Approval				
	Name	**Position**	**Date**	**Signature**
Revised by	Dagan Harris	VP Clinical and Regulatory affairs	10-Feb-2024	
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Approved by	Alon Ironi	CEO	10-Feb-2024	

Effective date of the document is from the date of approval.

Change History			
Rev	**Rev. Date**	**Revised by**	**Change description and reason for change**
1.0	01-Oct-2023	Dagan Harris	Initial version
2.0	10-Feb-2024	Dagan Harris	Increase sample size, add additional analysis

Clinical Study Protocol

A prospective, single arm, open label post market study assessing the safety and efficacy of Nerivio for the treatment of migraine in children under the age of 12

ClinicalTrials.gov Identifier: NCT06138756

Feb 01, 2024. Rev. 2

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1 TITLE PAGE

Study title:	A prospective, single arm, open label post market study assessing the safety and efficacy of Nerivio for the treatment of migraine in children under the age of 12
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-009
Clinical Phase:	Post market study
Study period:	First user first treatment - May 2020 Last user last treatment - October 2023
Investigators:	Dr Alit Stark Inbar
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2 RWE-009 Study Protocol

Title	A prospective, single arm, open label post market study assessing the safety and efficacy of Nerivio for the treatment of migraine in children under the age of 12
Investigational Device	Nerivio is an FDA-approved remote electrical neuromodulation (REN) device for the acute and/or preventive treatment of migraine with or without aura in patients 12 years of age or older. Nerivio delivers transcutaneous electrical stimulation to the upper arm to induce conditioned pain modulation (CPM) that activates a descending endogenous analgesic mechanism. The treatment is self-administered and controlled by a smartphone application.
Objectives	The study assessed the safety and efficacy of Nerivio for acute treatment of migraine in children under the age of 12.
Participant Population	Children who were prescribed with the Nerivio device for the treatment of migraine and were under the age of 12.
Sample size	The sample size was defined as all Nerivio users in the Nerivio database under the age of 12 in the day of their first treatment
Inclusion Criteria	• Prescribed with Nerivio device for the treatment of migraine • Age under 12 at their first Nerivio treatment • Treat with Nerivio at least once
Exclusion Criteria	• Treatments shorter than 30 minutes
Study Design	A prospective, data analysis of users that met the inclusion criteria was performed. All data that were reported prior and following the treatments by the users using the electronic diary within the Nerivio application were downloaded from Theranica server in an unidentified manner.
Primary endpoint - Safety	**<u>Rate of Device Related Adverse Events</u>** Incidence of device-related adverse events (DRAEs) reported by subjects. a) Percentage of patients reporting DRAEs b) Severity of reported DRAEs

Secondary endpoints - efficacy	**Consistent Headache Relief at 2 Hours Post-treatment.** The proportion of subjects reporting headache relief at 2 hours post-treatment in at least 50% of all their treatments. **Consistent Freedom from Headache at 2 Hours Post-treatment.** The proportion of subjects reporting freedom from headache at 2 hours post-treatment in at least 50% of all their treatments. **Freedom from a specific migraine associated symptom.** Freedom from a specific migraine associated symptom was calculated as the percent of patients reporting the presence of that symptom at baseline, and the lack of that symptom at 2-hours post-treatment in at least 50% of all their treatments. Per the ICHD-3, migraine associated symptoms are: a) Hyper sensitivity to light (phonophobia) b) Hyper sensitivity to sound (phonophobia) c) Nausea (with or without vomiting) **Functional disability relief** Functional disability relief was calculated as decrease of at least one level of functional disability from baseline to 2-hours post-treatment in at least 50% of all their treatments. Disability levels are (0) none (full function), (1) mild disability, (2) moderate disability, and (3) severe disability. **Freedom from functional disability** Freedom from functional disability was calculated as decrease from any disability level (3, 2, or 1) at baseline to no disability (i.e., return to full function) at 2-hours post-treatment in at least 50% of all their treatments.
Exploratory efficacy endpoints	**Use of migraine medications** Treatment patterns of Nerivio use as a standalone treatment vs. in combination with medications were extracted from the 2-hours post-treatment reports, as the percentage of treatments in which no rescue headache medications were used (Nerivio standalone), or Nerivio was used with over-the-counter (OTC) medications, or with prescription medications (Rx). **Nerivio treatment stimulation intensity** Treatment intensity (stimulation current) is set by patients via the smartphone app and automatically recorded. The average intensity over all treatments per patient was calculated to provide personal intensity levels, which was used for the analyses. Average personal intensity levels and the range for 80% of the users were calculated over the patient cohort. **Nerivio utilization** Average (and/or median) of number of Nerivio treatments per month. A specific cohort of this outcome considers safety in patients who use the device at high frequency, close to the every-other-day regime of preventive treatment.

Datasets	1. Intent to treat analysis set (ITT) The ITT analysis set includes all users who had at least one treatment 2. Modified intent to treat analysis set (mITT) The mITT analysis set includes all ITT participants who had at least 2 treatments with prospective electronic diary reports at the beginning of the treatment (“baseline”) and 2 hours post the beginning of the treatment.
Data Analysis	The ITT analysis set was used for the safety assessments and the mITT analysis set was used for the efficacy assessments.

STATISTICAL CONSIDERATIONS FOR RWE-009 STUDY

The study hypothesis was that treatments of migraine with the Nerivio device in children will be as safe and effective as previously described in adolescents and adults.

DATA COLLECTION

BASELINE DATA

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

TREATMENT DATA

Treatment data was 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...)

COMPUTER SOFTWARE

All statistical analyses and data presentations, including tabulations and listings, were performed using the SAS version 9.4 software.

STATISTICAL ANALYSIS

Demographic and Baseline Analysis

Demographic and baseline condition related characteristics will be tabulated and compared between the participant age data type. 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) was calculated ad the number of reported DRAE divided by the number of participants in the study.

Efficacy Endpoints Analysis

All the endpoints will be calculated for Qualified Attacks only, Qualifies treaterent was defined as

1 - Attacks treated with Nerivio for at least 30 minutes

2 – Pre and post treatment data wasreported 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 was 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 were 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) were marked as present or not.

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

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

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

Freedom from a specific migraine-associated symptom was calculated as the percentage of patients reporting the presence of that symptom at baseline and the lack of that symptom at 2 h post-treatment. Freedom from at least one associated symptom was calculated as the percentage of patients in which one or more associated symptom(s) were reported at baseline and the lack of at least one of those symptoms at 2 h post-treatment.