Pain Clinic, Ramat-Aviv Medical Center, Tel-Aviv, Israel

[6]Westport Headache Institute, Westport, Connecticut, USA

[7]Kahn-Sagol-Maccabi Research and Innovation Institute, Maccabi Healthcare Services, Tel Aviv, Israel

[8]BioStats Statistical Consulting Ltd., Modiin, Israel

[9]Tel-Aviv University Sackler School of Medicine, Tel-Aviv, Israel

[10]Department of Neurology, Chaim Sheba (Tel HaShomer) Medical Center, Ramat Gan, Israel

Correspondence
Stewart J. Tepper, MD, Neurology Department, Dartmouth-Hitchcock Medical Center, 1 Medical Center Drive, Lebanon, NH 03756, USA.
Email: sjtepper@gmail.com

Funding information
Neurolief Ltd

Abstract

Objective: To evaluate the efficacy and safety of concurrent non-invasive stimulation of occipital and trigeminal nerves in acute treatment of migraine with or without aura.

Background: Non-invasive neuromodulation devices stimulating a single peripheral nerve or anatomic distribution are routinely used by patients with migraine refractory to the first-line drugs or those who opt out of pharmaceutical treatment. Concurrent occipital and trigeminal stimulation was described in an invasive setting, and its safety cost outweighed its efficacy gain. This study evaluated the efficacy and safety of an external concurrent occipital and trigeminal device in acute treatment of migraine.

Design and Methods: This was a randomized, sham-controlled, double-blind, multicenter trial. Patients 18 years of age or older who met the International Classification of Headache Disorders (2018) diagnostic criteria for migraine with or without aura, reported 1–6 migraine attacks per month, and other headaches no more than 6 days per month were enrolled. Of 131 intention-to-treat participants (67 and 64 in the active and sham groups, respectively), 109 (50 and 59 in the active and sham groups, respectively) treated at least one migraine episode. Reduction of migraine headache (pain relief) 2 h after treatment initiation was the primary efficacy endpoint. Pain relief at 1 h, and pain freedom and relief in most bothersome symptom at 2 h after treatment initiation were the secondary endpoints. Freedom from most bothersome symptom at 2 h and sustained pain freedom 24 h after treatment initiation were among the exploratory endpoints.

Results: Sixty percent of participants (30/50) in the active arm reported pain relief at 2 h after initiation of the first eligible treatment (primary outcome) compared to 37% (22/59) in the control arm (difference, 23%; 95% confidence interval [CI], 2%–41%; $p = 0.018$). Pain freedom at 2 h without rescue medication was reported by 46% (23/50) of participants in the active arm and by 12% (7/59) of participants in the sham arm ($p < 0.001$). Pain freedom 2 h after the treatment and, subsequently, at 24 h, was reported by 4.25 times more participants in the active arm (36%; 18/50) than in the

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; eCOT-NS, external combined occipital and trigeminal neurostimulation; e-TNS, external trigeminal nerve stimulator; FA, full analysis; GEE, generalized estimating equations; IRB, institutional review board; ITT, intention to treat; MBS, most bothersome symptom; mITT, modified intention to treat; nVNS, non-invasive vagus nerve stimulation; OUS, outside the United States; PP, per protocol; REN, remote electrical neuromodulation; RIME, Relivion in Migraine study; SD, standard deviation; US FDA, US Food and Drug Administration.

sham arm (8%; 5/59). The 28% difference was statistically significant (95% CI, 1%–43%; $p < 0.001$). A 4.25-fold difference was also observed comparing the proportion of participants free from pain and most bothersome symptom 2 h after the stimulation (47% [17/36] and 11% [5/45] in the active and sham arms, respectively; 95% CI, 14%–54%; $p < 0.001$). Adverse events were not serious or severe. All study-related events resolved without treatment.

Conclusion: External concurrent occipital and trigeminal neurostimulation is a well-tolerated, safe, and effective migraine treatment that provided a fast and durable relief and freedom from migraine pain and associated symptoms in a randomized setting. The observed safety and performance suggest external concurrent occipital and trigeminal neurostimulation is a viable alternative to the currently available acute migraine treatments.

Trial registration: clinicaltrials.gov identifier NCT03631550.

KEYWORDS
headache, migraine, neuromodulation, neurostimulation, occipital nerve, trigeminal nerve

INTRODUCTION

Migraine is the second most common neurologic disorder affecting more than 1 billion people worldwide.[1,2] It is two to three times more likely to be experienced by women,[3] with prevalence peaking at 35–39 years of age in both sexes.[4]

Migraine spares no aspect of everyday life, and substantial impairment is registered in professional, academic, and social activities of people with migraine.[5,6] Often a debilitating condition, migraine is a prominent contributor to the global neurological disability-adjusted life years, second only to stroke.[7] It is also the seventh highest cause worldwide of years lost due to disability,[8] third in both sexes under 50.[2]

The underlying biology and pathophysiology pathways of migraine are complex,[9] which may explain the considerable rate of failure of the current first-line acute therapy agents, such as triptans, to provide relief of headache, the main migraine symptom.[10] Severe baseline headache as well as photophobia, nausea, and phonophobia, the three most bothersome symptoms (MBS) of migraine,[11] predict poor response to triptans, and nausea may be further exacerbated by these agents.[12–14] Switching to a different drug, class, or formulation may benefit some people.[14] However, a large fraction of patients remain refractory to pharmacological treatment, contraindications prevent use of certain agents in some people, and a minority of patients may experience uncommon but potentially harmful treatment intolerance.[15–17] Treatment alternatives are warranted.

Use of unifocal non-invasive neuromodulation devices is gaining acceptance in migraine care[18–27] and a non-invasive supraorbital trigeminal stimulation device (external trigeminal nerve stimulator [e-TNS])[18–20] was cleared by the US Food and Drug Administration (US FDA) for acute and preventive migraine treatment. Concurrent trigeminal and occipital stimulation was described only in an invasive setting.[28,29] Although the potential gain in efficacy was evident in the early clinical work and seemed to hold promise for further research, the discouragingly high rate of complications associated with the invasive nature of the procedure[30] may have dampened the enthusiasm of the technology developers.

The non-invasive Relivion MG system[30] (Figure 1), US FDA cleared[31] and CE-marked following the study described below, applies non-invasive external concurrent occipital and trigeminal neurostimulation (eCOT-NS) in a bid to harness the potential strengths of multifocal neural action and to mitigate the weaknesses

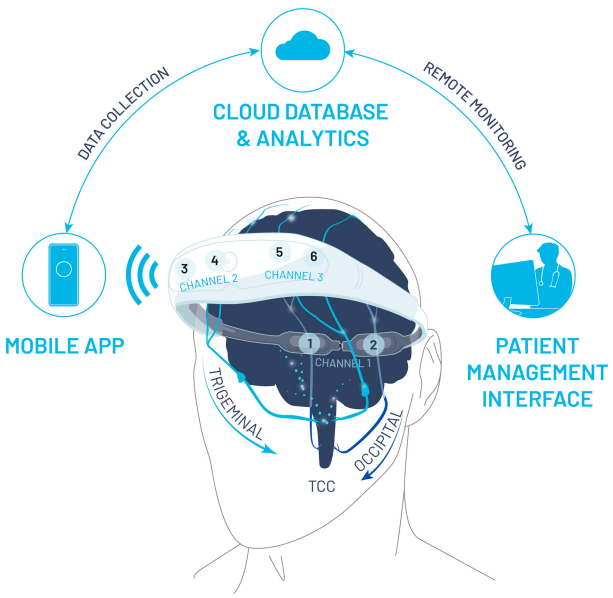

FIGURE 1 External combined occipital and trigeminal neurostimulation (eCOT-NS) system. TCC, trigeminocervical complex; Channel 1, occipital stimulation channel; Channel 2 and Channel 3, trigeminal (supraorbital/supratrochlear) stimulation channels; numbers 1–6 represent the six electrodes.

of the invasive approach. In this, randomized, double-blind, sham-controlled, multi-center Relivion in Migraine (RIME) study, efficacy and safety of the eCOT-NS device were evaluated in adults with migraine with or without aura. The primary endpoint was pain relief 2 h after treatment initiation. We hypothesized that the proportion of patients reporting pain relief level 2 h after treatment initiation will be higher in the active arm. The trial also assessed pain freedom and MBS absence 2 h after treatment initiation[32–34] in secondary and exploratory analyses, respectively. Sustained response was evaluated at 24 h after treatment initiation. This publication contains the primary analysis of data collected in the trial.

DESIGN AND METHODS

Study design and participants

This was a prospective, randomized, sham-controlled, double-blind clinical trial approved by institutional review boards (IRB) in the United States (Western Institutional Review Board, Inc. and Dartmouth-Hitchcock Medical Center) and by the Ethics Committee of the Israeli Ministry of Health. The trial was prospectively registered on clinicaltrials.gov, in accordance with the requirements in 42 CFR Part 11 (registration number NCT03631550). Patients known to sites participating in the study as migraine, and those responding to IRB-approved advertisements could be recruited. Written informed consent was obtained from all participants. The study was open for enrollment at six sites in the United States and six sites outside the United States (OUS), in Israel. The first participant provided informed consent on November 29, 2018, and the last participant made the last visit on August 4, 2020.

Investigators or site team members delegated by the investigators obtained written informed consent and assessed eligibility for this study. Patients 18 years of age or older who met the International Classification of Headache Disorders, 3rd edition diagnostic criteria for migraine with or without aura, reported one to six migraine attacks per month and other headaches no more than 6 days per month, and were willing to and capable of complying with the study requirements could be enrolled. Main exclusion criteria were onabotulinumtoxinA treatment in the head region in the 3 months preceding screening; supraorbital or occipital nerve blocks in the month preceding screening; history of chronic migraine, new daily persistent headache, or chronic tension-type headache in the 6 months preceding screening; >10 headache days per month; medication overuse headache at the time of screening; opioid or barbiturate use in the month preceding screening; metal/shrapnel or electrical devices implanted in the head (not including dental implants), a cardiac pacemaker, or an implanted or wearable defibrillator; parenteral infusions for migraine in the 2 weeks preceding screening; uncontrolled epilepsy; history of neurosurgical interventions; implanted neurostimulators, surgical clips (above the shoulder line) or any medical pumps; skin lesion or inflammation at the region of the stimulating electrodes; personality or somatoform disorder; documented history of cerebrovascular events; brain or facial trauma in the 3 months preceding screening; and participation in a previous study of the investigational device. Full list of the study eligibility criteria is provided in (Table 1).

The study included a 28-day screening period, at the beginning of which the participants completed a 3-month–retrospective migraine history questionnaire. During a 28-day run-in period, participants were asked to complete a run-in diary describing the migraine and headache days that occurred during that time.

Participants who completed the questionnaire and diary and were otherwise eligible for the study, as confirmed by the study investigators, were randomly allocated by the sites, through an interactive Web response system, 1:1 to either active or sham groups using a permuted block method stratified by center. The randomization scheme was prepared by the study statistician using the SAS software (version 9.4; SAS Institute) random number procedure. Randomization block size was random and known only to the unblinded statistician and the sponsor unblinding party not involved in the conduct of the study. The study electronic data collection system device management module assigned serial numbers of each study device, active or sham, to a participant number, according to the prespecified randomization scheme. Device appearance, packaging, and labeling were identical in both study arms.

After reading the device manual and watching an instructional video, participants trained on use of the device, the device-linked smartphone application, and completion of the outcome diary. After training, participants were equipped with their allocated device (same on which they were trained) and a dedicated smartphone.

Devices provided to participants randomized to the investigational arm administered symmetrical biphasic waveforms with phase duration of 330–400 ms at an 80-Hz pulse frequency and generated peak output current of up to 6 mA for the bilateral V1 ophthalmic trigeminal branches (bilateral supraorbital/supratrochlear) and up to 12 mA for the cervically derived bilateral greater occipital nerves. Devices assigned to participants in the control arm administered symmetrical biphasic waveforms with phase duration of 70–100 ms at a 0.33-Hz pulse frequency and generated peak output current of up to 5 mA for the trigeminal branches and up to 10 mA for the occipital nerves. Software discontinued stimulation after 60 min in both arms.

In the next 14 days (maximum), all participants self-administered one to two 30–60 min–long stimulations outside a migraine episode, for training, and completed the outcome diary. Failure to self-administer at least one treatment at a minimal stimulation intensity of 2 mA and/or complete the diary excluded participants from further involvement in the study.

Participants were allowed to take their prophylactic medications as prescribed and rescue medications as needed during run-in and self-training and were asked to document this in the participant diary.

During the treatment period that ensued after self-training and lasting until up to 70 ± 10 days after randomization, all participants were instructed to self-administer treatment at attack onset in up to five migraine episodes, excluding migraine attacks

TABLE 1 Eligibility criteria

Inclusion
Participants 18 years of age and older
Participant meets the ICHD-3 (2018) diagnostic criteria for migraine with or without aura
Participant reports 1–6 migraine attacks per month; other headaches no more than 6 days per month
Participant is willing to and capable of complying with the specified study requirements, provided written informed consent, can complete the electronic diaries, and can be contacted by telephone
Exclusion
Participant having received onabotulinumtoxinA treatment in the head region in the prior 3 months
Participant having received supraorbital or occipital nerve blocks in the prior month
Past 6 months of chronic migraine, new daily persistent headache, and chronic tension-type headache per ICHD-3 (2018) diagnostic criteria
Participant has >10 headache days per month
Current medication overuse headache
Use of opioid medications in the prior 1 month
Use of barbiturates in the prior 1 month
Implanted metal/shrapnel or electrical devices in the head (not including dental implants), a cardiac pacemaker, or an implanted or wearable defibrillator
Received parenteral infusions for migraine within the previous 2 weeks
Participant has known uncontrolled epilepsy
History of neurosurgical interventions
Participant with implanted neurostimulators, surgical clips (above the shoulder line) or any medical pumps
Current substance use disorders
Participant is participating in any other clinical study
Skin lesion or inflammation at the region of the stimulating electrodes
Personality or somatoform disorder
Pregnancy or lactation
Women with childbearing potential without medically acceptable method of contraception (NOTE: Females of childbearing potential must have a negative pregnancy test)
Documented history of cerebrovascular event
Participant with recent brain or facial trauma (occurred less than 3 months prior to this study)
Participant participated in a previous study with the Relivion device
The participant does not have the basic cognitive and motor skills needed to operate a smartphone
Participant with head circumference smaller than 51 cm or head circumference larger than 60 cm
Participant with other significant pain problem that in the opinion of the investigator may confound the study assessments

Abbreviation: ICHD-3, International Classification of Headache Disorders, 3rd edition.

upon awakening. For study treatment to be eligible, it had to be initiated as soon as possible but before 30 min from the headache onset, had to be administered for at least 30 min at a minimal intensity of 2 mA, no analgesics or other pain relief drugs could be taken and/or no cannabis products could be consumed within 4 h before treatment initiation, and more than 48 pain-free hours had to have passed since the previous migraine episode. Participants had to refrain from taking rescue medication and/or consuming cannabis for at least 2 h after initiating treatment. There were no other limitations on use of prescribed or rescue anti-migraine treatments.

Assessments

The primary efficacy endpoint was reduction of migraine headache (pain relief) 2 h after treatment initiation. The participant diary scored migraine headache pain on a four-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Participants recorded baseline pain and pain levels 1, 2, and 24 h after initiating treatment. Participants identified their MBS (nausea, photophobia, phonophobia, or none) before treatment and rated it present or absent and improved or not improved at 1 and 2 h after initiating treatment. Presence or absence of aura was also captured in the diary. Rescue medication intake was recorded at each time point.

Outcome measures

Endpoint analysis was performed on data from the first eligible treated migraine episode. A separate, ancillary analysis included data from all eligible treated episodes.

For the primary efficacy endpoint, participants were considered to have achieved pain relief if they reported a reduction of migraine headache pain from severe or moderate (2, 3) to mild or no pain (1, 0) or from mild (1) to no pain (0) 2 h after treatment initiation. This also applied to pain relief 1 h after treatment (secondary endpoint).

Participants scoring pain as "none" on the Likert scale at 2 h after treatment initiation were deemed pain-free for 2-h pain freedom (secondary endpoint). Participants reporting MBS freedom at 2 h were deemed MBS-free for the respective exploratory efficacy analysis. Use of rescue medication before 2 h from treatment initiation was interpreted as failure and participants who took rescue medication before 2 h from treatment initiation were interpreted to have failed to respond to treatment.

Sustained pain relief was defined as pain relief at 2 h from study treatment initiation without rescue medications and absence of moderate–severe headache in the next 22 h without using rescue medication.

Sustained pain freedom was defined as pain freedom at 2 h from study treatment initiation without rescue medications and pain freedom in the next 22 h without using rescue medication.

Adverse events (AEs) and device deficiencies were documented. Event severity was classified as mild (participant is aware of a sign or symptom, but it is easily tolerated), moderate (discomfort or interference with usual activity), or severe (incapacitating, with inability to engage in usual activity).

Statistical analyses

The sample size of 200 (100 per arm) with allowance for 10% attrition was calculated to test the null hypothesis of equal response rates with 80% power at a 5% level of significance, assuming that 45% of participants in the active treatment arm would have successful pain relief versus 25% with the sham.

The manufacturer identified a technical issue with the device during the course of the investigation. A corrective and preventive action was implemented by May 31, 2019. The issue was unlikely to have a significant impact on participant safety but could have affected treatment efficiency and, consequently, could have had significant impact on the scientific value of the data collected. To mitigate this risk, data of participants who completed the study or left the study without administering a treatment (including for training purposes) prior to May 31, 2019, were prospectively excluded from the intention-to-treat (ITT) analysis set. Both investigators and sponsor remained blinded to the results at this time. A request for a compensatory increase in the number of enrolled participants was submitted to and approved by all administrative bodies providing oversight.

In 2020, the COVID-19 pandemic severely affected trial recruitment and conduct and forced early trial stoppage before accrual of the initially approved number of participants could be completed, despite efforts of sponsor and investigators. On July 2nd, 2020, a premature trial termination notice was sent to all parties. Adaptations were made to the statistical analysis, before unblinding, in accordance with[35] and concurred by the US FDA. Eventually, the ITT population included all randomized participants, and safety analyses were conducted on the ITT dataset. A sensitivity safety analysis was conducted on the full analysis (FA) set, which contained data of participants excluded as explained above.

The modified ITT (mITT) dataset included data of all participants from the ITT analysis dataset who treated at least one eligible episode (excluding training sessions) and served as the principal dataset for the efficacy analyses. Participants in the mITT population were analyzed as treated.

The per-protocol (PP) analysis set included all participants in the mITT population who had no major protocol deviations. Major protocol deviations in this study included but were not limited to:

- Completion of baseline diary reporting more than 30 min before treatment initiation for the first eligible episode treatment or at any time after the first eligible episode treatment initiation; and
- Completion of outcome diary outside of window for the first eligible attack

Participants in the PP population were analyzed as treated.

Data were analyzed using SAS software. Continuous variables were summarized by a mean, standard deviation, minimum, and maximum and categorical variables by a count and percent. For continuous variable comparisons, an independent-samples t-test or analysis of covariance (ANCOVA) were used; when all valid episodes were analyzed, repeated measures ANCOVA was used. Appropriateness of each analysis method was verified visually using plots. For comparison of categorical variables in the first valid episode, the chi-squared test was used; when all valid episodes were analyzed, a repeated measures generalized estimating equations (GEE) model with identity link function and binary distribution, was used to account for within-participant correlation (variance components covariance structure). All statistical tests were two-sided. Required significance level of findings was lower than 5% ($p < 0.05$); nominal p values were presented. The hierarchy approach was adopted to control for type I error due to multiple endpoint testing. Thus, the primary endpoint was tested, and only if $p < 0.05$ were the following endpoints tested. For the three secondary endpoints, the Benjamini–Hochberg step-up method was used to adjust p-values to control familywise type I error rate.

Primary and secondary efficacy endpoints were summarized by a count and percentage and presented for both study groups with a two-sided 95% exact confidence interval (CI). The study arms were compared with a chi-squared test.

For primary endpoint analysis, when pain level at 2 h was not recorded, pain at 1 h was used instead. When the pain level was missing at both times, the participant was considered as not having pain reduction. Additional sensitivity analyses of the primary endpoint were performed to assess impact of missing data on study outcome using the following imputation methods for binary data:

- Participants with missing pain level at the 2-h assessment in their first treated valid episode were excluded from analysis.
- Participants with missing pain level at the 2-h assessment in their first treated valid episode were considered as having pain improvement.
- Participants with missing pain level at the 2-h assessment in their first treated valid episode were considered as having no pain improvement.

The study arms were compared with a chi-squared test, Fisher's exact test, and Mantel-Haenszel test. When all valid episodes were analyzed, a repeated measures GEE model with identity link function and binary distribution was used to account for within-participant correlation (variance components covariance structure).

Migraine pain levels were also reported as a numerical score (pseudo-continuous): "No pain" = 0, "Mild" = 1, "Moderate" = 2, and "Severe" = 3, as in other studies.[36] If rescue medication was

used within the 1–2-h– or 24-h–window, score at the corresponding hours post-treatment after rescue intake was set to the baseline value. The change from baseline in pain level at each time point was modelled with ANCOVA; baseline pain level and site were entered as covariates. Least-squares means were compared between groups. When all valid episodes were analyzed, a repeated statement (with variance components covariance structure) was added to the model (SAS PROC MIXED).

Blinding assessment and poolability of US and OUS data were analyzed by adding the variables to a logistic regression model; type III *p* values of the interaction terms with treatment group are reported. Incidence of AEs was compared between groups with a chi-squared test or Fisher's exact test, as appropriate.

RESULTS

Participant disposition and demographics

Of 245 people who provided informed consent to participate, 187 were found eligible and randomly assigned to receive active ($n = 94$) or sham ($n = 93$) eCOT-NS. Twenty-seven participants assigned to the active arm and 29 participants assigned to the sham arm who completed the study or did not treat any migraine episode before May 31, 2019, were excluded from analysis. Study participant disposition is in Figure 2.

Mean age was 40.3 years (range, 20–70.5, standard deviation [SD] = 12.7). Eighty-three percent (109/131) were female. There were no statistically significant differences in demographic characteristics between study arms (Table S1 in supporting information), except for body mass index (BMI), which was higher in the active arm (27.2 ±6.8 and 24.8 ±5.1, respectively, $p = 0.023$). There were no statistically significant differences between study arms in migraine characteristics, including mean onset age, aura presence, number of participants on prophylaxis at baseline (Table S2 in supporting information); number of migraine days, number of all migraine episodes, those preceded by an aura, and number of headaches that occurred during the run-in period (Table S3 in supporting information). Photophobia was the most common MBS in both groups (Table S4 in supporting information), matching demographics of other acute medication and device studies, and suggesting that the study observations are generalizable despite early termination.[11]

Twenty-two participants did not treat any eligible episode, leaving 109 (50 in the active and 59 in the sham group) analyzable

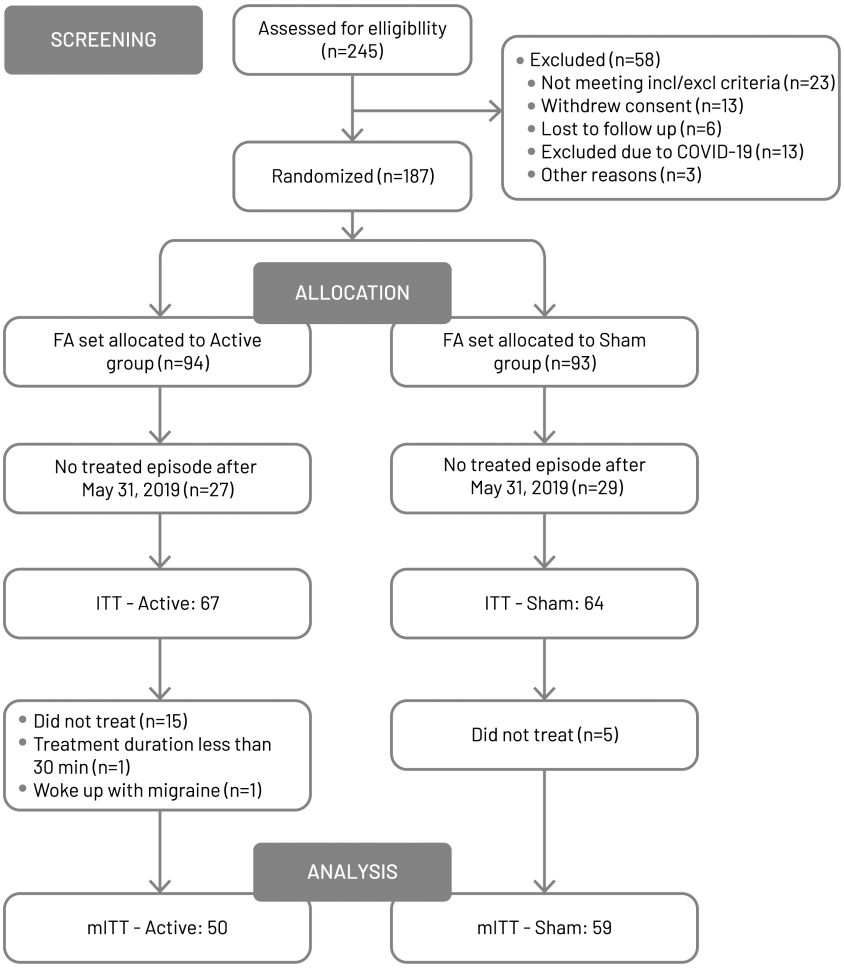

FIGURE 2 Disposition of participants. FA, full analysis; ITT, intention to treat; mITT, modified intention to treat.

participants in the mITT analysis set, and one participant from the sham group was removed from the PP analysis set due to reporting baseline pain level after initiation of treatment for the first eligible episode.

Two or more eligible episodes were treated by 58% (29/50) of participants in the active group and 61% (36/59) of participants in the sham group in the mITT analysis set. More specifically, two episodes were treated by 11 (22%) and 15 (25%) participants, three episodes—by 11 (22%) and 11 (19%) participants, four episodes—by 3 (6%) and 6 (10%) participants, and five episodes—by 4 (8%) and 4 (7%) participants in the active and sham group, respectively.

Aura was reported by 24% (12/50) of mITT participants in the active group and 27% (16/59) of participants with the sham ($p = 0.710$) in the first treated valid episode (first eligible treatment). Aura frequency was consistent with migraine epidemiology, suggesting a characteristic study population.

Pain and MBS relief

In the primary endpoint analysis, a substantial and statistically significantly greater proportion of participants in the active arm (30/50 participants—60%; 95% CI, 46%–72%) reported 2-h pain relief after initiation of the first eligible treatment than in the sham arm (22/59 participants—37%; 95% CI, 26%–50%) in the mITT analysis (absolute difference, 23%; $p = 0.018$; see Figure 4). Adjusting for missing values (three in the active and two in the sham) in a sensitivity analysis did not alter the result (Table S5 in supporting information). Data from US and OUS sites were similar and acceptable for pooling.

The proportion of participants reporting pain relief 1 h after initiation of the first eligible treatment, a secondary endpoint, was greater in the active arm (42%; 21/50) than in the sham arm (25%; 15/59; $p = 0.068$). In an analysis carried out in accordance with the US FDA guidance on "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency,"[35] migraine headache pain level was transformed into a pseudo-continuous numerical score (Figure 3). Upon rescue medication intake the score was set to the baseline value. In this analysis, mean percent pain reduction from baseline was 29% and 14% after 1 h ($p = 0.012$) in the active and sham arms, respectively (Table 2 and Table S6 in supporting information). Expanding this analysis to include datapoints from all eligible treatments produced a greater difference between the study arms (Table 3 and Table S7 in supporting information).

Two hours after initiation of the first eligible treatment, 81% (29/36) of participants in the active arm and 60% (27/45) of participants in the sham arm reported improvement in their MBS ($p = 0.047$), another secondary endpoint.

Pain and MBS freedom

Freedom from pain 2 h after initiation of the first eligible treatment without any rescue medication (secondary endpoint, Figure 4) was reported by 46% (23/50) of participants in the active arm and by 12% (7/59) of participants in the sham arm (absolute difference, 34%; $p < 0.001$). Differences in freedom from migraine headache

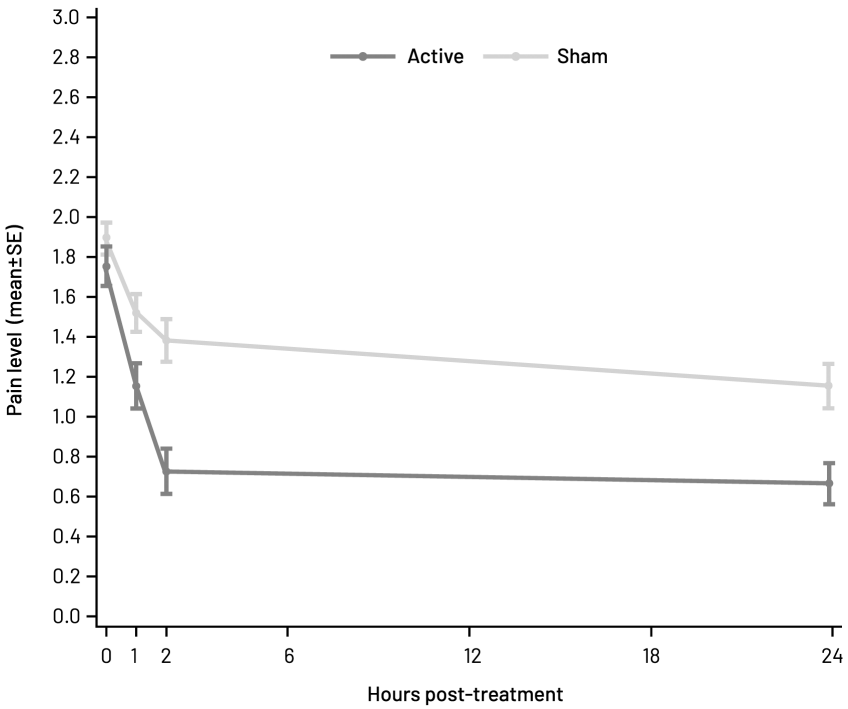

FIGURE 3 Pain relief over time after treatment.

TABLE 2 Change in pain level over time—first eligible treatment—mITT

Time point	Study arm (as randomized)	Least-squares mean (95% CI)	*p*-value*
1 h	Active	−0.6 (−0.9 to −0.4)	<0.001
	Sham	−0.3 (−0.5 to −0.1)	0.010
	Diff. (Active-Sham)	−0.3 (−0.6 to −0.1)	0.012
2 h	Active	−1.1 (−1.4 to −0.8)	<0.001
	Sham	−0.4 (−0.7 to −0.1)	0.003
	Diff. (Active-Sham)	−0.6 (−1.0 to −0.3)	<0.001
24 h	Active	−1.1 (−1.4 to −0.8)	<0.001
	Sham	−0.7 (−1.0 to −0.4)	<0.001
	Diff. (Active-Sham)	−0.4 (−0.7 to −0.0)	0.031

Abbreviations: CI, confidence interval; mITT, modified intention to treat.
*ANCOVA.

TABLE 3 Change in pain level over time—all eligible treatments—mITT

Time point	Study arm (as randomized)	Least-squares mean (95% CI)	*p*-value*
1 h	Active	−0.8 (−1.0 to −0.6)	<0.001
	Sham	−0.3 (−0.5 to −0.1)	<0.001
	Diff. (Active-Sham)	−0.5 (−0.7 to −0.3)	<0.001
2 h	Active	−1.0 (−1.3 to −0.8)	<0.001
	Sham	−0.5 (−0.7 to −0.2)	<0.001
	Diff. (Active-Sham)	−0.6 (−0.8 to −0.4)	<0.001
24 h	Active	−1.1 (−1.4 to −0.8)	<0.001
	Sham	−0.9 (−1.2 to −0.7)	<0.001
	Diff. (Active-Sham)	−0.2 (−0.4 to 0.1)	0.164

Abbreviations: CI, confidence interval; mITT, modified intention to treat.
*Repeated measures mixed model.

pain between the arms were substantial and statistically significant also at 1 h (absolute difference, 15%; $p = 0.012$) and at 24 h (absolute difference, 27%; $p = 0.044$) from treatment initiation (Table 4).

In the ad hoc assessment of sustained pain freedom, active treatment showed a prominent therapeutic gain of 28% over sham stimulation ($p < 0.001$; Figure 4 and Table 4). Exploratory analysis of pain freedom in all eligible treatments produced similar results (Table 4).

Freedom from MBS, an exploratory endpoint, was reported by 75% (27/36) and 47% (21/45) of participants in active and sham arms, respectively, at 2 h from treatment initiation (absolute difference, 28%; $p = 0.010$). Therapeutic gain of active over sham was also evident in the exploratory analysis of freedom from MBS in all eligible treatments at 1 h (52% vs. 21%; $p = 0.001$) and 2 h (70% vs. 39%; $p = 0.001$) after treatment initiation.

Finally, a significantly greater proportion of participants in the active arm reported both pain and MBS freedom 2 h after initiation of their first eligible treatment, an exploratory prespecified endpoint (Figure 4 and Table 5). Superiority of the active treatment was evident after pooling all eligible treatments (Table 5).

Pain relief and pain freedom in participants with moderate or severe pain at baseline

The differences observed between the study arms in the mITT assessment of pain relief and pain freedom in the first eligible treatment were more pronounced when only participants with baseline moderate-severe pain were included in an exploratory analysis at all time points (Table 6). Analysis of pain freedom showed greater absolute differences between study arms compared to the mITT analysis at all time points after treatment initiation (Table 6).

Rescue medication

After the first eligible treatment, 29% of participants (14/48) in the active group and 53% of participants (30/57) in the sham group reported rescue medication use ($p = 0.015$).

Safety and tolerability

None of the AEs reported in the study were serious or severe (Table 7). None of the events were caused by device deficiencies. All device- or procedure-related events resolved without treatment.

In the ITT analysis, 21 AEs were reported in 10 participants, 8 in the active arm (incidence, 12%; 8/67), and 2 with sham (incidence, 3%; 2/64). Differences in the incidence between groups were not statistically significant ($p = 0.097$). Sixteen events were causally, probably, or possibly related to the study device (of these seven occurred in five participants randomized to active arm; and nine were reported in two participants with sham).

In the FA analysis dataset, 51 AEs were reported in 21 participants, 12 in the active arm (incidence, 13%; 12/94), and 9 with sham (incidence, 10%; 9/93). Differences in incidence between groups were not statistically significant ($p = 0.503$).

Two participants in the ITT population assigned to the active arm at the same study site left the study during the training phase, citing inability to tolerate stimulation as reason for consent withdrawal. One additional participant withdrew from the study during the training phase citing discomfort during stimulation.

Blinding assessment

The majority of participants (70%) did not guess their treatment assignment. Only 10% of participants (6/59) in the sham group and 38% (19/50) in the active group correctly guessed their

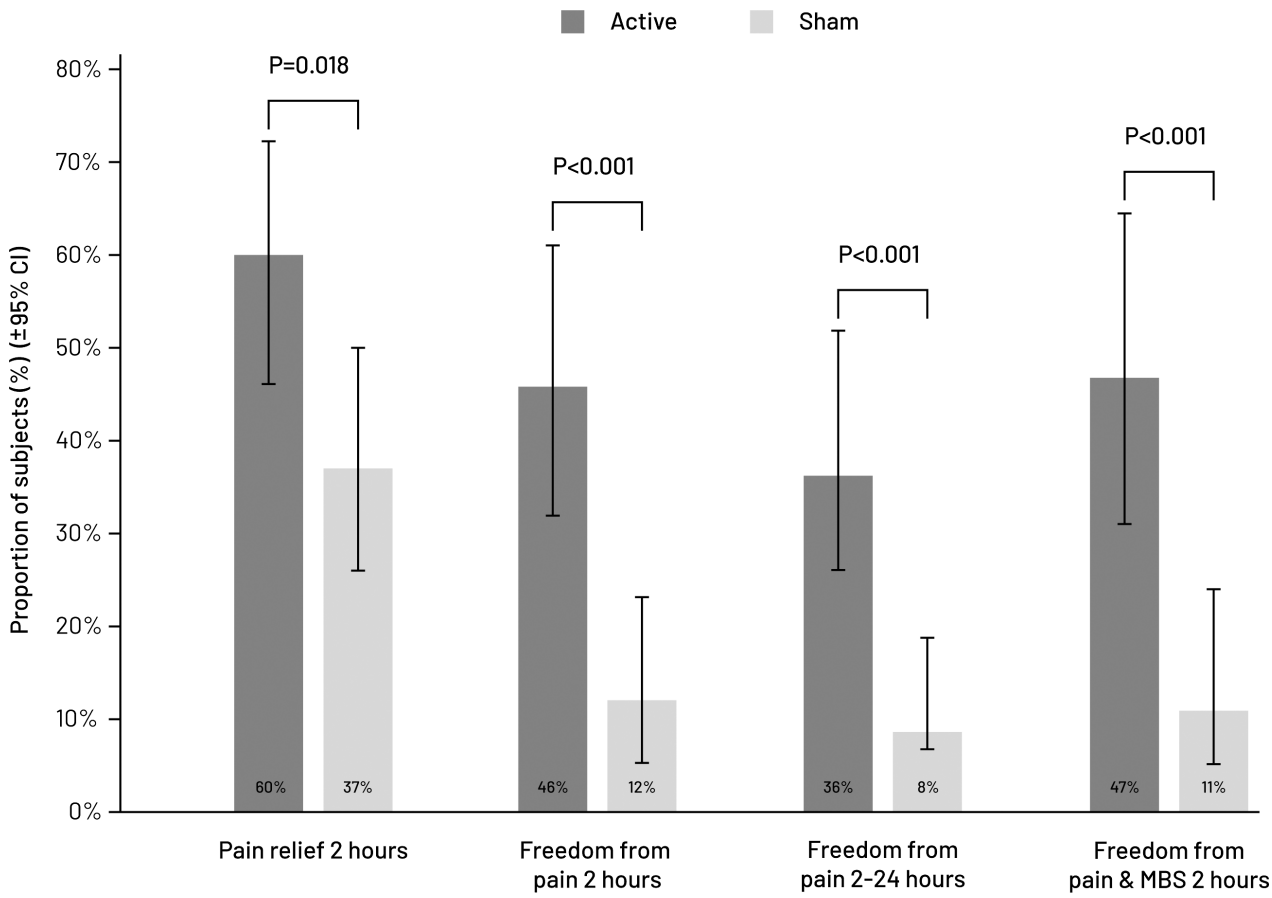

FIGURE 4 1st eligible treated episode mITT, left to right: Pain relief 2 h post-treatment; Freedom from pain 2 h post-treatment—; Freedom from pain 2–24 h post-treatment; Freedom from pain and MBS 2 h post-treatment. CI, confidence interval; MBS, most bothersome symptom; mITT, modified intention to treat.

TABLE 4 Freedom from pain—mITT

	First eligible treatment							All eligible treatments						
	Active			Sham				Active			Sham			
	n	*N*	%	n	*N*	%	*p*-value*	*n*	*N*	%	*n*	*N*	%	*p*-value**
2 h	23	50	46%	7	59	12%	<0.001	43	108	40%	17	130	13%	<0.001
1 h	9	50	18%	2	59	3%	0.012	27	108	25%	4	130	3%	<0.001
24 h	28	50	56%	17	59	29%	0.004	58	108	54%	50	130	38%	0.070
2–24 h	18	50	36%	5	59	8%	<0.001	32	108	30%	13	130	10%	0.002

Abbreviation: CI, confidence interval; mITT, modified intention to treat.

*χ^2 test; **Generalized estimating equations model.

assignment, demonstrating that the sham was effective in maintaining blinding.

DISCUSSION

The results of this pivotal randomized, double-blind, sham-controlled trial attest to the superiority of eCOT-NS compared to sham stimulation. The study met its primary endpoint by showing a statistically significant difference between the groups in 2-h pain relief. Higher mean BMI of participants in the active treatment arm, the only parameter not balanced between the groups, does not predict better migraine treatment outcome, hence, does not interfere with outcome interpretation.

Therapeutic gains of the eCOT-NS were also consistently evident in the secondary and exploratory analyses. Superiority of active stimulation over sham in providing pain freedom was seen as early as 1 h after treatment initiation. Differences became much more apparent 2 h after treatment initiation, with active stimulation presenting a 34% gain over sham (46% and 12%, respectively). Thirty-six percent were pain-free at 2 h and reported freedom from pain 24 h after the treatment, a sizable 27% advantage over the 9% of participants

TABLE 5 Freedom from pain and MBS—first eligible treatment—mITT

	Active			Sham			
	n	*N*	%	*n*	*N*	%	*p*-value
2 h							
First eligible treatment	17	36	47%	5	45	11%	<0.001***
All eligible treatments	34	86	40%	10	94	11%	<0.001**
1 h							
First eligible treatment	7	38	18%	2	46	4%	0.072*
All eligible treatments	19	90	21%	2	97	2%	0.003**

Abbreviations: MBS, most bothersome symptom; mITT, modified intention to treat.
*Fisher's exact test; **Generalized estimating equations model; ***χ^2 test.

TABLE 6 Pain relief and freedom from pain in participants with moderate or severe pain at baseline—first eligible treatment—mITT

	Active			Sham			
	n	*N*	%	*n*	*N*	%	*p*-value
Pain relief							
2 h	22	29	76%	20	43	47%	0.013*
1 h	19	31	61%	15	44	34%	0.019*
24 h	23	31	74%	21	44	48%	0.022*
Freedom from pain							
2 h	16	29	55%	5	43	12%	<0.001*
1 h	7	31	23%	2	44	5%	0.028**
24 h	21	31	68%	13	44	30%	0.001*

Abbreviation: mITT, modified intention to treat.
*χ^2 test; **Fisher's exact test.

TABLE 7 Summary of adverse events by type

	Active			Sham		
Adverse event term	# of reports	# of subjects	Incidence	# of reports	# of subjects	Incidence
Migraine	2	1	1%	–	–	–
Unpleasant sensation during treatment	1	1	1%	3	1	2%
Scalp numbness sensation	1	1	1%	–	–	–
Pain	2	1	1%	–	–	–
Skin redness	–	–	–	3	1	2%
Tingling	1	1	1%	–	–	–
Twitching	1	1	1%	–	–	–
Other	4*	3	4%	3**	1	2%

*COVID, upper respiratory infection, inner ear scratch, lip numbness; **Pressure/discomfort of head.

with sustained pain freedom in the sham arm. Therapeutic gains were even greater in the participants with moderate-severe pain intensity. All-around benefit was further underscored by a greater proportion of participants experiencing MBS freedom (group difference, 28%), and of those pain- and MBS-free at 2 h (group difference 36%).

Comparison of effect sizes reported in this study with those of other treatments should be interpreted with caution, as it can be obscured by several factors, for example, heterogeneity of participants between the studies. While systematic analysis of responses to treatment is not in the scope of this work, general observations based on assessment of comparable trials may still provide valuable insights.

In particular, with regard to pain freedom, Chou et al. evaluated e-TNS in a comparably sized study of 106 people for acute treatment

of migraine.[18] Seventeen percent of participants in the active arm and 7% of participants with sham reported 2-h pain freedom after treatment ($p = 0.15$). Sustained pain freedom for 24 h was reported by 6% (3/52) of participants in the active arm and by none with sham. Tassorelli and collaborators investigated safety and efficacy of non-invasive vagus nerve stimulation (nVNS).[24–26] Freedom from pain 2 h after treatment was reported by 30% and 20% of participants in the active and sham arm, respectively, and this difference also failed to reach statistical significance ($p = 0.067$). Yarnitsky and colleagues[21,22] assessed a remote electrical neuromodulation (REN) device, and 37% participants in the active arm experienced 2-h pain freedom post-treatment versus 18% with sham (therapeutic gain 19%, $p = 0.003$).[21,22] Overall, two of the three of the assessed non-invasive neurostimulators demonstrated a similar response pattern, with a minor and statistically non-significant effect on pain freedom at the 2-h mark.[18,24] The third showed a 19% gain over sham, substantially less than the 34% gain demonstrated in the present study. MBS freedom at 2 h for REN was not statistically different between study arms (41% vs. 36% for active and sham stimulation, respectively; $p = 0.559$).[21]

Seven participants (five and two in active and sham arms, respectively) in the Chou et al. trial left the study due to painful paresthesia and treatment-emergent nausea.[18] Two of the nVNS study participants (both in the sham arm) withdrew due to AEs.[24] Overall incidence of device-related AEs experienced with REN (4.8% vs 2.4% in active and sham arms, respectively)[21] and nVNS (6% and 8%)[24] was similar to results presented in the current study.

Results of the RIME trial suggest that in the most clinically important endpoints, pain freedom and MBS freedom, the eCOT-NS device may have a greater effect than e-TNS, nVNS, and REN neuromodulation devices. Oral triptan 2-h response rates are comparable to those reported in this trial.[37] The AE profile of the eCOT-NS device is likely more tolerable, and given the absence of triptan-induced vasoconstriction, also likely safer than triptans for acute treatment of migraine.

Multi-focal concomitant stimulation offers the prospect of additive or synergistic benefit.[38-41] Unfortunately, the burden of complications makes the invasive approach less attractive. On the other hand, eCOT-NS seemed a challenging endeavor, in view of the increased impedance due to the presence of hair and the potential of causing discomforting electrically induced contractions in neighboring cervical muscles.[30] The current study shows that eCOT-NS is not only feasible but is also highly effective. The US FDA-cleared and CE-marked device used in this study also offers flexibility of supervised adjustment of treatment by providing a patient-facing mobile application, a secure cloud database, and a web-based physician interface for monitoring of patient data by health-care providers.

This study is not free of limitations, such as its inability to meet the recruitment target, due to pandemic-imposed premature termination. However, the prospectively and carefully implemented statistical adjustments, which relied on the guidance published by the US FDA, in concert with the strict adherence to principles of good clinical practice likely minimized risk of bias.

CONCLUSIONS

eCOT-NS is a well-tolerated and safe non-invasive, self-administered, home-use device and demonstrated a substantial clinical benefit for those with migraine in providing a fast and durable relief and freedom of migraine symptoms. The RIME results show that the effect size of the eCOT-NS device is comparable and potentially higher than that of commercially available non-invasive neuromodulation devices for acute treatment of migraine. Efficacy, safety, and tolerability also suggest that eCOT-NS may be a viable alternative to first-line acute medication treatments, such as triptans.[37] Remote monitoring of patient data by health-care providers, allowing for in-line personalized treatment optimization, may also be of great value for patients' health and quality of life, especially in the era of social distancing and travel restrictions.

AUTHOR CONTRIBUTIONS

Study concept and design: Stewart J. Tepper, Brian Grosberg, Oved Daniel, Lisa Deutsch. *Acquisition of data*: Stewart J. Tepper, Brian Grosberg, Oved Daniel, Deena E. Kuruvilla, Gabriel Vainstein, Lisa Deutsch, Roni Sharon. *Analysis and interpretation of data*: Stewart J. Tepper, Lisa Deutsch, Roni Sharon. *Drafting of the manuscript*: Stewart J. Tepper, Lisa Deutsch, Roni Sharon. *Revising it for intellectual content*: Stewart J. Tepper, Brian Grosberg, Oved Daniel, Deena E. Kuruvilla, Gabriel Vainstein, Lisa Deutsch, Roni Sharon. *Final approval of the completed manuscript*: Stewart J. Tepper, Brian Grosberg, Oved Daniel, Deena E. Kuruvilla, Gabriel Vainstein, Lisa Deutsch, Roni Sharon.

ACKNOWLEDGMENTS

We thank Dr. Igor Ruvinsky for his help in drafting the manuscript.

FUNDING INFORMATION

Financial support for this study was provided by Neurolief Ltd. (Netanya, Israel).

CONFLICTS OF INTEREST

Stewart J. Tepper, MD: grants for research (no personal compensation): Allergan/Abbvie, Amgen, Eli Lilly, Lundbeck, Neurolief, Novartis, Satsuma, Zosano; consultant and/or Advisory Boards (honoraria): Aeon, Allergan/Abbvie, Alphasights, Amgen, Aruene, Atheneum, Axsome Therapeutics, Becker Pharmaceutical Consulting, BioDelivery Sciences International, Biohaven, ClearView Healthcare Partners, CoolTech, CRG, Currax, Decision Resources, Defined Health, DRG, Eli Lilly, ExpertConnect, FCB Health, Fenix, GLG, Guidepoint Global, Health Science Communications, HMP Communications, Impel, InteractiveForums, Keyquest, Krog and Partners, Lundbeck, M3 Global Research, MJH Holdings, Neurolief, Novartis, P Value Communications, Pain Insights, Inc, Palion Medical, Pulmatrix, Putnam Associates, SAI MedPartners, Satsuma, Spherix Global Insights, Strategy Inc, System Analytic, Taylor and Francis, Teva, Theranica, Trinity Partners, Unity HA, XOC, Zosano; Salary: Dartmouth-Hitchcock Medical Center, American Headache

Society, Thomas Jefferson University; CME honoraria: American Academy of Neurology, American Headache Society, Annenberg Center for Health Sciences, Catamount Medical Education, Diamond Headache Clinic, Forefront Collaborative, Haymarket Medical Education, Medical Education Speakers Network, Medical Learning Institute Peerview, Migraine Association of Ireland, Miller Medical Education, National Association for Continuing Education, North American Center for CME, The Ohio State University, Physicians' Education Resource, PlatformQ Education, Primed, Texas Neurological Society, Vindico Medical Education, WebMD/Medscape. Brian M. Grosberg, MD: grants for research (no personal compensation): Eli Lilly, Neurolief, Theranica; consultant and/or advisory boards (honoraria): Allergan/Abbvie, Amgen, Biohaven, Impel, Lundbeck, Neurolief, Theranica. Oved Daniel, MD: research grants/support from Teva Pharmaceutical Industries Ltd; consultancy and advisory board fees from Teva Pharmaceutical Industries Ltd. and Novartis Pharmaceuticals Corporation; speaker, Teva, Novartis, Eli-Lilly, Medison, Neurolief; Primary investigator in Teva, Novartis and Neurolief Clinical Trials; CGRP Forum editorial advisory board member; neurologist at the Ramat Aviv Medical Center Headache Clinic. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Deena E. Kuruvilla, MD, FAHS: consultant: Cefaly, Neurolief, Theranica, Nowwhat media, KX advisors; speakers bureau: Abbvie/Allergan, Amgen/Novartis, Lilly, American Headache Society, Biohaven, CME meeting; Advisory Board: Abbvie/Allergan, Lilly, Theranica, Amgen/Novartis; editor, associate editor: *Healthline*; Author: WebMD/Medscape, Healthline. Gabriel Vainstein, MD: consultant and/or advisory boards (honoraria): Eli Lilly, Novartis, Teva, Medison, Allergan, Neurolief, Abbvie. Lisa Deutsch, PhD: works as a biostatistician for hire and receives financial compensation for performing statistical analyses for companies in the medical device industry. There are no other conflicts of interest. Roni Sharon, MD: paid advisor/has done speaking engagements the following medications—Theranica, Neurolief, Abbvie, Teva, Novartis, Medison, Novartis, Eli Lilly, Clexio.

ORCID

Roni Sharon https://orcid.org/0000-0002-2452-8921

REFERENCES

1. Group GBDNDC. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Neurol*. 2017;16:877-897.
2. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1545-1602.
3. Allais G, Chiarle G, Sinigaglia S, Airola G, Schiapparelli P, Benedetto C. Gender-related differences in migraine. *Neurol Sci*. 2020;41:429-436.
4. Collaborators GBDH. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2018;17:954-976.
5. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68:343-349.
6. Doane MJ, Gupta S, Fang J, Laflamme AK, Vo P. The humanistic and economic burden of migraine in Europe: a cross-sectional survey in five countries. *Neurol Ther*. 2020;9:535-549.
7. Collaborators GBDN. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18:459-480.
8. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386:743-800.
9. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. *Physiol Rev*. 2017;97:553-622.
10. Thorlund K, Mills EJ, Wu P, et al. Comparative efficacy of triptans for the abortive treatment of migraine: a multiple treatment comparison meta-analysis. *Cephalalgia*. 2014;34:258-267.
11. Munjal S, Singh P, Reed ML, et al. Most bothersome symptom in persons with migraine: results from the Migraine in America Symptoms and Treatment (MAST) study. *Headache*. 2020;60:416-429.
12. Pierce M. Oral triptans and nausea: treatment considerations in migraine. *Headache*. 2013;53(Suppl 1):17-20.
13. Newman LC. Why triptan treatment can fail: focus on gastrointestinal manifestations of migraine. *Headache*. 2013;53(Suppl 1):11-16.
14. Leroux E, Buchanan A, Lombard L, et al. Evaluation of patients with insufficient efficacy and/or tolerability to triptans for the acute treatment of migraine: a systematic literature review. *Adv Ther*. 2020;37:4765-4796.
15. Loder E. Triptan therapy in migraine. *N Engl J Med*. 2010;363:63-70.
16. Lee AYS, Pucar PA, Smith AJF. Sumatriptan anaphylaxis: a headache of an allergy. *Neurol Clin Pract*. 2021;11:e344-e346.
17. Lombard L, Farrar M, Ye W, et al. A global real-world assessment of the impact on health-related quality of life and work productivity of migraine in patients with insufficient versus good response to triptan medication. *J Headache Pain*. 2020;21:41.
18. Chou DE, Shnayderman Yugrakh M, Winegarner D, Rowe V, Kuruvilla D, Schoenen J. Acute migraine therapy with external trigeminal neurostimulation (ACME): a randomized controlled trial. *Cephalalgia*. 2019;39:3-14.
19. Jiang L, Yuan DL, Li M, et al. Combination of flunarizine and transcutaneous supraorbital neurostimulation improves migraine prophylaxis. *Acta Neurol Scand*. 2019;139:276-283.
20. Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. *Neurology*. 2013;80:697-704.
21. Yarnitsky D, Dodick DW, Grosberg BM, et al. Remote electrical neuromodulation (REN) relieves acute migraine: a randomized, double-blind, placebo-controlled, multicenter trial. *Headache*. 2019;59:1240-1252.
22. Rapoport AM, Bonner JH, Lin T, et al. Remote electrical neuromodulation (REN) in the acute treatment of migraine: a comparison with usual care and acute migraine medications. *J Headache Pain*. 2019;20:83.
23. Silberstein SD, Calhoun AH, Lipton RB, et al. Chronic migraine headache prevention with noninvasive vagus nerve stimulation: the EVENT study. *Neurology*. 2016;87:529-538.
24. Tassorelli C, Grazzi L, de Tommaso M, et al. Noninvasive vagus nerve stimulation as acute therapy for migraine: the randomized PRESTO study. *Neurology*. 2018;91:e364-e373.
25. Grazzi L, Tassorelli C, de Tommaso M, et al. Practical and clinical utility of non-invasive vagus nerve stimulation (nVNS) for the acute

treatment of migraine: a post hoc analysis of the randomized, sham-controlled, double-blind PRESTO trial. *J Headache Pain*. 2018;19:98.
26. Martelletti P, Barbanti P, Grazzi L, et al. Consistent effects of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of migraine: additional findings from the randomized, sham-controlled, double-blind PRESTO trial. *J Headache Pain*. 2018;19:101.
27. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache S. The American Headache Society Consensus Statement: update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61:1021-1039.
28. Hann S, Sharan A. Dual occipital and supraorbital nerve stimulation for chronic migraine: a single-center experience, review of literature, and surgical considerations. *Neurosurg Focus*. 2013;35:E9.
29. Reed KL, Black SB, Banta CJ 2nd, Will KR. Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: initial experience. *Cephalalgia*. 2010;30:260-271.
30. Daniel O, Sharon R, Tepper SJ. A device review of Relivion(R): an external combined occipital and trigeminal neurostimulation (eCOT-NS) system for self-administered treatment of migraine and major depressive disorder. *Expert Rev Med Devices*. 2021;18:333-342.
31. *Relivion K203419*. Center for Devices and Radiological Health; 2021.
32. *Migraine: Developing Drugs for Acute Treatment*. (CDER) CfDEaR, ed.; 2018.
33. Diener HC, Tassorelli C, Dodick DW, et al. Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: fourth edition. *Cephalalgia*. 2019;39:687-710.
34. Houts CR, McGinley JS, Nishida TK, et al. Systematic review of outcomes and endpoints in acute migraine clinical trials. *Headache*. 2021;61:263-275.
35. *Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency*. (CDER) CfDEaR, (CBER) CfBEaR, (CDRH) CfDaRH, (CVM) CfVM, eds; 2020.
36. Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP. Disability in Strategies of Care Study g. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: a randomized trial. *JAMA*. 2000;284:2599-2605.
37. Cameron C, Kelly S, Hsieh SC, et al. Triptans in the Acute Treatment of Migraine: a Systematic Review and Network Meta-Analysis. *Headache*. 2015;55(Suppl 4):221-235.
38. Zhang J, Su J, Wang M, et al. The sensorimotor network dysfunction in migraineurs without aura: a resting-state fMRI study. *J Neurol*. 2017;264:654-663.
39. Coppola G, Di Renzo A, Tinelli E, et al. Thalamo-cortical network activity between migraine attacks: Insights from MRI-based microstructural and functional resting-state network correlation analysis. *J Headache Pain*. 2016;17:100.
40. Coppola G, Di Renzo A, Tinelli E, et al. Thalamo-cortical network activity during spontaneous migraine attacks. *Neurology*. 2016;87:2154-2160.
41. Reed KL, Will KR, Conidi F, Bulger R. Concordant occipital and supraorbital neurostimulation therapy for hemiplegic migraine; initial experience; a case series. *Neuromodulation*. 2015;18:297-303.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tepper SJ, Grosberg B, Daniel O, et al. Migraine treatment with external concurrent occipital and trigeminal neurostimulation—A randomized controlled trial. *Headache*. 2022;00:1-13. doi: 10.1111/head.14350