Approval				
	Name	**Position**	**Date**	**Signature**
Revised by	Tamar Lin	Chief Scientist		
Reviewed by	Dagan Harris	VP clinical and regulatory affairs		
Approved by	Alon Ironi	CEO		

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

Change History				
Rev	**Rev. Date**	**Revised by**	**Change description and reason for change**	**Training is required? Y/N**
1.0	01-July- 2019	Tamar Lin	Initial version	N

CLINICAL CLINICAL INVESTIGATION PLAN

STUDY TITLE:

A single arm, open label, multicenter study of the safety and efficacy of Nerivio™ for the acute treatment of migraine in adolescents

PROTOCOL NUMBER:	**TCH004**
REVISION:	1.0
RELEASE DATE:	01/July/2019
DEVICE:	Nerivio, a Neuromodulator device for the acute treatment of migraine
INVESTIGATOR:	_____
SPONSOR:	Theranica Bio-Electronics Ltd 4 Ha-Omanut st, Netanya, Israel
CONTACT DETAILS:	Dagan Harris, VP Clinical & Regulatory Tel: +972.72.390.9758 Fax: + 972.72.390.9762 Mobile: +972-0542220121 EMAIL: daganh@theranica.com

APPROVED BY:	POSITION:	DATE: (DDMMYY)	SIGNATURE:
_____	_____	_ _/_ _/_ _	_____
_____	_____	_ _/_ _/_ _	_____

The sponsor of this study, Theranica Bioelectronics Ltd, manufacturer of the Nerivio device for the acute treatment of migraine, states the following:

a) This study will be conducted in compliance with the protocol (after being approved by the local IRB/EC and, if required, by the relevant health care agencies), US 21 CFR Parts 50, 54, 56 and 812, 45 CFR Part 46, national laws and regulation concerning clinical trials, the Good Clinical Practices (GCP) set forth in ISO 14155 (2011) standard and the ethical principles that have their origin in the Declaration of Helsinki.

b) The Protocol, Informed Consent Form (ICF), patient's information material, and advertising material (if applicable) will be submitted and approved by the ethics and regulatory authorities, and any request by the IRB/EC or regulatory agencies will be complied with. Approval will be obtained prior to enrollment of any patients.

c) Adequate insurance policy will be held valid for the entire study duration as well as for the discovery period required per local regulation.

Protocol Signature Page for Investigator

The signing of this Clinical Investigation Plan (CIP) by the Principal Investigator signifies that the contents have been laid down in full agreement and that the study will be conducted per this CIP, its amendments, the clinical trial agreement and the applicable regulatory requirements.

The Principal Investigator confirms that written Institutional Review Board (IRB) Ethics Committee approval for the amended CIP will be obtained prior to commencing with data collection. This approval must be in the Principal Investigator's name and a copy sent to Theranica Bioelectronics. Additionally, the Principal Investigator must sign the declaration below:

I will provide copies of this CIP and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the conduct of the Study.

Investigator's Signature	Date
Investigator's Printed Name	
Site Name	Site #

A single arm, open label, multicenter study of the safety and efficacy of Nerivio™ for the acute treatment of migraine in adolescents

Table of contents

1. Synopsis

Title	A single arm, open label, multicenter study of the safety and efficacy of Nerivio™ for the acute treatment of migraine in adolescents
Sponsor	Theranica Bio-Electronics LTD. 45 HaMelakha st, Netanya, Israel
Investigational Device	Nerivio™ is an FDA-authorized remote electrical neuromodulation (REN) device for the acute treatment of migraine with or without aura in patients 18 years old or above who do not have chronic migraine. The device delivers transcutaneous electrical stimulation to the upper arm to induce conditioned pain modulation (CPM) that activates a descending endogenous analgesic mechanism. The electrical stimulation generated by the device is similar to other FDA approved electrostimulation devices. The treatment is self-administered and controlled by a smartphone application. A recent pivotal study in adults demonstrated that the device provides an effective acute migraine treatment with a favorable safety and tolerability profile.
Objectives	To evaluate the safety and efficacy of Nerivio™ in the acute treatment of migraine in adolescents (12 to 17 years of age).
Participant Population	Adolescents 12-17 years old meeting the International Headache Society criteria (ICHD-3) for migraine with or without aura, with a least 3- migraine attacks per month.
Sample size	Up to 130 participants
Inclusion Criteria	1. Participants age 12-17 years old at the time of informed consent, inclusive. 2. Participants have at least a 6-month history of headaches that meet the ICHD-3 diagnostic criteria for migraine with or without aura 3. History of at least 3 migraine attacks per month for each of the 2 months preceding study enrolment 4. Typical headache duration of at least 3 hours (when untreated or unsuccessfully treatment) 5. Stable migraine preventive medications during the 2 months prior to enrollment (no change in usage or dosage). 6. Participants have personal access to a smartphone (24/7) 7. Participants must be able and willing to comply with the protocol 8. Parents/Guardians must be able and willing to provide written informed consent 9. Participants must be able and willing to provide informed assent
Exclusion Criteria	1. Participants with an implanted electrical and/or neurostimulator device (e.g. cardiac pacemaker, cochlear implant). 2. Participants with congestive heart failure (CHF), severe cardiac or cerebrovascular disease. 3. Participants with epilepsy. 4. Medical use of cannabis or recreational use one month prior to enrollment. 5. Participants who have undergone nerve block (occipital or other) in the head or neck within the last 2 weeks 6. Treatment with onabotulinum toxin A (Botox) to the head and/or neck for 3 months before enrollment and/or during the study 7. Any history of anti-CGRP antibody treatment 8. Current participation in any other clinical study that includes treatment 9. Participants without basic cognitive and motor skills required for operating a smartphone.

	10. Pregnant or breastfeeding females 11. Pure menstrual migraine 12. Participants who received parenteral treatments for migraine within the previous 2 weeks. 13. Participants with other significant pain, medical or psychological problems that in the opinion of the investigator may confound the study assessments 14. Participants who have previous experience with the device 15. Participants with arm circumference below 7.9 inches (20 cm)
Study Design	A prospective, single arm, open label, multicenter trial. The study will be conducted in three phases: <u>Phase I - Run-in:</u> Eligible participants will be trained to use a smartphone migraine diary application for 4 weeks. Participants who report at least 3 migraine attacks with at least 3 hours duration (if not treated or if unsuccessfully treated), will be included in the treatment phase. <u>Phase II - Treatment phase:</u> Participants who meet the run-in requirements will receive an active Nerivio device. Participants will be instructed to use the device for the treatment of 4 qualifying migraine attacks (see below) within 60 minutes of onset during a period of up to 8-week. The participants will use the app to record pain intensity levels at baseline, 2- and 24-hours post-treatment, and to record the presence/absence of associated migraine symptoms (nausea, photophobia, phonophobia) at baseline and 2 hours post-treatment. The first reported treatment will be considered a "training" treatment, aimed to verify the participants use the device properly, and will only be included in the safety analysis. The first treatment of a qualifying attack after the training treatment is considered a test treatment and will be used for all efficacy analyses. The efficacy endpoints will be assessed on evaluable treatments of qualifying attacks. <u>Phase III (optional) - Free-use:</u> Participants who complete the treatment phase will be offered the opportunity to participate in an 8-week free-use phase in which they will be able to incorporate the Nerivio device into their usual care.
Qualifying migraine attack	A qualifying migraine attack is defined as a migraine attack that: 1. was not preceded by another migraine attack or other headache within the preceding 24 hours 2. was not preceded by the use of specific or non-specific acute migraine medications within the previous 24 hours 3. occurred in a setting in which the patient could properly administer the treatment (that is, it is possible to initiate a complete treatment within 60 minutes of onset and the participant will be able to complete the migraine diary at 2 hours after treatment)
Primary endpoints	1. <u>The safety of Nerivio</u> The incidence of adverse events in general and by seriousness, severity and association to the device. 2. <u>Treatment tolerability</u> The percent of subjects who fail to complete the study because of adverse events
Secondary endpoint	1. <u>Pain relief at 2 hours post-treatment</u>: The proportion of participants achieving pain relief at 2 hours post-treatment in the test treatment, with no use of rescue medication 2. <u>Pain-free at 2 hours post-treatment</u>:

	The proportion of participants achieving pain freedom at 2 hours post-treatment in the test treatment, with no use of rescue medication 3. Disappearance of associated symptoms at 2 hours post-treatment I. Disappearance of nausea in the test treatment at 2 hours post-treatment II. Disappearance of phonophobia in the test treatment at 2 hours post-treatment III. Disappearance of photophobia in the test treatment at 2 hours post-treatment
Exploratory endpoints	1. Sustained pain relief at 24 hours post-treatment: The proportion of participants achieving pain relief at 2 hours post-treatment in the test treatment, with no use of rescue medication and no relapse of headache pain within 24 hours 2. Sustained pain-free at 24 hours post-treatment: The proportion of participants achieving pain freedom at 2 hours post-treatment in the test treatment, with no use of rescue medication and no relapse of headache pain within 24 hours 3. Functional disability at 2 hours post-treatment The proportion of participants achieving improvement of at least one grade in functional disability in the test treatment at 2 hours post-treatment with no use of rescue medication 4. Functional disability at 24 hours post-treatment The proportion of participants achieving improvement of at least one grade in functional disability in the test treatment at 24 hours post-treatment with no use of rescue medication
Datasets	1. Intent to treat analysis set (ITT) The ITT analysis set includes all participants undergoing the treatment phase. 2. Modified intent to treat analysis set (mITT) The mITT analysis set includes all participants undergoing the treatment phase who treat a test treatment within 60 minutes of attack onset.
Data Analysis	The ITT analysis set will be used for the primary endpoints of safety and tolerability assessments. Safety assessments will include spontaneously reported adverse events. The mITT analysis set will be used for the efficacy assessments.

2. Background

Migraine is one of the most prevalent and disabling neurologic disorders [1], characterized by recurrent headache attacks with nausea, vomiting, photophobia, and phonophobia [2]. Migraine is also common in adolescents (12 to 17 years of age) [3]. Migraine in adolescents has also been associated with disability as evidenced by missed school days [4], poorer performance in school [5] and a negative impact on quality of life [6].

The majority of current migraine acute treatments for adolescents are pharmacological [7]. Not all adolescents find these to be effective, they can cause side effects, and their overuse may lead to medication overuse headache [8,9] and migraine chronification [10]. According to the American Academy of Neurology (AAN) and Child Neurology Society (CNS) evidence-based guidelines, ibuprofen, acetaminophen and sumatriptan nasal spray should be considered for the acute treatment of migraine in adolescents, but there is no supporting data for the use of oral triptans in adolescents [11]. Thus, there is a great unmet need for alternative acute migraine treatments that are both effective and well tolerated. Such developments hold the potential to improve the health and quality of life of youth with migraines.

Non-invasive neuromodulation is safe, well-tolerated, and may have fewer adverse effects than drugs [12,13]. However, the efficacy of current neuromodulation devices approved for migraine acute treatment in adults (above the age of 18 years) has not been established in adolescents. Thus, new non-pharmacological alternative acute migraine treatments are needed. Remote electrical neuromodulation (REN) [14] is a novel acute migraine treatment which stimulates upper arm peripheral nerves to induce conditioned pain modulation (CPM) - an endogenous analgesia mechanism in which conditioning stimulation inhibits pain in remote body regions [15].

The safety and efficacy of REN (Nerivio™, Theranica Bio-Electronics LTD., Israel) has been recently assessed in adults in a randomized, double-blind, sham-controlled multi-center study (NCT03361423). This study demonstrated that REN provides superior clinically meaningful relief of migraine pain and MBS compared to placebo, offering a safe and effective non-pharmacological alternative for acute migraine treatment. Specifically, the active stimulation was more effective than sham stimulation in achieving pain relief (66·7% [66/99; $CI_{95\%}$ 56·48-75·82] vs. 38·8%, p<0·001), pain-free (37·4% vs. 18·4%, p<0·005) and MBS relief (46·3% vs. 22·2%, p<0·001) at 2 hours post-treatment, and that the pain relief and pain-free superiority of the active treatment was sustained 48 hours post-treatment. In addition, the incidence of device-related adverse events was low and similar between treatment groups (4·8% vs. 2·4%, p=0·49). All device-related adverse events were mild, did not required medical intervention and resolved within 24 hours. The device was granted a 510k De novo approval (DEN180059)

The aim of the present study is to evaluate the safety and efficacy of REN for the acute treatment of migraine in adolescents.

3. Identification and description of the device information

3.1. Intended use

Current indication for use of the device:

The Nerivio™ is indicated for acute treatment of migraine with or without aura in patients 18 years of age or older who do not have chronic migraine. It is a prescription use, self-administered device for use in the home environment at the onset of migraine headache or aura.

This study aims to expand the current indication to include adolescents (12-17 years of age).

3.2. Device description

The device is a wireless wearable battery-operated stimulation unit controlled by a smartphone software application. Treatments with Nerivio™ are self-administered by the user at the onset of a migraine attack.

The Nerivio™ is a fully integrated unit similar in appearance to an adhesive armband made of thermoplastic polyurethane (TPU). The device includes several main components:

- A pair of electrodes covered with hydrogel and a removeable protective film
- An electronic circuitry and a battery contained in a plastic case
- A software that includes firmware and a software application for mobile platforms
- An armband to improve the adhesiveness and enable a discreet treatment

The external side of the Nerivio™ (Figure 1) includes an "on" switch and a LED indicator that signals various modes of operation, located on the enclosure. The internal side includes the electrodes and a biocompatible adhesive material that holds the device in its location. The armband is applied over the device to further secure its location on the arm and conceal the device to enable a discreet treatment.

The device produces a proprietary electrical signal comprising a modulated symmetrical quad-phasic 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).

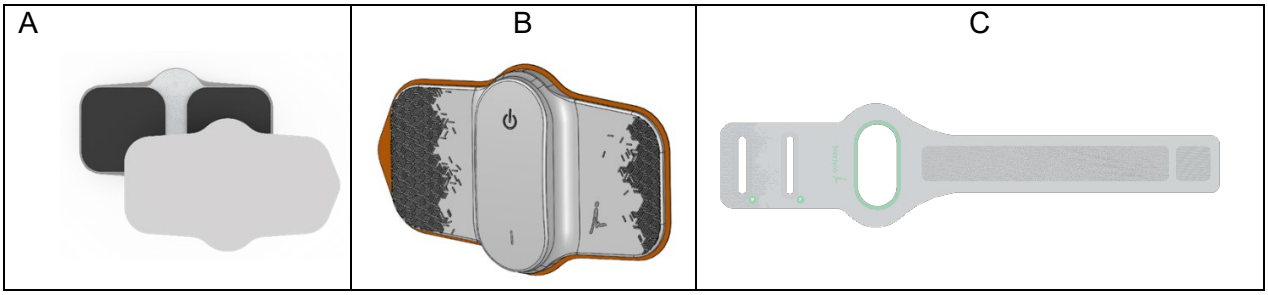

Figure 1 - Nerivio™ device. (A) Internal side, (B) External side, and (C) The armband

3.3. The application

Activation, control over stimulation intensity and termination of stimulation are performed via a dedicated smartphone application and installed on the user's cell phone. The application has a graphical user interface (GUI) which includes graphical controls that the user can select using a touch screen. The home screen (**Error! Reference source not found.**) provides access to information about migraine treatments and the system. In this screen the user can start treatments, review the history of migraine treatments and change device settings. A treatment is initiated, monitored and stopped in the treatment screen. In this screen the user sets the intensity level using "+" and "-".

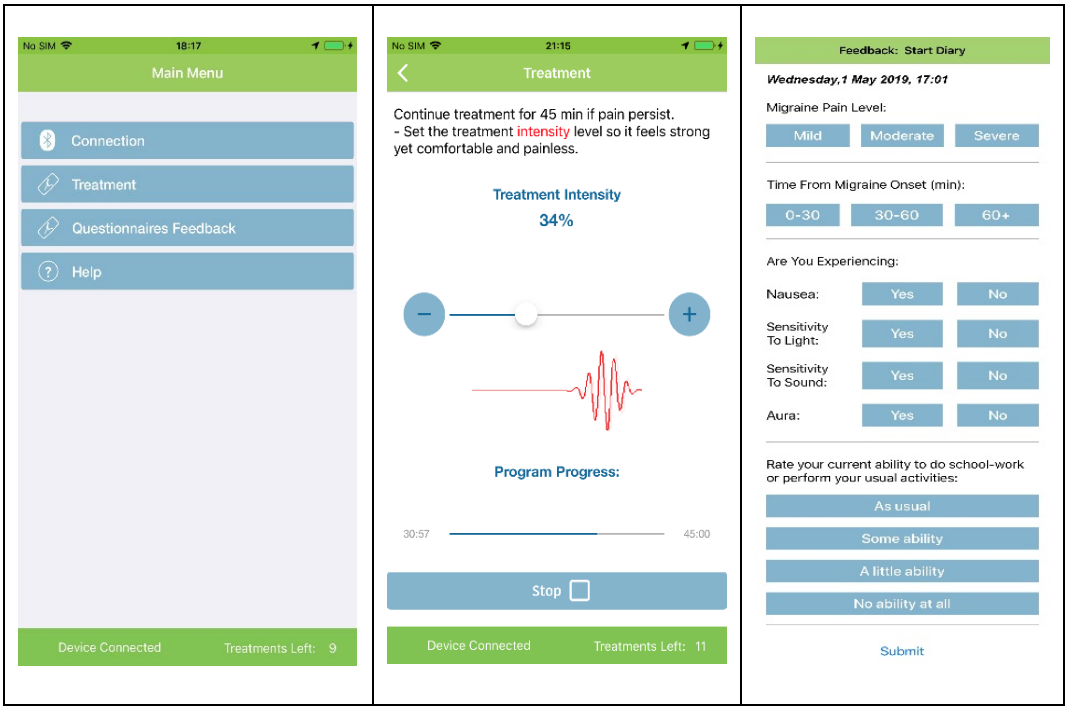

Figure 2: The app screens

The Nerivio application also includes a 'migraine diary' which collects information on the migraine episode and treatment (e.g. date & time, location, headache pain intensity, etc.). The application also provides notifications and indications on connection state and remaining number of treatments.

The device communicates with the mobile application software through a Bluetooth® radio protocol (BTLE) which uses 2.4GHz carrier.

The application can be installed from Google Play or the App store and supports Hebrew and English menu displays.

3.4. Operational context

Nerivio™ is a wearable, battery-powered medical device for the acute treatment of migraines with or without aura. Nerivio™ delivers transcutaneous electrical nerve stimulation (TENS) through the control of the Nerivio™ iOS or Android app. Nerivio™ is a home-use device that requires prescription but does not require training. The device is provided with a user manual. The first use of the device requires the user to install the app and pair the smartphone to the device. In each treatment, the intensity level should be individually set so it feels strong yet comfortable and painless. The battery of the device is non-rechargeable, the electrodes should be covered with protective liners and the device should be stored in its original package.

Nerivio™ should be placed on the user's arm (Figure 3) at the onset of a migraine episode, the device should then be turned on and a treatment can be activated via the mobile application. The treatment includes a weak electrical current delivered to the skin via the electrodes. The arm was chosen for several reasons. First, it is distal from the head, enabling to produce CPM. Second, it may be easily accessed independently by the user without the help of others. Finally, it provides a discrete location that maintains the privacy of the user and enables to continue with ongoing activities during treatment.

Figure 3 - Nerivio™ location of treatment

3.5. Principle of operation

Conditioned pain modulation (CPM) is a descending endogenous analgesic mechanism that originates in the brainstem (rostral ventromedial medulla), in which pain in one part of the body inhibits pain in multiple remote body regions [15]. According to this well-established mechanism, also known as "pain inhibits pain", the intensity of a painful stimulus can be reduced by a second painful stimulus at a different location [16,17]. Notably, it has been shown that very strong but subjectively non-painful stimulus is sufficient to trigger pain inhibitory effects [18].

From a neuronal level, noxious sensory information is carried by two primary afferent fibers – the Aδ and C fibers (Table 1). Aδ fibers are small myelinated afferents that respond to mechanical and thermal stimuli, and carry rapid, sharp pain. These fibers are responsible for the initial withdrawal reflex responses. C fibers are unmyelinated and have a small diameter and low conduction velocity. These fibers respond to chemical, mechanical and thermal stimuli and produce slow, burning pain. The headache of migraine is believed to be mediated by activation of both types of fibers that innervate meningeal blood vessels [19]. CPM inhibits the responses of these fibers, with an inhibitory preference towards the C fiber mediated responses [20]. Another type of primary sensory afferent fibers is the Aβ fibers which are large and thickly myelinated, enabling rapid signal conduction (Table 1). These fibers have a low activation threshold and transmit tactile information.

Table 1 – Characteristics of nerve fibers

Nerve fiber type	A-delta	C	A-beta
Diameter	Medium (1-5 microns)	Small (< 2 microns)	Large (> 5 microns
Myelination	Thinly myelinated	Unmyelinated	thickly myelinated
Signal propagation	Medium (5-30 mS^{-1})	Slow (< 2mS^{-1})	Fast (>35mS^{-1})
Activation threshold	High and Low	High	Low
Sensation with stimulation	Rapid, Sharp. Localized pain	Slow, diffuse. Dull pain	Tactile information

In Nerivio™, the stimulation (secondary stimulus) is engineered to produce a strong but non-painful stimulus that invokes the CPM as a pain relief mechanism for the migraine headache (initial stimulus). The patient is instructed to adjust the intensity to the strongest stimulation which is still below the perceived pain level. The area of the electrodes of Nerivio™ is relatively large, enabling to recruit a large number of fibers

during treatment. The pulse frequency and duration are designed so that C fibers and Aδ fibers are stimulated below their thresholds, aiming to produce a local sensation below the pain threshold, as well as to avoid excitation of motor nerves. Furthermore, the local pain sensation in the arm may be inhibited by Aβ fibers through the "gate control" theory of pain [21], further preventing the perception of pain. In addition, the pulses frequency gradually changes during the stimulation to avoid pain habituation, and a low frequency modulating waveform is added to invoke the release of neurotransmitters to further enhance the analgesic impact.

3.6. Output parameters

Output parameters of the Nerivio™ are similar to those of other transcutaneous electrical nerve stimulation (TENS) devices previously approved by the FDA for adults and are currently marketed for different indications.

The Nerivio™ output parameters and its comparison to other approved devices are described in Table 2.

Table 2 - Key output parameters comparison

Parameter	Nerivio™	Cefaly	Sys*Stim TENS
Mode or Program name	TENS	TENS	TENS
Waveform	Biphasic, symmetrical	Biphasic, symmetrical	Asymmetrical biphasic with zero net DC
Shape	Rectangular	Rectangular	Rectangular
Maximum output voltage (V) 500Ω 2KΩ 10KΩ	 20 60 60	 8 32 60	 92 ±20% 144 ±20% 166 ±20%
Maximum output current (mA) 500Ω 2KΩ 10KΩ	 40 30 6	 16 16 6	 184 ±20% 72 ±20% 17 ±20%
Duration of primary (depolarizing) phase (μsec)	200	250	200μs ±10%
Frequency (Hz)	100-120	60	1-80Hz ±10%
Maximum average power density (mW/cm²)500Ω	1.14	0.017	12
Maximum phase charge (μC)			

500Ω	8	4	33.5u ±10%
Maximum current density (mA/cm², r.m.s) 500Ω	1.6	2.37	

The user controls the stimulation intensity within the specified limits. A dedicated mechanism controls speed of intensity adjustment in order to protect the user from unexpected strong stimulation intensity variations.

3.7. Instructions for use

Device instructions for use be will available in a separate document which will be provided to the participants with the device and its package.

3.8. Identification of the medical device

Since the device has not been approved by the FDA for adolescents yet, the device will be labeled for clinical investigation use only. The label includes the address of the legal manufacturer and all other essential information, enabling complete traceability of the medical device, consistent with the regulatory labeling requirements.

3.9. Training

Participants will receive general instruction and will undergo training on using the device. The intended study population does not require special training but is expected to be familiar with smartphone use. The training will be administered by designated study personnel and will be recorded in a corresponding CRF. In addition, records of the training session will be documented in the study data base with a label “training”. The criteria for training effectiveness will be the ability of the participant to independently administer a training treatment session.

The sponsor representative will be responsible to provide a formal training to the investigator and site personnel, which will include a demo and training activities. In order to provide additional support to the clinical personnel, a training video clip will be used at all training sessions for the study personnel and the participants.

4. Preliminary investigations and justification for the study design

4.1. Previous pre-clinical experience

No animal studies were conducted with the Nerivio™ device. The necessity for an animal study has been deemed unnecessary since the device utilizes similar output parameters to those of FDA approved TENS devices, and in accordance with the application of risk

management according to EN ISO14791. Furthermore, there is no valid animal model to test the effectiveness of this device.

4.2. Previous clinical experience

The clinical data was obtained in one prospective, double-blind, randomized, crossover, sham-controlled pilot study and one prospective, randomized, double-blind, sham-controlled pivotal studies (TCH-003). Both studies were conducted on adults (ages 18 years or above). Each of these studies is briefly summarized below.

4.2.1. Pilot study (NCT02453399)

The pilot study was a single-center, prospective, double-blind, randomized, crossover, sham controlled pilot study to collect clinical data related to the safety and effectiveness of non-invasive remote electrical neuromodulation with Nerivio™ for the acute treatment of migraine. The results of this study have been published in Neurology [14]. Briefly, 86 people with migraine with or without aura (in accordance with ICHD classification criteria) who had 2–8 attacks per month without preventive medications for at least 2 months were recruited. The participants were requested to treat migraine episodes at home using the device, which randomly provided five 20-minute-long stimuli programs differentiating in pulse width; 4 active programs at 80–120 Hz, with pulse widths of 200 (P200), 150 (P150), 100 (P100), and 50 (P50) ms, and 1 placebo stimulation protocol (P0) at 0.1 Hz frequency with 45-ms-long pulses.

Pain levels were self-reported using a 0-10 numeric rating scale (NRS) [22] via a smartphone application at onset and 10, 20, and 120 minutes after stimulation onset. The primary endpoint was the proportion of participants reporting pain decrease of at least 50% at 2 hours posttreatment in at least 50% of completed treatments.

Participants

A summary of the demographic characteristics of the participants is presented in Table 3. The final analysis was performed on 71 participants who successfully treated at least one migraine attack and have not used rescue medications concurrently with the electrostimulation treatments.

Table 3: demographic characteristics

	Female	Male
Sample size, n (%)	69 (80)	17 (20)
Age, y, mean (min–max, SD)	45.2 (22–72, 11.7)	48.8 (26–67, 11.7)
Migraine attacks per month, mean (SD)	5.1 (2.7)	5.34 (2.3)
Migraine attacks per month, mean (SD)	8.9	8.6
Occurrence of aura, n (%)	40 (58)	11 (65)

Efficacy

The analysis of the primary endpoint revealed a 64% rate of at least 50% pain reduction (defined as a reduction from sever to moderate pain to mild or no pain) at 2 hours post-treatment, in at least 50% of completed active treatments. This rate was significantly higher than the 26% rate found for the sham treatment (p=0.005). The data demonstrated that the P200 program was most effective for headache relief. Thus, the following pivotal study was conducted with the P200 program.

Safety

In this study no device-related adverse events and no side effects were reported.

4.2.2. TCH-003 Pivotal study (NCT03361423)

This was a randomized, double-blind, sham-controlled study conducted at 7 USA and 5 Israeli sites from December 2017 to October 2018. This study aimed to assess the efficacy and safety of Nerivio™.

Participants

Eligible patients were 18–75 years old females and males who met the International Classification of Headache Disorders (ICHD) third edition criteria for migraine with or without aura, with at least two and no more than eight migraine headaches per month, with no more than 12 headache days per month, and with stable (or no) migraine preventive medications in the last two months prior to recruitment. Exclusion criteria were: 1) pregnancy, nursing, trying to conceive; 2) pure menstrual migraine (excluded because these attacks are often longer); 3) implanted electrical device(s); 4) treatment with OnabotulinumtoxinA in the prior month; 5) nerve blocks in the preceding two weeks; 6) current use of cannabis; 7) uncontrolled epilepsy; 8) receiving parenteral infusions for migraine in the preceding two weeks; 9) other significant pain, medical or psychiatric illness that in the opinion of the investigator may confound the study assessments; 10) unable to use a smartphone; 11) previous experience with REN in clinical trials for migraine.

Randomization and masking

Before each site initiation, randomization schemes of blocks of eight participants per site (four active and four sham) were developed. Group allocation was concealed by randomization lists for each smartphone operating system (Android or iOS) prepared by the statistician of the data monitoring committee (DMC), which included the device media access control (MAC) address (the unique device identification number) and an assigned randomization number identifier. Participants were randomized based on the type of operating system of their phones (Android or iOS) and their order of arrival to the randomization visit. To assess blinding, participants were asked at the end of study which

group they thought they had been assigned to (active, sham, do not know). The participants, investigators and clinic personnel were unaware of group assignment until the completion of the double-blind treatment phase. Each device was programmed with one of two versions of firmware that delivered either active or sham electrical stimulation (see above for detailed electrical properties). In all other aspects, the active and the sham conditions were kept similar.

Procedures

After enrollment, participants were trained to use the electronic diary application, installed on their own smartphones, and then completed a one-month migraine diary ("roll-in" phase). Eligible participants were then randomized in a 1:1 ratio to either active (active group) or sham stimulation (sham group), in a double-blind manner. During the randomization visit, participants were trained to use the device assigned to them, including finding the optimal individual stimulation intensity level (perceptible but not painful). Participants treated their migraine attacks for 4-6 weeks ("double-blind treatment" phase), starting at their optimal stimulation intensity, as soon as possible after migraine headache began and always within one hour of symptom onset. Participants were instructed to avoid taking rescue medications within two hours post-treatment, if possible. Pain scores (none, mild, moderate, or severe) were recorded at baseline, 2- and 48-hours post-treatment. Migraine associated symptoms including nausea, photophobia and phonophobia were recorded at the time of treatment. Participants declared their most bothersome migraine symptom (MBS) for each treated attack and reported absence and presence of all associated symptoms (including their MBS) at baseline and 2 hours post-treatment. At 2 hours, participants also subjectively reported whether they feel that a significant MBS relief was achieved.

Outcomes

The primary efficacy endpoint was the proportion of participants who achieved pain relief at 2 hours post-treatment in the "test treatment", defined as improvement from severe or moderate pain to mild or none, or, improvement from mild pain to none. The secondary efficacy endpoints pain-free (improvement from mild, moderate, or severe pain to none), MBS relief, pain relief & MBS relief, and MBS freedom at 2 hours post-treatment. Exploratory endpoints included 48-hour sustained pain-free and pain relief responses. An additional exploratory endpoint was within-subject consistency, defined as the proportion of participants achieving pain relief at 2 hours post-treatment in at least 50% of their treated attacks. Pain relief at 2 hours post-treatment as function of baseline pain level was also explored.

Results

296 participants were enrolled; 252 were randomized after the "run-in" phase, 126 were assigned to the active group and 126 to the sham group. Of the 44 who were not randomized, 33 failed to meet the "roll-in" criteria, 9 withdrew from the study and 2 were

withdrawn by the investigator due to migraine misdiagnosis. Among the 252 randomized participants (intent-to-treat population), 7 withdrew from the study, 3 (1 sham, 2 active) due to intolerance to the stimulation and 4 (2 sham, 2 active) were lost to follow up. 237 participants completed at least one treatment (the "run-in" treatment) and 203 participants completed the “test treatment”. 202 participants (99 in the active group and 103 in the sham group) started the “test treatment” within one hour from symptom onset and reported pain level at 2 hours, forming the mITT population with evaluable data. 37 participants who did not complete the “test treatment”, due to insufficient migraine attacks (n=18), participant’s decision not to use the device (n=4), other (n=6) or unknown (n=9), were excluded from the efficacy analyses.

The demographic and clinical characteristics were similar between treatment groups (Table 4). The characteristics of treated migraine headaches were comparable to those reported in previous migraine studies [23–25].

Table 4: Demographic and clinical characteristics (intent-to-treat population)

Characteristic	**Active group (n=126)**	**Sham group (n=126)**	
Age, y (SD)	43.8 (12.25)	41·6 (11.81)	
Female, % (n/N)	80.9% (102/126)	80.9% (102/126)	
Caucasian, % (n/N)	86.5% (109/126)	88.9% (112/126)	
Triptan users, % (n/N)	51.6% (65/126)	44.4 (56/126)	
Migraine with aura, % (n/N)			
Often	30.2% (38/126)	26.2% (33/126)	
Rarely	20.6% (26/126)	23.8% (30/126)	
None	49.2% (62/126)	50.0% (63/126)	
MBS % (n/N)*			
None	3.2% (4/126)	0.8% (1/126)	
Nausea	29.4% (37/126)	24.6% (31/126)	
Photophobia	43.7% (55/126)	57.1% (72/126)	
Phonophobia	20.6% (26/126)	17.5% (22/126)	
Preventive medication use, % (n/N)	28.6% (36/126)	37.3% (47/126)	
Migraine attacks in the “roll-in” phase, n	440	437	
Treated migraine attacks in the “double-blind treatment” phase, n**	385	388	
Characteristics of the test treatment (mITT)			**P value**
Presence of aura in the “test treatment”, % (n/N)†	19.2% (19/99)	19.4% (20/103)	0.96
Baseline pain severity in the “test treatment”, % (n/N)†			0.11
Mild	35.4% (35/99)	41.7% (43/103)	
Moderate	57.6% (57/99)	44.7% (46/103)	
Severe	7.1% (7/99)	13.6% (14/103)	
Presence of baseline associated symptoms in the “test treatment”, % (n/N)†			
Nausea	25.3% (25/99)	24.3% (25/103)	0.87
Photophobia	63.6% (63/99)	75.7% (78/103)	0.06
Phonophobia	55.6% (55/99)	56.3% (58/103)	0.91

* Four participants in the active group reported allodynia as MBS (data not shown) **Participants were asked to treat up to four episodes †modifed intent-to-treat population

In the active group, 66.7% participants (66/99; $CI_{95\%}$ 56.48-75.82) achieved pain relief for the test treatment, compared to 38·8% (40/103; $CI_{95\%}$, 29.39-48.94) in the sham group, a therapeutic gain of 27.9% (p<0.001;Figure 4A). Similar results were found when missing data was imputed using a worst-case scenario (66/103=64.1% for active versus 41/104=39.4% for sham, p<0.001). Furthermore, more participants in the active group were pain-free at 2 hours post-treatment (37.4% [37/99; $CI_{95\%}$ 27.85-47.67]) compared with the sham group (18.4% [19/103; $CI_{95\%}$ 11.49-27.30]; a therapeutic gain of 19.0%; P=0.003, adjusted; Figure 4A). Rescue medication within 2 hours post-treatment was used by 1% of the participants in the active group and 3.8% in the sham group (p=0.19).

The active treatment was also significantly more effective than sham for MBS relief (46.3% [44/95] vs. 22.2% [22/99]; $CI_{95\%}$ 36.02-56.85 and 14.48-31.69 respectively; p<0.001, adjusted) and for combined pain relief & MBS relief (40.0% vs. 15.2%; $CI_{95\%}$ 30.08-50.56 active and 8.74-23.76 sham; p<0.001, adjusted) at 2 hours post-treatment (Figure 4B and Table 4). There was no statistically-significant difference between treatment groups in the 2 hours post-treatment MBS free response (40.7% [33/81] vs. 36.4% [32/88]; CI 29.95-52.23 active and 26.37-47.31 sham; p=0.55, adjusted; Figure 4B).

The 2-hours pain relief and pain-free superiority of the active treatment were sustained 48 hours post-treatment. Sustained pain relief at 48 hours post-treatment was achieved in 34 of 87 (39·1%) participants in the active group, and in 15 of 89 (16.9%) participants in the sham group (P<0.005; Figure 4A). Sustained pain-free at 48 hours was achieved in the active group by 18 of 87 (20.7%) participants, and in the sham group by 7 of 89 (7.9%) participants (P<0.05; Figure 4A).

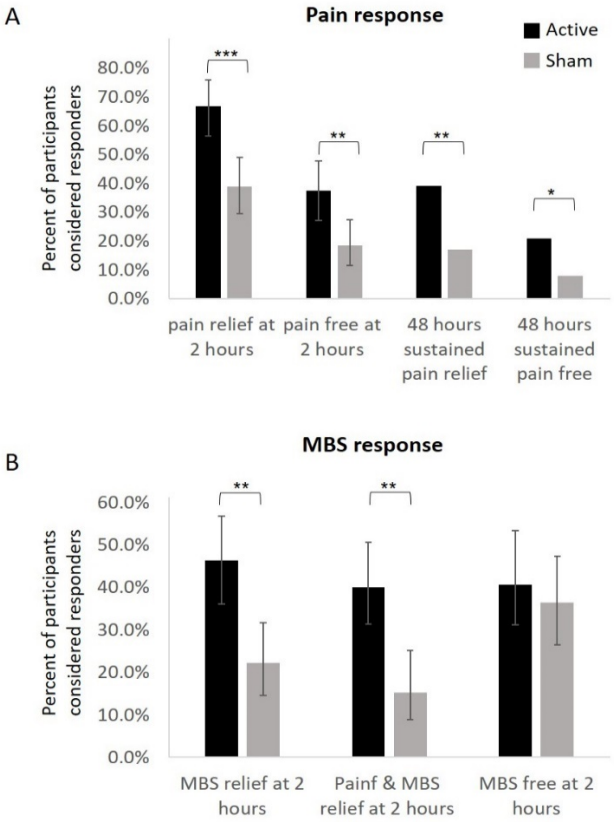

Figure 4: Efficacy endpoints. A. Pain response at 2- and 48-hours post-treatment. **B.** MBS response at 2 hours post-treatment. The error bars represent 95% confidence intervals.
***p<0.001, **p<0.005, *p<0.05. MBS=most bothersome symptom.

During the 4-6 weeks period of the double-blind treatment phase, participants in the active group treated an average of 3.5 attacks per participant versus an average of 3.6 attacks per participant in the sham group. Pain relief at 2 hours post-treatment for at least 50% of treated attacks was higher in the active group compared to the sham group (62.6% [62/99] vs. 45.6% [47/103], p=0.015).

The primary endpoint was also evaluated as a function of baseline pain intensity. The interaction between baseline pain intensity and response rate was not found significant (p=0.84), indicating that the treatment effect was similar across baseline pain intensity levels.

Table 5: Incidence of adverse events and device-related adverse events in the ITT population

	Active (n=126)	Sham (n=126)	P value
Patients reporting at least one adverse event, % (n/N)	15.1% (19/126)	11.9% (15/126)	0.58
Device-related adverse events, % (n/N)	4.8% (6/126)	2.4% (3/126)	0.49
Device-related adverse events incidence			
Warmth sensation, % (n/N)	2.4% (3/126)	0.8% (1/126)	0.62
Numbness in the arm/hand, % (n/N)	0.8% (1/126)	0% (0/126)	1.00
Redness, % (n/N)	1.6% (2/126)	0.8% (1/126)	1.00
Itching, % (n/N)	0.8% (1/126)	0% (0/126)	1.00
Neck and shoulder pain, % (n/N)	0% (0/126)	0.8% (1/126)	1.00
Pain in the arm, % (n/N)	1.6% (2/126)	0% (0/126)	0.49
Tingling, % (n/N)	0% (0/126)	0.8% (1/126)	1.00
Muscle spasms, % (n/N)	0.8% (1/126)	0% (0/126)	1.00

Safety analyses were performed on all 252 participants (ITT population). The percentage of participants experiencing at least one adverse event was 13.5% (34/252) and was comparable across treatment groups (15.1% [19/126] active and 11.9% [15/126] sham, p=0.58). 23 device-related adverse events were reported during 773 treatments (2.7%), 14 in the active group and 9 in the sham group. The incidence of device-related adverse events was low (3.6%), and similar between treatment groups (6/126 [4.8%] vs. 3/126 [2.4%]; p=0.49). Device-related adverse events included warmth sensation, temporary arm/hand numbness, redness, itching, tingling, muscle spasm and pain in the arm, shoulders or neck (Table 5). All device-related adverse events were mild, resolved within 24 hours and did not require medical treatment. There were no device-related serious adverse events, no unanticipated adverse device effects and none of the participants withdrew from the study due to adverse events.

The findings of this study suggest that remote electrical neuromodulation with Nerivio™ is an effective acute migraine treatment with a favorable safety and tolerability profiles. REN may be an alternative acute migraine treatment with comparable or superior efficacy to commercially available neuromodulation devices [23,26]. REN has the potential to increase patient adherence, improve migraine management and improve the health and quality of life of people with migraines.

4.3. Clinical investigation risks and benefits

4.3.1. Anticipated benefits to participants

The clinical studies conducted in adults demonstrated that REN provides superior clinically meaningful relief of migraine pain and MBS compared to sham-device with a favorable safety profile, offering a safe and effective non-pharmacological alternative for acute migraine treatment. It is anticipated that adolescents with migraine will experience a similar clinically beneficial effect.

4.3.2. Risks and adverse effects

The results of the pivotal study demonstrate a favorable safety profile of the device. In this study, adverse event incidence was low; mainly reports of sensation of warmth, redness and numbness of the arm/hand. All device-related adverse events were mild, resolved within 24 hours and did not require medical treatment. There were no device-related serious adverse events, no unanticipated adverse device effects and none of the participants withdrew from the study due to adverse events. The safety profile of the device is favorable compared to triptans [27] and to new pharmacological agents, such as centrally acting serotonin (5-HT1F) agonists that lack cardiac vasoconstrictive activity [28]. Furthermore, the device has comparable or superior efficacy to commercially available neuromodulation devices [23,26].

4.3.3. Risk-benefit balance

The data collected in the randomized controlled clinical study in adults demonstrated that acute treatment of migraine with Nerivio™ results in most important clinical benefits with a very low risk to the patient. Invoking conditioned pain modulation using peripheral neurostimulation that induces a general analgesic effect resulted in favorable 2-hour pain relief and pain-free responses which are comparable with pharmacological acute migraine treatments such as triptans with a more favorable safety profile. Overall, the benefit-risk balance of Nerivio™ is favorable. The overall risk posed by the device is minimal. The device offers a major benefit by providing a novel acute treatment of migraines which is highly effective and reduces the side effects of current pharmacological treatments. Therefore, the device may offer an alternative non-pharmacological treatment approach to the limited effective treatment options in adolescents and has the potential to decrease the reliance of patients on pharmacological treatments, improve treatment adherence, reduce the risk of medication overuse and considerably improve the health and quality of life of adolescents with migraine.

5. Objectives & hypotheses

5.1. Study objectives

The objective of this study is to evaluate the safety and efficacy of Nerivio™ for the acute treatment of migraine with or without aura in adolescents. The goal of this study is to demonstrate migraine headache relief without unexpected device-related adverse effects.

5.2. Study hypothesis

The hypothesis of this study is that in adolescents, REN with Nerivio™ will provide clinically meaningful relief of migraine pain with a favorable safety profile.

6. Study design

6.1. Participants

This study will be conducted on up to 130 eligible participants.

6.1.1. Inclusion criteria

- Participants age 12-17 years old at the time of informed consent, inclusive.
- Participants have at least a 6-month history of headaches that meet the ICHD-3 diagnostic criteria for migraine with or without aura
- History of at least 3 migraine attacks per month for each of the 2 months preceding study enrolment
- Typical headache duration of at least 3 hours (when untreated or unsuccessfully treatment)
- Stable migraine preventive medications during the 2 months prior to enrollment (no change in usage or dosage).
- Participants have personal access to a smartphone (24/7)
- Participants must be able and willing to comply with the protocol
- Parents/Guardians must be able and willing to provide written informed consent
- Participants must be able and willing to provide informed assent

6.1.2. Exclusion criteria

- Participants with an implanted electrical and/or neurostimulator device (e.g. cardiac pacemaker, cochlear implant).
- Subjects with congestive heart failure (CHF), severe cardiac or cerebrovascular disease.
- Participants with epilepsy.
- Medical use of cannabis or recreational use one month prior to enrollment

- Participants who have undergone nerve block (occipital or other) in the head or neck within the last 2 weeks
- Treatment with onabotulinum toxin A (Botox) to the head and/or neck for 3 months before enrollment and/or during the study
- Any history of anti-CGRP antibody treatment
- Current participation in any other clinical study that includes treatment
- Participants without basic cognitive and motor skills required for operating a smartphone.
- Pregnant or breastfeeding females
- Pure menstrual migraine
- Participants who received parenteral treatments for migraine within the previous 2 weeks.
- Participants with other significant pain, medical or psychological problems that in the opinion of the investigator may confound the study assessments
- Participants who have previous experience with the device
- Participants with upper arm circumference below 7.9 inches (20 cm)

6.1.3. Contraindications

- The device should not be used by people with congestive heart failure (CHF), severe cardiac or cerebrovascular disease.
- The device should not be used by people with uncontrolled epilepsy.
- The device should not be used by people with active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device. Such use could cause electric shock, electrical interference or serious injuries or medical conditions.

<u>Main warnings and precautions:</u>

- The device should not be used over skin conditions, such as open wounds or rashes, or over swollen, red, infected or inflamed areas or skin eruptions or fragile skin on the upper arm at the treatment location.
- The device should not be shared with other people. The device is intended to be used by a single person to avoid skin disease or any transmissible disease.
- The device should not be used on the heart, chest, neck, head or any other body location other than the upper arm, because this could cause severe muscle spasms resulting in closure of your airway, difficulty in breathing, or adverse effects on heart rhythm or blood pressure.
- The device has not been evaluated for use in pregnant women

6.1.4. Withdrawal/discontinuation

Participants may withdraw consent at any time without and do not have to provide an explanation.

Participant may be withdrawn from the study by the PI or sponsor due to one or more of the following reasons:

- Participant is lost to follow-up
- Refusal of the participant to continue treatment and/or follow-up observations
- Serious adverse event
- Participants encountering difficulties with the investigational product (IP) (e.g. cannot tolerate the treatment, unable to operate the application)
- Significant protocol deviation/violation or noncompliance, either by the patient or the investigator
- Decision made by the investigator that termination is in the patient's best medical interest
- Device malfunction
- Other ethical or clinical considerations upon investigator discretion

6.2. Stimulation program

The 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 minutes.

6.3. Procedures

This open label study includes 3 phases and up to 4 visits. All visits will be conducted in the presence of a parent/guardian.

First visit – enrollment: The first visit will include screening, enrollment and training on the application in diary mode. The screening process will include an eligibility assessment and a urine pregnancy test. Following successful screening, enrollment interview and signing an informed consent by the parent/guardian and an informed assent by the participant. The participants will be trained to use the electronic diary application, installed on their own smartphones. The site personnel will be required to document the training session in the CRF. During this visit, participants will complete baseline questionnaires that included information on the frequency and severity of their migraine attacks, typical associated symptoms, use of preventive and acute treatments, and the effect that their migraine attacks have on their daily routine and quality of life.

Phase 1 – run-in phase: After the enrollment visit, participants will undergo a 4-week migraine diary phase aimed to collect baseline migraine characteristics and further assess eligibility. Participants will be asked to report in the application each migraine attack. These reports will be transferred by the application to the electronic data collection (EDC) system, where they will be collected and registered. Participants who did not have at least 3 migraine attacks will be excluded from the study. Eligibility will also be determined based on the compliance of participants to report the attacks within one hour from attack onset and report the pain level at 2 hours post-treatment in at least 66.7% of the reported attacks.

Second visit – Device training visit: Eligible participants who meet the run-in requirements will receive the Nerivio™ device. The device will be registered and connected by Bluetooth to their smartphone. During this visit, participants and their parent/guardian will be trained to use the device, including finding the optimal individual stimulation intensity level (perceptible but not painful). The site will also carefully review with the patient and parent/caregiver how to identify a qualifying migraine attack (see below) and provide detailed instructions on study procedures.

The individual intensity level identified during this visit will be recorded, and the participants will be asked to treat their migraine headaches with the device using the identified intensity. If the research staff recognizes that the participant cannot tolerate the feeling of the electrical stimulation, the participant may be withdrawn from the study.

During the training, participants will also be informed on the key elements which are critical for the successful conduct of the study:

- Treatments of attacks with Nerivio™ should be performed as soon as possible after migraine headache or aura began and always within one hour of symptoms onset. Treatments of mild headaches are accepted.
- Avoid taking rescue medications within two hours post-treatment (2 hours from start of treatment), if possible.
- The treatment should be performed for at least 30 minutes (the recommended treatment duration is 45 minutes).

Phase 2 –Treatment phase: Participants will be instructed to use the device for the treatment of 4 qualifying migraine attacks (see below) as soon as possible and always within 60 minutes of onset during a period of up to 8 weeks. Participants will be instructed to use the device with the intensity level identified during the device training visit (with a range of ±5 units) and make sure the stimulation is perceptible but not painful. Participants will be instructed to avoid taking rescue medications within 2 hours post-treatment. If medications are used, participants will be instructed to record in the app when and which medication was taken. The participants will use the app to record pain intensity levels (none, mild, moderate, or severe) at baseline, 2- and 24-hours post-treatment, and to record the presence/absence of associated migraine symptoms (nausea, photophobia,

phonophobia) at baseline and 2 hours post-treatment. To assess functional disability, participants will also record at baseline, 2- and 24-hours post-treatment their response to the following question in their diary: "How do you rate your ability to do school-work or perform your usual activities?" using a 4-point scale ('as usual', 'some ability', 'a little ability', 'no ability at all'). At the beginning of each treatment, participants will also be asked to report the time elapsed from attack onset. Adverse events will be reported throughout this phase of the study.

Participants who do not achieve satisfactory relief at 2 hours post-treatment may treat again with the Nerivio™ device or may treat with usual care at that time or any time thereafter if the headache does not resolve. Participants will also be able to treat headache recurrence with the device. Attacks that are not treated with the device may be treated with usual care.

The first reported treatment will be considered a "training" treatment, aimed to verify that the participants use the device properly, and will only be included in the safety analysis. The efficacy evaluation will be performed on the first treatment of a qualifying attack (see below) following the training treatment (hereby termed "test treatment").

Qualifying migraine attack

A qualifying migraine attack is defined as a migraine attack that:

1. Was not preceded by another migraine or other headache within the preceding 24 hours
2. Was not preceded by the use of specific or non-specific acute migraine medications within the previous 24 hours
3. Occurred in a setting in which the patient could properly administer the treatment (that is, it is possible to initiate a complete treatment within 60 minutes of onset and the participant will be able to complete the migraine diary at 2 hours after treatment)

Third visit – Termination of the treatment phase and free-use phase initiation: Following the 8-week period of the treatment phase, participants will return to the clinic to return the device and fill questionnaires assessing satisfaction and user experience. All participants who complete the treatment phase will be offered to participate in an additional 8-week phase in which the device can be incorporate into usual care.

Phase 3 – Free-use phase: Participants will continue in an 8-week phase in which they will be able to use the device according to their preferences for the treatment of their migraine attacks.

Fourth (final) visit – End of study: Participants will return to the clinic following the end of the 8-week free-use phase, at which time they will return the device.

6.3.1. Study duration

The duration of the study for each participant is expected to be ~12 weeks for the run-in and treatment phases and additional 8 weeks for those participating in the free-use phase.

6.4. Study endpoints

6.4.1. Primary endpoints

1. <u>The safety of Nerivio</u>
   The incidence of adverse events in general and by seriousness, severity and association to the device.

2. <u>Treatment tolerability</u>
   The percent of subjects who fail to complete the study because of adverse events

6.4.2. Secondary endpoints

1. Pain relief at 2 hours post-treatment:
   The proportion of participants achieving pain relief, defined as improvement from severe or moderate pain to mild or none, or improvement from mild pain to none, at 2 hours post-treatment in the test treatment, with no use of rescue medication
2. Pain-free at 2 hours post-treatment:
   The proportion of participants achieving pain freedom, defined as improvement from mild, moderate, or severe pain to none, at 2 hours post-treatment in the test treatment, with no use of rescue medication
3. Disappearance of associated symptoms at 2 hours post-treatment
   a. The proportion of participants reporting nausea at baseline and achieving absence of nausea at 2 hours post-treatment in the test treatment
   b. The proportion of participants reporting phonophobia at baseline and achieving absence of phonophobia at 2 hours post-treatment in the test treatment
   c. The proportion of participants reporting photophobia at baseline and achieving absence of photophobia at 2 hours post-treatment in the test treatment

6.4.3. Exploratory endpoints

1. Sustained pain relief at 24 hours post-treatment:
   The proportion of participants achieving pain relief at 2 hours post-treatment in the test treatment, with no use of rescue medication and no relapse of headache pain within 24 hours

2. Sustained pain-free at 24 hours post-treatment:
   The proportion of participants achieving pain freedom at 2 hours post-treatment in the test treatment, with no use of rescue medication and no relapse of headache pain within 24 hours

3. Functional disability at 2 hours post treatment
   The proportion of participants who achieve improvement of at least one grade in functional disability in the test treatment at 2 hours post-treatment, with no use of rescue medication

4. Functional disability at 24 hours post treatment
   The proportion of participants who achieve improvement of at least one grade in functional disability in the test treatment, with no use of rescue medication

6.5. Methods and timing of assessing and analysing variables

Once the last patient will complete the treatment phase of the study and all the queries will be resolved, the database will be locked, cleaned and exported for final statistical analysis. A study report will be issued following the final database lock.

6.6. Data management

The data management function will be supported by a cloud-based electronic data capture (EDC) system developed by FlaskData.IO (Modi'in, Israel). FlaskData.IO provides services for collection and remote monitoring of clinical trials data, compliant with HIPAA and 21 CFR Part 11. EDC portals with secure authorized access will be made available to every participating site, as well as to the study monitor.

Data captured by the clinical personnel will be entered directly into pre-specified eCRF screens by the site personnel. Data from paper sources will be entered into the study database. Automatic data checks will be implemented for majority of entry fields to provide opportunity for resolving data inconsistencies as soon as possible to its occurrence. Efforts will be made to identify missing or incorrect data and promptly resolve these issues.

Data collected by the smartphone application will be directed to a secured cloud-based database where it will undergo analysis aimed at detecting of missing data and other inconsistencies. The smartphone will transmit PRO and technical data containing activation times, stimulation intensity and ePRO via the smartphone to a central electronic database for analysis. Activities such as repeatedly aborted programs, missing feedbacks, inconsistent stimulation intensity adjustments, will be communicated to the research coordinator of the corresponding site, using the participants' ID codes. Automated means were developed to identify and provide corresponding notifications regarding events that

may lead to protocol deviations and/or missing data, and which resolution may require involvement of study personnel. Examples of such events include missing PRO data or low device battery level. An automated system was implemented to notify the participant, site study coordinator and the sponsor's study monitor of such issues. Missing data will be automatically identified by a script running on the cloud of FlaskData.IO, and queries will be generated to the participants and the corresponding site study coordinator. Near real time detection of problems in accumulating data will allow timely generation and resolution of queries. Intermediate data processing and translation into eCRF format will be performed. Processed data are further pushed into the EDC system.

A daily back-up of the database will be performed. In addition, a copy of each participant's ePROs and other activities will be stored in his/her smartphone memory and can be retrieved if needed.
EDC tools will be used for locking the database and exporting to SAS compatible format for interim and final statistical analyses. Query resolution will also be performed using EDC tools.
All paper-based source data and relevant medical documents that also serve as source documents will be maintained by the sites and will be available as eCRF attachments. participant identification will be removed from all data and the participants will be identified by their codes. The site investigator is responsible for ensuring that eCRFs are filled in a timely manner and that relevant paper documents are properly stored. The investigators will provide the documents to the sponsor either through the sponsor representative or by mail per the sponsor's request.
Access to data will be authorized and controlled, in accordance with relevant regulations and guidelines.

The study will be performed according to the protocol. At each site, the PI will appoint staff member(s) that will be responsible for completing the CRFs supplied by the sponsor.
Specifics of data query handling are given in data management and monitoring plans.
Audit trail for data entry and corrections will be maintained.

6.7. Monitoring plan

An independent data monitoring committee (DMC) will be responsible for providing oversight of the data monitoring issues. The DMC will periodically review and evaluate the accumulated data. The DMC will make recommendations regarding enrollment, continuation, modification, or termination of the study. The data reviewed by the DMC will include a summary of the following topics:

- Study progress: subject recruitment, comparison with recruitment targets, retention, protocol adherence, and quality of data collection procedures
- Treatment monitoring: data on treatment integrity and adherence

• Safety monitoring: data related to the safety of the subjects, including any device-related adverse events or side effects related to the treatment

7. Statistical Considerations

7.1. Study design and aim

The study is designed as a prospective, open label, multicenter clinical trial. This study aims is to evaluate the safety and efficacy of Nerivio™ for the acute treatment of migraine with or without aura in adolescents (ages 12-17 years).

7.2. Endpoints

7.2.1. Primary endpoints

The primary endpoints of the study are related to the safety of the device. Safety and tolerability will be assessed by review of all safety parameters, including adverse events. The incidence of adverse events will be assessed as a function of severity and association to the device. The time of resolution of the adverse events and need for treatment will also be analyzed.

7.2.2. Secondary endpoints

Secondary efficacy endpoints include:

- Proportion of subjects reporting, for the test treatment, pain relief at 2 hours post treatment without use of rescue medication. Pain relief is defined as an improvement from severe or moderate pain to mild or no pain, or from mild pain to no pain.
- Proportion of subjects reporting, for the test treatment, pain-free at 2 hours post treatment without use of rescue medication. Pain free is defined as an improvement from mild, moderate or severe pain to no pain.
- Proportion of subjects reporting, for the test treatment, nausea at baseline and achieving absence of nausea at 2 hours post treatment without use of rescue medication.
- Proportion of subjects reporting, for the test treatment, phonophobia at baseline and achieving absence of phonophobia at 2 hours post treatment without use of rescue medication.
- Proportion of subjects reporting, for the test treatment, photophobia at baseline and achieving absence of photophobia at 2 hours post treatment without use of rescue medication.

7.2.3. Exploratory endpoints

Exploratory efficacy endpoints include:

- Proportion of subjects achieving, for the test treatment, pain relief at 2 hours post treatment without use of rescue medication and no relapse of headache pain within 24 hours.
- Proportion of subjects achieving, for the test treatment, pain freedom at 2 hours post treatment without use of rescue medication and no relapse of headache pain within 24 hours.
- Proportion of subjects achieving, for the test treatment, improvement of at least one grade in functional disability at 2 hours post treatment without use of rescue medication.
- Proportion of subjects achieving, for the test treatment, improvement of at least one grade in functional disability at 24 hours post treatment without use of rescue medication.

7.3. Sample size

A sample size was calculated on the efficacy endpoint of pain relief at 2 hours post-treatment. Calculations show that a sample size of 110 participants would provide 80% power to determine that 60% (±6%) of the participants will achieve pain relief at 2 hours post-treatment. The sample size may be increased to up to 130 participants to account for a potential ~15% drop-out rate and/or missing data.

7.4. Analysis sets

Intent to treat analysis set (ITT)
The ITT analysis set includes all patients undergoing the treatment phase.

Modified intend to treat analysis set (mITT)
The mITT analysis set includes all patients undergoing the treatment phase and treat a test treatment within 60 minutes of attack onset. Subjects with no valid post baseline assessment will not be included in the relevant analysis.

Per-protocol analysis set (PP)
The PP analysis set includes all patients from the mITT analysis set without major protocol deviations. Main protocol instructions include:

- has started within 60 minutes of attack onset
- was administered to treat a qualifying migraine attack
- was administered for at least 30 minutes
- includes data on pain intensity at 2 hours post-treatment
- rescue medication was not used before or within 2 hours post-treatment

Statistical analysis of the analysis sets

The ITT analysis set will serve as the main set for safety assessments.
The mITT analysis set will serve as the primary set for the efficacy assessment.

7.5. Statistical analysis

7.5.1. General considerations

Statistical analyses will be performed using SAS® v9.4 or higher (SAS Institute, Cary NC, USA).
Baseline demographic and other baseline characteristics, together with safety analyses will be performed on all participants who underwent the treatment phase. Baseline values are defined as the last valid value prior to treatment.
Where confidence limits are appropriate, a two-sided 95% confidence interval will be constructed.

7.5.2. Demographic and other baseline variables

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

7.5.3. Safety analysis

Safety and tolerability will be assessed by review of all safety parameters, including adverse events. Serious adverse events, device-related SAEs, adverse events (by type and overall), device-related AE, adverse device reactions and device malfunction rates will be documented. Treatment tolerability, the number and percent of subjects who fail to complete the study and the number and percent of subjects who fail to complete the study because of adverse events will be presented. Time to withdrawal will also be assessed and presented by Kaplan-Meier curves.

7.5.4. Efficacy analysis

The efficacy endpoints will be assessed on evaluable treatments of qualifying attacks. The first use of the device is considered a training treatment and will not be included in the efficacy analyses. The first treatment of a qualifying attack after the training treatment is considered a test treatment and will be used for all efficacy assessments. If this treatment is not evaluable (i.e., no pain data at 2 hours post-treatment), a subsequent treatment of a qualifying attack with evaluable data will be considered the test treatment.

Use of rescue medication before the 2-hours assessment will be considered a treatment failure for the 2-hours endpoints, and before the 24 hours assessment for the sustained

24-hours endpoints. The percentage of participants achieving each of the efficacy outcomes will be presented in a tabular form along with two-sided 95% exact confidence intervals.

For the associated symptoms outcomes, the observed response proportions and corresponding 95% exact confidence intervals for each associated symptom will be provided. All patients with baseline and 2 hours values will be included in the analyses. A response in each associated symptom (nausea, vomiting, photophobia, phonophobia) is defined as change from presence of a specific associated symptom at baseline to absence of the same associated symptom at 2 hours post-treatment.

In addition, logistic regression models will be used to assess the efficacy. Baseline value and site will serve as covariates.

The first secondary endpoint (pain relief at 2 hours) may also be evaluated in attacks with aura and attacks without aura separately.

7.5.5. Treatment by sites interaction

Poolability across centers may be assessed using logistic regression. Centers with less than 10 subjects will be grouped together by geographical area. If the center term is found significant ($p<0.1$), the reason for this interaction will be further explored. This evaluation may include demographic features, symptoms at presentation, clinical and treatment history, and site comparability in the features found to be associated with the primary endpoint variables. Adjustment for other covariates such as demographics or other baseline subject characteristics may be performed by adding these variables into a logistic regression model.

The analysis may be repeated for US sites vs. out of US (OUS) sites.

7.5.6. Handling of missing data

Sensitivity analyses of the efficacy endpoints may be performed to assess the impact of missing data of pain severity at 2 hours post-treatment on the efficacy outcomes. This will be performed using several possible imputation methods including, but not limited to:

- Observed data: use only treatments with non-missing pain data who did not withdraw early from study.
- Dropout/AE Imputation: a subject with no post baseline measurement of pain or a subject withdrawn due to an adverse event or treatment intolerability should be considered as a non-responder for this analysis.

- Worst Case Scenario: assumes that all subjects with missing pain data are failures.
- Best Case Scenario: assumes that all subjects with missing pain data are successes.

8. Data management

8.1. Data capture

Data capture will be performed using an electronic data collection (EDC) system in conjunction with electronic patient reported outcome (PRO) collection tools implemented in the smartphone application. The clinical sites will use electronic case report forms (eCRFs) to document the information required by the study CIP.

The EDC provider is FlaskData.IO. The EDC enables secure collection, transmission, validation, monitoring and real-time administration of the data collected at the sites and by the smartphone application. The system offers a password-restricted access to clinical trial information based on individuals' roles and responsibilities. The EDC is compliant with *21 CFR Part 11* and FDA's "*Guidance: Computerized Systems Used in Clinical Investigations.*"
Except for patient reported outcomes which are directly reported by the participants in the smartphone application, data reported on the eCRF should be driven from source documents and should be consistent with these source documents. Editing of data will be done with a full audit trail.
PRO data collected from the smartphone application will be saved in dedicated log files on the smartphones for backup purposes and transferred to the EDC system.

8.1.1. Direct data entry

For several CRF fields, source data verification (SDV) may not be possible as entries may not be found in source documents (e.g., migraine diary or other patient reported outcome completed directly into the smartphone app). Therefore, the CRF may be used for direct data entry, but only in pre-defined fields.

8.2. Data quality assurance

To ensure the quality of clinical data across all subjects, a clinical data management review of the patient data in the CRF will be performed by the sponsor. During this review, patient data will be assessed for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the CIP and relevant regulations. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be issued by the sponsor. Discrepancy resolution will be documented within the database audit trail.

8.3. Electronic signatures

The PI will electronically sign each individual eCRF after the data has been cleaned, monitored and reviewed. The electronic signature asserts that the investigator reviewed the eCRFs, the data queries, and the site notifications, and agrees with the content. Any changes made to the data after an electronic signature has been applied will result in invalidation of the original signature, and the PI will be required to re-sign the data after reviewing the change(s).

8.4. Verification, validation and securing of electronic data capture system

Verification and validation of the EDC and eCRFs will be performed by a team comprising representatives of the developer, the sponsor and at least one of the participating sites. A verification and validation report will be detained by the sponsor.

8.5. Records and data retention

A copy of all records (e.g., informed consent documents, source data, safety reports, study device dispensing records, etc.) which support case report forms for this study, will be retained in the files of the responsible investigator for a minimum of five (5) years following notification by the sponsor that all investigations (not merely the investigator's portion) are completed, terminated and/or discontinued. If the principal investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian within 5 days after such transfer occurs.

The database will be retained by the EDC system provider for a minimum of 5 years.

8.6. Other aspects of clinical quality assurance

The site PI or a person designated by the site PI is responsible for establishing and maintaining compliance with the study protocol. The study PI is responsible for addressing quality assurance issues (e.g. correcting procedures that are not in compliance with the protocol). The study coordinator is responsible for quality control issues (e.g. correcting errors in data entry). The sponsor will monitor the investigational sites throughout the study. All outstanding issues and findings that site personnel become aware of will be communicated and handled in agreement with a monitoring plan. An independent DMC will be responsible for providing oversight of the data monitoring issues and conducting periodical reviews that may include recommendations regarding enrollment, continuation, modification, or termination of the study.

Site audits by the sponsor may be conducted before the completion of the study to ascertain data quality and integrity.

The Food and Drug Administration (FDA) and/or the local state health authorities may request access to all study records, including source documents, for inspection. The investigator and site staff agree to cooperate with these audits. The investigator must notify the sponsor of any health authority audit as soon as notification of such audit is made. A representative or designee of sponsor may be present during a health authority audit.

9. Amendments and deviations from the protocol

9.1. Protocol amendments

The protocol cannot be amended by the investigator without obtaining the sponsor's approval. Protocol amendments will be submitted for approval to local IRB/EC and, if applicable, to the respective regulatory authority (RA). The amendments can be implemented in the study only after an IRB/EC and/or RA approval are obtained. Non-substantial changes (e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance) which do not affect the rights, safety and well-being of human subjects and/or are not related to the clinical investigation objectives or endpoints, may only require a notification to the IRB/EC and/or regulatory without protocol amendment.
The following documents are relevant to the protocol but are not considered part of the protocol. These documents are stored and modified separately. As such, modifications to these documents do not require protocol amendments:

- Site roster
- Case report forms
- Data management plan
- Monitoring plan
- Statistical analysis plan
- DMC

9.2. Protocol deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or related SOPs requirements. The deviation may be associated with the subject, the investigator, or study personnel. The investigator/co-investigators must obtain the sponsor's approval for all protocol deviations, except for cases in which the safety and well-being of a patient will be affected, as stated in section 4.5.4 b of the ISO 14155 (2011).

Compliance with the protocol will be assessed by the study monitor during the monitoring visits as well as remotely, using designated reports provided by the EDC system.
All protocol deviations will be addressed in study subject source documents and promptly reported to the site IRB, according to local requirements.

9.3. Procedures for recording, reporting and analyzing protocol deviations

All protocol deviations will be documented in source documents and appropriate eCRFs.

The study monitor is responsible for identifying and reviewing protocol deviations with the investigator or designee and documenting the issue and action/outcome of the protocol deviation in the MVR and any follow up letter/communication with the principal investigator.
The study monitor will ensure that major protocol deviations are discussed with the investigator. Major deviations include deviations that:

- impact patient safety
- alter the risk/benefit ratio
- compromise the integrity of the data
- affect willingness of the patient's participation in the study

The deviations will be reported to the IRB/EC periodically or as specified by the local regulations. Further documentation of any changes in research activity should be submitted to the sponsor and the IRB/EC if the deviations are related to any instance of serious or continuing non-compliance with governing regulations/requirements of the IRB/EC, and/or related to changes in protocol specified patient activity and procedures.

In addition to the immediate reporting, the study monitor will document all deviations in the monitoring visit report and follow-up letters. The monitor will discuss deviations with relevant site personnel. If needed, a note to file will be issued and filed in the relevant file and a copy will be sent to the sponsor. The sponsor or its designee will review records of deviations and will consider the need for corrective and preventive action and further external reporting to regulatory authorities. Deviations will be summarized and included in the study report. The potential impact/lack of impact of the deviations on the study results will be assessed.

9.4. Notification requirement and timelines

Major deviations should be escalated to the sponsor within 5 business days. Protocol deviations must be reported to local IRB/EC according to their guidelines. The site PI or other designated site staff member is responsible for adhering to local IRB/EC requirements.

10. Device accountability

The devices will be provided by Theranica Bioelectronics (sponsor), with all required labeling. The device number will be documented in the CRF and in the site log when provided to the participant. Each batch of devices delivered to the clinical sites for allocation to study participants will be accompanied with a shipment note. The device shipment records will be maintained by the sponsor as well as on site.

Prior to distribution, the devices will be stored in a designated locked cabinet. The access to the investigational devices will be controlled by the research staff. The devices will only be used in the clinical investigation and according to the study protocol.

Each device has a sticker on it with a unique number. When a device will be provided to the participant, it will be paired with the participant's smartphone using Bluetooth connection. During device allocation, application installation and device–smartphone pairing, a site allocated user ID will be entered by the study coordinator via the application. The three IDs (user ID, phone ID, device ID) provide a mean for identifying technical and PRO data from each participant in the electronic database while protecting participant's privacy.

The investigators will be responsible for the safe storage of the devices according to the instructions provided by Theranica Bioelectronics, with restricted access to the investigational materials in their possession, thereby preventing use of any materials by any person not participating in the study. The device accountability records will be reviewed during the monitoring visits.

The investigator will be responsible for providing device use training to the participants according to the instructions for use and protocol and for maintaining product inventory and records. As part of study closure, all unused devices must be returned in their original packaging to Theranica Bio-Electronics.

11. Informed consent process

Informed consent and assent must be obtained from the parent/caregiver and participant, respectively, before any protocol-related activities are performed. Participants must be provided with a signed copy of the consent and assent forms. The eCRFs will be updated that informed consent and assent have been signed.

12. Adverse events

Adverse event (AE) is defined as any unfavorable and unintended medical change, temporally associated with the use of the sponsor's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse

change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the sponsor's product, is also an adverse experience. An adverse device effect (ADE) is an adverse event related to the use of the investigational device. In this study the ADE refers to side effect and complications.

A serious adverse event (SAE) is defined as an adverse event that leads to
a) death,
b) serious deterioration in the health of the subject, that either resulted in
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or body function
c) fetal distress, fetal death or a congenital abnormality or birth defect

A serious device related adverse effect (SADE) is an adverse event related to the use of the investigational device and that is considered by regulations and definitions as serious.

12.1. Characteristics of AEs

An investigator who is a qualified physician, will evaluate all adverse events as to:

Maximum intensity
Mild: awareness of symptom, but easily tolerated
Moderate: definitely acting like something is wrong
Severe: extremely distressed or unable to do usual activities

Duration
Record the start and stop dates of the adverse experience. If less than 1 day, indicate the appropriate length of time and units

Relationship of an AE and SAE to the study device
The relationship of the adverse event to the study device is defined as:

Definitely related: There is evidence of exposure to the device. The temporal sequence of the AE onset relative to use of the device is reasonable. The AE is more likely explained by the device than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the device.

Probably related: There is evidence of exposure to the device. The temporal sequence of the AE onset relative to use of the device is reasonable. The AE is more likely explained by the device than by another cause. Dechallenge (if performed) is positive.

Possibly related: There is evidence of exposure to the device. The temporal sequence of the AE onset relative to use of the device is reasonable. The AE could have been due to another equally or less likely cause. Dechallenge (if performed) is positive.

Definitely not related: The subject/patient did not use the device; or temporal sequence of the AE onset relative to device use is not reasonable; or there is another obvious cause of the AE.

12.2. Reporting of AEs and SAEs

All adverse events will be recorded in appropriate adverse events case report form. The adverse events will be used for the safety assessment. An on-site visit to monitor the adverse event will be conducted if the principal investigator determines it is needed. These visits will be reported using designated case report forms. If during the last visit, an ongoing device-related AE is present, the participant will be monitored for approximately 2 weeks, until the AE resolves or a steady state is achieved.

The PI must report any SAE or SADE to the sponsor within 1 business day:
Theranica Bioelectronics
Dr. Dagan Harris
Tel: +972.72.390.9758
Fax: + 972.72.390.9755
Email: dagah@theranica.com

The sponsor is responsible for reporting the adverse events to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

12.3. Anticipated device-related AEs

Possible adverse events associated with remote electrical neuromodulation include, but are not limited to, the following:

- Numbness of the hand/arm
- Itching
- Muscle spasms
- Redness
- Warmth sensation
- Tingling
- Pain in the arm

All anticipated devoice-related AEs, if present, are temporary and should disappear shortly after the treatment.
The following migraine symptoms are foreseeable and will not be considered as device related: headache, nausea, light sensitivity, sensitivity to noise, allodynia, abdominal pain,

loss of appetite, cold or heat sensation, paleness, fatigue, dizziness, anxious mood, fever (rare), blurred vision, vision symptoms such as bright flashing dots or lights, blind spots, wavy or jagged lines (aura).

12.4. Device malfunction

Device malfunction is an inadequacy of the device with respect to its identity, quality, durability, reliability, safety, or performance, such as failure, use error or inadequate labeling. Device malfunctions may or may not be associated with an adverse event.
All device malfunctions will be reported in the eCRF. Device malfunctions that were associated with an SAE or that could have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstance had been less fortunate, will be reported within 24 hours of occurrence. If possible and needed, the device(s) associated with malfunction or failure will be retained until arrangements for its collection are made by the sponsor.

All device malfunctions will be summarized and reported in the clinical study report and will be reported to the regulatory authorities according to local reporting requirements.

13. Early termination

13.1. Criteria and procedures

The study may be discontinued if:

The sponsor decides to terminate the study due to company considerations (e.g. the data monitoring committee recommends terminating the study based on the interim analysis)

If in the opinion of study PI, the study presents an unreasonable medical risk to the patients, the PI may close the site under his/her responsibility.

If the clinical investigation terminated early or suspended, the sponsor will send a report justifying this decision to the corresponding IRB/EC, regulatory body and all investigators. A suspended or terminated clinical investigation may not be re-initiated without approval of the corresponding IRB/EC and relevant RA, as applicable. Enrolled subjects will be followed according to the institution’s standards and guidelines.

13.2. Requirements for patient follow-up in case of withdrawal

If a patient withdraws consent, all efforts will be made to collect the final visit observations as soon as possible.

14. Publication policy

The publication policy is defined in the sponsor-investigator agreement.

15. Patient confidentiality & data protection

The privacy of the participants and the confidentiality of all personal data will be maintained in reports and publications and will not be otherwise published in any way.
The privacy will be maintained according to prevailing national data protection, privacy and secrecy laws. Each patient will be identified by a unique patient identification number. However, the sponsor's monitor or representative and regulatory representatives, auditors and inspectors may have access to medical files in order to verify the authenticity of the data collected, as documented in the informed consent form.

16. Guidelines and applicable documents

- EN ISO 14155; (2011): Clinical investigation of medical devices for human patients
- EN ISO 14971; (2012): Medical devices – Application of risk management to medical devices
- International Conference of Harmonization Good Clinical Practice guidelines
- FDA Guidance for Industry: Computerized Systems Used in Clinical Investigations

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