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RESEARCH SUBMISSIONS

Remote electrical neuromodulation for migraine prevention: A double-blind, randomized, placebo-controlled clinical trial

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Abstract

Objective: To assess the clinical efficacy of remote electrical neuromodulation (REN), used every other day, for the prevention of migraine.

Background: Preventive treatment is key to managing migraine, but it is often underutilized. REN, a non-pharmacological acute treatment for migraine, was evaluated as a method of migraine prevention in patients with episodic and chronic migraine.

Methods: We conducted a prospective, randomized, double-blind, placebo-controlled, multi-center trial, with 1:1 ratio. The study consisted of a 4-week baseline observation phase, and an 8-week double-blind intervention phase in which participants used either REN or a placebo stimulation every other day. Throughout the study, participants reported their symptoms daily, via an electronic diary.

Results: Two hundred forty-eight participants were randomized (128 active, 120 placebo), of which 179 qualified for the modified intention-to-treat (mITT) analysis (95 active; 84 placebo). REN was superior to placebo in the primary endpoint, change in mean number of migraine days per month from baseline, with mean reduction of 4.0 ± SD of 4.0 days (1.3 ± 4.0 in placebo, therapeutic gain = 2.7 [confidence interval −3.9 to −1.5], $p < 0.001$). The significance was maintained when analyzing the episodic (−3.2 ± 3.4 vs. −1.0 ± 3.6, $p = 0.003$) and chronic (−4.7 ± 4.4 vs. −1.6 ± 4.4, $p = 0.001$) migraine subgroups separately. REN was also superior to placebo in reduction of moderate/severe headache days (3.8 ± 3.9 vs. 2.2 ± 3.6, $p = 0.005$), reduction of headache days of all severities (4.5 ± 4.1 vs. 1.8 ± 4.6, $p < 0.001$), percentage of patients achieving 50% reduction in moderate/severe headache days (51.6% [49/95] vs. 35.7% [30/84], $p = 0.033$), and reduction in days of acute medication intake (3.5 ± 4.1 vs.

Abbreviations: AEs, adverse events; AHS, American Headache Society; ANCOVA, analysis of covariance; BMI, body mass index; CGRP, calcitonin gene–related peptide; CI, confidence interval; CPM, conditioned pain modulation; FDA, Food and Drug Administration; HIT-6, headache impact test short form; ICHD-3, International Classification of Headache Disorders, 3rd edition; IHS, International Headache Society; ITT, intention to treat; mAbs, monoclonal antibodies; mITT, modified intention-to-treat; MSQ, migraine specific quality of life questionnaire; REN, remote electrical neuromodulation; SD, standard deviation; SE, standard error; t-SNS, transcutaneus supraorbital nerve stimulation; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation.

1.4 ± 4.3, $p = 0.001$). Similar results were obtained in the ITT analysis. No serious device-related adverse events were reported in any group.

Conclusion: Applied every other day, REN is effective and safe for the prevention of migraine.

KEYWORDS
headache, migraine, neuromodulation, non-pharmacological, prevention, prophylaxis

INTRODUCTION

Migraine affects more than 1 billion people worldwide causing significant disability and a huge socioeconomic burden.[1] Preventive treatment is key in the management of migraine and mitigation of burden.[2] The American Headache Society (AHS) Consensus Statement recommends preventive therapy in patients with frequent disabling migraine attacks (≥4 monthly headache days), or contraindication to or overuse of acute medications, or adverse events (AEs) in response to acute therapies.[3]

Significant advances in migraine prevention have reduced the number of migraine attacks and improved the quality of life of some patients.[4] However, suboptimal efficacy and tolerability of some of the migraine prevention treatments has led to low adherence to oral preventive treatment, and adequate migraine prevention remains an unmet need.[5] Adherence with more novel therapies, like calcitonin gene–related peptide (CGRP) monoclonal antibodies (mAbs) injection, is better than for oral preventives, but there are still significant rates of discontinuation.[6] The 2021 AHS Consensus Statement on integrating new migraine treatments into clinical practice states that only 3%–13% of patients with migraine use preventive treatment, even though nearly 40% of those with migraine, and all of those with chronic migraine, may benefit from preventive treatment.[7] The Consensus Statement further asserts that the poor adherence is caused by low-to-moderate efficacy of many oral preventive treatments, moderate-to-high rates of AEs, contraindications, or drug–drug interactions that limit use. Evidence from a large US health-care database (more than 8000 patients) indicates that more than 80% of patients with chronic migraine discontinue oral preventive therapy within the first year.[8] Thus, there is an unmet need for non-pharmacological migraine prevention that is both effective and well tolerated.

Remote electrical neuromodulation (REN) is a drug-free acute treatment for migraine[9,10] that activates an endogenous pain management mechanism, conditioned pain modulation (CPM). CPM is a descending analgesic mechanism in which a sub–pain-threshold stimulation (e.g., in the arm) inhibits pain in remote body regions (e.g., in the head).[11,12] The REN device (Nerivio®) is a US Food and Drug Administration (FDA)-cleared wearable, wireless, battery-operated stimulation unit, controlled by a smartphone application. For the acute treatment of migraine attacks the device is applied for 45 min to the lateral upper arm.

The efficacy of REN in acute treatment of migraine was established in adults and adolescents with chronic and episodic migraine, with and without aura.[11,13–15] These data, as well as additional studies indicating REN's efficacy,[16–22] were further supported by a real-world evidence analysis of more than 23,000 treatments[23] indicating that REN provides a safe and effective acute treatment for migraine. Two recent systematic reviews and meta-analyses found REN effective for acute treatment of migraine.[24,25] Furthermore, neuromodulation treatment (including REN) is recommended by the recent AHS Consensus Statement as an adjunct to the existing treatment plan for patients with an inadequate response to a migraine-specific acute medication, as well as for those with frequent attacks who may be at risk of developing medication-overuse headache and/or chronic migraine due to overuse of acute medication.[7]

Given that CPM is an endogenous central nervous system mechanism,[12] and as its deficiency was related to prevalence of migraine[26] it was hypothesized that repeated activation ("training") of this mechanism using an external stimulus may potentially strengthen the associated neural networks. Considering previous findings indicating that the effect of a single REN treatment may persist for (at least) 48 h,[14] it was hypothesized that repeated treatment sessions, applied every other day, could activate the CPM in a sustained manner, thus exerting a preventive effect and reducing the monthly number of migraine attacks. The aim of the present clinical trial was to evaluate the efficacy and safety of REN, applied every other day, for the preventive treatment of migraine in a large, multi-center, randomized, double-blind, placebo-controlled study.

METHODS

Participants

The study (ClinicalTrials.gov NCT04828707) was conducted in 15 US centers. Participants were men and women aged 18–75. The main inclusion criteria were: (1) 6-month history of headaches that meet the International Classification of Headache Disorders, 3rd edition (ICHD-3) diagnostic criteria for migraine with or without aura, either chronic or episodic migraine[27]; (2) 6 to 24 headache days (a headache day is defined throughout the study as a calendar day with headache report, at any severity, i.e., severe, moderate, or mild, regardless of the duration of the headache) per 28-day period in each of the 3 months preceding study enrollment; (3) participants either did not use preventive medications, or were on a stable dose of a single migraine preventive medication during the 2 months before enrollment, and throughout the study period.

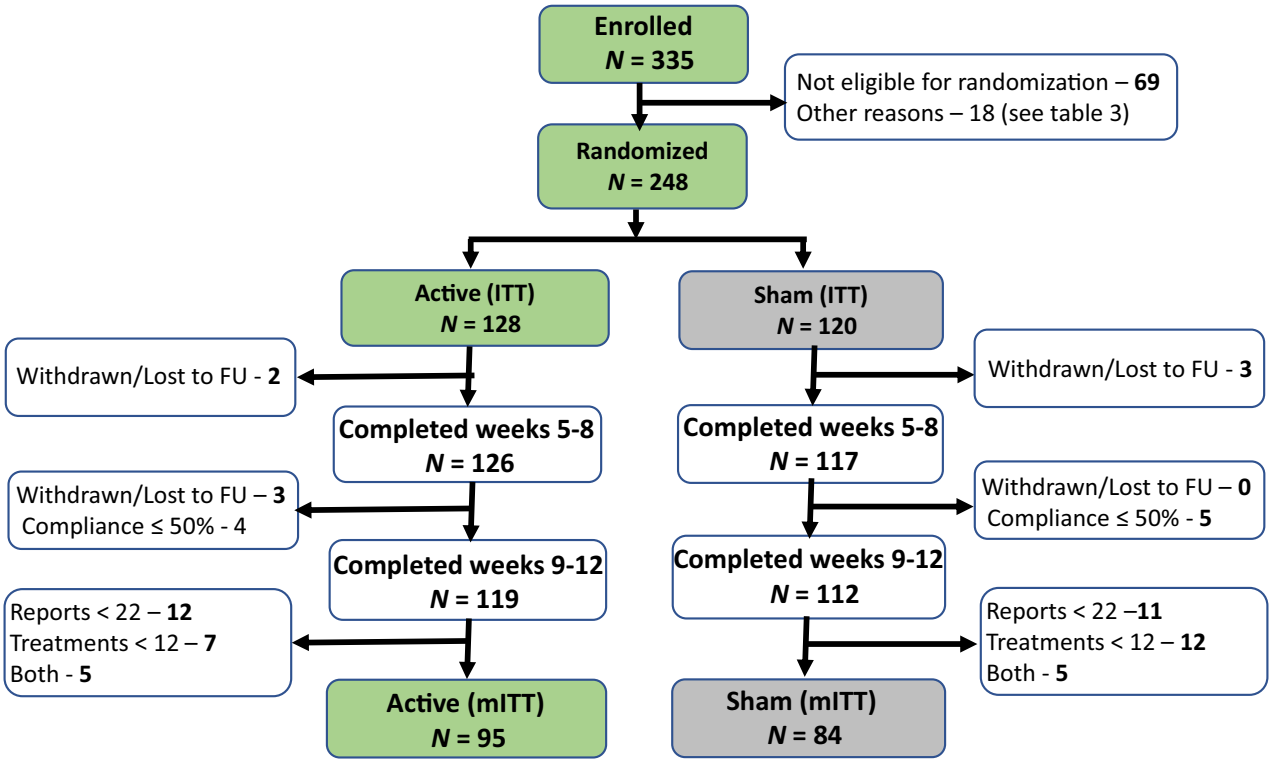

FIGURE 1 CONSORT (subject disposition) chart. FU, follow-up; ITT, intention to treat; mITT, modified intention to treat.

The main exclusion criteria were: (1) use of opioids/barbiturates on more than 4 days per month in the last 6 months; (2) current participation in another interventional study; (3) pregnant or breastfeeding; (4) other significant pain, or medical or psychological condition that may confound the assessments; (5) prior use of REN (Nerivio).

Participants were recruited via study sites (approached by study staff), and via advertisement in migraine advocacy group media. The study was approved by Western Institutional Review Board (tracking number 20210751) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Study design

This was a prospective, randomized, double-blind, placebo-controlled, multi-center trial. The study consisted of a baseline (observation) phase, and an intervention phase (see CONSORT chart, Figure 1).

Participants used a designated electronic diary via the Nerivio app to complete a report every evening (regardless of whether they had a headache that day). The collected data included: pain level ratings using a 4-point scale (none, mild, moderate, severe); functional disability (no limitation, some limitation, moderate limitation, severe limitation); presence/absence of nausea and/or vomiting, photophobia, and phonophobia; and acute medication intake. The first question was about pain level, and the following questions were presented only if the participant reported having pain. For the full daily questionnaire see Table S1. A list of minor pre-registered protocol amendments implemented during the trial can be found at: https://clinicaltrials.gov/ct2/history/NCT04828707?A=1&B=1&C=Side-by-Side#StudyPageTop.

Baseline phase

The study began with a 4-week baseline phase, in which participants were instructed to complete the daily report and continue using their regular medications when needed, as before. Data from this phase served as a baseline for comparison with the intervention's effects (i.e., pre vs. post treatment), and to verify eligibility for participation in the intervention phase.

Intervention phase

Eligibility criteria for the intervention phase, based on the 4-week baseline phase were: (1) 6 to 24 headache days during the 28-day baseline period; (2) at least four headache days during baseline fulfilling the ICHD-3 criteria for migraine (migraine with or without aura/probable migraine/headaches requiring the use of migraine-specific medications including triptans, gepants, ditans, or ergot derivatives); (3) completed the diary on at least 22 days out of the four baseline weeks (80.0% compliance).

The intervention phase was 8 weeks long. Eligible participants were randomized in a 1:1 ratio to active or placebo group. Randomization lists, in blocks of six, were prepared for each site prior to the initiation of the site, by the study biostatistician via a computer-generated list of random numbers. The active and sham devices were visually identical, keeping both the staff and participants blind to the type of device. The devices carried an identification code (associating it with the active/sham groups), which was kept blind to all parties until the end of the study. Devices were allocated by ID numbers to preserve future allocations, and the randomization scheme was per site (each site had its own randomization list, independent of other sites). Participants were instructed to conduct a full 45-min treatment with REN every other day, and to complete the daily diary. Participants were instructed not to use REN for acute treatment, and, when needed, treat their migraine/headache with their usual acute treatments.

Study device

The REN device has been described in detail elsewhere.[10] Briefly, the active device produces a proprietary electrical signal comprising a modulated symmetrical biphasic square pulse with a modulated frequency of 100–120 Hz, pulse width of 400 μs, and up to 40 mA output current (adjusted by the participant). The duration of the treatment is 45 min, as the indicated acute REN treatment of migraine.

The sham device produces electrical pulses of the same maximum intensity (34 mA) and overall energy, but with different pulse durations and much lower frequencies compared to the active device.[11] The sham stimulation is strongly perceivable by the user but is designed to not activate nociceptive nerve fibers and thus to not activate the CPM. Participants were requested, at the end of their intervention phase, to indicate which device they believed they had, to assess blinding (see the Blinding assessment section).

Participants were instructed to adjust the intensity individually, in each treatment (using a simple ± graphical interface on the app), so that the stimulation on the arm felt strong yet not painful.

Participants received guidance on how to use the device by designated staff at the study sites (or via teleconference for those who could not come in person due to the COVID-19 pandemic). Additionally, all participants received video instructions, and a written manual, both available on the REN App.

Outcome measures

All prospective endpoints were compared between the 4-week baseline phase (weeks 1–4) and the last 4 weeks of the intervention phase (weeks 9–12). Given that preventive processes may require time to exert their effect, only data from the second month of the intervention phase were included in the statistical analysis (a common timeframe for efficacy analysis in migraine prevention studies, e.g., rimegepant,[28] erenumab,[29] vagus nerve stimulation[30]).

Primary efficacy endpoint

Difference between the groups in the mean change in number of migraine days per month compared the 4-week baseline phase (weeks 1–4) to the last 4 weeks of the treatment phase (weeks 9–12).

A migraine day was defined as a calendar day with headache that is accompanied by at least one of the following: aura, photophobia, phonophobia, nausea and/or vomiting; or with a headache that is treated with a migraine-specific acute medication.

A predefined subanalysis of the primary endpoint examined the episodic and chronic subgroups separately, comparing the results of each subsample to that of placebo stimulation.

Another subanalysis examined the results of the subsamples taking and not taking migraine prophylaxis, separately. The results of each subsample were compared to that of placebo stimulation.

Early response, that is, response at the end of the first month of treatment (week 8) was also analyzed. This analysis was performed on the intention to treat (ITT) data (given that this is first month data, and modified ITT [mITT] was defined based on second month data).

Secondary and exploratory efficacy endpoints

All outcome measures were compared between the 4-week baseline phase (weeks 1–4) and the last 4 weeks of the intervention phase (weeks 9–12), evaluating differences between the groups in:

1. Mean change in number of moderate/severe headache days.
2. Mean change in the number of headache days (any severity).
3. Percentage of participants achieving at least 50% reduction from baseline in the mean number of headache days (all severities), and of moderate/severe headache days.
4. Mean change from week 1 to week 12 in the Headache Impact Test short form (HIT-6[31]) total score.
5. Mean change from week 1 to week 12 in the Migraine Specific Quality of Life Questionnaire (MSQ) Role Function Domain (restrictive and preventive combined score; i.e., MSQ role[32,33]) function.
6. [Exploratory efficacy endpoint:] Reduction in the mean number of days of acute headache/migraine medication intake.

The HIT-6 and MSQ questionnaires were completed at the beginning of the baseline phase (beginning of week 1) and the end of the treatment phase (end of week 12), pertaining retrospectively to the prior month in each case. As such, secondary endpoints 4,5 are retrospective, while all other endpoints are prospective, based on daily collected data.

Safety endpoints

Difference between the groups in percentage of device-related AEs was measured. The incidence of AEs was assessed per severity and association to the device.

Analysis sets

Intent to treat

The ITT dataset included all randomized participants and served as the dataset for safety assessments.

Modified intent to treat

The mITT analysis set included all ITT participants with at least 22 daily reports and at least 12 treatments in the last month of treatment (weeks 9–12). The treatment adherence criterion was chosen to ensure sufficient treatment, and diary adherence criterion was set to ensure a sufficient number of daily reports to allow for a per-month analysis of reduction in number of migraine days. To maintain an equal timeframe across participants, data were standardized to 28 days in the following manner: 28*(reported migraine days)/(report days). These procedures are similar to those taken in other migraine prevention studies, for example, the rimegepant prevention study.[28]

The mITT was defined as the main efficacy dataset. All efficacy analyses were repeated on the ITT as well.

Missing data

Analyses on the ITT dataset were calculated using last observation carried forward for all ITT efficacy outcomes. Specifically, data of participants who dropped out during the first 4 weeks of the intervention phase (weeks 5–8) was normalized to 28 days and then carried forward and served to replace data from the final 4 weeks of the intervention (weeks 9–12).

Blinding assessment

Immediately at the end of the intervention phase, participants were asked about their presumed group assignment (active, placebo, do not know).

Sample size

A sample size of 234 participants, 117 per each treatment arm, was estimated prior to the beginning of the study to provide 80% power to detect a mean (± standard deviation [SD]) difference of 2.0 ± 3.0 in the change in number of migraine headache days from the baseline to weeks 9–12 of the treatment phase, between the active group and the sham group at a two-sided alpha level of 0.05. With an anticipated discontinuation rate of about 20%, 300 participants are planned to be enrolled. Following the interim analysis (blinded to all study staff), it was recommended by the data monitoring committee to stop the enrollment at 100 participants per arm. No additional adjustments were made following the interim analysis.

Statistical analysis

Independent *t*-tests were used for comparing continuous variables between study groups. Means are presented along with SD for baseline variables, and standard error (SE) for change from baseline. Chi-square tests were used to compare nominal variables. Fisher's exact test was used for nominal variables with low occurrence (AEs). Data for all nominal variables are presented as the number and percentage of participants. Effect sizes were calculated using Cohen's *d* (for continuous variables) and Cohen's *w* (for nominal variables). The hierarchy approach was adopted for the primary and secondary endpoints to control type I error due to multiple endpoint testing. Thus, an endpoint was first tested and only if $p < 0.05$, the following endpoints were tested. Analyses were not multiplicity corrected. The analysis of the primary endpoint was also conducted as an analysis of covariance (ANCOVA) controlling for age, sex, body mass index (BMI), and number of migraine days at baseline. All the required statistical assumptions for the tests performed were met.

All tests were two-tailed, and *p*-value <0.05 was considered statistically significant.

Data were analyzed using IBM SPSS statistics software version 28.0.

The study's hypothesis was that the active and the sham groups will differ in the mean change in monthly migraine days from the baseline phase to the last 4 weeks of treatment phase.

Data from participants with <28 report days was standardized to 28 days, for all efficacy endpoints (except for the percentage of participants achieving at least 50% reduction from baseline in the mean number of headache days). While most endpoints are calculated as a subtraction, this third secondary endpoint is calculated as a ratio (i.e., number of headache days in weeks 9–12 divided by number of headache days in weeks 1–4), and thus was not normalized.

RESULTS

Participants

The study period was April 13, 2021, to August 11, 2022. Of 335 enrolled participants, 248 participants (74.0%) were eligible at the end of the baseline phase and were randomized and received a device

(128 active: 120 placebo). Of these, 179 (72.2%) were included in the mITT arm (95 active: 84 placebo; see disposition chart, Figure 1). Among the randomized participants, eight (3.2%) withdrew or were lost to follow-up during the treatment phase ($n = 5$ [3.9%] and $n = 3$ [2.5%] in the Active and Sham groups, respectively). During weeks 9–12, 23 (9.3%) participants did not complete at least 22 daily reports ($n = 12$ [9.4%] and $n = 11$ [9.2%] in the Active and Sham groups, respectively), 19 (7.7%) participants did not perform at least 12 treatments ($n = 7$ [5.5%] and $n = 12$ [10.0%] in the Active and Sham groups, respectively), and 19 (7.7%) participants did not complete both ($n = 9$ [7.0%] and $n = 10$ [8.3%] in the Active and Sham groups, respectively).

Overall, 85.9% of the participants were female, mean age of 41.7 (±12.9), and the ratio of episodic to chronic patients was 47.6%:52.4%. Demographic and clinical characteristics of the ITT dataset, along with statistical comparison, are presented in Table 1. No statistical difference was found between the groups in any of the parameters. Similar values were reported in the mITT dataset, with no significant differences between the groups.

Primary endpoint

The mean change in number of migraine days per month was −4.0 ± 4.0 in the REN group, versus −1.3 ± 4.0 in the placebo. The net therapeutic gain (difference between active and placebo) was 2.7; $p < 0.001$ (reduction in active: from 11.8 migraine days in baseline to 7.8 in weeks 9–12; in placebo: from 12.0 to 10.7), see Figure 2.

The subanalyses of the episodic ($n = 45$:42 [active:placebo]) and chronic ($n = 50$:42) subsamples were both significant (Figure 3): The mean change in the episodic subsample was −3.2 ± 3.4 in the REN arm, versus −1.0 ± 3.6 in the placebo arm with a net therapeutic gain of 2.3; $p = 0.003$.

The mean change in the chronic subsample was −4.7 ± 4.4 in the REN arm, versus −1.6 ± 4.4 in the placebo arm with a net gain of 3.0; $p = 0.001$.

Of the participants, 40.8% used a preventive medication in addition to REN. The REN and placebo arms did not differ in the distribution of types of prophylactic medications ($p = 0.413$ in mITT, 0.240 in ITT). Half of the preventive medication users were on first-line preventives (i.e., generic oral drugs), while the other half on second-line

TABLE 1 Demographic and clinical characteristics of the ITT dataset.

		All ($n = 248$)	Active ($n = 128$)	Placebo ($n = 120$)	p-value[a]
Age (years)	Average ± SD	41.7 ± 12.9	41.0 ± 12.0	42.6 ± 13.6	0.299
Sex	Female	213 (85.9%)	110 (85.9%)	103 (85.8%)	0.585
	Male	35 (14.1%)	18 (14.1%)	17 (14.2%)	
Race	White	222 (89.5%)	116 (90.6%)	106 (88.3%)	0.484
	Asian	4 (1.6%)	1 (0.8%)	3 (2.5%)	
	Black/African American	15 (6.0%)	6 (4.7%)	9 (7.5%)	
	Native Hawaiian	1 (0.4%)	1 (0.8%)	0 (0.0%)	
	Other	6 (2.4%)	4 (3.1%)	2 (1.7%)	
Height (cm)	Average ± SD	166 ± 8.3	166 ± 8.4	165 ± 8.2	0.315
Weight (kg)	Average ± SD	84.5 ± 25.0	84.0 ± 25.6	85.0 ± 25.2	0.815
BMI (kg/m^2)	Average ± SD	30.4 ± 7.7	30.7 ± 8.3	31.2 ± 8.4	0.572
Chronic migraine[b]	*N* (%) (in baseline)	130 (52.4%)	67 (52.3%)	63 (52.5%)	0.981
Migraine with aura[b] (%)	*N* (%)	62 (25.0%)	33 (25.8%)	29 (24.1%)	0.799
On preventive medication (%)	*N* (%)	102 (41.1%)	46 (35.9%)	56 (46.7%)	0.094
Type of preventive	Generic oral (e.g., amitriptyline, topiramate)	43 (17.3%)	23 (18.0%)	20 (16.7%)	0.242
	mAbs	22 (8.9%)	8 (6.3%)	14 (11.7%)	
	OnabotulinumtoxinA	13 (5.2%)	5 (3.9%)	8 (6.7%)	
	Gepants	6 (2.4%)	2 (1.6%)	4 (3.3%)	
	Other	18 (7.3%)	8 (6.3%)	10 (8.3%)	
Baseline migraine days[b]	Average ± SD, in baseline	12.2 ± 4.5	12.1 ± 4.3	12.4 ± 4.9	0.546
Baseline headache days[b]	Average ± SD, in baseline	15.6 ± 4.6	15.6 ± 4.5	15.5 ± 4.8	0.833

Abbreviations: BMI, body mass index; ITT, intention to treat; mABs, monoclonal antibodies; SD, standard deviation.

[a]*T*-test for continuous variables, chi-square test for nominal variables.

[b]Determined based on the 28-days baseline phase.

(i.e., anti-CGRP mAbs, onabotulinumtoxinA, gepants), which means first-line preventives had failed in the past. For detailed distribution of preventive medications, see Table 1.

Subanalyses of the subsamples not using (62:44) and using (33:40) prophylaxis were calculated (mITT dataset): The mean change of migraine days in the no-prophylaxis subsample was −4.5 ± 4.0 in REN arm, versus −1.5 ± 3.6 in the placebo arm with a net therapeutic gain of 3.0 days; $p < 0.001$.

The mean change in the prophylactic subsample was −3.5 ± 3.5, versus −1.5 ± 4.1 in the placebo arm with a net gain of 2.0 days; $p = 0.032$.

The same subanalysis in the ITT dataset produced similar results: in the no-prophylaxis subgroup: −4.3 ± 4.7 versus −1.1 ± 3.7, $p < 0.001$; in the prophylaxis subgroup −3.1 ± 3.8 versus −1.3 ± 5.1, $p = 0.055$.

Early response, that is, response at the end of the first month of treatment (week 8) indicated a mean change in number of migraine days per month of −3.1 in the REN group, versus −1.5 in the placebo.

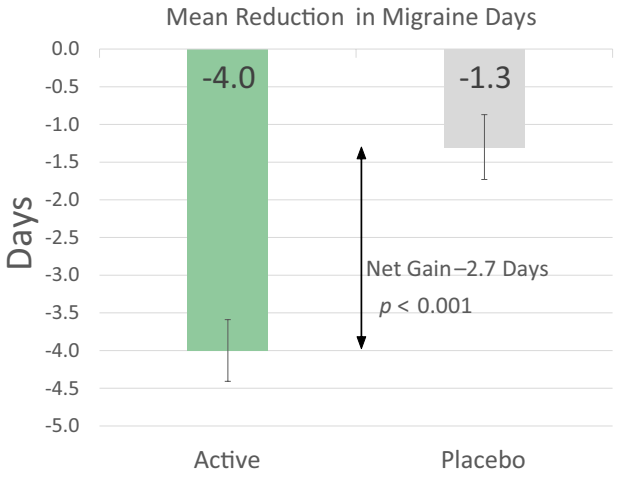

FIGURE 2 Mean reduction in migraine days per month. Error bars represent ± standard error.

The net therapeutic gain (difference between active and placebo) was 1.6; $p < 0.001$ (reduction in active: from 11.8 migraine days in baseline to 8.7 in weeks 5–8; in placebo: from 12.0 to 10.5). The analysis of the primary endpoint was also conducted as an ANCOVA controlling for age, sex, BMI, and number of migraine days at baseline (see Table S2), and the corrected model reached the same level of significance as the main analysis, $p < 0.001$.

Secondary and exploratory endpoints

Out of the five secondary endpoints, all three prospective endpoints were found statistically significant in order, and these were: mean change per month in the number of moderate/severe headache days (net gain = 1.6; $p = 0.005$), number of headache days (gain = 2.7; $p < 0.001$), percentage of patients achieving at least 50% reduction from baseline in headache days (26.3%:11.9%; $p = 0.015$), and achieving at least 50% reduction in moderate/severe headache days (51.6%:35.7%; $p = 0.033$; Figure 4).

There were quantitative differences in the REN arm from week 1 to week 12 in the two retrospective questionnaire-based endpoints

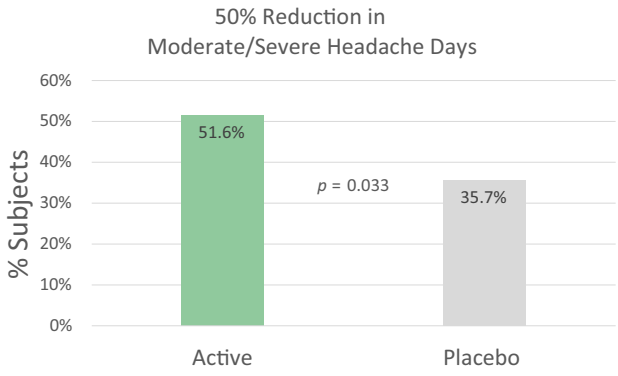

FIGURE 4 Percent of participants reporting at least 50% reduction in moderate/severe headache days.

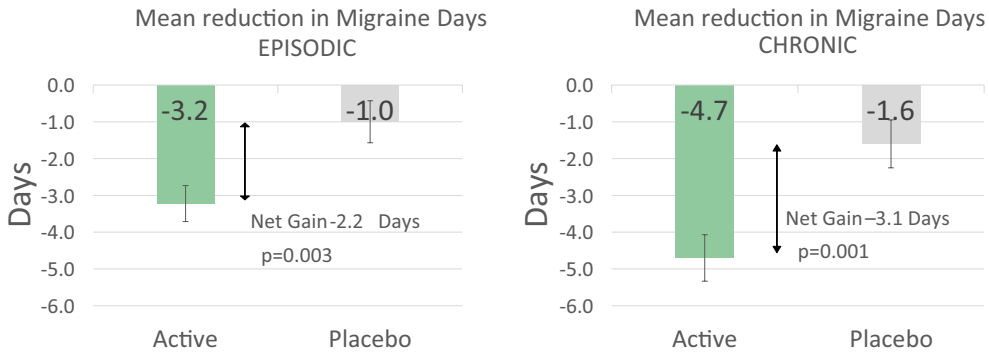

FIGURE 3 Subanalysis of the mean reduction in migraine days, in episodic and chronic subgroups. Error bars represent ± standard error.

of HIT-6 score (5.2 points) and MSQ score (−11.6 points); however, none was statistically significant compared to the placebo.

A significant difference was found in the prospective exploratory endpoint of reduction from baseline in the mean number of acute headache/migraine medication days per month (active −3.5 ± 4.1: sham −1.4 ± 4.3; therapeutic gain = 2.1; $p = 0.001$).

Detailed results of the primary, secondary, and exploratory endpoints in the ITT and mITT datasets are shown in Table 2.

Analysis of adherence to treatment protocol

The treatment adherence of participants in the ITT dataset was analyzed (Table 3). Of the randomized patients, 89.5% (222/248) completed at least 22 out of the 28 required treatments (i.e., at least 78.6% of the per-protocol number of treatments during the 2-month treatment phase). Evaluation of the primary endpoint in this subgroup shows a mean reduction of −3.8 migraine days in the REN arm from baseline to weeks 9–12, compared to a reduction of −1.0 day in the placebo arm (net gain of 2.8 days, $p < 0.001$). Sixteen of the 248 participants (6.5%) completed between 50% and 75% of the required per-protocol number of treatments during the 2-month treatment phase (i.e., between 15 to 21 treatments out of 28). The seven REN users had a reduction of −1.8 migraine days from baseline to weeks 9–12, compared to a reduction of −1.4 days in the nine placebo users. Ten of the 248 participants (4.0%) completed less than 50% of the required treatments.

Safety

Safety analyses were performed on the full ITT dataset ($N = 248$). Results are shown in Table 4.

There were two non–device-related serious AEs (SAEs), both in the REN arm: a suicide attempt and an appendicitis surgery. Both were deemed by the principal investigators (PIs) as non-related to the study device or study procedures. Two participants discontinued due to non–device-related AEs, one in the REN arm and the other in the placebo arm.

There was a single device-related AE, which occurred in the sham group (0.8%, [1/120]). In this AE, the participant reported worsening of fibromyalgia pain with use of the study device. The severity of the AE was defined as moderate. The participant decided not to continue with the study and withdrew consent. No device-related AEs were reported in the active group.

Blinding

Of the mITT dataset, 43.2% (41/95) of the participants in the REN group and 34.5% (29/84) of the placebo made a correct guess, while most participants in both groups made a wrong guess, did not know, or did not answer. The difference between the correct guesses in the two groups was analyzed using a 2 × 2 chi-square test, indicating lack of statistically significant difference ($p = 0.237$).

A similar analysis was done on the ITT dataset, in which 39.1% (50/128) of the REN and 30.8% (37/120) of the placebo group participants correctly guessed their device, without a statistically significant difference ($p = 0.175$).

DISCUSSION

The current study indicates that preventive REN treatment, applied every other day, results in a statistically significant and clinically meaningful decrease in number of migraine days, compared to placebo stimulation. Active preventive REN treatment resulted in a mean decrease of −4.0 ± 4.0 migraine days per month, compared to a much smaller reduction of −1.3 ± 4.0 in the placebo group. The average therapeutic gain was thus 2.7 migraine days per month. Very similar results, with the same therapeutic gain of 2.7, were also found in the analysis of the ITT group. The statistically significant results were maintained in separate subanalyses of the chronic and episodic subsamples, as well as in the separate subanalyses of participants who used and did not use migraine prophylaxis, despite smaller sample sizes in each of the subgroups in these two subanalyses. Early response, that is, response at the end of the first month of treatment, was also statistically significant, with a therapeutic gain of 1.6 migraine days at this early point in the intervention.

While comparison of efficacy across different studies should be interpreted very cautiously, it appears that REN's efficacy (therapeutic gain of 2.7 reduction in migraine days per month) is similar to those of leading FDA-approved migraine prevention treatments. For example, rimegepant and atogepant, two FDA-approved oral CGRP antagonists for prevention of episodic migraine reported net therapeutic gains of 0.8[28] and 1.7[34] migraine days per month, respectively. Erenumab,[29] an injectable CGRP mAb with the highest to-date efficacy in the migraine prevention study literature, reported net therapeutic gain of 2.4 migraine days per month in chronic migraine patients.

A significant difference between REN and placebo was also found in all prospective secondary and exploratory endpoints, decrease of the mean number of moderate/severe headache days and headache days of any severity, decrease of the mean number of acute medication days, and proportion of participants achieving at least 50% reduction in headache days (all severities) and moderate/severe headache days. These findings point to the various ways in which REN relieves the burden of migraine, and further support the clinical significance of the reduction in the number of migraine days. Additionally, the statistical significance was maintained in an analysis of the ITT as well, across all endpoints. These results rule out any possibility that the significance of the results stems from any potential selection bias associated with the mITT criteria.

No significant differences between REN and the placebo were found in the improvements from week 4 to week 12 in HIT-6 and MSQ questionnaire scores. The lack of difference between the

TABLE 2 Primary, secondary, and exploratory efficacy endpoints (mITT and ITT datasets.)

	mITT data set		ITT data set	
Endpoint	**REN (*N* = 95)**	**Sham (*N* = 84)**	**REN (*N* = 128)**	**Sham (*N* = 120)**
Primary efficacy end point				
Migraine days per month				
Mean no. of days at baseline (days ± SD)	11.8 ± 4.4	12.0 ± 4.4	12.1 ± 4.3	12.4 ± 4.9
Change from baseline—mean no. of days ± SD (SE)	−4.0 ± 4.0 (0.4)	−1.3 ± 4.0 (0.4)	−3.8 ± 4.5 (0.4)	−1.1 ± 4.4 (0.4)
Difference versus placebo (95% CI)	−2.7 (−3.9 to −1.5)		−2.7 (−3.8 to −1.6)	
p-value	<0.001		<0.001	
Effect size effect size Cohen's D (95% CI)	−0.7 (−1.0 to −0.4)		−0.6 (−0.8 to −0.3)	
Secondary and exploratory efficacy endpoints				
Moderate/severe headache days per month				
Mean no. of days at baseline (days ± SD)	8.5 ± 3.9	8.3 ± 4.1	8.4 ± 3.8	8.5 ± 4.2
Change from baseline—mean no. of days ± SD (SE)	−3.8 ± 3.9 (0.4)	−2.2 ± 3.6 (0.4)	−3.5 ± 3.9 (0.3)	−2.1 ± 3.9 (0.4)
Difference versus placebo (95% CI)	−1.6 (−2.7 to −0.5)		−1.4 (−2.4 to −0.4)	
p-value	0.005		0.005	
Effect size effect size Cohen's D (95% CI)	−0.4 (−0.7 to −0.1)		−0.5 (−0.8 to −0.3)	
Headache days per month				
Mean no. of days at baseline (days ± SD)	15.7 ± 4.7	15.0 ± 4.5	15.6 ± 4.5	15.5 ± 4.8
Change from baseline—mean no. of days ± SD (SE)	−4.5 ± 4.1 (0.4)	−1.8 ± 4.6 (0.5)	−4.2 ± 4.5 (0.4)	−2.0 ± 4.5 (0.4)
Difference versus placebo (95% CI)	−2.7 (−3.9 to −1.5)		−2.2 (−3.3 to −1.0)	
p-value	<0.001		<0.001	
Effect size effect size Cohen's D (95% CI)	−0.6 (−0.9 to −0.3)		−0.4 (−0.6 to −0.1)	
≥50% reduction in headache days				
Participants	25	10	40	22
Percent	26.3%	11.9%	31.3%	18.3%
p-value	0.015		0.019	
Effect size Cohen's W (95% CI)	0.2		0.1	
≥50% reduction in moderate/severe headache days				
Participants	49	30	71	48
Percent	51.6%	35.7%	55.5%	40.0%
p-value	0.033		0.015	
Effect size Cohen's W (95% CI)	0.2		0.2	
HIT-6 score				
Baseline	64.5 ± 6.0	64.2 ± 5.6	64.0 ± 7.3	64.6 ± 6.1
Change from baseline ± SD (SE)	5.2 ± 6.2 (0.6)	4.4 ± 5.6 (0.6)	4.7 ± 7.0 (0.6)	3.9 ± 6.2 (0.6)
Difference versus placebo (95% CI)	0.8 (−1.0 to 2.5)		0.9 (−0.8 to 2.5)	
p-value	0.399		0.328	
Effect size effect size Cohen's D (95% CI)	0.1 (−0.2 to 0.4)		0.1 (−0.1 to 0.4)	
MSQ score				
Baseline	49.6 ± 13.2	49.7 ± 13.2	48.7 ± 13.7	48.7 ± 13.4
Change from baseline ± SD (SE)	−11.4 ± 13.2 (1.4)	−10.4 ± 13.5 (1.5)	−11.5 ± 12.8 (1.1)	−9.8 ± 13.6 (1.2)
Difference versus placebo (95% CI)	−1.1 (−5.0 to 2.9)		−1.7 (−5.0 to 1.7)	
p-value	0.587		0.326	
Effect size effect size Cohen's D (95% CI)	−0.1 (−0.4 to 0.2)		−0.1 (−0.4 to 0.1)	

(Continues)

TABLE 2 (Continued)

Endpoint	mITT data set		ITT data set	
	REN (*N* = 95)	Sham (*N* = 84)	REN (*N* = 128)	Sham (*N* = 120)
Medication days per month				
Mean no. of days at baseline (days ± SD)	11.6 ± 4.6	11.1 ± 5.1	11.3 ± 4.8	11.4 ± 5.1
Change from baseline—mean no. of days ± SD (SE)	−3.5 ± 4.1 (0.4)	−1.4 ± 4.3 (0.5)	−3.9 ± 4.5 (0.4)	−2.2 ± 4.4 (0.4)
Difference versus placebo (95% CI)	−2.1 (−3.3 to −0.8)		−1.7 (−2.8 to −0.6)	
p-value	0.001		0.005	
Effect size effect size Cohen's D (95% CI)	−0.5 (−0.8 to −0.2)		−0.4 (−0.6 to −0.1)	

Note: As the previous secondary endpoint was not statistically significant, the *p*-value was not calculated here. The next endpoint was exploratory; thus, its *p*-value is calculated.

Abbreviations: CI, confidence interval; HIT-6, Headache Impact Test short form; ITT, intention to treat; mITT, modified intention to treat; REN, remote electrical neuromodulation; SD, standard deviation; SE, standard error.

TABLE 3 Analysis of treatment adherence (ITT dataset).

Number of treatments in intervention phase (weeks 5–12 of the study)	15–21 out of 28 treatments	22–28 out of 28 treatments
Participants in REN arm (*n*, [%])	7 (5.5%)	115 (89.8%)
Participants in placebo arm (*n*, [%])	9 (7.5%)	107 (89.2%)
Mean reduction of migraine days in REN ± SD (SE)	−1.8 ± 3.8 (1.4)	−3.8 ± 4.4 (0.4)
Mean reduction of migraine days in placebo ± SD (SE)	−1.4 ± 6.1 (2.0)	−1.0 ± 4.1 (0.4)
Net gain: diff. between REN and placebo	−0.4	−2.8
p-value	0.880	<0.001
Effect size	0.09	0.62

Note: Participants with <15 treatments per month (active *n* = 6, sham *n* = 4) are not included in the table.

Abbreviations: ITT, intention to treat; REN, remote electrical neuromodulation; SD, standard deviation; SE, standard error.

groups in the HIT-6 and MSQ could be due to several reasons. One possibility stems from the fact that, unlike the other endpoints, these two scales are rated retrospectively and thus may be more prone to a potential recall bias. Additionally, the 8-weeek intervention period may be too short to allow for the significant clinical changes to translate into a subjective perception of improvement.

Analysis of sensitivity to adherence indicated that nearly 90% (89.8% in the active group and 89.2% in the placebo group) of the participants completed more than 75% of the per-protocol number of treatments, and even those with subprotocol adherence (50%–75% of per-protocol) obtained statistically significant reduction in migraine days.

A subanalysis of participants who used migraine prophylaxis (a stable dose of a single migraine preventive medication) versus those that did not use migraine prophylaxis, indicated that in both of these subsamples a statistically significant effect was found. It should be noted, though, that the effect was qualitatively somewhat stronger in the group not taking prophylaxis (therapeutic gain of 3.0 days, vs. 2.0 days in the prophylaxis group), and that no participants have taken two or more additional prophylactic medications.

A very low rate of device-related AEs was found in the safety and tolerability analyses across the 8-week intervention phase, with no differences compared to placebo. No SAEs were related to treatment with REN. These findings accord with the safety results of previous clinical trials of REN[11,13–15] and extend its favorable safety profile.

REN's efficacy and tolerability profile can additionally be evaluated against other placebo-controlled studies in migraine prevention. An efficacy-tolerability review was done by Vandervorst et al., in 2021,[35] comparing anti-CGRP mAbs to the most commonly prescribed drugs for the prevention of episodic and chronic migraine. Analyzing the current data within the framework of the Vandervorst et al. review (see Figures S1 and S2 for episodic and chronic migraine, respectively) provides a perspective on the potential importance of REN in preventing migraine, and indicates REN's favorable efficacy-tolerability profile.

To provide a wider context of the placebo effect in the current study, the placebo group in the current study demonstrated a reduction of 1.3 migraine days, which is lower than most CGRP studies, but higher than that of transcutaneus supraorbital nerve stimulation (t-SNS; 0.3),[36] and comparable to those of vagus nerve stimulation (VNS; 1.5)[30] and topiramate (1.1).[37] A low placebo effect could potentially contribute to a higher therapeutic gain (i.e., a higher difference between the groups); however, it is probable that in both arms of the study there was a similar placebo effect. Additionally, the therapeutic gain found in the current study (2.7 days) was higher than that of the three aforementioned studies with lower placebo effects (t-SNS 1.7,[36] VNS 0.7,[30] topiramate 1.3[37]), so that no indication for such an effect rises from these studies.

Four other neuromodulation devices for migraine are FDA cleared and are in clinical use in the United States. One is the aforementioned t-SNS device, called Cefaly™, which is indicated for acute and preventive treatment in adults. A recent meta-analysis

TABLE 4 Adverse events rate (ITT dataset).

Participants reported at least one AE	All	Active	Sham	*p*-value
Serious adverse events (SAE) (*n*, [%])	2 (0.8%)	2 (1.6%)	0 (0.0%)	0.498
Device-related SAEs (*n*, [%])	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
All AEs (*n*, [%])	41 (16.5%)	20 (15.6%)	21 (17.5%)	0.730
Device-related AEs (*n*, [%])	1 (0.4%)	0 (0.0%)	1 (0.8%)	0.484
Discontinuation due to AE (*n*, [%])	2 (0.8%)	1 (0.8%)	1 (0.8%)	>0.999

Abbreviations: AE, adverse event; ITT, intention to treat.

on neuromodulation techniques for migraine treatment by Moisset et al. finds that "Based on current evidence, it appears to be useful for preventive treatment and possibly acute treatment."[24] The VNS device, termed Gammacore™, is indicated for acute and preventive treatment in adults and adolescents aged 12 or more but "the Moisset meta-analysis" finds that it "cannot be recommended for migraine treatment based on the presented data."[24] The third device is spring TMS™, a portable single pulse transcranial magnetic stimulation device, which is indicated for acute and preventive treatment in adults. Last, an external combined occipital and trigeminal neurostimulation device called Relivion MG™ was recently FDA cleared for acute treatment for migraine in adults. The quality of this study was not reviewed by the meta-analysis.

The duration of the double-blind phase of the current study was 8 weeks long. While this is shorter than the recommended 12-week duration by the International Headache Society (IHS) guidelines for pharmacological therapies and neuromodulation devices,[37] demonstrating efficacy in a shorter period of time has the advantage of providing faster relief to patients.

With respect to limitations of the study, the subanalyses differentiating between participants who took additional preventive medications and those who did not are based on a partial, smaller sample size of those who took preventive medications. Moreover, medical history regarding failure on previous preventive medications was not collected during the study, yet half of the participants who took an additional preventive medication took second-line preventives, suggesting that first-line preventives had failed in the past. Thus, for a more profound assessment of the different responses among users of different preventive drugs, as well as history of preventive failures, a designated study may be required. Another limitation is that the definition of a migraine day included a possible combination of headache and aura, which is not in accordance with IHS guidelines;[38] however, no such instances were recorded, and thus this has no bearing on the study's results. Last, the study's inclusion criteria allowed for a single preventive agent, potentially limiting generalizability of the results in those taking two or more preventives. Relatedly, onabotulinumtoxinA injections as well CGRP mAb injections were allowed (provided that treatment has been stable for at least 2 months), and the specific timepoint in the cycle, and administration schedule (every 1/3 months) was not monitored, with some patients potentially experiencing a wearing off effect or a boost effect associated with the injection.

CONCLUSIONS

The use of REN every other day for preventive treatment of migraine was shown to result in a statistically significant and clinically meaningful reduction of migraine frequency, the primary endpoint, above and beyond the placebo effect. The significant results were also maintained in separate subanalyses of the chronic and episodic subsamples, and in participants using and not using pharmacological preventive medications. Significant reductions from baseline were also found in the mean number of headache days, moderate/severe headache days, acute migraine medication intake days, and proportion of participants achieving at least 50% reduction from baseline in number of headache days and moderate/severe headache days. The incidence of side effects was low, and no serious device-related AEs were reported.

These results indicate that REN is a safe and effective preventive treatment for migraine, offering a much-needed non-pharmacological alternative either as a stand-alone preventive therapy or in combination with pharmacological therapies to further enhance preventive impact. Given the previously well-established clinical efficacy and high safety profile in acute treatment of migraine, REN can cover the entire treatment spectrum of migraine, including both acute and preventive treatments.

AUTHOR CONTRIBUTIONS

Study concept and design: Robert P. Cowan, Brian M. Grosberg, Alon Ironi, Dagan Harris, Liron Rabany, Maya Vizel. *Acquisition of data*: Robert P. Cowan, Timothy R. Smith, Brian M. Grosberg, Bradley D. Torphy, Dagan Harris, Maya Vizel. *Analysis and interpretation of data*: Stewart J. Tepper, Liron Rabany, Alon Ironi, Alit Stark-Inbar, Dagan Harris, Andrew M. Blumenfeld. *Drafting of the manuscript*: Liron Rabany, Alon Ironi, Alit Stark-Inbar. *Revising it for intellectual content*: Stewart J. Tepper, Liron Rabany, Robert P. Cowan, Timothy R. Smith, Brian M. Grosberg, Bradley D. Torphy, Dagan Harris, Maya Vizel, Alon Ironi, Alit Stark-Inbar, Andrew M. Blumenfeld. *Final approval of the completed manuscript*: Stewart J. Tepper, Liron Rabany, Robert P. Cowan, Timothy R. Smith, Brian M. Grosberg, Bradley D. Torphy, Dagan Harris, Maya Vizel, Alon Ironi, Alit Stark-Inbar, Andrew M. Blumenfeld.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

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

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