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Study title:	Real-World Evidence (RWE) of Usage of Nerivio, a Remote Electrical Neurostimulation (REN) Device In Adolescents Patients With Migraine
Test Device:	Nerivio
Indication studied:	Acute treatment of migraine
Study description:	Prospective, single arm, open label post market study
Sponsors:	Theranica Bioelectronics Ltd
Protocol:	RWE-003 ver 1.0 01-Jan-2021
Clinical Phase:	Post market study

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Study RWE-003

Title	Real-World Evidence (RWE) of Usage of Nerivio, a Remote Electrical Neurostimulation (REN) Device In Adolescents Patients With Migraine
Sponsor	Theranica Bio-Electronics Ltd. 4 Ha-Omanut St., Netanya, Israel
Investigational Device	Nerivio is a Remote Electrical Neuromodulation (REN) wearable, battery-powered medical device for the acute and/or preventive treatment of migraine with or without aura in patients 12 years of age or older. Nerivio is controlled by a mobile application. Nerivio is intended for self-administration in a home healthcare environment. The device is worn on the upper arm and transmits transcutaneous remote electrical nerve stimulation by applying weak electrical pulses that invoke conditioned pain modulation (CPM) to inhibit migraine pain. Nerivio is intended for self-administration at the onset of a migraine episode.
Objectives	To evaluate the safety, utilization and efficacy of Nerivio in adolescent patients (Age 12-18) who used the Nerivio device for treating their migraine
Patient Population	Nerivio users aged 12-18 years old who registered a Nerivio account and used the Nerivio device for the acute treatment of migraine.
Sample size	The sample size will includes all Nerivio users in the age of 12-18 in the Nerivio database who treated with Nerivio at least once between Jan 01, 2021 and May 31, 2022
Inclusion criteria	• Age between 12-18 years • REN user across the United States who created Nerivio account on January 1st, 2021 until May 31, 2022. • Had at least two evaluable treatments with the Nerivio device (for consistent efficacy analysis).
Exclusion criteria	• Treatments shorter than 20 minutes will not be included in the analysis

Study Design	The analysis included patients at the age of 12-18 (at the day of opening a Nerivio account) with migraine across the USA who used Nerivio at least once between January 01, 2021, and May 31, 2022. Treatment data will be collected through the Nerivio app (Nerivio®) which is required for treatment. Device output current is set by the user to be strong but not painful and is equivalent to treatment dosage (max device current 40 mA on 0-100 units user-facing scale). Additionally, patients can voluntarily log details about their symptoms at both treatment onset and 2-hours post-treatment status. Treatment efficacy will be measured by consistent reduction in headache pain intensity and functional disability at 2-hours post-treatment, based on data from patients who voluntarily will answer the pre and post treatment questionnaires. Safety will be assessed by the rate of device related adverse event reported by the patients.
Evaluable Treatment	Evaluable treatment is a treatment that meets all the following criteria: • Baseline and 2-hour post-treatment pain intensity and functional disability scores were recorded. • The participant did not use any concomitant acute migraine medication during the treatment.
Efficacy endpoints	1. **Pain Relief:** Reduction in pain intensity from moderate or severe (baseline score of 2 or 3) to mild or no pain (score of 1 or 0) at 2 hours post-treatment. 2. **Pain Freedom:** Reduction in pain intensity from mild, moderate, or severe (baseline score of 1, 2, or 3) to no pain (score of 0) at 2 hours post-treatment. 3. **Functional Disability Relief:** Reduction in functional disability by at least one point from baseline at 2 hours post-treatment. 4. **Functional Disability Freedom:** Reduction in functional disability from mild, moderate, or severe (baseline score of 1, 2, or 3) to no disability (score of 0) at 2 hours post-treatment.
Utilization endpoints	5. **Consistent Usage of Migraine Abortive (Rescue) Medications:** The proportion of subjects with REN treatments without the use of pharmacological migraine abortive (rescue) medication (either over the counter or prescribed), or with a combination of rescue medication or without any treatment at all at 2 hours post-treatment in at least 50% of all their treatments. **6. Treatment intensity distribution:** The mean intensity of the stimulation collected for all treatments that were performed within the study
Safety endpoints	Rate of serious adverse events, adverse events and device-related adverse events

Data collection	Data will be collected prospectively through the Nerivio smartphone application, At the time of creating a Nerivio account on the App, patients (and their parents, in case of patients younger than 18) are required to sign a consent statement presented to them, where they agree that their deidentified data may be collected and used for reserve purposes. Prospective data was collected for Nerivio users in the United States who treated their migraine attacks with the Nerivio device. Nerivio utilization, and Nerivio treatment reports at T=0h and T=2h were extracted from the Nerivio server in an unidentified manner. Data will be analyzed per user following additional analysis per the target population. The following data will be extracted: • Demographics: Age at registration, gender. • Treatment Details: Treatment date, baseline pain intensity, pain intensity at 2 hours post-treatment, baseline functional disability, functional disability at 2 hours post-treatment. • Treatment Frequency: Number of treatments per month over the 12-months period. • Pain Intensity: 0 (no pain), 1 (mild), 2 (moderate), 3 (severe). • Functional Disability: 0 (no disability), 1 (mild interference), 2 (moderate interference), 3 (severe interference). • Additional migraine symptoms (Nausea/ vomiting, Photophobia, Phonophobia)
Statistical considerations	See at the end of the document
Responder Definition	For each efficacy endpoint, a participants will be considered a responder in if they achieved the defined outcome in at least 50% of their evaluable treatments during that study period.

STATISTICAL CONSIDERATIONS FOR RWE-003 STUDY

The study hypothesis was that treatments of migraine with the Nerivio device In adolescents will demonstrate similar results to the results previously found in adults

DATA COLLECTION

BASELINE DATA

Baseline participant characteristics (age, gender) will be collected from the Nerivio account of each participant.

UTILIZATION DATA

Utilization information is pulled out from the Nerivio server for each treatment

TREATMENT DATA

Treatment data will be retrieved from the Nerivio app for each treatment. Data includes automatic parameters (e.g time of treatment, location, device serial number, treatment intensity etc...) and individual information completed by the participant (pain level before and after the treatments, migraine symptoms, functional disability before and after the treatment etc...)

SAFETY DATA

All safety information will be pulled out from the Nerivio support center and/or additional safety reports from other sourced that are register in Nerivio database.

STATISTICAL ANALYSIS

Demographic and Baseline Analysis

Demographic and baseline condition related characteristics will be tabulated and compared between the participant data types. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum and categorical variables by a count and percentage.

Safety Endpoints Analysis

The rate of device related adverse event (DRAE) will be calculated ad the number of reported DRAE divided by the number of participants in the study.

Efficacy Endpoints Analysis

Generalized linear mixed model (GLMM) will be used to compare the effect of treatment month on efficacy rate outcomes.

Utilization Endpoints Analysis

Utilization outcome will be calculated from the treatment parameters (intensity levels) and the treatment reports (usage of rescue medications), and will be presented in appropriate distribution tables.

Qualifies treatment was defined as

1 - Attacks treated with Nerivio for at least 20 minutes

2 – Pre and post treatment data were reported by the participant for the specific treatment

3 – No rescue medications were taken before and during the 2 hours post treatment, according to the participant report

Consistent efficacy will be conducted in cases where at least two qualified treatments were performed. Patients who experienced the outcome (e.g., pain freedom) in at least 50% of their reported treatments, during which they did not report the use of rescue medications, were considered responders.

Headache pain and functional disability will be rated at baseline and at 2 h post-treatment on a 4-point scale: severe, moderate, mild, or none. Migraine associated symptoms (photophobia, phonophobia, and nausea/vomiting) will be marked as present or not.

Pain relief will be calculated as a decrease from severe or moderate levels at baseline to mild or none at 2 h posttreatment.

Functional disability relief will be calculated as any improvement in disability from baseline to 2 h posttreatment.

Pain/functional disability freedom will be calculated as a decrease from any pain/disability level at baseline to none at 2 h post-treatment.