Approval				
	Name	**Position**	**Date**	**Signature**
Revised by	Maya Vizel	Clinical Research Director		
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-Feb-2021	Maya Vizel	Initial version	N
2.0	01-Sep-2021	Maya Vizel	Minor changes in study efficacy endpoints and dataset definition, revised definition of migraine day, definition of a visit permitted timeframe, addition of study TCH004 synopsis. Correction of grammar and typo errors	N
3.0	10-Mar-2022	Maya Vizel	Sample size increase. Adjusted definition of mITT set, adding exploratory endpoints	N

CLINICAL INVESTIGATION PLAN

STUDY TITLE:

A prospective, Randomized, double-blind, sham-controlled multi-center clinical study assessing the safety and efficacy of Nerivio for the preventive treatment of migraine.

PROTOCOL NUMBER:	TCH008
REVISION:	3.0
RELEASE DATE:	10/March/2022
DEVICE:	Nerivio, a Neuromodulation device for the prevention 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 (2020) 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 #

Table of contents

1. Synopsis

Title	A prospective, randomized, double-blind, sham-controlled multi-center clinical study assessing the safety and efficacy of Nerivio for the preventive treatment of migraine.
Investigational Device	Nerivio is an FDA-approved remote electrical neuromodulation (REN) device for the acute treatment of migraine with or without aura. 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. The study will assess Nerivio for the preventive treatment of migraine using a 45-minute treatment given every other day.
Objectives	To evaluate the safety and efficacy of Nerivio for migraine preventive treatment.
Participant Population	Adults (18-75) meeting the International Headache Society criteria (ICHD-3) for migraine with or without aura, with 6-24 headache days per 28-day period and at least 4 days fulfilling ICHD-3 criteria for migraine without aura (code 1.1; C and D) or with aura (code 1.2; B and C), probable migraine, or requiring the use of triptans or ergot derivatives.
Sample size	Up to 375 participants
Inclusion Criteria	1. Age 18-75 years old 2. Must have at least a 6-month history of headaches that meet the ICHD-3 diagnostic criteria for migraine with or without aura, either chronic or non-chronic migraine. 3. History of 6 to 24 headache days per 28-day period for each of the 3 months preceding study enrolment (based on patient report). 4. Subjects on prophylactic migraine treatment are permitted to remain on 1 medication with possible migraine-prophylactic effects if the dose has been stable for at least 2 months prior to the screening visit, and the dose is not expected to change during the course of the study. 5. Have personal access to a smartphone (24/7). 6. Must be able and willing to comply with the protocol. 7. Must be able and willing to provide informed consent.
Exclusion Criteria	1. An active implanted electrical and/or neurostimulator device (e.g. cardiac pacemaker, cochlear implant).

	2. Uncontrolled epilepsy. 3. History of use of opioids or barbiturates on more than 4 days a month in the last 6 months. 4. Current participation in any other interventional clinical study 5. Participants without basic cognitive and motor skills required for operating a smartphone. 6. Pregnant or breastfeeding. 7. Other significant pain, medical or psychological problems that in the opinion of the investigator may confound the study assessments. 8. Prior experience with the Nerivio device.
Study Design	A prospective, randomized, double blind, sham controlled, multicenter trial, conducted in three phases. The trial will consist of a screening/enrollment visit, followed by a 4-week (28 days) baseline phase. Eligible participants will enter an 8-week double-blind preventive treatment phase. Following the preventive treatment phase, patients will be offered to participate in a 4-week open label pre-emptive treatment phase or continue their prevention treatment with an active device, according to their eligibility. Patients will complete an electronic diary throughout the study; this includes a daily evening report (completed regardless of whether the patient had a headache) and a treatment feedback during the follow up pre-emptive phase <u>Phase I – Baseline - 4 weeks (weeks 1 through 4):</u> Eligible participants will install the Nerivio app on their smartphones and will be instructed to record daily their migraine/headaches symptoms and medication use on the Nerivio app. <u>Transition to the treatment phase:</u> Participants who meet the following criteria in the baseline phase will be eligible to continue to the treatment phase: • Complete the diary in at least 22 out of the 28 days during the baseline phase (80%) • Have between 6 to 24 headache days during the 28-day baseline period. • At least 4 of their headache days during the baseline phase fulfill the ICHD-3 criteria for migraine (migraine without aura [code 1.1; C and D] or with aura [code 1.2; B and C], or probable migraine, or headaches

	requiring the use of migraine-specific medications including triptans, gepants or ergot derivatives) Phase II - treatment phase (prevention) – 8 weeks (weeks 5 through 12): Participants who meet the baseline phase requirements will be randomized in a 1:1 ratio to active and sham groups. Participants will be instructed to complete a daily diary (in the Nerivio app) about their headaches, associated symptoms, and medication use. They will also be instructed to conduct a 45-minute treatment with Nerivio every other day. Transition to the follow-up phase (open label): At the end of the treatment phase, participants from both arms (active and sham) may continue to a follow-up phase in which they will receive an active device that can be used during this phase. The data of all participants will be used for safety analyses. The data of participants from the baseline and treatment phases will be used to assess their eligibility to participate in the pre-emptive follow-up phase. Participants eligible for the follow-up phase meet the following conditions: • Between 6-16 headache days during the baseline phase. • Participants experience prodrome symptoms within 24 hours prior to the onset of their migraine headache in at least half of their migraine attacks during the baseline phase. • Participants completed the daily questionnaires in at least 70% of the days during the treatment phase. • Treated every other day in at least 24 and less than 33 days during the 56 days of the treatment phase. Phase III – Follow-up phase (open label) - 4 weeks (weeks 13 through 16): All participants will receive an active Nerivio device to use during the follow-up phase. Participants who do not meet the above requirements will be able to enter into the safety follow-up and continue to use Nerivio every other day for the preventive treatment of migraine. They will be instructed to compete a daily diary as was done in the treatment phase.

	Participants who meet the above requirements will enter the pre-emptive follow-up phase and be instructed to conduct a 45-minute device treatment within 60 minutes of prodrome symptom onset. Participants will be instructed to complete questionnaires regarding their headache, prodrome symptoms, and medication use at baseline (start of treatment), 2 hours post-treatment, and 24 hours post-treatment. In addition, participants will be instructed to continue to report the daily diary, as performed in the other phases of the study.
Primary efficacy endpoint	Mean change in number of migraine headache days per month comparing the 4-week baseline phase (weeks 1 through 4) with the last 28 days of the treatment phase (weeks 9 through 12). A migraine headache day is defined as a calendar day with headache that is accompanied by at least one of the following symptoms: aura, photophobia, phonophobia, nausea and/or vomiting; or a calendar day with a headache that is treated with a migraine-specific acute medication.
Secondary efficacy endpoints	1. Mean change in number of moderate/severe headache days per month comparing the 4-week baseline phase (weeks 1 through 4) with the last 28 days of the treatment phase (weeks 9 through 12) A moderate/severe headache day is defined as a calendar day with moderate or severe headache. 2. Mean change in the number of headache days per month from the 4-week baseline phase (weeks 1 through 4) to the last 4 weeks of the treatment phase (weeks 9 through 12). A headache day is defined as a calendar day with headache (at any severity). 3. Percentage of patients achieving at least 50% reduction from baseline in the mean number of headache days (all severities) per month in the last 4 weeks of the treatment phase (weeks 9 through 12). 4. Mean change in the HIT-6 total score from baseline to the last 4 weeks of the treatment phase (weeks 9 through 12). 5. Mean change in the MSQ role function from baseline the last 4 weeks of the treatment phase (weeks 9 through 12).
Exploratory efficacy endpoints	1. Reduction in the mean number of acute headache/migraine medication days per month in the last 4 weeks of the treatment phase (weeks 9 through 12) compared to Baseline (weeks 1 through 4). An acute headache/migraine medication day is a calendar day on which the

	patient consumes at least one dose of any medication (OTC or prescribed) for acute treatment of headache or migraine. [Endpoints 2-6 below relate to the pre-emptive follow-up phase] 2. Percentage of patients who treat for the first treatment in the pre-emptive phase, during a prodrome, when they are pain free, and remain pain free during the following 2 hours after the treatment, without use of acute medication. 3. Percentage of patients who treat for the first treatment in the pre-emptive phase, during the prodrome, when they are pain free, and remain pain free during the following 24 hours after the treatment, without use of acute medication. 4. Percentage of patients who treat for the first treatment in the pre-emptive phase, during the prodrome, when they are pain free, and remain either pain free or with mild pain during the following 24 hours after the treatment without use of acute medication. 5. Mean change in the percentage of prodromes which were followed by a headache within 24 hours from baseline to the end of the pre-emptive follow-up phase. 6. Mean change in the average number of moderate/severe headache days per month in the pre-emptive phase compared to the 4-week baseline phase. [Endpoint 7 relate to Health Economics analysis] 7. Differences between active and sham groups in reduction of the following events from baseline (weeks 1-4) to the last 4 weeks of treatment phase (weeks 9-12): (a) Absenteeism, (b) Presenteesim, (c) Healthcare provider appointments, (d) ED/ER visits, (e) Brain MRI/CT scans [Endpoint 8 relate to migraine prediction analysis]8. Feasibility of a migraine prediction algorithm: Analysis of the daily information provided by the participants during the baseline period (weeks 1-4) for the purpose of predicting their migraine days
Safety endpoints	1. The incidence of adverse events in general and by seriousness, severity and association to the device. 2. Treatment tolerability (by electronic patient report).

Datasets	1. Intent to treat analysis set (ITT) The ITT analysis set includes all randomized participants 2. Modified intent to treat analysis set (mITT) The mITT analysis set includes all ITT participants who had at least 22 days of efficacy assessments in the last 4 weeks of the treatment phase (weeks 9 through 12) and at least 12 treatments performed throughout weeks 9-12.
Data Analysis	The ITT analysis set will be used for the safety assessments and 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]. The International Headache Society defines migraine as a recurrent headache disorder manifesting in attacks lasting 4-72 hours. In addition to the disabling pain attacks, migraines can be either with or without aura, and accompanied by at least one of the symptoms: nausea, photophobia and phonophobia. Some patients also experience additional symptoms occurring hours or days before the headache, known as the prodromal phase, or after pain resolves, known as the postdromal phase. The prodrome symptoms include food cravings, repetitive yawning, fatigue and neck stiffness.[2].

Patients experiencing a frequent number of migraine attacks and a myriad of related symptoms require a treatment regime to manage their pain levels and extensive accompanying symptoms. Current treatment strategies for migraine consists of both preventive treatment and acute treatment. Preventive treatments have been shown to be efficacious for patients in reducing the number and severity of headache days, making it the primary treatment plan for chronic migraine patients [3].

However, current preventive treatments demonstrate only up to 50% response rate [4-6] and only 30% adherence rate [7], requiring additional new preventive treatments for these non-responders. Moreover, even when highly effective, preventive treatments do not prevent all migraine attacks, thus requiring the use of acute treatment [8], and if used excessively, acute medications can often lead to medication overuse headache (MOH) [9]. Thus, there is a great unmet to have a preventive treatment that does not increase medication intake on one hand, and on the other hand reduces the number of headache days and pain severity.

This unmet need can be met using remote electrical neuromodulation (REN) [10]. REN 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 [11]. The safety and efficacy of REN (Nerivio®, Theranica Bio-Electronics LTD., Israel) have already been established for acute treatment [12,13]. Nerivio was assessed for migraine 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) for the acute treatment of migraine in people who do not have chronic migraine. In addition, two open label studies of the Nerivio for acute treatment of migraine in chronic migraine patients demonstrated similar patterns of pain relief, pain free and consistency of pain relief across treatments. Based on these studies, the device was granted a 510k pre-market notification (K201824) for the acute treatment of migraine in people 18 years and older.

The aim of the present study is to evaluate the safety and efficacy of Nerivio for a preventive treatment of migraine, thus establishing Nerivio as a digital health tool offering a complete treatment management of migraine. Since already demonstrated to be effective for acute treatment, Nerivio can provide a complete management of migraine pain and symptoms that will greatly benefit the quality of life of migraine patients, improving adherence and lowering the side effects.

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. 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 the preventive treatment of migraine in patients 18 years of age or older.

3.2. 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.

Main warnings and precautions:

- 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 and people less than 18 years of age

3.3. 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 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 bi-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).

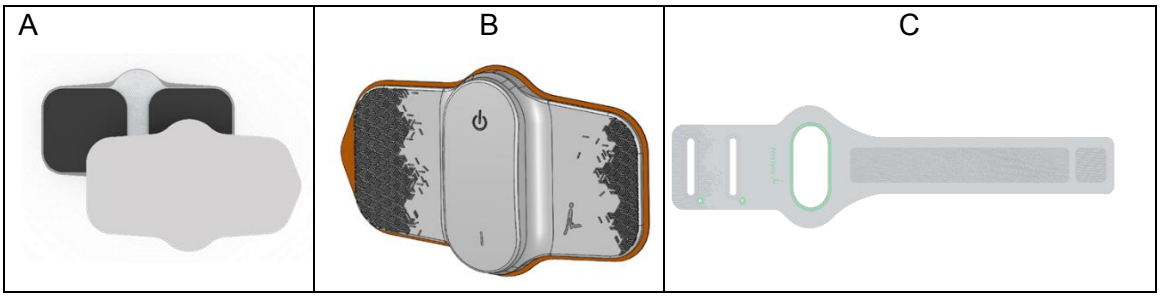

Figure 1: Nerivio device. (A) Internal side, (B) External side, and (C) The armband

3.4. The application

Activation, control over stimulation intensity and termination of stimulation are performed via a dedicated smartphone application and installed on the user's

smartphone (Figure 2). The application has a graphical user interface (GUI) which includes graphical controls that the user can select using a touch screen. The app enables the user to start treatments and control them.

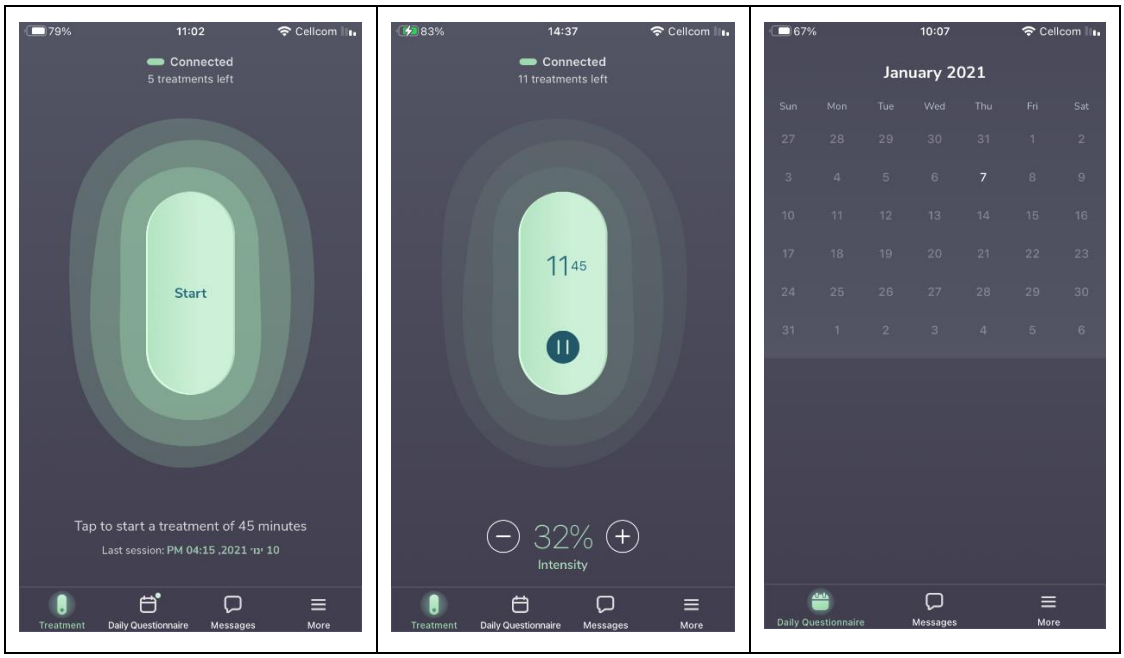

Figure 2: The app screens

In addition, the application sends the user a daily questionnaire of migraine related symptoms. 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.

3.5. 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 printed QuickStart guide and a user manual in the app. 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), currently – per the present indication - 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 response. Second, it may be easily accessed independently by the user without the help of others. Finally, it provides a discreet location that maintains the privacy of the user and enables to continue with ongoing activities during treatment.

Figure 3: Nerivio location of treatment

3.6. 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 [13]. 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 [14,15]. Notably, it has been shown that very strong but subjectively non-painful stimulus is sufficient to trigger pain inhibitory effects [16].

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 [17]. CPM inhibits the responses of these fibers, with an inhibitory preference towards the C fiber mediated responses [18]. 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.

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

Table 1: Characteristics of nerve fibers

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 [19], 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.

The expansion of this mechanism of action to prevention is based on the hypothesis that frequent triggering of the CPM mechanism (in this case, every other day) train this mechanism for rapid activation upon need.

3.7. Output parameters

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.

The Nerivio output parameters is described in Table 2.

Parameter	Nerivio Device
Mode or program name	REN
Waveform	Biphasic, symmetrical
Shape	Rectangular
Maximum output voltage (V) 500Ω 2KΩ 10KΩ	 20 60 60
Maximum output current (mA) 500Ω 2KΩ 10KΩ	 40 30 6
Duration of primary (depolarizing) phase (μsec)	200
Frequency (Hz)	100-120
Maximum average power density (mW/cm²)500Ω	1.14
Maximum phase charge (μC) 500Ω	 8
Maximum current density (mA/cm², r.m.s) 500Ω	 1.6

Table 2: Key output parameters of Nerivio

3.8. Instructions for use

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

3.9. Identification of the medical device

The device 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. Investigational sites outside the USA, where the device is not yet approved, will receive a device with an additional label for clinical investigation use only.

3.10. 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 device described in this submission is identical to the version in K201824, and accordingly, the nonclinical testing that supported this clearance remains fully applicable to the device for the proposed modified indications for use. No additional bench testing will be conducted. A brief summary of the existing clinical experience with the device is summarized in this section.

Clinical data supporting the safety and performance of the Nerivio device for the treatment of migraine headaches has been collected across a series of studies:

Study number	Design	Population	Submission
TCH-001	prospective, double-blind, randomized, crossover, sham-controlled pilot study	Patients with migraines, aged 18-75 years old	DEN180059
TCH-003	prospective, randomized, double-blind, sham-controlled pivotal study	patients with migraines, aged 18-75 years old	DEN180059
TCH-005	prospective, open-label, single arm, dual-center study	patients with chronic migraine aged 18–75 years	K201824

TCH-006	prospective, open-label, single arm, multicenter study	patients with chronic migraine aged 18–75 years	K201824
TCH-004	prospective, open-label, single arm, multicenter study	patients with episodic **and chronic** migraine aged 12–17 years	K203181

Table 3 - Prospective clinical data supporting prior clearances

4.2.1. **Pilot Study TCH-001 (NCT02453399)**

As previously presented to the agency in DEN180059, 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 stimulation with Nerivio device for the acute treatment of migraine. Briefly, 86 migraineurs 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 four different stimuli programs (P200, P150, P100 and P50 with frequencies of 100-120Hz each and pulse width of 2x200msec, 2x150msec, 2x100msec and 2x50msec, respectively).

Stimulation period was set to 20min and the intensity was self-adjusted to a "well perceived, but non-painful" level. Stimuli were given at random sequence. Pain levels were self-reported using the numeric rating scale (NRS) of 0 – 10 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 post-treatment in at least 50% of completed treatments.

The other primary endpoint was the relative pain reduction by NPS at two hours post-treatment as a percentage of pre-treatment pain. This was calculated per each type of stimulation.

The analysis of the primary endpoint revealed a 64% rate of at least 50% pain reduction at 2 hours post-treatment, in at least 50% of completed active treatments. Pain reduction was defined as a reduction from severe or moderate pain to (i) mild or no pain; and (ii) to no pain This rate was significantly higher than the 26% rate found for the sham treatment (p=0.005). The data demonstrated that the P200 program presented the most potential effect of migraine headache reduction. Moreover, no device-related adverse events were reported. The next studies utilized devices with the P200 program only.

4.2.2. **TCH-003 Pivotal Study (NCT03361423)**

As previously discussed in DEN180059, this study was a prospective, randomized, double-blind, sham controlled multi-center pivotal study aiming to demonstrate the efficacy and safety of Nerivio. The study was performed in 7 sites in the USA and 5 sites in Israel.

Eligible patients were 18–75 years old females and males who met the inclusion/exclusion criteria of the study. The study included two phases. In the first ("roll-in") phase, participants were asked to keep a headache diary for one month in which all migraine episodes were documented. The second phase was a double-blind treatment phase, in which eligible participants were randomly allocated in a 1:1 ratio to either active stimulation (treatment group) or sham stimulation (sham group), in a double-blind manner. Participants were then asked to treat their migraine episodes for 6 weeks using the device and to treat each migraine episode within 60 minutes of symptom onset. The participants used the application (installed on their personal phones) to record pain scores (scale: none, mild, moderate, or severe) at baseline, 2 hours post-treatment and 48 hours post-treatment, and to record the presence/absence of associated migraine symptoms (nausea, photophobia, phonophobia). The first reported treatment was considered a "run-in test" treatment, aimed to verify that the participants use the device properly, and was only included in the safety analysis. The efficacy endpoints were evaluated on the first reported treatment following the "run-in test" treatment (hereby termed "Test treatment").

Results

In the mITT analysis set, the proportion of participants achieving a pain-relief response 2 hours after treatment was 66.7% (66/99) in the treatment group compared to 38.8% (40/103) in the sham group (therapeutic gain 27.9%; p<0.0001). The active treatment was also superior to the sham for the reduction of pain for each one of the possible baseline pain levels (severe, moderate, and mild). Furthermore, the active stimulation treatment was significantly more effective than the sham treatment for the proportion of participants achieving 2 hours of MBS relief (46.3% vs. 22.2%; p=0.0.0008) and for the proportion of participants who achieved both headache relief and MBS relief at 2 hours post-treatment (40.0% vs. 15.2%; p=0.0004. There was no significant difference between active and sham treatment for MBS-free 2 hours post-treatment (40.7% vs. 36.4%; p=0.0.55). For pain-free 2 hours post-treatment, the active device was superior to the sham device, with statistical significance (37.4% vs. 18.4%; p=0.0036).

The active treatment was significantly more effective than the sham treatment for all measures of sustained efficacy, including 48-hour sustained pain-free response with device single use (p=0.007), 48-hour sustained headache reduction with device single use (p=0.0015), 48-hour sustained pain-free response with device reuse (p=0.0148), and 48-hour sustained headache reduction with device reuse (p=0.0010). In addition, the consistency of pain reduction over multiple treatments was also significantly higher in the treatment group (62.6%) compared to the sham group (45.6%, p=0.0154).

With regard to safety, the incidence of device-related adverse events was low (3.6%), and similar between treatment groups (active group: 6/126 [4.8%]; sham group: 3/126 [2.4%]; pFisher's=0.4998). There were no unanticipated adverse device effects and all device-related adverse events reported were mild in severity, did not require treatment and were self-resolved. No serious adverse events related to the device were reported.

No statistically significant differences were found between treatment groups in either the type or rate of adverse events during the double-blind treatment phase.
In this randomized, double-blind, sham-controlled study, the Nerivio was effective and well-tolerated for the acute treatment of migraine. From a risk-benefit perspective, treatment with Nerivio achieved significant pain relief without serious side effects. Therefore, Nerivio demonstrated that it offers an alternative for current pharmacological and non-pharmacological treatments that combines efficient treatment with minimal side effects.

4.2.3. Clinical study TCH-005 (NCT04161807)

A prospective, open-label, single arm, dual-center study pilot study of the Nerivio device in patients with chronic migraine was performed to assess the performance of Nerivio in people with chronic migraine across two clinical sites: one site in the USA and one site in Israel. Specifically, it assessed the capability of the Nerivio device to alleviate migraine headache and additional symptoms in patients with chronic migraine and support the submission of a 510(k) notice with an expanded indication for use of Nerivio in people with chronic migraine, compared to the original De Novo submission. This study has been previously presented to FDA in the 510k pre-market notification (K201824) and summarized below.
The study included patients with chronic migraine aged 18–75 years old, who met the International Classification of Headache Disorders (ICHD-3) criteria for chronic migraine (at least 15 headache days a month, with at least eight days a month on which their headaches and associated symptoms meet diagnostic criteria for migraine).

Study design and procedures

Participants treated their migraine attacks at home for 4 weeks (treatment phase), with their optimal stimulation intensity, as soon as possible after migraine headache began and always within one hour of attack onset. Participants were instructed to avoid taking rescue medications within the first two hours post-treatment. Pain scores (none, mild, moderate, or severe), absence/presence of migraine associated symptoms including nausea/vomiting, photophobia and phonophobia, and functional disability were recorded at baseline, 2- and 24-hours post-treatment in electronic diary application included in the Nerivio mobile application that was installed on the participants' smartphones.

Results

A total of 296 qualifying migraine headaches (defined as a migraine headache that is of moderate or severe intensity and preceded by 24 hours of no pain or mild intensity pain; or is of mild intensity and preceded by 24 hours of no pain) were treated with Nerivio (average of 7.8 treatments per participant per 4 weeks for 38 participants), of which baseline pain level was reported in 270 treatments.
A total of 210 evaluable treatments (excluding the training treatment) of qualifying migraine headaches were conducted by the 38 participants included in the analyses, with an average of 5.5±2.6 evaluable treatments per patient per 4 weeks. Rescue

medication at 2 hours was used across 16 subjects in 22 of the 210 treatments (89.5% compliance rate). 22 (57.9%) of the patients did not use any medication during the trial (for all their treatments). Use of medication was considered a failure for the specific treatment.

The primary, secondary and exploratory endpoints of a single attack were conducted on the test treatment of the final analysis set of 38 participants. Pain relief and pain-free at 2 hours were achieved by 50.0% (19/38; CI95% 33.4-66.6%) and 26.3% (10/38; CI95% 13.4-43.1%) participants, respectively. Pain relief was sustained for 24 hours in 83.3% (10/12; CI95% 51.6-97.9%) of the participants who achieved relief at 2 hours (7 participants did not report pain level at 24 hours and were thus, excluded from the analysis). Nausea, photophobia, and phonophobia disappeared at 2 hours in 58.8% (10/17; CI95% 32.9-81.6%), 37.5% (9/24; CI95% 18.8-59.4%), and 50.0% (8/16; CI95% 24.7-75.3%) participants, respectively. Furthermore, 46.7% (14/30; CI95% 28.3-65.7%) participants experienced improvement in functional ability at 2 hours and 72.7% (16/22; CI95% 49.8-89.3%) participants experienced improvement in functional ability at 24 hours (8 participants with missing data at 24 hours were excluded from the analysis).

Consistency analyses across all attacks (excluding the training treatment) demonstrated that 73.7% (28/38) of the participants experienced pain relief in at least 50% of their treated attacks. Mean pain relief rate across subjects was 58.8%, median pain relief rate across subjects was 60% and the inter quartiles rang (IQR) was 43.67 - 87.50%.

According to the safety analyses, the percentage of participants experiencing at least one adverse event was 4.7% (2/42) with 95% confidence interval of (0.6 – 16.2%). A single device-related adverse event was reported (2.3% [1/4])). The device-related adverse event was moderate, resolved within 48 hours following drug therapy (triptan). There were no serious adverse device-related events and none of the participants withdrew from the study due to adverse events.

The findings of the study demonstrated that Nerivio is effective for the acute treatment of migraine in people with chronic migraine. Acute treatment of migraine headaches resulted in clinically meaningful benefits. Pain relief and pain-free rates were generally similar to those found in people with non-chronic migraine as reported in the Nerivio clinical study presented in DEN180059. Overall, the data reveal consistent response rates from treatment to treatment, with no evidence of reduction in therapeutic benefits over time. Specifically, over 73% of the patients achieved pain relief at 2 hours in more than half of their attacks. The findings of this study also show that the device is safe and well-tolerated. No safety issues were associated with the more frequent use of the device in patients with chronic migraine.

4.2.4. **Clinical study TCH-006 (NCT04194008)**

A large multicenter study of the Nerivio device in patients with chronic migraine was performed to further assess the performance of Nerivio in the chronic migraine population. This study has also been previously presented to FDA in the 510k pre-market notification (K201824) and summarized below for completeness.

The study included patients, aged 18-75 years, with chronic migraine who met the International Classification of Headache Disorders (ICHD-3) criteria for chronic migraine (at least 15 headache days a month, with at least eight days a month on which their headaches and associated symptoms meet diagnostic criteria for migraine).

Study design and procedures

This study was a prospective, open-label, single arm, multicenter study conducted across 9 clinical US sites. Participants entered a 4-week "Run-in" phase in which they had to report their migraine attacks and continue with their usual treatment care. Participants who reported at least 6 qualifying migraine headaches with pain data at baseline and 2 hours post-treatment were eligible to continue to the "Treatment" phase. During the "Treatment" phase, participants were asked to treat their migraine attacks at home for 4 weeks with their optimal stimulation intensity, as soon as possible after migraine headache began and always within one hour of attack onset. Participants were instructed to avoid taking rescue medications within the first two hours post-treatment. Pain scores (none, mild, moderate, or severe), absence/presence of migraine associated symptoms including nausea/vomiting, photophobia and phonophobia, and functional disability were recorded at baseline, 2- and 24-hours post-treatment in electronic diary application included in the Nerivio mobile application that was installed on the participants' smartphones.
Participants who finished the "Treatment" phase were offered to continue to an 8-week follow-up phase in which they could incorporate the device into their usual care. Following the 8 weeks of "Follow up" phase, participants fill out their end of study questionnaire and completed the study.

Results

Run-in phase
A total of 997 qualifying migraine attacks were reported during the run-in phase by the 126 enrolled patients, with an average of 7.9 attacks per participant. Of these, pain level at baseline was reported on 993 reported attacks.

Treatment phase
A total of 711 qualifying migraine headaches were treated with Nerivio (average of 7.3 treatments per participant per 4 weeks for 97 participants [2 participants had no qualifying migraine attacks]), of which baseline pain level was reported in 635 treatments. Pain severity of treated migraine headaches was mostly moderate (57.2% [363/635]). 157/635 (24.7%) of the treated migraine headaches were severe and 115/635 (18.1%) of the treated migraine headaches were mild. Generally, the characteristics of treated migraine headaches were comparable to those reported in previous migraine studies and are consistent with the pain intensity characterization of the target patient population of the device.
A total of 493 evaluable treatments (excluding the training treatment) of qualifying migraine headaches were conducted by the 91 participants included in the analyses,

with an average of 5.4±2.8 evaluable treatments per patient per 4 weeks. Medication at 2 hours was used in 54 of the 493 treatments (89.0% compliance rate). Use of medication was considered a treatment failure.

The primary, secondary and exploratory endpoints of a single attack were conducted on the test treatment of the final analysis set of 91 participants. Pain relief and pain-free at 2 hours were achieved by 59.3% (54/91; CI95% 48.5-69.5%) and 20.9% (19/91; CI95% 13.0-30.6%) of the participants, respectively. Pain relief was sustained for 24 hours in 73.3% (33/45; CI95% 58.0-85.3%) of the participants (9 participants did not report pain level at 24 hours and were thus excluded from the analysis). Nausea, photophobia, and phonophobia disappeared at 2 hours in 48.8% (20/41; CI95% 32.8-64.8%), 40.5% (30/74; CI95% 29.2-52.5%), and 44.6% (29/65; CI95% 32.2-57.4%) participants, respectively. Furthermore, 59.4% (19/32; CI95% 40.6-76.3%) of the participants experienced improvement in functional ability at 2 hours (participants with missing data at baseline or at 2 hours were excluded from the analysis) and 50.0% (7/14; CI95% 23.0-76.9%) of the participants experienced improvement in functional ability at 24 hours (participants with missing data at baseline or at 24 hours were excluded from the analysis).

Consistency analyses across all attacks (excluding the training treatment) demonstrated that 57.1% (52/91; CI95% 46.3-67.4%) of the participants experienced pain relief in at least 50% of their treated attacks. Mean pain relief rate across subjects was 50.4%, and median pain relief rate across subjects was 50%. Pain relief in at least 2 of 3 consecutive treatments (first 3 treatments excluding the training treatment) was reported by 64.4% (47/73; CI95% 52.3-75.3%) of the participants.

The percentage of participants experiencing at least one adverse event was 9.1% (9/99) with 95% confidence interval of (4.2 – 16.6%). One device-related adverse event was reported (1.0% [1/99]) in which pain in the arm was felt following the use of the device on that arm. The device-related adverse event was mild, resolved within 24 hours without medication. The other adverse events which were deemed unrelated to the device.

The findings of the study show that Nerivio is effective for the acute treatment of migraine in people with chronic migraine. Acute treatment of migraine headaches resulted in clinically meaningful benefits. Pain relief and pain-free rates were generally similar to those found in people with non-chronic migraine, indicating that Nerivio provides an alternative acute migraine treatment independent of the frequency and severity of migraine headaches.

The data inspected for all treatments reveal consistent response rates from treatment to treatment with no evidence of tolerance to the therapeutic benefits. In at least two of the first three attacks treated with Nerivio, about 65% of patients achieved pain relief at 2 hours post-treatment. The study also demonstrated that Nerivio relieves the associated symptoms of migraine, including nausea, photophobia and phonophobia and has clinical benefit on the MBS.

The results of the study show that Nerivio is safe to use and is well-tolerated. The incidences of device-related adverse events were low with no device-related serious

adverse events. The rate of all device-related adverse events was below 2%, which compares favorably to the reported rates for current pharmacological treatments.

4.2.5 Clinical study TCH-004 (NCT04089761)

A multicenter study of the Nerivio device in adolescent patients (age 12-17, inclusive) with migraine was performed to assess the performance of Nerivio in the adolescent migraine population. This study has also been previously presented to FDA in the 510k pre-market notification (K203181) and is summarized below for completeness.

Study design and procedures

This study was a prospective, open-label, single arm, multicenter study conducted across 12 clinical US sites. Participants entered a 4-week "Run-in" phase in which they had to report their migraine attacks and continue with their usual treatment care. Participants who reported at least 3 qualifying migraine headaches with pain data at baseline and 2 hours post-treatment were eligible to continue to the "Treatment" phase. During the "Treatment" phase, participants were asked to treat their migraine attacks at home for 8 weeks with their optimal stimulation intensity, as soon as possible after migraine headache began and always within one hour of attack onset. Participants were instructed to avoid taking rescue medications within the first two hours post-treatment. Pain scores (none, mild, moderate, or severe), absence/presence of migraine associated symptoms including nausea/vomiting, photophobia and phonophobia, and functional disability were recorded at baseline, 2- and 24-hours post-treatment in electronic diary application included in the Nerivio mobile application that was installed on the participants' smartphones.

Participants who finished the "Treatment" phase were offered to continue to an 8-week follow-up phase in which they could incorporate the device into their usual care. Following the 8 weeks of "Follow up" phase, participants fill out their end of study questionnaire and completed the study.

Results

Run-in phase

A total of 267 qualifying migraine attacks were reported during the run-in phase by 54 of the 60 enrolled patients (6 patients did not report any migraines during the run-in phase), with an average of 4.9 migraine attacks per participant

Treatment phase

A total of 159 qualifying migraine headaches were treated with Nerivio for which pain data was recorded at baseline and at 2 hours post-treatment (average of 3.5 treatments per participant). Pain severity of treated migraine headaches was mostly

moderate (48.4% [77/159]). 57/159 (35.8%) of the treated migraine headaches were severe and 25/159 (15.7%) of the treated migraine headaches were mild

Pain relief and pain-free at 2 hours were achieved by 71.8% (28/39) and 35.9% (14/39) participants, respectively. Pain relief was sustained for 24 hours in 90.9% (20/22) of the participants, and pain freedom was sustained for 24 hours in 90.9% (10/11) of the participants. Nausea, photophobia, and phonophobia disappeared at 2 hours in 54.5% (12/22), 41.9% (13/31), and 40.0% (10/25) participants, respectively. Furthermore, 69.7% (23/33) participants experienced improvement in functional ability at 2 hours and 69.0% (20/29) participants experienced improvement in functional ability at 24 hours.

a consistency analyses was conducted across all treated attacks (excluding the training treatment). This analysis demonstrated that 66.7% (26/39) of the participants experienced pain relief in at least 50% of their treated attacks, and 33.3% (13/39) of the participants experienced pain-free in at least 50% of their treated attacks.

Safety analyses were performed on all 45 participants who used the device at least once. 10 participants (22.2%) reported at least one adverse event. There was one device-related adverse event reported (2.2%) in which a temporary feeling of pain in the arm was felt. This adverse event was mild and resolved after the treatment without requiring medication or any other intervention. The other adverse events which were deemed unrelated to the device.

The findings of the study show that Nerivio is effective for the acute treatment of migraine in the adolescent population. The results of the study show that Nerivio is safe to use and is well-tolerated by adolescence migraineurs. The incidence of device-related adverse events was low with no device-related serious adverse events.

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 the use for preventive treatment will be experienced with a similar safety profile.

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 [26] and to new pharmacological agents, such as centrally acting serotonin (5-HT1F) agonists that lack cardiac vasoconstrictive activity [27]. Furthermore, the device has comparable or superior efficacy to commercially available neuromodulation devices [21,24].

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 neuromodulation 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, and was not changed when frequency of use was increased significantly for over 15 times per month by chronic migraine patients. Using the device for a preventive treatment is not expected to pose any new risks, since the device will be used every other day, resulting in ~15 days per month. The overall risk posed by the device is minimal. The device may offer an alternative non-pharmacological treatment that includes both acute and preventive treatments, without needing a variety of pharmacological agents that increases the risk of medication overuse, improve treatment adherence and considerably improve the health and quality of life of patients 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 preventive treatment of migraine. The goal of this study is to demonstrate a reduction in the number of migraine headache days per month while maintaining a favorable safety profile.

5.2. Study hypothesis

The hypothesis of this study is that treating with Nerivio every other day will reduce monthly migraine headache days, while maintaining a favorable safety profile. This will be demonstrated by a significant difference between the active and the sham groups in the mean change in monthly migraine days from the baseline phase to the last 4 weeks of treatment phase.

6. STUDY DESIGN

6.1. Participants

This study will be conducted on up to 375 participants.

6.1.1. Inclusion criteria

- Age 18-75 years old
- Must have at least a 6-month history of headaches that meet the ICHD-3 diagnostic criteria for migraine with or without aura, either chronic or non-chronic migraine.
- History of 6 to 24 headache days per 28-day period for each of the 3 months preceding study enrolment (based on patient report).
- Subjects on prophylactic migraine treatment are permitted to remain on 1 medication with possible migraine-prophylactic effects if the dose has been stable for at least 2 months prior to the screening visit, and the dose is not expected to change during the course of the study.
- Have personal access to a smartphone (24/7).
- Must be able and willing to comply with the protocol.
- Must be able and willing to provide informed consent.

6.1.2. Exclusion criteria

- An active implanted electrical and/or neurostimulator device (e.g. cardiac pacemaker, cochlear implant).
- Uncontrolled epilepsy.
- History of use of opioids or barbiturates on more than 4 days per month in the last 6 months.
- Current participation in any other interventional clinical study.
- Participants without basic cognitive and motor skills required for operating a smartphone.
- Pregnant or breastfeeding.
- Other significant pain, medical or psychological problems that in the opinion of the investigator may confound the study assessments.
- Prior experience with the Nerivio device.

6.1.3. Withdrawal / Discontinuation

Participants may withdraw consent at any time 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

Nerivio device - The device produces a proprietary electrical signal comprising a modulated symmetrical biphasic square pulse with a modulated frequency of 100-120Hz, pulse width of 400μs, and up to 40mA output current (adjusted by the participant). The duration of the treatment is 45 minutes.

Sham device- The device produces electrical pulses of similar width and intensity, but much lower frequency compared to the active device. It produces an electrical signal comprising a modulated symmetrical biphasic and rectangular pulse with a modulated frequency of 0.11-0.2Hz, pulse width of 300-1700μs, and up to 34mA output current (adjusted by the participant). The duration of the treatment is 45 minutes. This sham program produces pulses that are perceivable by the user, thus maintaining the blinding, but on the other hand do not intend to activate the CPM as a pain relief mechanism.

6.3. Procedures

This study includes up to four visits. Each visit can be performed either on-site or remotely, using a teleconference software. The means of remote visits will be documented in the site binder prior to site initiation. Each visit will have a time window of 10 days after the perspective visit date to complete the study visit.

Pre visit evaluation-

A candidate patient for the study will be asked by the clinic to complete an online questionnaire that will assess the patient compliance to participate in the study. A summary of the questionnaire will be sent to the clinic for review. The PI will use the data from the questionnaire to evaluate the patient ability to comply with the study requirements.

First visit –

The first visit will include screening, enrollment and training on the application.

Enrollment: The screening process will include an eligibility assessment and a urine pregnancy test. Following successful screening, the site staff will provide the participants

with study related information, perform an enrollment interview and receive an informed consent from the participants. During this visit, participants will complete baseline questionnaires that includes information on frequency of 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 (HIT-6 and MSQ questionnaires).

Application training: Eligible participants who enroll to the study will be trained to use the application that will be installed on their own smartphones. The participants will be instructed to complete a daily diary that included information on, headache with time of onset, migraine symptoms, and medication use. The site personnel will be required to document the training session in the CRF.

Baseline phase:
After the enrollment visit, participants will undergo a 4-week baseline phase aimed to collect headache days, medication use, migraine symptoms, and further assess eligibility. Participants will use the app daily to record headache with time of onset, migraine symptoms and medication use. To ensure compliance, the app will send daily reminders/notifications in a pre-specified time in the evening chosen by the participant, but the questionnaire will be available throughout the day. The daily reports will be transferred by the application to the electronic data capture (EDC) system, where they will be collected and registered.

Qualification to enter into the treatment phase: Participants who complete the diary in at least 22 out of the 28 days during the baseline phase (80%), have between 6 to 24 headache days during the 28-day baseline period, at least 4 of their headache days during the baseline phase fulfill the ICHD-3 criteria for migraine (migraine without aura [code 1.1; C and D], or with aura [code 1.2; B and C], or probable migraine, or headaches requiring the use of migraine-specific medications such as triptans, gepants or ergot derivatives) will continue to the treatment phase. Participants who fail these criteria will be excluded from the study and considered screen failure.

Second visit-
Device training: Eligible participants who successfully complete the baseline phase will be randomized in a 1:1 ratio into one of the two groups: either active (treatment with Nerivio active device) or sham group (treatment with Nerivio sham device). During this visit, participants will receive general instructions on study procedures, device mode of operation and warnings/precautions. After the training, patients will be instructed to use the device at home every other day.
The site personnel will be required to document the training session in the CRF. If the visit is conducted remotely, the devices will be shipped/mailed to the participant beforehand, with clear instructions not to open the device before the training.

Before the first device use, the participants will watch a short instructional video that includes how to pair the device, finding the optimal individual stimulation intensity level (perceptible but not painful, just below the pain threshold), and instruction to use the device every other day for 45 minutes and to complete a daily questionnaire.

Treatment phase:

During this 8-week phase, participants will be instructed to use the device every other day for 45 minutes. Participants will also be instructed to continue completing a daily diary with information on their headaches with time of onset, migraine symptoms and medication use, as performed in the baseline phase. Participants will be instructed to use the device with an intensity level that is perceptible but not painful. Adverse events will be reported throughout this phase of the study directly to the site staff and recorded in the CRF.

Participants can treat their migraine and headaches with their usual acute treatments. (Nerivio will not be used for acute treatment to avoid bias between the groups).
Blinding will be assessed at the end of the treatment phase when participants will be asked of their presumed group assignment (active, sham, do not know).

Third visit-

Transition to the follow-up phase (open label):

During the visit, participants will complete the following questionnaires:

1. Patient assessment of treatment group during the treatment phase
2. HIT questionnaire regarding weeks 9-12
3. MSQ regarding weeks 9-12

At the end of the 8-week treatment phase, participants from both arms (active and sham) may continue to an open-label follow-up phase in which they will receive an active Nerivio device to use during the follow-up phase.

Participants who meet the following conditions will be offered to enter the **pre-emptive follow-up phase**:

- Between 6 to 16 headache days during the baseline phase.
- Participants experience at least one prodromal symptom, within 24 hours prior to the onset of their migraine headache, in at least half of their migraine attacks during the baseline phase.
- Participants completed the daily questionnaires in at least 70% of the days during the treatment phase
- Treated every other day on at least 24 and no more than 32 days during the 56 days of the treatment phase.

All other patients will be offered to receive an active device and continue in a safety follow-up, using Nerivio for preventive treatment of migraine, as instructed in the treatment phase.

Follow-up phase (open label):
Participants who continue into this 4-week period of follow-up phase, will receive an active device. Those who do not meet the requirements (see above) will use Nerivio for preventive treatment of migraine, as performed during the treatment phase. Participants will continue to complete a daily diary and use the device every other day for 45 minutes.

Participants who meet the requirements (see above) will receive the device for pre-emptive treatment of migraine. Participants will be instructed to use Nerivio within 60 minutes of prodrome symptoms onset, prior to the start of a headache, for a 45-minute treatment. The participants will be instructed to complete questionnaires regarding their headache, prodrome symptoms, and medication use at baseline (start of treatment), 2 hours post-treatment and 24 hours post-treatment. In addition, participants will be instructed to continue to complete the daily diary as in the baseline and treatment phases.

Participants will be permitted to take their usual care medications during this phase, except for the timepoint between starting a device treatment until 2 hours after treatment start.

Fourth (final) visit – End of study:
During the final visit, participants may be asked to fill additional questionnaires on their migraine and their experience with the device. In addition, all study devices will be returned to the clinic, either in person or by mail/shipment.

Study design is summarized in Figure 4 below.

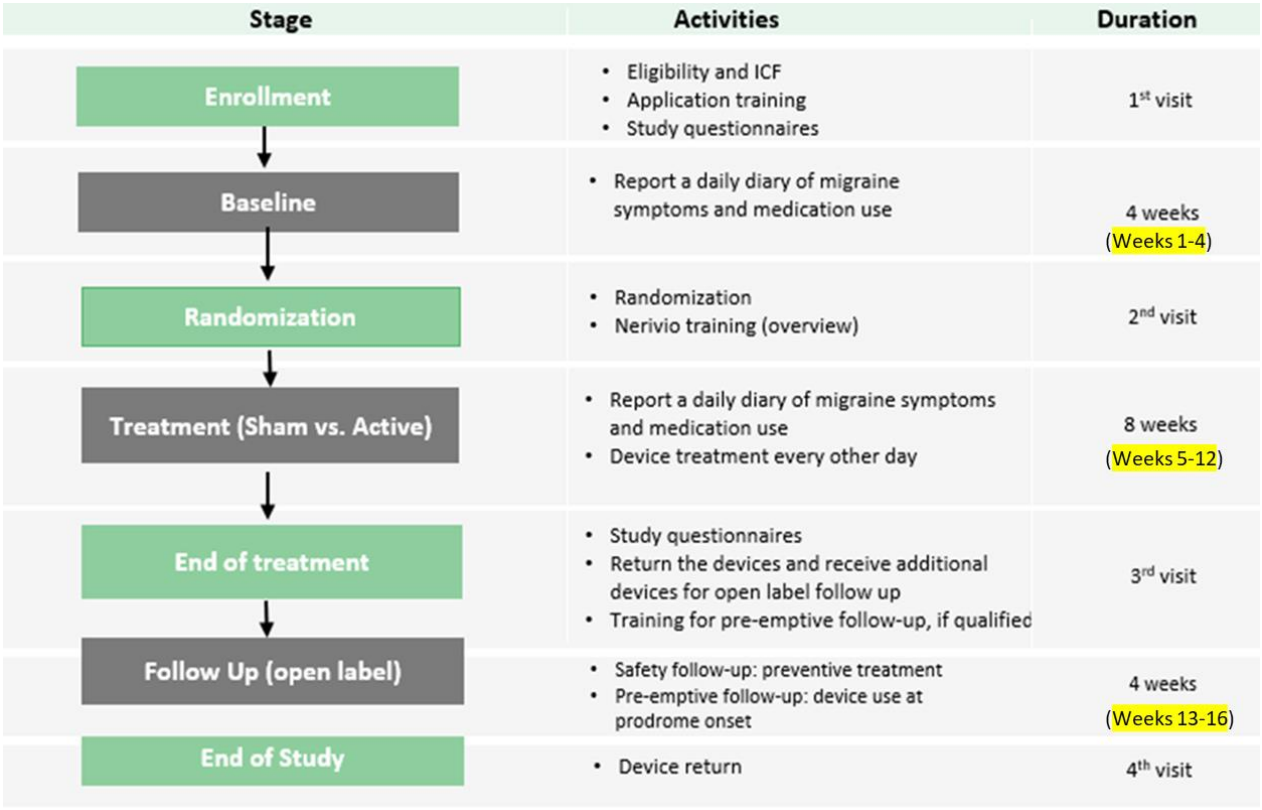

Figure 4: Study design

6.3.1. Study duration

The duration of the study for each participant is expected to be up to 16 weeks.

6.4. Study endpoints

6.4.1. Primary efficacy endpoint

Difference between treatment groups in the mean change in number of migraine headache days per month comparing the 4-week baseline phase (weeks 1 through 4) with the last 28 days of the treatment phase (weeks 9 through 12).

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

6.4.2. Secondary efficacy endpoints

1. Difference between treatment groups in the mean change in number of moderate/severe headache days per month comparing the 4-week baseline

phase (weeks 1 through 4) with the last 28 days of the treatment phase (weeks 9 through 12).
A moderate/severe headache day is defined as a calendar day with moderate or severe headache.

2. Difference between treatment groups in the mean change in the number of headache days per month from the 4-week baseline phase (weeks 1 through 4) to the last 4 weeks of the treatment phase (weeks 9 through 12). A headache day is defined as a calendar day with headache (at any severity).

3. Difference between treatment groups in the percentage of patients achieving at least 50% reduction from baseline in the mean number of headache days (all severities) per month in the last 4 weeks of the treatment phase (weeks 9 through 12).

4. Difference between treatment groups in the mean change from baseline in the HIT-6 total score in the last 4 weeks of the treatment phase (weeks 9 through 12).

5. Difference between treatment groups in the mean change from baseline in the MSQ role function in the last 4 weeks of the treatment phase (weeks 9 through 12).

6.4.3. Exploratory efficacy endpoints

1. Difference between treatment groups in the reduction in the mean number of acute headache/migraine medication days per month in the last 4 weeks of the treatment phase (weeks 9 through 12) compared to Baseline (weeks 1 through 4).
An acute headache/migraine medication day is a calendar day on which the patient consumes at least one dose of any medication (OTC or prescribed) for acute treatment of headache or migraine.

[Endpoints below relate to the pre-emptive follow-up phase]

2. Percentage of patients who treat for the first treatment in the pre-emptive phase, during a prodrome, when they are pain free, and remain pain free during the following 2 hours after the treatment, without use of acute medication.
3. Percentage of patients who treat for the first treatment in the pre-emptive phase, during the prodrome, when they are pain free, and remain pain free during the following 24 hours after the treatment, without use of acute medication.
4. Percentage of patients who treat for the first treatment in the pre-emptive phase, during the prodrome, when they are pain free, and remain either pain free or

with mild pain during the following 24 hours after the treatment without use of acute medication.

5. Mean change in the percentage of prodromes which were followed by a headache within 24 hours from baseline to the end of the pre-emptive follow-up phase.
6. Mean change in the average number of moderate/severe headache days per month in the pre-emptive phase compared to the 4-week baseline phase.

[Endpoint below relate to Health Economics analysis]

7. Differences between active and sham groups in reduction in the means of the following events from baseline (weeks 1-4) to second month of treatment (weeks 9-12):
   a. Absenteeism – number of missed work/school days
   b. Presenteeism – number of work/school days with moderate/severe functional disability
   c. Healthcare provider appointments
   d. ED/ER visits
   e. Brain MRI/CT scans

8. Feasibility of a migraine prediction algorithm:
   Analysis of the daily information provided by the participants for the purpose of developing a migraine prediction algorithm.

6.4.4. Safety endpoints

1. Device safety
   The incidence of adverse events in general and by seriousness, severity and association to the device.

2. Treatment tolerability
   The percent of subjects who fail to complete the study because of device-related adverse events.

6.5. Methods and timing of assessing and analysing variables

Once the last patient completes 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. Procedures to ensure blinding

This is a double-blind study: neither the patient, nor the investigators will be aware of arm allocation of each study participant. Maintaining double blind design is a known challenge in non-invasive neuromodulation devices trials. Several means are planned to ensure the double-blind aspect of this trial.

- Selection of identically looking active and sham devices as control means is only a single step aimed at maintaining blindness.
- Adherence to randomization procedure by clinical staff is critically important.
- Importance of adherence to study design and procedures will be explained to participants during enrollment.
- No information regarding expected stimulation perception will be provided, except for the fact that stimulation intensity adjustment control will allow to adjust intensity to a ”strong but not painful” level.
- Before the end of the treatment phase, participants will not be asked directly any questions regarding treatment perception.
- The clinical staff will be instructed to not engage in any discussions regarding anticipated treatment perception.
- Device training will be performed using a training video with minimal contact with the site staff to maintain the blinding.
- The patient will use only the allocated device following the randomization procedure.

To assess blinding, participants will be asked at the end of the treatment phase which group they think they had been assigned to (active, sham, do not know).

6.7. 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.

6.8. 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 adverse events or side effects related to the treatment
- Efficacy monitoring: interim efficacy analysis and recommendations
- Futility monitoring: futility will be assessed during the interim analysis

7. STATISTICAL CONSIDERATIONS

7.1. Study design and aim

The study is designed as a prospective, double-blind, sham-controlled, multicenter study. This study aim is to evaluate the efficacy and safety of Nerivio for the preventive treatment of migraine.

7.2. Endpoints

7.2.1. Primary efficacy endpoint

The primary efficacy endpoint of the study is the difference between the groups in the mean change in the average of migraine headache days per month comparing the 4-week baseline phase (weeks 1 through 4) with the last 28 days (4 weeks) of the treatment phase (weeks 9 through 12). The groups will be compared with the independent t-test.

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

Subset Analyses

The primary endpoint will also be evaluated stratified by center using a General Linear Model ANOVA test.

A sensitivity analysis of the primary endpoint will be performed to assess the impact of missing data on the study outcome. This will be performed using several possible imputation methods.

Adjustment for other covariates such as demographics or other baseline participant characteristics may be performed by adding these variables into a multivariate linear regression.

7.2.2. Secondary efficacy endpoints

Secondary efficacy endpoints include:

1. Difference between treatment groups of mean change in the average number of moderate/severe headache days per month comparing the 4-week baseline phase (weeks 1 through 4) with the last 28 days of the treatment phase (weeks 9 through 12).

   A moderate/severe headache day is defined as a calendar day with moderate or severe headache.

2. Difference between treatment groups in the mean change in the average number of headache days per month in comparing the 4-week baseline phase (weeks 1 through 4) with the last 4 weeks of the treatment phase (weeks 9 through 12). A headache day is defined as a calendar day with headache (at any severity).
3. Difference between treatment groups in the achievement of at least 50% reduction from baseline in the mean number of moderate to severe headache days per month in the last 4 weeks of the treatment phase (weeks 9 through 12).
4. Difference between treatment groups in the the mean change from baseline in the HIT-6 total score.
5. Difference between treatment groups of the mean change from baseline in the MSQ role function.

The secondary efficacy variables will be summarized by a count and percentage and compared with a chi-squared test or a Fisher's exact test.

7.2.3. Exploratory efficacy endpoints

Exploratory efficacy endpoints include:

1. Difference between treatment groups in the reduction of mean number of headache/migraine acute medication days per month in the last 4 weeks of the treatment phase (weeks 9 through 12). An acute headache/migraine medication day is a calendar day on which the patient consumes at least one dose of any medication (OTC or prescribed) for acute treatment of headache or migraine.
2. Percentage of patients who treat for the first treatment during a prodrome, when they are pain free, and remain pain free during the following 2 hours after the treatment, without use of acute medication.
3. Percentage of patients who treat for the first treatment in the pre-emptive phase during a prodrome, when they are pain free, and remain pain free during the following 24 hours after the treatment, without use of acute medication.
4. Percentage of patients who treat for the first treatment in the pre-emptive phase during a prodrome, when they are pain free, and remain either pain free or with mild pain during the following 24 hours after the treatment without use of acute medication.
5. Mean change in the percentage of prodromes which were followed by a headache within 24 hours from baseline to the end of the follow-up phase.
6. Mean change in the average number of moderate/severe headache days per month comparing the 4-week baseline phase with the follow-up phase.

7. Difference between treatment groups in the reduction of the health economics metrics: absenteeism days, presenteeism days, ED/ER visits, physician appointments visits and CT/MRI scans – from weeks 1-4 to weeks 9-12.
8. Feasibility of a migraine prediction algorithm:
   Analysis of the daily information provided by the participants for the development of a prediction algorithm for the purpose of predicting a migraine attack on the following day.

7.2.4. Safety endpoints

The safety endpoints of adverse events and tolerability will be assessed by review of all safety parameters, including adverse events.
The incidence of treatment related 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 analysed.

7.3. Statistical hypothesis

In this study, we will test the following hypothesis:

- H_0 : MD_a-MD_s=0
- H_1: MD_a-MD_s≠0

Where MD_a is the mean change in number of migraine days in the in the active arm, and MD_s is the mean change in number of migraine days in the sham arm.

7.4. Sample size

A sample size of 234 participants, 117 per each treatment arm, was determined to provide 80% power to detect a mean (±SD) difference of 2±3.0 in the reduction in number of migraine headache days from the baseline to weeks 9-12 of the treatment phase, between the active group and the sham group at a two-sided alpha level of 0.05. With an anticipated discontinuation rate of about 35%, up to375 participants are planned to be enrolled. In case of higher dropout or non-eligible participants or missing data, enrollment may be extended in order to reach the desired sample size.

7.5. Analysis sets

Intent to treat analysis set (ITT)
The ITT analysis set includes all randomized patients.

Modified intend to treat analysis set (mITT)

The mITT analysis set includes all ITT participants who had at least 22 days of efficacy assessments in weeks 9-12 of the treatment phase and at least 12 treatments performed in weeks 9-12.

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.

7.6. Statistical analysis

7.6.1. General considerations

Statistical analyses will be performed using a statistical software such as SAS® (SAS Institute, Cary NC, USA), or SPSS statistic program version 27.0 (or higher) software.
Baseline demographic and other baseline characteristics, together with safety analyses will be performed on all participants who were randomized. 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.

7.6.2. 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.

7.6.3. Efficacy analysis

The efficacy endpoints will be assessed on evaluable reports of daily symptoms.
A modified intent to treat analysis set (mITT) will include all ITT participants who had at least 22 days of efficacy assessments in the last 4 weeks of the treatment phase (weeks 9 through 12) and at least 12 treatments performed in the last 4 weeks of the treatment phase (weeks 9 through 12). The efficacy analyses will be conducted on the mITT analysis set. The mITT will be assessed for the mean change in migraine days from the 4-week baseline phase (weeks 1 through 4) to the last 4 weeks of the treatment phase (weeks 9 through 12) and will be compared between treatment groups with a significance level $p<0.05$.

7.6.4. Safety analysis

Safety and tolerability will be assessed on the ITT analysis set by reviewing 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.

7.6.5. 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, if applicable.

7.6.6. Handling of missing data

For management of missing data in the primary analysis, i.e., missing daily reports, the number of migraine days per each 28-day period in the Treatment phase will be prorated (normalized) to a 28-day. For example, if a patient had 24 reported days during weeks 9-12, with 7 migraine days, her number of migraine days in this period will be normalized to (7/24) * 28 = 8.17

7.6.7. Interim analysis

One interim analysis is planned after at least 35% of the data is collected (~84 participants in both arms [42 per arm]). The study will continue to the originally planned sample size if the results are favorable (difference between groups in the mean reduction of migraine days of at least 1 migraine day). The interim analysis will be performed on both the mITT and ITT analysis sets, and the enrollment may be stopped due to futility if the interim effects fall below the threshold.

7.6.7.1. Procedure

After all the relevant data will be entered into the database, a soft lock to the database will be performed. An independent unblinded statistician will perform the assessments described below. A designated decision committee will recommend whether to continue or stop the study once the interim results are available.

In the interim analysis, the data of all evaluable subjects enrolled up to that point will be analyzed.

7.6.7.2. Blinding

Only the unblinded statistician and the two other members of the DMC will be exposed to the interim report. This team may also have access to the unmasked information of the interim analysis. The investigators and company directors will only be informed of a decision to continue or to discontinue the trial, or to implement modifications in trial procedure and/or sample size. The unblinded statistician who is responsible for conducting the interim analyses should ensure that the unmasked data is not available to any unauthorized person within or outside the company.
Only the decision and recommendation will be shared with the sponsor and the study personnel.

7.7. Randomization

After a subject meets the eligibility criteria, he/she will be equally allocated (with a 1:1 ratio) to one of the following treatment groups based on a randomization scheme with blocks stratified by center:

- Active
- Sham

Subjects will be stratified according to their headache days frequency reported during the baseline phase, to achieve approximately equal numbers of chronic and non-chronic participants. High frequency (HF) group will contain all subjects reported 15 headache days or more, and low frequency (LF) group will contain all subjects reported less than 15 headache days. The stratified randomization will allow a balance in the number of headache days between treatment groups and prevent bias in the mean change of migraine/headache days.
The randomization scheme will be prepared by a biostatistician using a random number generating procedure.

7.8. Blinding

This is a double-blind study, the subjects, and investigators will be blinded to the treatment allocated to each subject. The study personnel will be blinded to the randomization block size.

Each device will be programmed with one of two versions of firmware that deliver either active or sham electrical stimulation. In all other aspects, the active and the sham conditions will be kept identical.

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 (i.e. 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

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 analysing 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 must be obtained from the participant before any protocol-related activities are performed. Participants must be provided with a signed copy of the consent form. The eCRFs will be updated that the informed consent form has 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.

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.

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.

Unlikely related: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

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: daganh@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 device-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

17. REFERENCE

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