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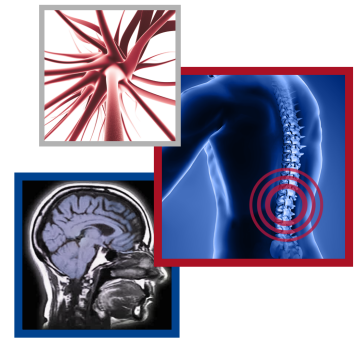

Temporal analysis of remote electric neuromodulation for the prevention of migraine

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Aim: To evaluate the onset, magnitude and persistence of efficacy of remote electrical neuromodulation (REN) compared with placebo for the preventive treatment of migraine. **Materials & methods:** Analysis was conducted on data from a prospective, double-blind, placebo-controlled clinical trial, which assessed the efficacy of REN for the prevention of migraine. The number of monthly migraine days (MMD) per group was calculated in 2-week intervals and compared between the groups. **Results:** Differences between the active (N = 95) and placebo (N = 84) groups reached significance at 2 weeks: therapeutic gain 0.84 MMD, $p = 0.036$. Four weeks gain 1.59 MMD; $p = 0.025$, 6 weeks gain 2.27 MMD; $p < 0.001$, 8 weeks gain 2.68 MMD; $p < 0.001$. **Conclusion:** REN provides rapid and consistent efficacy in preventive treatment of migraine.

First draft submitted: 9 April 2023; Accepted for publication: 28 July 2023; Published online: 24 August 2023

Keywords: headache • migraine • neuromodulation • nerivio • prevention • prophylaxis • remote electric neuromodulation • REN • treatment • timing

Preventive treatment is essential for effectively managing migraine and mitigating its burden [1]; however, adequate migraine prevention remains an unmet need [2]. The American Headache Society (AHS) Consensus Statement emphasizes the importance of preventive treatment in individuals with frequent disabling migraine attacks, contraindication to or overuse of acute medications or adverse events (AEs) [3].

While there has been substantial progress in migraine prophylaxis, resulting in reduced attack frequency and improved quality of life for some patients [4], migraine prevention and adherence to treatments remain significant challenges in the field [2]. With the growing interest in patient-centered drug development, there has been an increasing interest in patient preferences among physicians, regulators and healthcare technology appraisers [5].

People with migraine consider rapid impact as one of the most valued characteristics of preventive therapy. In a 2023 survey study that was conducted among 604 US adults diagnosed with migraine, the speed of onset was rated as a key preference (together with durability of effectiveness and mode of administration) [6]. In another study, participants were asked to rate seven different factors contributing to treatment satisfaction. The speed of onset was ranked as a top factor, second only to efficacy [7]. Similar results were found in additional studies that examined patients' preferences for migraine prevention [8,9]. Yet, the therapeutic benefits of some oral preventive drugs may take several weeks or months to manifest [10,11]. Given the substantial toll of migraine on patients' lives, there is a need for treatments that reliably address a person's preference and provide a rapid onset of action [12].

Nerivio® (Theranica Bioelectronics Ltd, Israel) is a remote electrical neuromodulation (REN) device [13,14] for the prevention and/or acute treatment of (episodic or chronic) migraine, with or without aura, in patients ages 12 and above [15–19], that is cleared by the US FDA. It is a wearable, wireless, battery-operated medical device, controlled by a smartphone application, that is applied for 45 min to the lateral upper arm.

Future Medicine

A recent randomized multi-center placebo-controlled clinical trial has demonstrated that REN is effective and safe for the prevention of migraine [19]. REN treatment, applied every other day, resulted in a significant improvement in the primary efficacy end point of mean monthly migraine days (MMD) assessed at the end of the 2 months of the double-blind intervention period; however, the temporal patterns of response, including onset and persistence of efficacy, have not been reported to date. The aim of the current analysis was to evaluate the onset, magnitude of response and persistence of benefit of REN compared with placebo, for the preventive treatment of migraine.

Methods

Dataset

The current *post-hoc* analysis was conducted on data from a prospective, double-blind, placebo-controlled multi-center randomized clinical trial (RCT), which evaluated the efficacy of REN treatment, applied every other day, for the prevention of migraine (NCT04828707) [19]. The information regarding the dataset and study design is identical between the RCT and the current *post-hoc* analysis, and thus these segments hereinafter are similar to those presented in the RCT publication [19]. The clinical trial was approved by Western Institutional Review Board (WIRB; approval number 20210751) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participants prior to the start of that study. The dataset analyzed in the current study is based on the Modified Intend to Treat (mITT) dataset of the RCT, as pre-registered (NCT04828707) and specified in the RCT publication [19]. It includes 95 participants in the active treatment group, and 84 participants in the placebo group.

The ITT dataset included all randomized participants. The mITT dataset included all ITT participants with at least 22 daily reports and at least 12 treatments in the last month of treatment (weeks 5–8). The treatment adherence criterion was selected to ensure sufficient treatment, and diary adherence criterion was used to ensure a sufficient number of daily reports to allow for a per-month (MMD) analysis of the reduction in the number of migraine days. To maintain an equal timeframe across participants, data were standardized to 28 days in the following manner:

$$28 \times \frac{(\text{reported migraine days})}{\text{report days}}$$

These procedures are common in migraine prevention studies, e.g., the Rimegepant prevention study [20].

Participants were men and women aged 18–75. The main inclusion criteria were: 6-month history of headaches that meet the ICHD-3 diagnostic criteria for migraine with or without aura, either chronic or episodic migraine [21]; 6–24 headache days (a headache day is defined throughout the study as a calendar day on which a headache is reported, of 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; 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. The main exclusion criteria were: use of opioids/barbiturates on more than 4 days per month in the last 6 months; current participation in another interventional study; pregnant or breastfeeding; other significant pain, medical or psychological condition that may confound the assessments; prior use of REN (Nerivio®).

Study design

The clinical trial included a 4-week baseline (observation) phase and an 8-week double-blind intervention phase. Participants used a designated electronic diary via the Nerivio app to fill 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); the presence or absence of nausea and/or vomiting, photophobia and phonophobia; and acute medication intake.

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.

Baseline phase

The study began with a 4-week baseline phase, in which participants were instructed to fill 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.

Double-blind intervention phase (weeks 0–8)

The intervention phase was 8 weeks long. Eligible participants were randomized in a 1:1 ratio to active or placebo groups. The active and placebo devices were visually identical, keeping both the staff and participants blind to the type of device. Participants were instructed to conduct a full 45-minute treatment with Nerivio every other day, and to fill the daily diary. Participants were instructed not to use Nerivio for acute treatment, and, when needed, treat their migraine/headache with their usual acute treatments.

Outcome measures

Monthly migraine days

Monthly migraine days (MMD) was calculated using a sliding window, so that for each bi-weekly time point, we totaled the number of migraine days in the preceding month (28 days). MMD was calculated throughout the intervention phase, in 2-week intervals (weeks 0, 2, 4, 6, 8) for each of the study groups.

Mean change from baseline

The mean change from baseline in MMD was calculated throughout the intervention phase, as a subtraction between the group's MMD value at that week and the group's MMD value at baseline (week 0).

Mean change from prior evaluation

The mean change from the prior evaluation in MMD was calculated throughout the intervention phase, as a subtraction between the group's MMD value at that week and the group's MMD value at the previous evaluation timepoint.

Group differences

Differences between the active and placebo groups in the reduction of MMD from baseline and from the prior evaluation were calculated throughout the double-blind period: i.e., weeks 2, 4, 6 and 8.

Statistics

A repeated measure analysis of variance (ANOVA) model was used, with group as a between-subjects factor, and week number as a within-subject factor. For each timepoint the mean change is presented per group, along with an SE, and a p-value for the comparison between the groups (statistical significance set at $p < 0.05$). The primary analysis includes all mITT participants, and the change from baseline analysis is repeated as sub-analyses of the episodic and chronic sub-sets (the data were not *apriori* powered to perform subgroup analyses). Demographic and clinical characteristics were compared between the groups using a two sample *t*-test.

Results

Participants

Demographic and clinical characteristics of the mITT study sample are presented in Table 1. No statistical difference was found between the groups in any of the parameters (for subject disposition data including ITT details and withdrawal rates see Appendix 1).

Timeline of preventive effect

Change from baseline in the number of migraine days per month per study group is presented in Table 2, along with a p-value representing the significance of the difference between the groups. The results indicate an onset of the difference between the groups starting at the first evaluated time point of 2 weeks from the beginning of the intervention. For monthly number of migraine days per group see also Figure 1.

The group comparison of change from prior evaluation was statistically significant at each of the tested timepoints: 2 weeks; $p = 0.036$, 4 weeks; $p = 0.038$, 6 weeks; $p < 0.001$, 8 weeks; $p = 0.002$.

Table 1. Demographic and clinical characteristics of the modified intend to treat dataset.

Parameter		All (n = 179)	Active (n = 95)	Sham (n = 84)	p-value[†]
Age (years)	Average (SD)	42.9 (13.1)	42.5 (12.3)	43.3 (14.0)	0.685
Gender	Female, n (%)	151 (84.4%)	80 (84.2%)	71 (84.5%)	0.954
	Male, n (%)	28 (15.6%)	15 (15.8%)	13 (15.58%)	
Race (n)	Caucasian, n (%)	167 (93.3%)	88 (92.6%)	79 (92.6%)	0.705
	Asian, n (%)	2 (1.1%)	0 (0.0%)	2 (2.4%)	
	Black/African–American, n (%)	8 (4.5%)	5 (5.3%)	3 (3.6%)	
	Other, n (%)	2 (1.1%)	2 (1.1%)	02 (0.0%)	
Chronic migraine[‡]	n (%)	124 (69.3%)	62 (65.2%)	62 (73.85%)	0.323
Preventive medications	n (%)	69 (38.5%)	32 (33.7%)	37 (44.0%)	0.136
Aura[§]	n (%)	43 (24.0%)	26 (27.4%)	17 (20.2%)	0.265

[†] *T*-test for continuous variables, chi-square test for nominal variables.
[‡] Diagnosed prior to enrollment.
[§] Aura preceding a migraine attack.

Table 2. Mean change from baseline in the number of migraine days per month.

Week	Active group (n = 95)		Placebo group (n = 84)		Group comparison	
	Mean migraine days per month	Mean change from baseline	Mean migraine days per month	Mean change from baseline	Therapeutic gain	Significance (p-value)
0	11.76	–	11.98	–	–	–
2	10.09	-1.67	11.15	-0.83	**0.84**	**0.036**[†]
4	8.69	-3.07	10.50	-1.48	**1.59**	**0.025**[†]
6	8.18	-3.58	10.67	-1.31	**2.27**	**<0.001**[†]
8	7.79	-3.97	10.69	-1.29	**2.68**	**<0.001**[†]

[†] Indicate statistical significance ($p < 0.05$).

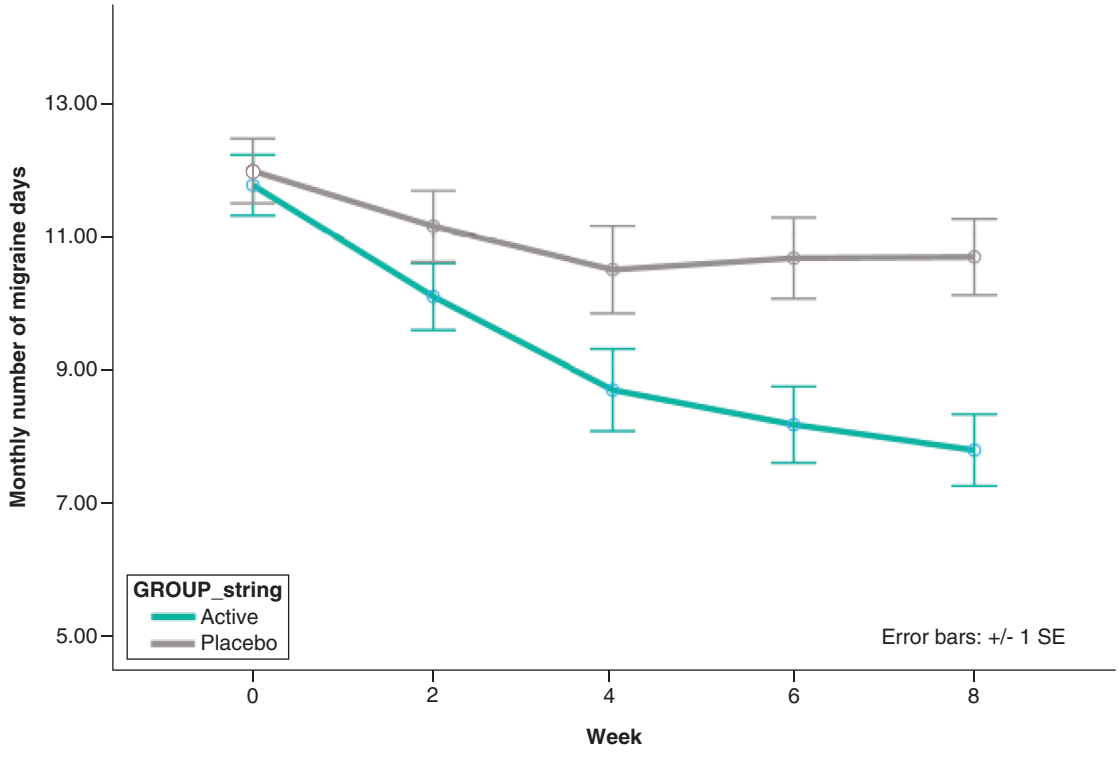

Figure 1. Monthly migraine days per group.

Table 3. Sub analysis of episodic and chronic sub-samples.

Characteristic	Week	Active group		Placebo group		Group comparison	
		Mean migraine days per month	Mean change from baseline	Mean migraine days per month	Mean change from baseline	Therapeutic gain	Significance (p-value)
Episodic n = 45:42	0	9.60	–	9.46	–	–	–
	2	7.87	-1.73	8.77	-0.69	**1.04**	**.039**†
	4	6.69	-2.91	8.49	-0.97	**2.13**	**.021**†
	6	6.66	-2.94	8.59	-0.87	**2.07**	**.008**†
	8	6.37	-3.23	8.50	-0.96	**2.27**	**.003**†
Chronic n = 50:42	0	13.71	–	14.49	–	–	–
	2	12.10	-1.61	13.52	-0.97	**0.64**	**.303**
	4	10.50	-3.21	12.50	-1.99	**1.22**	**.282**
	6	9.54	-4.17	12.75	-1.74	**2.4**	**.019**†
	8	9.07	-4.64	12.87	-1.62	**3.02**	**.002**†

†Indicate statistical significance ($p < 0.05$).
The bold text indicates the main results shown in the table.

Episodic & chronic sub-analysis

The sub-analyses of change from baseline in MMD in the episodic and chronic sub-samples is presented in Table 3.

Discussion

The current findings build upon the pivotal trial results and provide valuable clinical information on the efficacy time course of REN as a preventive migraine treatment.The results indicate a rapid and effective response to REN treatment, applied every-other-day, as early as 2 weeks from the beginning of the treatment, with an increased impact over time.

The differences between the active and placebo groups demonstrated statistical significance as early as the first tested timepoint of 2 weeks from the beginning of the intervention, with a therapeutic gain of 0.84 monthly migraine days at this early timepoint. The differences between the groups continued to show significant reductions over time: 4 weeks therapeutic gain of 1.59 MMDs ($p = 0.036$), at 6 weeks therapeutic gain of 2.27 MMDS ($p < 0.025$), and peak therapeutic gain of 2.68 MMDs ($p < 0.001$) after 8 weeks. A comparison of each evaluation to the prior timepoint indicated that the differences between the groups were not only maintained over time, but demonstrated a statistically significant increase during each interval.

These results are similar to those of some of the new oral CGRP migraine prevention medications, such as Atogepant [12], and superior to some current oral preventive drugs that necessitate several weeks or months of administration before demonstrating therapeutic benefits [12,22,23]. The results thus suggest that Nerivio provides a treatment option that addresses patients' preference by providing rapid onset of action, coupled with the high efficacy and low occurrence of side effects [19].

Analyses of the chronic and episodic sub-sets indicate a similar trend in both sub-groups. The episodic sub-set displayed statistical significance starting at the first measure timepoint of 2 weeks, with a therapeutic gain 1.04 MMD ($p = 0.039$). The effect grows over time and reaches its peak at 8 weeks (therapeutic gain 2.27 MMD, $p = 0.003$). The chronic sub-set starts with a therapeutic gain of 0.64 MMD ($p = 0.303$) at the 2-week timepoint, that becomes statistically significant at the 6-week timepoint with a therapeutic gain of 2.4 MMD ($p = 0.019$). The effect reaches its peak at 8 weeks, with a therapeutic gain of 3.02 ($p = 0.002$). While the therapeutic gain was not statistically significant until week 6 in chronic migraine patients, it should be noted that this is a *post-hoc* analysis of data from a clinical trial, the data were *apriori* powered to detect changes in the clinical study's primary and point (change from baseline to week 8 in MMD). The data were not powered to detect early sub-group response, and a bigger sample could have potentially detected statistically significant changes at an earlier timepoint. It is also important to note that most migraine prevention studies focus on either episodic or chronic participants (e.g. Atogepant [12], Topiramate [24], Cefaly [25]), and the separate analyses of these sub-groups provides important insights into the response patterns of these two populations.

The study's main limitation is its duration. Given that the double-blind period of the RCT was limited to 8 weeks, longitudinal data regarding the temporal dynamics of distinctions between the active treatment and placebo is not available. Such a study is currently being conducted.

Additionally, the analyze data were taken from a clinical RCT setting. While RCTs are considered to provide the highest standard of clinical data (in terms of adverse events monitoring, efficacy and more), they may also induce some degree of bias (e.g. via specification of admission criteria). A real-world analysis of the temporal patterns would complement the presented results, and is currently being conducted.

Conclusion

REN treatment applied every other day for the prevention of migraine was found superior to placebo as early as 2 weeks after the beginning of the intervention in both the whole group analysis and the episodic migraine sub-group. In the chronic migraine sub-sample statistical significance was achieved after 6 weeks of treatment. The difference between the active and placebo groups grew in magnitude at each bi-weekly measured time point, reaching a peak at 8 weeks. Collectively, the results indicate that REN provides effective early and sustained reduction in monthly migraine days.

Summary points

- Remote electrical neuromodulation (REN) has been previously shown to be safe and effective for the prevention of migraine.
- The current analysis was performed to assess the temporal patterns of response to REN treatment, used every-other-day over 2 months, for the prevention of migraine.
- Participants were randomly assigned to receive either a REN device (Nerivio®), or a placebo device. All participants were instructed to use the device every-other-day for 8 weeks, and to report their migraine attacks daily via a designated smartphone app.
- The mean number of monthly migraine days per group was calculated, in 2-week intervals (using a sliding window of 4 weeks).
- REN treatment was found superior to placebo at as early as 2 weeks after the beginning of the intervention, in both the whole group analysis and the episodic migraine sub-group.
- In the chronic migraine sub-sample statistical significance was achieved after 6 weeks of treatment.
- The difference between the active and placebo groups grew in magnitude at each bi-weekly measured time point, reaching a peak at 8 weeks.
- Collectively, the results indicate that REN provides effective early and sustained reduction in monthly migraine days.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/pmt-2023-0039

Financial & competeing interests disclosure

The study was funded by Theranica Bio Electronics LTD. AM Blumenfeld: speaker bureau/ advisory board – Abbvie, Allergan, Aeon, Biohaven, Lilly, Impel, Collagium, Amgen, Lundbeck, Theranica, Axsone, Revance. L Rabany, A Stark-Inbar, D Harris and A Ironi are Thranica employees. They receive a salary and hold stock options. AM Harrriott: Science Committee American Academy of Neurology, Board of Directors of the American Headache Society, Board of Directors American Migraine Foundation, Board of Directors Headache Cooperative of New England, Scientific Advisory Board for Theranica, Authorship agreement Abbvie, Received study drug for research from Praxis Inc. RB Halker Singh: Royalties – Oxford University Press, Editorial services – Current Neurology and Neuroscience Reports, Headache Journal. 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.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The clinical trial from which the presented dataset is taken was approved by Western Institutional Review Board (WIRB; approval number 20210751) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the participants prior to the start of that study.

Data sharing statement

Data will be shared upon request from the authors.

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