“Migraine Treatment with Nerivio Migra neurostimulation device”

Pivotal prospective randomized double-blind, sham controlled multi-center clinical trial

Clinical Investigation Plan

CLINICAL CLINICAL INVESTIGATION PLAN

STUDY TITLE:

Migraine Treatment with Nerivio Migra Neurostimulation device

PROTOCOL NUMBER:	**TCH_002**
REVISION:	1.4
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DEVICE:	Nerivio Migra migraine treatment device, model 1.0. SW Final version 1.2, 22 November 2016
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version 1.4

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Change control table

Rev. no.	Change rationale	Date
1.0	Release for FDA review following pre-sub meeting on Sept. 13, 2016	Nov. 06, 2016
1.1	Release for IRB submission	Nov. 15, 2016
1.2	Additional amendments: procedures	Nov. 22, 2016
1.3	Correction of mistakes in section 14.7	Feb 2, 2017
1.4	Addition of open label phase, addition of one secondary endpoint, a few modifications following comments from FDA	Feb 14, 2017

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

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

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

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

Protocol Signature Page

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.

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

Contents

1 SYNOPSIS

Sponsor	Theranica Bioelectronics Ltd. 45 HaMelakha st, Netanya, Israel
Title	A prospective, randomized, double-blind, sham controlled multi-center clinical trial “Migraine Headache Treatment with Nerivio Migra neurostimulation device”
Investigational Device	Nerivio Migra neurostimulation device is intended for acute treatment of migraine headache with and without aura via delivery of transcutaneous electrical stimulation below pain threshold to patient upper arm at the onset a migraine pain. The level of generated stimuli is similar to other FDA approved electro stimulation devices. Nerivio Migra treatment is self-administered by the patient. It is intended to alleviate pain through conditioned pain modulation. The device is controlled by a dedicated smartphone application.

Study Design	A prospective, randomized, double-blind, sham controlled multi-center trial. Ratio between treatment and control groups will be 1:1, stratified by center and use of preventive medications. The study will be conducted in three stages. Enrolled participants will be provided with an active Nerivio Migra or an identically looking sham device and trained to perform treatment and provide feedback via the smartphone application**.** Investigational devices will be programmed in active or sham mode with a 1:1 ratio, in order to achieve the desired ratio between active and control groups sizes. Following successful completion of device and application training, subjects will be discharged. <u>Stage One.</u> Roll-in. Participants will be reporting their migraine attacks using an electronic migraine diary installed on their smartphones. Duration of this phase is one month. <u>Stage Two.</u> Parallel arm treatment stage. Following successful completion of Stage 1, the application will be activated in treatment mode. Subjects will be asked to apply the device and administer treatment at onset of their migraine pain. Subjects will be reporting their feedback via the smartphone application. Duration of Stage Two will be determined by treatment of four attacks over the course of two months (whichever is achieved first). Stage Three. Open label extended treatment. Following the completion of the study by all subjects and the return of all study devices, subjects will be offered a 2-month period of using active device, at no cost.
Objectives	The purpose of this study is to evaluate the safety and performance of the Nerivio Migra Migraine device for the treatment of non-chronic migraine patients with and without aura
Primary Endpoint	<u>Primary Performance Endpoint.</u> Proportion (%) of patients reporting freedom from pain (pain grade 0) 2 hours post treatment without rescue medications in at least 50% of treated attacks <u>Primary Safety Endpoint.</u> Device related adverse effects
Secondary & Exploratory Endpoints	Performance endpoints: <u>Secondary:</u> 1. The proportion (%) of subjects reporting treatment response at 2 hours post treatment without medications in at least 50% of treated attacks. Treatment response is defined as pain level reduction from moderate or severe at baseline to mild or pain level of none if treatment started with mild pain. 2. Proportion (%) of patients reporting, 2 hours post treatment: ▪ freedom from pain (pain grade 0) and their most bothersome migraine-associated symptom (MBS) in at least 50% of treated attacks ▪ freedom from nausea in at least 50% of treated attacks

	▪ freedom from photophobia in at least 50% of treated attacks ▪ freedom from phonophobia in at least 50% of treated attacks <u>Exploratory:</u> 3. The proportion (%) of patients reporting freedom from pain (pain grade 0) 48 hours post treatment without medications in at least 50% of treated attacks 4. The percent of subjects who are pain-free at 2 hours with no use of rescue medication, and either have no relapse of pain within the subsequent 46 hours, or, if they have a relapse of pain in this time window, it disappears every time, after two hours, using the device, with no use of rescue medications. 5. Patient global impression of change, with emphasis on *disability and quality of life.*
Safety Endpoints	• Treatment tolerability • Adverse events and complications whether related or unrelated to study device.
Patient Population	Adults 18-75 years old meeting International Headache Society criteria for migraine with and without aura, who are reporting 2-8 migraine attacks per month.
Number of Patients	Up to 248 patients with evaluable data, equally distributed between US and non-US sites
Inclusion Criteria	1. Patient is 18-75 years old. 2. Patient meeting the ICHD-3 diagnostic criteria for migraine with and without aura 3. Patients reporting 2-8 migraine attacks per month. 4. Patient must be able and willing to comply with the protocol 5. Patient must be able and willing to provide written informed consent 6. Male or non-pregnant / non-lactating female (NOTE: Females of child bearing potential must have a negative pregnancy test and must be willing to use adequate contraceptive means during the study 7. Possesses the basic cognitive and motor skills needed to operate android cell phone
Exclusion Criteria	1. Has other significant pain problem that in the opinion of the investigator may confound the study assessments 2. Is currently implanted with an electrical and/or neurostimulator device (e.g. cardiac pacemaker or defibrillator, vagus nerve neurostimulator ,deep brain stimulator, spinal stimulator, bone growth stimulator cochlear implant, Sphenopalatine ganglion stimulator or Occipital nerve stimulator). 3. Known uncontrolled epilepsy. 4. Use of Cannabis including medical use. 5. Has chronic migraine (more than 15 headache days per month).

	6. Changed usage or dosage of migraine preventive medications in the last two months 7. Has undergone nerve block (occipital or other) in the head or neck within the last 2 weeks. 8. Is participating in any other clinical study.
Study Procedures	Following successful screening, enrollment interview and signing of informed consent, participants will be provided with an active Nerivio Migra or identically looking sham device and trained to perform treatment and provide feedback via the smartphone application**.** Baseline information including mean frequency and severity of migraine attacks, occurrence of other headaches, presence of ICHD-3 diagnostic criteria for migraine with and without aura and use of preventive and rescue medications will be recorded. During roll-in stage, migraine status will be recorded and participants will be requested to complete a quality of life questionnaire. Participants who successfully completed the roll-in stage will continue to the stage involving treatment of four qualifying migraine attacks. A qualifying migraine attack shall be preceded by at least 48 hours of freedom from headache. Participants will be instructed to activate the device at the onset of a qualifying migraine attack and manually adjust stimulation intensity to a level within the pre-defined range where it is perceivable but not painful. Patients will be requested to refrain from use of rescue medications prior to and during the first two hours after treatment with the device, and if they can not comply with this, record their use of medications in the smartphone application. Via the application, each participant will be asked to rate his/her migraine pain level using Pain Grades Scale with values 0-3 (no pain, mild, moderate, severe): (1) upon starting the treatment, (2) two hours after starting treatment, (3) 48 hours after start of the first treatment corresponding to current migraine attack. Participants will be also asked to provide feedback using the application regarding the time elapsed from start of migraine attack to start of the treatment. In addition, participants will be reporting their use of rescue medication and presence of nausea, photophobia, phonophobia and allodynia, as well as additional migraine symptoms. In case of failure to provide feedback regarding pain level post-treatment, queries will be generated via EDC system and telephone follow-up will be performed by study investigator staff to solicit such feedback. After providing feedback at two hours post start of treatment and in case of pain recurrence, participants will be allowed to re-treat the attack using Migra device. Adverse events will be reported. Post study questionnaire will include patient global impression of change, blinding and usability assessments.

	Unscheduled visits will be recorded and termination visit will be scheduled upon the completion of the study. In the event of premature discontinuation an early discontinuation visit will be scheduled.
Study Duration	Duration of study participation for each subject will be approximately three months, one month of roll-in stage and treatment of four qualifying migraine attacks over the course of two months (whichever is achieved first).
Sample Size Estimation	Sample size calculation is based on responders rate, defined as the proportion of patients that achieved pain free status (pain grade 0) at two hours post treatment.
Investigational Sites and Principal Investigators	Current list is kept on file

2 BACKGROUND

2.1 Introduction

Migraine is a common neurovascular disorder manifesting itself in attacks of headaches that can reach a level of severe pain in many patients, leading to substantial functional impairment [1]. The recent Global Burden of Disease Study 2010 (GBD2010), conducted by the World Health Organization, estimates a worldwide prevalence of migraine of 14.7%, ranking it third place among the most common diseases and at the seventh place among specific causes of disability and top of all neurological disorders as cause of total years lived with disability [1]. Migraine, thus, affects millions of people [1]. Up to date, pathophysiology of migraine is not fully understood [2]. Current approach to migraine treatment is predominantly pharmacological [3].

Transcutaneous electrical stimulation (ES) is a non-invasive technique that delivers series of weak electrical pulses to patient's skin. ES has been used for decades for treatment of variety of painful conditions [3, 4], with application of the stimulation adjacent to, or at least within the dermatome of the painful body site. Recent clinical data provide evidence that electro stimulation is an effective approach providing relief to chronic headaches and, among them, migraine. It is highly tolerable by patients and associated with no adverse effects [4-6]. There are currently two approved non-invasive devices intended for providing migraine relief via transcutaneous electro stimulation. The first device, Cefaly, is used for treatment and prophylaxis of chronic migraines, was developed by STX-Med [4]. The device applies electro stimulation to the forehead, within trigeminal nerve territory. The second device, GammaCore, was developed by ElectroCore [6], vagus nerve stimulation is approved for marketing in Europe and is used for treatment of migraine pain. Both devices deliver stimulation at relatively low intensity (16mA). At the same time, both devices target electro stimulation to major specific nerves in close proximity to patient's head. Both trigeminal and vagus nerves are responsible for multiple functions of major importance. The list includes, but is not limited to, facial sensation, biting, chewing for trigeminal nerve; heart rate,

sweating and speech for vagus nerve. From this prospective, safety of treatment is of great concern.

These commercially available treatment approaches are associated with significant usability challenges due to the bulkiness of the applied devices and their cumbersome self-application (Cefaly device is mounted on forehead and the GammaCore is hand held throughout the treatment session).

In addition, burden of treatment with these devices defined as the 'work' of being a patient and its effect on the quality of life (QOL) including challenges associated with lifestyle changes, reaction of others, etc. [21, 22] may be quite high.

In summary, there exists recognized clinical need for a non-pharmacological solution for acute migraine.

3 IDENTIFICATION AND DESCRIPTION OF THE DEVICE

Theranica has developed Nerivio Migra ("Migra" or "the device"). Nerivio Migra is intended for acute treatment of non-chronic migraines with and without aura. The device is designed to be self-applied to the upper arm. Treatments with Nerivio Migra are intended to be self-administered by the user at onset of a migraine headache. The device delivers transcutaneous electrical stimulation below pain threshold to peripheral nerve system at the onset of an acute migraine attack. Migra is operated via a mobile application.

Nerivio Migra utilizes electro stimulation in order to achieve conditioned pain modulation (CPM) effect at the onset of a migraine headache. Conditioned Pain Modulation (CPM) [7] is a paradigm used in pain research, in which a "conditioning" (also referred to as secondary) stimulus is applied such as to influence the subject's perception of a "conditioned" (primary) painful stimulus, delivered (or originating) at a different body location. Based on diffused noxious inhibitory control (DNIC) mechanism [14], and sometimes referred to as "pain inhibits pain" principle, CPM allows to evoke powerful endogenous analgesic mechanism, by which a painful stimulus may be inhibited. The modulatory effect is diffuse, over the whole body, and can be induced by conditioning that can be applied anywhere in the body. Thus, use of this approach allows applying the conditioning stimuli away from the painful site.

The conditioning stimulus is given at an intensity which is well felt, but below pain threshold, so it is not painful. Experimental human data shows that in the majority of tested subjects, a conditioning stimulus which is slightly lower than pain threshold is sufficient to activate CPM [8, 9]. This is probably due to different summation requirements of the brainstem pain modulation centers and of the cortex; it seems that more intensive peripheral nociceptive activity is needed for the latter than for the former. Since the 'inhibitory power' activated by the CPM via this peripheral non-painful stimulation is limited, the time window at migraine pain onset, where activity of the nociceptive pathways is still just starting, seems to be an ideal target for stimulation. It is well known [10] that nociceptive pathways undergo a process of sensitization during the first two hours or so of the migraine attack, such that it is easier to abort an attack earlier within this window, and more difficult later. Thus, application of the stimulation early in the attack is expected to alleviate pain substantially, or abort the attack.

The device delivers electrical currents that are within the range of FDA approved battery operated Transcutaneous electrical nerve stimulation (TENS) devices to treat pain [18, 19].

The use of TENS has proved effective in clinical studies and its safety is well established [15-17]. Multiple TENS devices are being marketed for over-the-counter use for a wide range of indications and anatomical locations. Many approved devices are used to treat chronic conditions.

Two main groups of electro stimulation protocols have been described and evaluated for pain relief: high frequency (80-200Hz) and low frequency (1-5Hz) [18]. Nerivio Migra operates in high frequency domain.

To the best of our knowledge this is the first device based on application of electrical stimulation to treat migraine headache through conditioned pain modulation allowing for the application of the stimulator remotely to head and neck.

The device is comprised of 3 main components: (1) Arm-band with attached electrodes, (2) Electronics case and (3) Software including Firmware and Mobile Application software to be run on a mobile platform. Each of these components is briefly described below.

3.1 Intended Use

The Nerivio Migra device is intended for acute treatment of adult episodic migraine with and without aura. It is intended for self-administration in home setting.

3.2 The Device

The Device is a fully integrated unit similar in appearance to a sports armband. The device includes an arm band, electronic circuitry and battery contained in a plastic case, and a pair of electrodes with hydrogel.

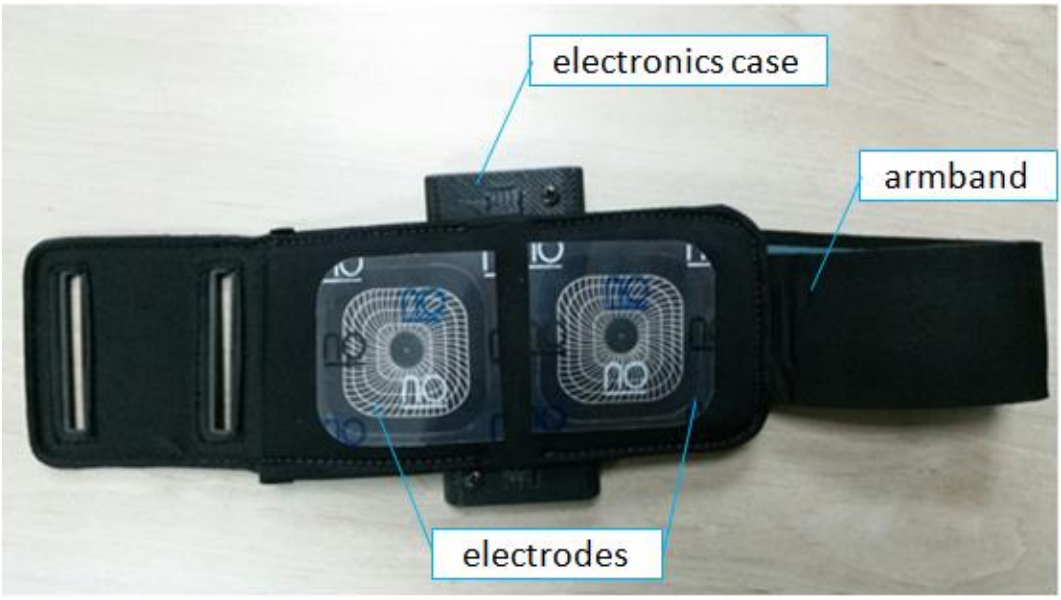

Figure 1. Internal side of Nerivio Migra device

The armband is based on a standard, off the shelf, smartphone armband made from a durable light neoprene material. It is thin and stretchable, as to not impede the user's movement. The Velcro strip allows convenient placement of the device at intended arm area for variety of arm sizes.

A pair of electrodes is attached to the internal side of the armband. The 5cm x 5cm Ultra Slim Electrodes with multistick gel (Model SN2020) are manufactured by Axelgaard Manufacturing Co. Ltd (Fallbrook CA). The electrodes are incorporated into the armband and are not to be replaced by participants throughout the course of the study.

The plastic case, made of non-flammable ABS type plastic, is placed on the armband in a manner that does not result in its contact with the body. The plastic case contains the device's electronics circuitry. It is attached to the external surface of the armband and wired to the electrodes that are housed on the inside of the armband. The case dimensions are 10cm x 5cm x 1.5cm.

The electronic circuitry housed within the plastic case contains a small printed circuit board (PCB) with the electronics components that are needed to generate and operate the electro stimulation functions (delivered via the electrodes) as well as the wireless communication with the user's smartphone or tablet (via standard Bluetooth protocol). The PCB connects to a battery located inside the case, and is wired to the pair of stimulation electrodes.

The outside of the plastic case contains an on-off switch and LED indicator of working state.

Figure 2. External side of Nerivio Migra device

The device includes current source circuitry that ensures steady stimulation current output. The current output is limited by the current source hardware design to 60mA. The output voltage is further limited by the power supply hardware design to 60V.

The device uses a controlled current source to output steady and controlled current via a pair of electrodes. The stimulation program is stored in device memory. The waveform is generated by the Pulse Generator unit and controlled by a programmable microcontroller (µCPU) to follow pre-set stimulation program parameters. Intensity of the output current can be controlled via mobile app software by Bluetooth wireless connection (BT/BLE). Once stimulation has been started by user, the device can operate in a stand-alone fashion without wireless connection to the mobile app software and will automatically cease stimulation after reaching the program's time limit.

The provided battery is sufficient to provide power required for stimulation throughout the duration of the whole experiment. The device will not be connected to power outlet by study participants.

An ID sticker used to uniquely identify the device, as well as assist with a quick Bluetooth pairing is placed on the external side of the device.

3.3 The Application

Activation, control over stimulation intensity and termination of stimulation are performed via a dedicated smartphone application developed by Theranica and installed on the user's cell phone.

The Nerivio Migra Application provides user interface for operating and managing the device, means for collecting Patient Reported Outcomes (PRO) and the link to the secure cloud and study database (DB). Captures of main Application screens are shown in figure 4.

The Application is installed from a standalone APK file, fully independent and distributable; implementation for Android only (4.1 and above).

- Upon activation, the Application shows the main window with the following options for the user to select:

- Connection – handles the Bluetooth connection to the device
- Diary/Treatment – collects information regarding migraine symptoms, controls the stimulation programs, as well as user feedback regarding the treatment
- Help – provides online help to the user

- The Application logs and records every operation of the device into NVM on the Smartphone. Subsequently, this information is also relayed to the Cloud (see **Figure 5**).
- The Application is able to query device battery status and notify the user of its condition.
- Supports menus and display language in Hebrew, English and Russian (according to phone's language set)
- Supports PRO collection
- Keeps logs of the actions performed by the user, including:
  - Device's connection and disconnection
  - Activation and deactivation periods
  - User stimulation intensity adjustments
  - Feedback from the user (before, during and after activation)

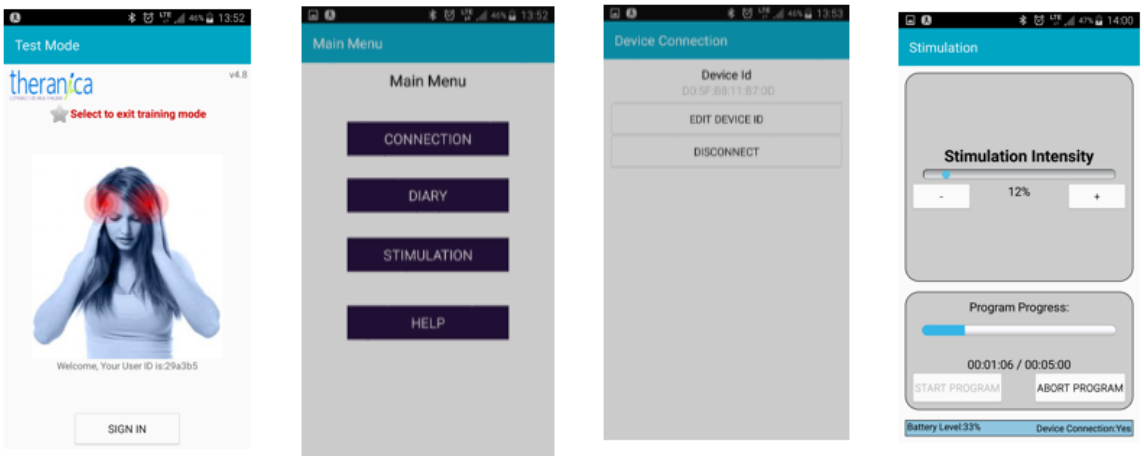

Figure 4. Application screens. Left to right: start screen, main menu, connectivity screen, treatment management screen

3.4 Energy output

Output parameters of the Migra are similar to those of other TENS devices previously cleared by the FDA and currently marketed for variety of indications for over the counter use.

Parameter	Nerivio Migra 1	Cefaly	Sys*Stim TENS
Mode or Program name	TENS	TENS	TENS
Waveform	Biphasic, symmetrical	Biphasic, symmetrical	Asymmetrical biphasic with zero net DC
Shape	Rectangular	Rectangular	Rectangular

Maximum output voltage (V)			
500Ω	30	8	92 ±20%
2KΩ	60	32	144 ±20%
10KΩ	60	60	166 ±20%
Maximum output current (mA)			
500Ω	60	16	184 ±20%
2KΩ	30	16	72 ±20%
10KΩ	6	6	17 ±20%
Duration of primary (depolarizing) phase (µsec)	200	250	200µs ±10%
Frequency (Hz)	100-120	60	1-80Hz ±10%
Maximum average power density (mW/cm²)500Ω	3.17	0.017	12
Maximum phase charge (µC)			
500Ω	12	4	33.5u ±10%
Maximum current density (mA/cm², r.m.s)			
500Ω	0.50	2.37	

Table 1 - Key output parameters comparison

User has control over stimulation intensity within the specified limits. A dedicated mechanism controls speed of intensity adjustment in order to protect the user from unexpectedly strong stimulation intensity variations.

3.5 Verification and validation

The design of the Nerivio Migra device has been verified and validated as per the design control requirements (FDA 21 CFR part 820.30 and ISO 13485). The device successfully passed basic safety and EMC tests per applicable standards (leakage current, power consumption and radiation emission) at Hermon Laboratories.

3.5.1 Performance testing

All features and output specifications identified in Tables 1-2 were verified under various loading conditions meant to simulate those the device could encounter during use.

Bench tests of the device included

- Verification of stimulation programs – pulses characteristics, program duration, and stimulation intensity. The tests were performed using e*Scope TDS3012B manufactured by Tektronix (USA).
- Mechanical testing
- Bluetooth connectivity – distance and robustness
- Battery lifetime for active and passive states.

3.5.2 Software validation

Validation of software (smartphone application) relating to the function of the device was performed for variety of use cases providing coverage of device requirements.

It includes:

- Application in general
- Authorization
- Connectivity with the device
- Help / troubleshooting messages
- Programs execution
- Activation
- Amplitude control
- User feedback
- Battery measurement
- Android version
- Logs
- Application dialogs
- Client/server communication
- Notifications
- User feedback –additional data
- Notification to switch down device

3.6 Principle of Operation

Once Migra is placed on the patient's arm (see Figure 3) at the onset of a migraine headache, the user turns the device ON and activates therapy via the Mobile Application.

Figure 3 - Nerivio Migra ready for use

This target location is easily accessed independently by the patient without help and is discrete to maintain treatment privacy. The treatment delivered to the user is a weak electrical current to the skin via the electrodes.

The operation of Migra is controlled by mobile application software that was developed by the company. The application is installed and operated from the patient's smartphone device, and is used for the activation, termination and control (e.g. stimulation intensity control, status indications and more) of the device.

The communication between the Migra device and the Application software is performed wirelessly via standard Bluetooth protocol.

Duration of the stimulation program is pre-set to 25 minutes. At any point in time, however, the patient is able to stop treatment by one of three methods:

- Terminating the stimulation via the Mobile Application
- Turning off the device switch located on the outside of the armband
- Carefully removing the armband

Migra delivers a single, pre-set, active stimulation program, or a sham program. Programs characteristics are given in Appendix XX.

Device operation flow is presented in the figure below.

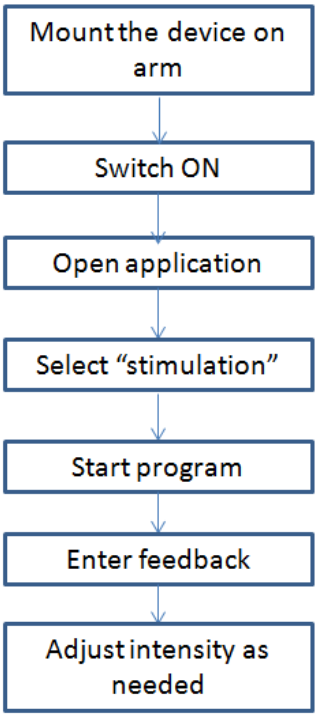

Figure 5. Device operation flow

At any moment in the course of treatment, user can stop treatment by terminating the stimulation via the smartphone application, or by turning off the switch on the wearable unit, or by simply removing the armband.

3.7 Identification of the Medical Device

The medical device will be labeled for clinical investigation use only. The label includes the address of the legal manufacturer and all other essential information to allow full traceability of the medical device as per the regulatory labeling requirements.

3.8 Instructions for Use

Device Instructions for Use are available as a separate document to study personnel. Printed instructions for Use are handed to study participants along with the device. Electronic version of IFU is accessible from the Application at any time. A brief description of principle of operation can be found in sections 3.1, 3.4 above.

3.9 Summary of Necessary Training

General instructions and training in device use as peer the IFU will be provided to study participants at the participating sites. No specific skills are required from study participants beyond basic level of experience with general purpose Android applications. Training will be delivered by designated study personnel and will be recorded in a corresponding CRF. In addition,

records of the training session will be recorded in the study DB with label “training”. The criteria for training effectiveness will be ability of the participant to run a training treatment session independently. At the end of the session, the device will be switched into operational mode by “sliding off” training mode indicator on the main screen of the application.

Training to the investigator and staff will be delivered by Theranica representative in a frontal session including demo and training activations. In order to provide additional support to clinical personnel, a training clip was recorded and will be available at all training sessions for staff and participants.

4 PRELIMINARY INVESTIGATIONS AND JUSTIFICATION FOR THE STUDY DESIGN

4.1 Previous Pre-Clinical Experience

There were no animal studies with the Nerivio Migra device. Since it is applying energy output similar to that of FDA approved TENS devices, and in accordance with the application of risk management as per EN ISO14791, the necessity for such a study has been precluded. There is no valid animal model to test the effectiveness of this device.

4.2 Previous Clinical Experience

Theranica has completed a prospective, randomized, double-blind, sham controlled, cross-over, multiple treatment arms single center study **“Relief of migraine pain through electro stimulation”** at the Neurology Department, Rambam Medical Center (Haifa, Israel). A brief summary of this pilot study protocol is provided below, along with an overview of the procedures utilized and the results observed.

Pilot Study Objective

The purpose of the investigation was to evaluate the safety and performance of the Nerivio Migra for the treatment of non-chronic migraine patients with and without aura and provide comparative data regarding performance and tolerability of the evaluated treatment programs.

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Adult male and female ages 18-75.
2. Patients meeting International Headache Society criteria for migraine with and without aura.
3. Patients reporting 2-8 migraine attacks per month.
4. Patient must be able and willing to comply with the required follow-up schedule
5. Patient must be able and willing to provide written informed consent
6. Patient was not on preventive medications for at least two months

Exclusion Criteria

1. Has other significant pain problem (e.g. cancer pain ,fibromyalgia or other head or facial disorder) that in the opinion of the investigator may confound the study assessments

2. Has severe cardiac or cerebrovascular disease.
3. Has uncontrolled high blood pressure (systolic > 160 mmHg, diastolic > 100 mmHg after 3 repeated measurements within 24 hours).
4. Is currently implanted with an electrical and/or neurostimulator device (e.g. cardiac pacemaker or defibrillator, vagus nerve neurostimulator ,deep brain stimulator, spinal stimulator, bone growth stimulator cochlear implant, Sphenopalatine ganglion stimulator or Occipital nerve stimulator).
5. Known epilepsy.
6. Use of Cannabis including medical use.
7. Has chronic migraine (more than 15 headache days per month).
8. Has undergone nerve block (occipital or other) in the head or neck within the last 2 months.
9. Has received Botox injections within the last 6 months.
10. Is pregnant or thinking of becoming pregnant during the study period, or of childbearing years and is unwilling to use an accepted form of birth control.
11. Is participating in another clinical study in Migraine treatment or prevention.
12. Does not possess the basic cognitive or motor skills needed to operate android cell phone.

Study Procedures

Potential patients signed informed consent prior to any study procedure. The patient medical history, migraine history, use of concomitant medications and diagnosis were recorded. Patients found eligible by meeting all of the inclusion criteria and none of the exclusion criteria received documented training whereupon its successful completion the investigational device was provided to study participants for home use.

As per the instructions for use, participants were instructed to activate the device at the onset of a migraine attack and manually adjust stimulation intensity to a level where it is perceivable but not painful. Patients were requested to refrain from use of rescue medications prior to and during the first two hours following treatment by the device, and if they could not comply with this, record medications usage in the smartphone application.

Five 20-minute long stimulation protocols were programmed into each unit; four active programs at 100-120 Hz, with primary phase widths of 200 (P200), 150 (P150), 100 (P100) and 50 (P50) microseconds, and one placebo stimulation protocol (P0) at 0.1 Hz frequency with 45 microseconds long pulses. Stimuli were given at random sequences with the following distribution: P0 and P200: probability of 1/3 each, P50, P100, P150: probability of 1/9 each. Randomized sequences of programs were generated independently for each participant.

Both patients and study personnel were blinded to the order of individual treatments.

Via the smartphone application, each participant was asked to rate his/her migraine pain level four times using a Numeric Pain Rating Scale (NPS, values 0-10): (1) upon starting the treatment, (2) during (halfway through treatment program), (3) at the end of treatment, as well as (4) two hours after treatment.

At the beginning of each treatment, participants were asked to provide feedback using the application regarding the time elapsed from start of migraine attack to start of the treatment. In case of failure to provide feedback regarding pain level post-treatment, telephone follow-up was performed by study investigator staff to solicit such feedback. Follow up phone calls were

performed to record changes in medical condition, concomitant medication, migraine therapy and adverse effects. Unscheduled visits were recorded and termination visit were scheduled upon the completion of the study as defined by a maximal number of 20 complete treatment cycles but no longer than 6 months from enrollment. (whichever is fulfilled first). In the event of premature discontinuation an early discontinuation visit was scheduled. End of study interview was performed soliciting feedback regarding device usability, burden of treatment, use of migraine medications during the study period, as well as free comments.

Study Endpoints

- The primary efficacy endpoint of the study was the proportion of responders, where a responder is defined as subject with clinically significant decrease in pain score measured by Numeric Pain Rating Scale (NPS) of at least 50% 2 hours post treatment as compared to baseline in at least 50% of treatments.
- The second primary performance endpoint was relative pain reduction at 2 hours post treatment as compared to baseline.
- The primary safety endpoint was evidence of device related adverse effects.

Burden of treatment was assessed by mean scores of post-study questionnaire. Success was defined as superior performance of active treatments as compared to sham treatment. The protocol provided for enrollment of up to 100 patients.

Summary of Results

The pilot study was performed between June 2015 and March 2016. A total of 86 participants were provided with the Nerivio Migra devices for use as part of this clinical study.

A summary of participants' demographic characteristics is presented in Table 2 below.

	Female	Male
N (%)	69 (80%)	17 (20%)
Age mean (min-max, STD)	45.2 (22-72, 11.7)	48.8 (26- 67, 11.7)
Migraine attacks per month, mean (STD)	5.1 (2.7)	5.34 (2.3)
Mean pain intensity during attack	8.9	8.6
Occurrence of aura	40 (58%)	11 (65%)

Table 2 – Pilot Study Population

Seventy-two participants successfully treated at least one migraine attack. The remainder of participants either did not treat their attacks per protocol, or failed to provide complete feedback. One participant was excluded from statistical analysis due to repeated use of rescue medications concurrently with the electro stimulation treatments. Complete reporting was obtained for 70% of activations for P200, P150, P100 programs, 58% of activations of P50 and 28% of placebo activations.

No adverse events related to the device and no side effects were reported.

Observed outcome measures based on ITT analysis are summarized in Table 3 below.

	Sham	Active programs				
	P0	P200	P150	P100	P50	Overall active programs (p vs. placebo)
%50% (% responders), N=71	26%	46% (0.04)	48% (0.06)	39% (0.4)	44% (0.14)	64% *(significance level 0.005)*
Relative pain reduction (%)	-2	-20 NS	-26 P=0.02	-16 NS	-18 NS	Model p=0.031
Pain grade reduction (% responders), N=57	24%	58% (0.02)	52% (0.08)	40% (0.44)	48% (0.20)	76% *(significance level 0.005)*
No pain after two hours (% responders), N=57	6%	30% (0.004)	12% (0.56)	23% (0.06)	26% (0.14)	44% *(significance level 0.005)*

Table 3 – Pilot Study Results

Our results show that remote electrical stimulation allowed to achieve significant reduction in the migraine pain. Analysis per pain grades, as has been used for triptans, shows results similar to the triptans per pain reduction and pain elimination. When taking all active stimulation protocols together, 64% of the patients had more than 50% pain reduction, in more than half of their treated attacks. Relative pain reduction for the active stimuli ranged between 16 and 26%, while for the placebo stimulation the reduction was of 2% only. Mean pain level at device activation point was 4.6. Overall ANOVA based effect was significant (p=0.031), with significant effect in post hoc analyses for the P150 protocol.

In terms of change in pain grades, reduction from moderate or severe to mild or none was reported by 58% of the participants in response to the strongest stimulation program (P200, widest pulse), as opposed to 24% for placebo. Overall, 76% of subjects reported such reduction to active stimulation (significant at 0.005 level vs. placebo). Reduction to no pain outcome occurred in more than 50% of activations for 30% of participants when the strongest program was activated, as opposed to 6% for placebo. In the course of the study, 64% of participants who provided feedback on at least one active program activation reported at least 50% pain reduction in more than half of their activations and are considered responders to the evaluated treatment. This is significantly higher than the 26% responder to placebo activations (p=0.005).

In the end-of-trial interviews, subjects indicated (i) Reduction in amount of migraine medications during study period (mean questionnaire score was 1.5, where 1 means “same amount”, 2 means “less”); (ii) overall burden of treatment was considered very low – mean score was 2.5 (between “neutral” and “not at all”); and (iii) the device and application were found easy to use by a majority of study participants (mean questionnaire score was 3.85 (between “easy” and “very easy”)).

4.3 Clinical Investigation Risks and Benefits

4.3.1 Anticipated Benefits

Theranica's pilot study demonstrated a significant effect of Nerivio Migra in alleviating migraine pain (see pilot study results above). It is anticipated that patients will experience similar effect under the setting of the current study.

Another known benefit to patients participating in such a study is the ability to learn more about their medical condition through the assessments that will be performed throughout the course of the study. Additionally, patients will be closely observed by the study staff throughout their participation in the study. Last, all assessments associated with the study, as well as the study device, are provided at no charge to the participants.

4.3.2 Risks and Adverse Effects

Technical characteristics and electrical output of Nerivio Migra device are similar to other known and approved for personal use TENS devices applying electrical stimulation for pain relief purpose (see Table 1). Safety of the Nerivio Migra has been extensively tested and confirmed through bench performance testing (see section3.5.1) as well as throughout Theranica's pilot clinical study with the device. No device related adverse events were recorded in the course of the pilot study, and treatment was well tolerated by participants.

Current study design does not require application of electrical stimulation for unusually prolonged periods, or other circumstances where the use of the device has not yet been validated. Hence this protocol presents minimal risks to the subjects and adverse events are not anticipated beyond those reported for other TENS devices. Potential expected device side effects are listed in section 14.7.

No information is available for use of the Nervio Migra and pregnancy, so women who are pregnant are not eligible for inclusion in this study.

As discussed with the FDA at a Pre-submission meeting (September 2016), the proposed clinical study meets the criteria of a Non-Significant Risk (NSR) device study.

4.3.3 Risk Control and Mitigation

The following efforts will minimize risks to patients in the study:

- Conduct of the study following successful completion of extensive bench performance testing and careful risk analysis.
- Selection of investigators who are experienced and skilled in management of patients with migraine.
- Establishment of a training program for study staff members (investigators and coordinator) and use of tools that will ensure proper training to the patients for home use of the device.
- Clearly defining the inclusion and exclusion criteria such that only appropriate patients are enrolled in the study.

4.3.4 Risk-to-Benefit Rationale

We believe that the Nerivio Migra device holds great potential to provide an efficient and low risk treatment option to the population of migraine sufferers. Assessing the risks against the potential benefits of the use of the Nervio Migra for alleviating migraine pain, Theranica and the principal investigators (PIs) have determined that there is a high likelihood that the expected benefit may outweigh the risk in patients fulfilling the study eligibility criteria.

5 OBJECTIVES & HYPOTHESES

5.1 Objective

The study purpose is to demonstrate safety and effectiveness of the Nerivio Migra electro stimulation device for treatment of migraine attacks with and without aura.

5.2 Hypothesis

The hypothesis is that the electro stimulation delivered transcutaneously to the peripheral nervous system at onset of a migraine headache will abort the attack, as indicated by significant difference between proportions of responders to the sham control stimulation and the active treatment without unexpected device related adverse effects.

6 DESIGN OF THIS CLINICAL STUDY

6.1 Description

This is a prospective, randomized, double-blind, sham controlled multi-center clinical trial "Migraine Treatment with Nerivio Migra electro stimulation device". The study will enroll up to 248 patients diagnosed with migraine with and without aura, per the inclusion and exclusion criteria. These patients will be individually and randomly assigned to either treatment group or control group. For sham control, short electrical pulses of amplitude range similar to that of the treatment programs will be administered at very low frequency (0.1-0.5 Hz). The rationale underlying selection of sham control settings is that, on the one hand, pulses are perceivable and the user is able to manipulate their intensity similarly to the case of treatment programs, while, on the other hand, no clinically relevant treatment is delivered, based on existing knowledge of parameters range of electro stimulation treatments [5-7, 18].

Following successful screening, enrollment interview and signing of informed consent, participants will be provided with an active Nerivio Migra or identically looking sham device and trained to perform treatment and provide feedback via the smartphone application**.** Ratio between treatment and control groups will be 1:1.

Baseline information including mean frequency and severity of migraine attacks, occurrence of other headaches, presence of ICHD-3 diagnostic criteria for migraine with and without aura and use of preventive and rescue medications will be recorded.

Investigational devices will be programmed in active or sham mode with a 1:1 ratio, in order to achieve the desired ratio between active and control groups sizes, stratified with by use of preventive medications.

Study flow is schematically presented in the figure below.

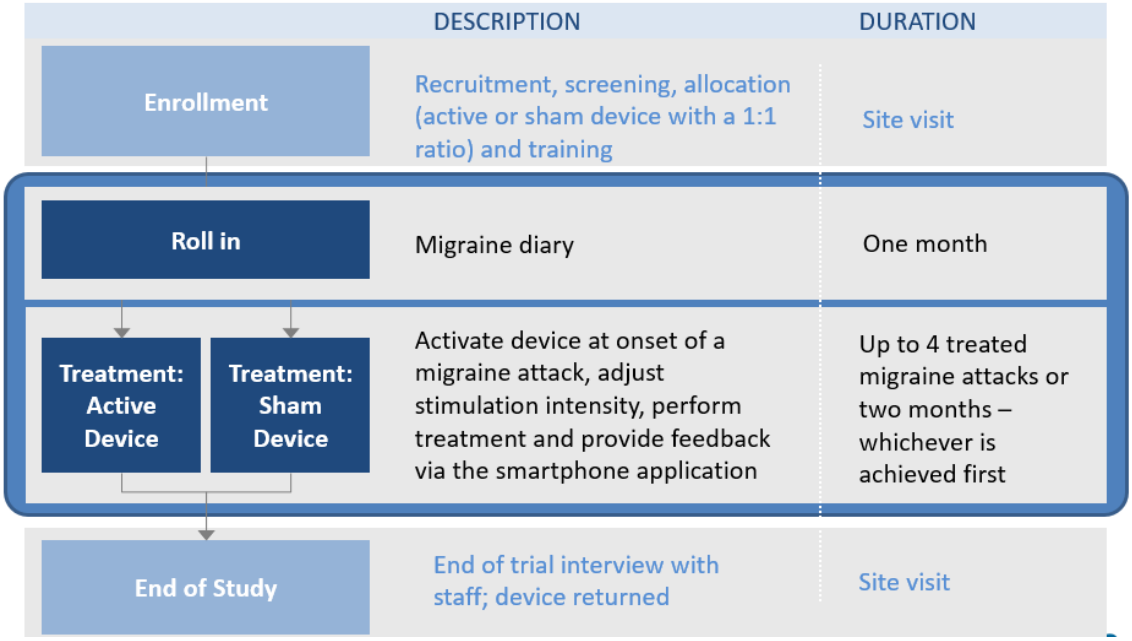

Figure 4. Study Design

Following enrollment, the study will be conducted in three stages.

Stage One. In stage one (roll-in phase) recruited participants will be reporting their migraine attacks per ICHD-3 diagnostic criteria, including presence of aura, using an electronic migraine diary installed on their smartphones. Duration of this phase is one month.

Stage Two. This will be the parallel arm treatment stage.

Participants will be instructed to activate the device at onset of a qualifying migraine attack and manually adjust stimulation intensity to a level within the pre-defined range where it is well perceived but not painful. A qualifying migraine attack shall be preceded by at least 48 hours of freedom from headache. Patients will be requested to refrain from use of rescue medications prior to and during the first two hours after treatment with the device, and if they can not comply with this, record their use of rescue medications (migraine specific drugs or other medications or therapies that may be used to treat pain, from a pre-specified list) in the mobile application.

Via the smartphone application, each participant will be asked to rate his/her migraine pain level three times using Pain Grades Scale (0 - no pain, 1- mild pain, 2- moderate pain, 3 – severe pain): (1) upon starting the treatment, (2) two hours after start of treatment, (3) 48 hours after start of attack. At the start of each treatment, participants will be also asked to provide time elapsed from start of migraine attack to start of the treatment. Participants will be also asked to provide feedback regarding their use of medication (migraine specific drugs or other medications or therapies that may be used to treat pain, from a pre-specified list), presence of nausea, photophobia and phonophobia, and treatment perception. After providing feedback at two hours

after start of treatment and in case of pain recurrence, participants will be allowed to re-treat the attack using Migra device.

Adverse events will be reported.

Duration of study participation for each patient will be up to three months, determined by one month of the roll-in stage followed treatment of four qualifying attacks over the course of two months (whichever is achieved first).

Post study questionnaire will include patient global impression of change [27], blinding and usability assessments.

Stage Three. This part will include open label extended treatment. Following the completion of the study by all subjects and the return of all study devices, subjects will be offered a 2-month period of using active device, at no cost.

6.2 Measures to Minimize Bias

A number of measures are built into the study design and procedures in order to minimize various potential sources of bias.
Implementation of the one-month roll-in period in conjunction with baseline assessment (questionnaire) mitigates recall bias and allows more reliable assessment of baseline headaches frequency, duration and severity.
Gender selection bias will be eliminated due to recruiting patients in headache clinics, emergency and neurology departments.
Randomization is employed to avoid bias in participants' allocation to study arms.
Double blind design is ensures collection of bias free efficacy data. Specific measures will be taken to ensure blindness (refer to Section 6.2.2).
Detailed statistical analysis plan will be developed prior to study start to mitigate interpretation bias.

6.2.1 Randomization

Randomized allocation of active and sham devices with stratification to use of preventive medications will be performed. Every site will be allocated a stock of identically looking, numbered devices of both kinds.

6.2.2 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. A number of means are planned to ensure the double blind aspect of this trial.

Selection of identically looking, active sham devices as control means is only a single step aimed at maintaining blindness. Each device will be numbered with 3 digit numbers, first digit site number and two digit subject numbers. Each new patient will be provided with d next consecutive numbered device.

Adherence to randomization procedure by clinical staff is critically important.

Importance of adherence to study design and procedures will be explained to participants in the course of 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 well perceived but non-painful" level.

In order to achieve blinding, participants will be trained individually. A training clip will be used for training, in order to minimize staff exposure to participants' reaction to and tolerability of treatment intensity.

In the course of the trial, 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.
End of study questionnaire will include individual blinding assessment to examine whether the blinding was well maintained throughout the study.

6.3 Study Endpoints

6.3.1 Primary Endpoints

Performance

Proportion (%) of patients reporting freedom from pain (pain grade 0) 2 hours post treatment without medications in at least 50% of treated attacks

6.3.2 Secondary Endpoints

Secondary Performance Endpoints

1. The proportion (%) of subjects reporting treatment response at 2 hours post treatment without rescue medications in at least 50% of treated attacks. Treatment response is defined as: pain level reduction from moderate or severe at baseline to mild or pain level of none if treatment started with mild pain

2. Proportion (%) of patients reporting, 2 hours post treatment:
   - freedom from pain (pain grade 0) and their most bothersome migraine-associated symptom (MBS) in at least 50% of treated attacks
   - freedom from nausea in at least 50% of treated attacks
   - freedom from photophobia in at least 50% of treated attacks
   - freedom from phonophobia in at least 50% of treated attacks

6.3.3 Exploratory Endpoints:

1. The proportion (%) of patients reporting freedom from pain (pain grade 0) 48 hours post treatment without medications in at least 50% of treated attacks

2. The percent of subjects who are pain-free at 2 hours with no use of rescue medication, and either have no relapse of pain within the subsequent 46 hours, or, if they have a relapse of pain in this time window, it disappears every time, after two hours, using the device, with no use of rescue medications.
3. Patient global impression of change, with emphasis on disability and quality of life.

6.3.4 Safety Endpoints:

- Treatment tolerability
- Adverse events and complications whether related or unrelated to study device.

6.4 Methods and Timing of Assessing, Recording and Analyzing Variables

Data capture and management are described in detail in the Data Management Plan.
List and structure of individual eCRFs are also given in the Data Management Plan.
Data monitoring procedures are described in detail in the study's Monitoring plan.
The study will rely to a large degree on electronic data capture methods.

6.4.1 Types of Data

Overall, data collected in the course of the study may be divided into three categories:

1. captured by clinical personnel. This includes demographic characteristics, baseline migraine parameters, end of study questionnaires, adverse events reports. Source data may be paper worksheets, further transferred into eCRFs maintained by the EDC system.
2. patient reported outcomes. This includes feedback entered via the smartphone application regarding migraine pain level, migraine symptoms, treatment perception, rescue medications. These data are used for calculation of study endpoints. Here, source data will be electronic, followed by automatic transfer to eCRFs.
3. additional information and technical data, captured by means of a system of log files by the Application. This includes stimulation activation times, applied stimulation intensity, device defects information, and other.

6.4.2 Clinical Study Variables and Data Capture Tools

This section provides an overview of collected PRO data and its capture tools.

6.4.2.1 Start attack/episode PRO feedback data

The screen provides for collection of the following data:

Item	Description	Control type	Values range
Current migraine pain level	Current migraine pain level in pain grade categories	Dropdown list	Mild (1), Moderate (2), Severe (3).

Time from onset of migraine pain	Time from onset of migraine pain	Dropdown list	under 10 minutes 10-20 minutes 20-60 minutes 1-2 hours 2-4 hours over 4 hours
Nausea	Presence of nausea	Radio buttons	Y/N
Sensitivity to light	Presence of photophobia	Radio buttons	Y/N
Sensitivity to sound	Presence of phonophobia	Radio buttons	Y/N
Increased skin sensation	Presence of allodynia	Radio buttons	Y/N

6.4.2.2 2h PRO

This feedback dialog appears 2h after the treatment program has started.

The screen provides for collection of the following data:

Item	Description	Control type	Values range
Current migraine pain level	Current migraine pain level in pain grade categories	Dropdown list	No pain (0), Mild (1), Moderate (2), Severe (3).
Medication	Whether rescue medication was taken	Radio buttons	Y/N
Medication name	Rescue medication	Dropdown list	From a pre-defined list
Nausea	Presence of nausea	Radio buttons	Y/N
Sensitivity to light	Presence of photophobia	Radio buttons	Y/N
Sensitivity to sound	Presence of phonophobia	Radio buttons	Y/N

Increased skin sensation	Presence of allodynia	Radio buttons	Y/N
Arm side where device was applied	Left or right arm	Radio buttons	L/R
Pain location (side)		Dropdown list	L R both
Additional feedback	Additional, free style feedback	Textbox	Free text, optional

6.4.2.3 48h PRO

The screen shall provide for collection of the following data:

Item	Description	Control type	Values range
Current migraine pain level	Current migraine pain level in pain grade categories	Dropdown list	No pain (0), Mild (1), Moderate (2), Severe (3).
Medication	Whether rescue medication was taken	Radio buttons	Y/N
Medication name	Rescue medication	Dropdown list	From a pre-defined list
Additional feedback	Additional, free style feedback	Textbox	Free text, optional

6.4.3 Methods and Timing of Assessing, Recording and Analyzing Variables

Once the last patient will have completed the study and all the queries have been resolved, database will be locked, cleaned and exported for final statistical analysis. Study report will be issued following final database lock.

Recurrent treatments within 46 hours from first treatment of an attack are allowed, and are collected and analyzed as exploratory data. Use of rescue medication within the 48 hours from start of 1st treatment of the attack is considered a failure for sustained relief assessment.

6.4.4 Data Flow and Management

Data management function will be supported by a cloud based EDC system developed by Clear Clinica (Modi'in, Israel). Clear Clinica 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 clinical personnel will be entered directly into pre-specified eCRF screens by 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 close as possible to real time. Effort will be made to identify missing or incorrect data and resolve the issues promptly.

Data collected onto the smartphone application will be directed to a secure cloud based database where it will undergo analysis aimed at detection of missing data and other inconsistencies. The smart phone 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, and similar, will be communicated to research coordinator of the corresponding site, using 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 staff. 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 Sponsor study monitor on the above events. Missing data will be identified automatically by a script running on Clear Clinica's cloud, and queries will be generated to participants and 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 are performed at this stage. Processed data are further pushed into the EDC system.
Schematics of data flow are presented in **Figure 5**.

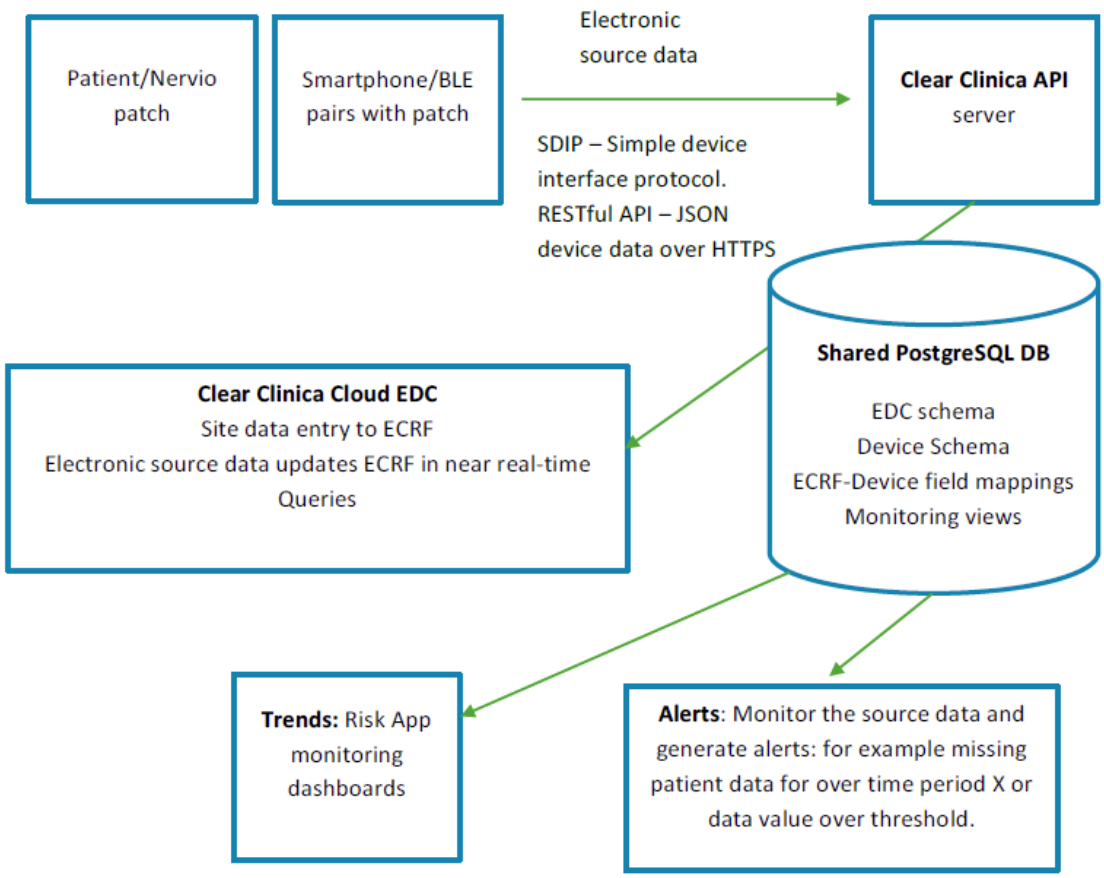

Figure 5. Schematics of data flow

Back-up of the database is performed daily. In addition, copy of each participant's ePROs and other activity is stored in his/her smartphone memory and can be retrieved in case such need occurs.
Study database will be locked and exported using EDC tools into SAS compatible format for interim and final statistical analyses.

Query resolution will be performed using EDC tools.
All paper based source data and relevant medical documents meant to serve also as source documents will be maintained by the sites and available as eCRF attachments. Patient identification will be blackened from all data. Patients will be identified by their codes. The site investigator is responsible for ensuring that eCRFs are filled in a timely manner and relevant paper documents are properly stored. Investigator will provide the documents to the sponsor either through the sponsor representative or by mail per sponsor request.

Access to data will be authorized and controlled, in accordance with relevant laws and guidelines.

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 Case Report Forms 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.

6.4.5 Procedures for Review of Data

A detailed description of data queries, their resolution and overall data flow can be found in the Data Management Plan.

Missing PRO data will be identified by a dedicated software running on the cloud closely to real time. Corresponding queries will be issued to study participants and site study coordinator. Effort will be made to resolve such queries as close as possible to real time.

6.4.6 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) is charged with the task of providing regular oversight of the data monitoring issues as detailed in the document: "DMC". These experts will periodically review and evaluate the accumulated data for study progress. The DMC will make recommendations concerning 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 targeted recruitment, 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 is to be performed per algorithm presented in Section 7.5.

• Futility monitoring: Futility will be assessed at the time of interim analysis.

6.4.7 Total Expected Duration of the Clinical Investigation

The anticipated duration of the study is up to 18 months.

6.5 Subjects

6.5.1 Inclusion Criteria

Patients need to fulfill all the below Inclusion criteria:

1. Patient is 18-75 years old.
2. Patient meeting the ICHD-3 diagnostic criteria for migraine with and without aura
3. Patient reporting 2-8 migraine attacks per month.
4. Patient must be able and willing to comply with the protocol
5. Patient must be able and willing to provide written informed consent
6. Male or non-pregnant / non-lactating female (NOTE: Females of child bearing potential must have a negative pregnancy test and must be willing to use adequate contraceptive means during the study)
7. Possesses the basic cognitive and motor skills needed to operate android cell phone

6.5.2 Exclusion Criteria

Patients are excluded if they have any of the following:

1. Has other significant pain problem that in the opinion of the investigator may confound the study assessments
2. Is currently implanted with an electrical and/or neurostimulator device (e.g. cardiac pacemaker or defibrillator, vagus nerve neurostimulator ,deep brain stimulator, spinal stimulator, bone growth stimulator cochlear implant, Sphenopalatine ganglion stimulator or Occipital nerve stimulator).
3. Known uncontrolled epilepsy.
4. Use of Cannabis including medical use.
5. Has chronic migraine (more than 15 headache days per month).
6. Changed usage or dosage of migraine preventive medications in the last two months
7. Has undergone nerve block (occipital or other) in the head or neck within the last 2 weeks.
8. Is participating in any other clinical study.

6.5.3 Contraindications

Contraindications for the use of the Nerivio Migra device include those known for transcutaneous electrical stimulation procedures. In addition to restrictions described in exclusion criteria, Nerivio Migra shall not be placed over open wounds or burns, or on irritated skin.

The Nerivio Migra is **NOT** intended for use in any other location except the upper arm.

6.5.4 Number of Subjects

The total number of patients to be treated in this study is up to 248 eligible patients (see section 7.5).

6.5.5 Expected Study Duration for Each Subject

Study duration per patient is 4 complete treatment cycles and no longer than 3 months from enrollment (whichever is fulfilled sooner).

6.5.6 Point of Enrollment

Patients are formally enrolled in the study once they are found eligible by inclusion and exclusion criteria, have signed an informed consent and received training on the use of the device. If the patient was not treated with the investigational device, the patient will be excluded from the mITT data analysis set.

6.5.7 Patient Withdrawal Criteria

Patients may be withdrawn from the study by the PI or sponsor, if any one or more of the following events occur:

- The patient wishes to withdraw from the study without providing any explanation.
- Patient is lost to follow-up.
- Refusal of the patient to continue treatment and/or follow-up observations.
- Serious adverse event.
- Significant protocol deviation/violation or noncompliance, either on the part of the patient or investigator.
- Decision made by the investigator that termination is in the patient's best medical interest.
- Device failure.
- Other ethical or clinical considerations upon investigator discretion.

6.5.8 Handling of Withdrawals

In accordance with the Declaration of Helsinki, a patient has the right to withdraw from the study at any time, for any reason, without prejudice to any future medical care by the physician or the institution. The investigator and the sponsor also have the right to withdraw patients from the study in the event of serious adverse events, protocol departures (deviations, violations and exemptions), or other reasons. Should a patient (or the patient's legally authorized representative) decide to withdraw, all efforts will be made to collect and report the next visit observations, and the reasons for withdrawal, as thoroughly and timely as possible.

Withdrawals will be recorded, analyzed and reported to local ethical committee according to local regulations.

6.5.9 Patient lost to follow-up

If a patient does not show for a end-of-study visit and cannot be contacted to collect follow-up information, he/she will be counted as a 'missed visit'. Prior to counting the patient as a 'missed visit' the following will be performed:

- Repeated, documented attempts to contact the patient via all available means.
- Repeated, documented attempts to contact the patient's general practitioner or referring physician.
- If a visit cannot be arranged, obtain as much information as possible through all communication means with the patient and/or his/her treating physician.

If a patient is lost to follow-up, the methods used to attempt to contact the patient should be noted. At least three attempts should be made to contact the patient and/or his/her treating physician via all available routes, and a certified letter should be sent to the permanent address on file.

6.5.10 Enrollment Period

The anticipated enrollment rate is expected to be approximately 6-15 patients per month, depending on participating site. Enrollment period is expected to be up to six months long.

6.5.11 Procedures for Replacement of Subjects

No subject replacement is planned.

6.6 Study related Procedures

6.6.1 General

The potential candidates will be screened to assess whether they are appropriate candidates for inclusion in this study. Informed consent will be obtained prior to initiation of any of the following clinical procedures that are performed solely for the purpose of determining eligibility for research. Pregnancy test for female patients with childbearing potential will be performed. The patient medical history, migraine history and diagnosis will be recorded and verified, the use of concomitant medication will be recorded in designated case report forms. Eligible patients will receive a documented training, and upon its successful completion the investigational device will be handed to study participants for home use. As per the IFU, participants are instructed to activate the device at the onset of a migraine headache and manually adjust stimulation intensity to a level where it is perceivable but not painful. Participants are requested to refrain from use of rescue medications prior to and during the first two hours after treatment and, if could not comply with this, record their use in the cellular application. Via the smartphone application, each participant will be asked to rate his/her migraine pain level three times: (1) upon starting the treatment, (2) two hours after treatment, (3) 48 hours after first treatment corresponding to the current migraine attack, using Pain Grades Scale (0 - no pain, 1- mild pain, 2- moderate pain, 3 – severe pain). At the end of each treatment, participants will be asked to provide feedback using the application regarding the time elapsed from start of migraine attack to start of the treatment, their use of medication. In case of failure to provide feedback regarding pain level post-treatment, telephone follow-up will be performed by study investigator staff to solicit such feedback. Additional migraine symptoms will be self-reported using the application. Follow up phone calls will be scheduled to record change in medical condition, concomitant medication and migraine therapy. Unscheduled visits will be recorded and termination visit will be scheduled upon the completion of the study as defined by treatment of four qualifying attacks over the course of two months (whichever is achieved first). In the event of premature discontinuation an early discontinuation visit will be scheduled.

6.6.2 Visit and assessment schedule

The study requires two hospital visits: (1) for screening and device training and (2) end of study visit when the device is returned and end of study assessment is performed.

Screening and enrollment visit

During the screening visit, the following procedures will be performed:

- Review Inclusion /exclusion criteria and evaluate eligibility
- Informed consent signing
- Demographics and medical history review.
- History of migraines.

- Medication history and concomitant medication(s) review.
- Enrollment and randomization.
- Patients will receive the Narivio device and smart phone (per need)
- Patients will receive training on device and application operation and schedule of reporting.
- Completion of a questionnaire.
- Urine pregnancy test

End of study visit (3 months after enrollment)

During the screening visit, the following procedures will be performed:

- Participants will be asked about changes in concomitant medications and adverse events that have occurred during the study.Devices and smartphones will be returned.
- Completion of a questionnaire

6.6.3 Activities performed by sponsor representatives

It is the sponsor's responsibility to train the site staff and supply the devices in a timely manner.

It is also the sponsor's responsibility to communicate to other sites' representatives serious adverse events, device malfunctioning findings and other relevant information that may affect study operation.

6.7 Monitoring Plan

A detailed Monitoring Plan was developed for this study by the sponsor.

Monitoring functions will be performed in compliance with Good Clinical Practices guidelines per forth in ISO 14155 (2011). The major function of the clinical monitor is to observe and assess the quality of the clinical study and the data generated from it, and to ensure that patients' welfare is being kept.

Based on implementation of an EDC platform, remote monitoring will be possible and will be performed on a regular basis between monitoring visits. The Study Monitor/CRA will access the EDC to perform remote review of the data. Attention will be paid (but not limited to) to the following:

- Number of patients enrolled, per site.
- Timely data entry.
- Timely resolution of queries.
- AE/SAE and device deficiencies reporting in accordance with the protocol and according to the timelines, including adequate follow-up.
- Non-compliances documentation.
- Timely follow-up.
- Devices accountability

Due to utilization of integrated ePRO tools and EDC platform for data collection and management, electronic source data will be considered verified by nature of process validation and verification performed jointly by Theranica and the EDC vendor and documented separately.

A well planned and prepared Initiation Visit will take place to address and train the site on aspects of protocol adherence and data monitoring processes.

The following monitoring visits are planned in the course of the study:

- After the Site Initiation, a monitoring visit close to the first few (3-5) subjects' enrollment.
- After the study completion by first few patients
- After completion of study by all planned patients

In cases where the monitor notices that the PI is performing not according to the protocol or relevant regulation, the monitor should notify the sponsor by means of the monitoring report, email notification or a separate report if needed (i.e. Deviation Report Form). A follow-up letter to the PI should include the key findings. Site revisiting regarding GCP and protocol adherence should be done by the monitor in case of repetitive deviations.

7 STATISTICAL CONSIDERATIONS

7.1 Study Design and Aim

The study is designed as a prospective, randomized, double-blind, sham controlled multi-center clinical trial. The study aim is to demonstrate safety and effectiveness of Nerivio Migra electro stimulation device for treatment of migraine attacks with and without aura.

7.2 Study Variables

7.2.1 Primary performance variable

The primary performance endpoint, the proportion (%) of patients reporting freedom from pain (pain grade 0) 2 hours post treatment without rescue medications in at least 50% of treated attacks, will be measured in the form of a binary variable which will be assigned the value of "1" if the subject reports freedom from pain (pain grade 0) 2 hours post treatment without rescue medications in at least 50% of his/her treated attacks, and "0" otherwise.

7.2.2 Secondary performance variables

The secondary performance endpoints will all be expressed in the form of binary variables as in the representation of the primary performance variable.

7.2.3 Exploratory performance variables

The exploratory performance endpoint, the proportion (%) of patients reporting freedom from pain (pain grade 0) 48 hours post treatment without rescue medications in at least 50% of treated attacks, will be measured in the form of a binary variable which will be assigned the value of "1"

if the subject reports freedom from pain (pain grade 0) 48 hours post treatment without rescue medications in at least 50% of his/her treated attacks, and "0" otherwise.

Patient global impression of change is measured via a questionnaire.

7.2.4 Safety variables

Incidence of all adverse events and complications by severity and relationship to study device.

Treatment tolerability as measured by a questionnaire.

7.3 Study Hypothesis

H_0: The proportion (%) of subjects reporting freedom from pain at 2 hours post treatment without rescue medications in the treated group = The proportion (%) of subjects reporting freedom from pain at 2 hours post treatment without rescue medications in the sham group.

H_A: The proportion (%) of subjects reporting freedom from pain at 2 hours post treatment without rescue medications in the treated group ≠ The proportion (%) of subjects reporting freedom from pain at 2 hours post treatment without rescue medications in the sham group.

7.4 Sample Size Estimation

The sample size for this study was calculated to test the above described null hypothesis with a chi-squared test, even though the final analysis may employ a regression model.

In the pilot study, the percentage of responders in the relevant treatment arm was 30%, while the percentage of responders in the sham group was 6%. The latter result is consistent with sham response rates referenced in IHS Guidelines for Migraine Trials. Sample size calculations are based on a more conservative estimate of the sham group response rate of 10%, then a sample size to detect a difference between treated and sham groups (of 20%) with 80% power at a 5% level of significance will result in a total of 124 evaluable subjects, with 62 subjects randomized to the treated arm and 62 to the sham arm. Allowing for a ~10% drop-out rate, a total of 136 (68 treated vs. 68 sham) subjects may be enrolled in the study.

Statistical considerations require availability of 124 evaluable subjects, i.e. with data available for analyses. The study recruitment will be monitored closely via the EDC system and, as soon as the evaluable data target is achieved, the Study Monitor will receive notification. If the number of subjects enrolled in the US is at least 50% of the accumulated population, recruitment will be stopped.

7.5 Interim Analysis

According to [24-26], planning an interim analysis that permits an increase in the sample size as described below does not inflate the type I error. In addition, the final analysis is performed using the conventional test as appropriate for the statistical hypothesis.

One interim analysis is planned once 50% of the information is collected, i.e. the interim look will be performed after 62 evaluable subjects have been accrued. After all the relevant data will be

entered into the database, a soft lock to the database will be performed. An unblinded statistician will perform the assessments described below. A designated Data Monitoring Committee will recommend whether to stop the study once the interim results are available.

The study will then either continue to the originally planned sample size if the result is "favorable", stop for futility if the result is "unfavorable", or an increase will be made to the sample size if the result is "promising". These decisions will be made based on the conditional power (CP), defined as the conditional probability that the result will exceed a critical value at the interim given the observed effect size $\widehat{\delta_1}$ = difference between response rates treated versus control at the interim look.

Notation:

n1= sample size at interim analysis

n2= sample size calculated based of effect size obtained at interim

nmax = the highest sample size the company is willing to use/ can afford, nmax = 248 subjects and is calculated based on a smaller effect size of 15% in the same manner as above.

CPmin=is the calculated minimum CP based on the ratios nmax/n2, n1/n2 and the target study power (80%).

The following are the decision rules for the interim analysis which will be performed upon accrual of 50% (n1/n2) of the sample size, i.e. 62 evaluable subjects. These depend on the zone into which CP falls at the interim, the calculated CPmin, the maximum sample size designated for the study and the % of the originally planned sample size at which the interim analysis will be performed. Following this principle does not inflate the Type I error.

1. If the result is "Unfavorable", i.e. CP < CPmin = 36% (interim result is so disappointing that it is not worth increasing the sample size to retrieve conditional power), continue to the original sample size of 124. If the difference between response rates at the interim (Pt-Pc) is less than 0 (i.e. control is better than treatment) stop the trial for futility.
2. If the result is "Promising", i.e. 36% ≤ CP < 80%, the sample size is increased to recover the targeted power of 80%. The sample size used will be either the new calculated sample size based on the conditional power (as described in Sample size re calculation using conditional power Jonathan S. Denne Statist. Med. 2001; 20:2645–2660) or the predetermined maximum sample size of 248 subjects whichever lower.
3. If the result is "Favorable", i.e. CP ≥ 80% the interim results are sufficiently favorable and trial continues to the original sample size planned of 124 without the need to adaptively increase the sample size.

7.6 Randomization

After a subject meets the eligibility criteria, he/she will be randomly allocated (with a 1:1 ratio) to one of the following 2 treatment groups based on a randomization scheme using the permuted block method stratified by preventive medications use and center:

- Sham Control
- Nerivio Migra group

The randomization scheme will be prepared by the study statistician using the SAS (version 9.4.) random number procedure. The block size will be fixed and study personnel will be blinded to the randomization block size.

7.7 Analysis sets

7.7.1 Intent to treat analysis set (ITT)

The ITT analysis set will consist of all subjects randomized. In accordance with the ITT principle, all subjects randomized will be kept in their originally assigned treatment group.

7.7.2 Modified intent to treat analysis set (mITT)

The mITT set will consist of all subjects in the ITT set who completed at least one study treatment, assigned a treatment group as treated.

7.7.3 Per protocol analysis set (PP)

The Per-Protocol (PP) analysis set includes all patients from the mITT analysis set without any major protocol deviation who have evaluable data on at least one qualifying migraine attack.

7.7.4 Statistical analysis of analysis sets

The ITT analysis set will serve as the main set for safety assessments and the mITT set for all performance assessments.

The primary performance assessment will also be performed on the PP analysis set as a sensitivity analysis.

7.8 Statistical Analyses

Amendments to the statistical analyses section will not require IRB approval, unless driven by protocol or study design change. In that case a standalone SAP will be prepared prior to data lock for each analysis milestone.

7.8.1 General Considerations

Statistical analyses will be performed using SAS® v9.4 (SAS Institute, Cary NC, USA).

All statistical tests will be two-sided. The required significance level of findings will be equal to or lower than 5%, nominal p-values will be presented. Where confidence limits are appropriate, the confidence level will be 95%.

Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage. For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test will be used as appropriate. For comparison of proportions (categorical variables), the Chi-squared test or Fisher's exact test will be used as appropriate.

If multiple measurements are taken in a single patient, statistics described below will be appropriately modified to accommodate the within patient correlation.

7.8.2 Significance levels and handling of type I error

7.8.2.1 Type I Error

The overall significance level for this study is 5% using two-tailed tests, except for treatment by site interaction that will be tested at a significance level of 10%.

7.8.2.2 Hierarchy Approach for Secondary Endpoints Analysis

The hierarchy approach will be adopted for the primary and secondary endpoints to control type I error due to multiple endpoint testing. Thus, the primary endpoint will first be analyzed and only if $p<0.05$, will the secondary endpoints be analyzed.

7.8.3 Demographic and Other Baseline Characteristics

Demographic and baseline condition related characteristics will be tabulated and compared between the study groups by data type. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage.
This data will include:

- Demographic data
- Medical history
- Migraine preventive medication
- Other concomitant medication
- Migraine attacks characteristics per ICHD-3 diagnostic criteria for migraine with and without aura
- Physical examination
- Laboratory (pregnancy) tests for women of childbearing potential

7.8.4 Disposition of Patients

The numbers of patients who entered the study and completed each stage of the study will be provided per month, as well as the reasons for all post randomization discontinuations, grouped by major reason, e.g., lost to follow-up, adverse event, poor compliance, did not administer any treatment (with reasons). A list of discontinued patients, protocol deviations, and patients excluded from the performance analysis will be provided as well.

7.8.5 Performance Analyses

Primary Performance Analyses:
The primary endpoint is freedom from pain at 2 hours post treatment without rescue medications in at least 50% of treated attacks, a count and percentage of subjects free from pain will be calculated and presented for both study groups each with a two-sided 95% exact confidence interval. The groups will be compared with a chi-squared test.

If the null hypothesis is rejected in favor of the alternative hypothesis and the proportion (%) of subjects reporting freedom from pain at 2 hours post treatment without rescue medications in the treated group is greater than that of the sham group, the study will be deemed successful.

The primary endpoint will also be evaluated stratified by center using a Mantel-Haenszel test to assess the center by group interaction.

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

Subset analysis:

Adjustment for other covariates such as demographics or other baseline patient characteristics may be performed by adding these variables into a logistic regression model.

Subgroup analysis according to use of preventive medications will be performed and reported by adding these variables to a logistic regression model.

Secondary performance analyses:

The secondary performance variables will be summarized by a count and percentage and compared with a chi-squared test.

Exploratory performance analyses:

A count and percentage of patients reporting freedom from pain (pain grade 0) 48 hours post treatment without rescue medications in at least 50% of treated attacks will be presented, the groups will be compared with a chi-squared test.

Use of rescue medications will be summarized by descriptive statistics per treatment group and compared between the groups with a t-test.

Patient global impression of change will be summarized by descriptive statistics per treatment group and compared between the groups with a t-test.

Ease of use will be summarized by descriptive statistics.

7.8.6 Safety Analysis:

The primary safety variable, the cumulative incidence (and 95% CI) of device related adverse events (AEs) throughout the study, will be presented in tabular format and will include incidence tables by severity.

Adverse event rates will be compared between the study groups with a chi-squared test.

Serious adverse events will be listed and discussed individually.

Treatment tolerability will be compared between the study groups, 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 as well.

7.8.7 Handling of Missing Data

A sensitivity analysis of the primary end-point will be performed to assess the impact of missing data on the study outcome using possible imputation methods for binary data. A “worse case” scenario analysis will be performed as well where subjects with missing data for the binary response assessment will be considered as a non-responder/ non-success.

Imputation of missing data may be performed on secondary and exploratory endpoints as well.

7.9 Pooling

Subgroup analysis of the primary performance endpoint by center, and US vs OUS, will be used to evaluate the poolability of the results. The significance of center-to-center variability in treatment effect will be evaluated by including an interaction term of treatment group by center in a logistic regression model. In the case that poolability is questionable, the reasons for differential treatment effect, such as patient and clinical characteristics, will be investigated and reported.

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 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 ClearClinica. The EDC allows for the secure collection, transmission, validation, monitoring and real-time administration of study data gathered at investigative sites, and by the patient via the smartphone application. The system allows 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 Trials.*”

Except for Patient Reported Outcome entered directly by the patient to the smartphone App, data reported on the eCRF should be driven from source documents and be consistent with these source documents. Editing of data is done under full audit trail.

PRO data collected from the smartphone applications will be saved in dedicated log files on the smartphones for backup purposes and transferred to the EDC system at end of study visit.

8.1.1 Direct Data Entry

For several CRF fields Source Data Verification (SDV) may not be possible as entries may not be found in source documents (*e.g.*, migraine diary or other Patient Reported Outcome completed directly into the smartphone App). Therefore, it is allowed to use the CRF for direct data entry, but only for pre-defined fields.

8.2 Data Quality Assurance

To ensure the quality of clinical data across all subjects, a clinical data management review will be performed by Theranica on patient data submitted in the CRF. During this review, patient data will be checked 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 Theranica. 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 data reviewed. The electronic signature asserts that the investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content. Any changes made to the data after 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. Verification and validation report will be held by the sponsor.

8.5 Records and Data Retention

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.

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

8.6 Other Aspects of Clinical Quality Assurance

Site PI or a person designated by the site PI is responsible for establishing and maintaining adherence to the study protocol. Study PI is responsible for addressing quality assurance issues (correcting procedures that are not in compliance with protocol). Study Coordinator is responsible for quality control issues (i.e. correcting errors in data entry).

Theranica will assign a monitor to 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 Monitoring Plan.

Sponsor auditing of the site may be done 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 health authority audit.

9 AMENDMENTS TO THE CLINICAL INVESTIGATION PLAN

The protocol is not to be amended by the investigator without first obtaining sponsor's approval. Amendments initiated by the sponsor, or initiated by the investigator and then approved by the sponsor, will be submitted for approval to local IRB/EC and, if applicable, to the respective Regulatory Authority (RA). Protocol amendments should receive the IRB/EC approval, and if submitted to the RA, a regulatory approval as well, prior to implementation in the study. For non-substantial changes (e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance) not affecting the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints, a simple notification to the IRB/ EC and, where appropriate, regulatory authorities can be sufficient.
The following documents are relevant to the protocol, but are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Site Roster
- Case report forms
- Data Management Plan
- Monitoring Plan
- Statistical Analysis Plan
- DMC

10 CLINICAL INVESTIGATION PLAN DEVIATIONS

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or related SOPs requirements. The noncompliance may be on the part of the subject, the investigator, or study staff.

The protocol is not to be deviated by the investigator or the co-investigators without first obtaining sponsor approval except in cases where 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 to the protocol will be assessed by study monitor during monitoring visits as well as remotely, using designated reports provided by the EDC system.

All deviations from the protocol will be addressed in study subject source documents and promptly reported to the site IRB, according to local requirements.

10.1 Procedures for Recording, Reporting and Analyzing Protocol Deviations

All protocol deviations need to be documented in source documents and appropriate eCRF.

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 to the principal investigator.

The Study Monitor will ensure that major protocol deviations are discussed with the Investigator. Major deviations are those deviations that:

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

Deviations will be reported to the IRB/EC periodically or as specified by local regulations. Further documentation of any changes in research activity should be submitted to the sponsor and the IRB/EC if:

- They 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.

The Study Monitor will, in addition to the above immediate reporting, 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 sent to Theranica.

Theranica 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. Assessment and discussion of their potential impact / lack of impact on study results will be addressed.

10.2 Notification Requirement and Timelines

Major deviations should be escalated to the sponsor within 5 business days.

11 PROTOCOL DEVIATIONS

Protocol deviations must be reported to local IRB/EC per their guidelines. The site PI or other designated site staff member is responsible for knowing and adhering to local IRB/EC requirements.Device Accountability

Devices will be provided by Theranica Bioelectronics, bearing required labeling. Upon being handed to study participant, device number will be documented in CRF and in site log. Each batch of devices delivered to clinical sites for allocation to study participants is accompanied by a shipment note. Device shipment records are maintained by sponsor and on site.

Prior to distribution, the devices are stored in a designated locked cabinet. Access to investigational devices is controlled by the research staff. The devices are only 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 is handed to a study participant, it is coupled to the participant's smartphone by means of Bluetooth connection.

In the course of device allocation, application installation and device – application connection establishment, site allocated User ID is entered by study coordinator via the Application.

The triplet of IDs (User ID, phone ID, device ID) provides means of identifying technical and PRO data from each participant in the electronic database while protecting participant's privacy.

The clinical investigator will be responsible for the safe storage of devices in accordance with instructions given 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. Device accountability records will be reviewed during monitoring visits.

The investigator will be responsible for providing device use training to the patients according to the IFU 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 Bioelectronics.

12 STATEMENTS OF COMPLIANCE

This study will be conducted in compliance with the protocol (after being approved by the local EC and, if required, by the local RA), the Good Clinical Practice (GCP) per ISO 14155 (2011) standard and the ethical principles that have their origin in the Declaration of Helsinki.

The Informed Consent Form (ICF), patient's information material, and advertising material (if applicable) must be submitted and approved by the IRB/EC (and RA when needed), and any request by the IRB/EC or RA will be followed. Written approval of the protocol, ICF, patient's information material, and any advertising material (if applicable) must be obtained from the EC and if applicable the corresponding RA prior to any patient enrollment.

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

13 INFORMED CONSENT PROCESS

Written informed consent must be obtained from each study patient prior to commencing any CIP-specific procedures. A written informed consent (approved by Theranica and the IRB/EC) must be signed and dated by the patient, and the person who conducted the informed consent discussion. Additionally, the person who conducted the informed consent discussion will indicate that Informed Consent has been obtained by noting so in the appropriate section of the. Patients will be given a copy of the signed informed consent document. The signed informed consent will be retained with the study records at the investigational site. New findings relevant to the patient's continued participation will be made available to the patients after approval of such updates by the IRB/EC.

Informed consent accurately describes all aspects of the clinical investigation that are relevant to the subject's decision to participate in the study.

14 ADVERSE EVENTS

Capturing of adverse events will serve for safety evaluation.

Adverse events encountered during treatment will be captured via end of study questionnaire and interview.

This study will use the list in section 14.7 below for nomenclature of adverse events complications reported in the CRF for Device related side effects.

Non-Device adverse events will be graded according to section 14.2.1 below. AE resulting from a procedure that is not related to the device, are considered as general AEs.

On-site visits to investigate adverse events and follow them up will be scheduled at the discretion of the principal investigator. Unscheduled visits and termination visit will be reported using designated case report forms.

If at the last visit there will be a Device related AE/side effect that is still active, the patient will be followed to completion or until a steady state is achieved for a continuous period of 2 weeks.

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14.1 Characteristics of an Adverse Event

14.1.1 Severity of the Adverse Event

Severity of AEs will be determined using the following scale:

- Mild: The patient is aware of a sign or symptom, but it is easily tolerated
- Moderate: Discomfort or interference with usual activity
- Severe: Incapacitating, with inability to engage in usual activity

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14.1.2 Relationship of an AE and SAE to the Study Device

The relationship of the adverse event to the study device is defined as follows:
Definite: An adverse event has a definite determination that it was caused due to the device.
Probable: An adverse event has a strong temporal relationship to study device or recurs on rechallange, and another etiology is unlikely or significantly less likely.
Possible: An adverse event has a strong temporal relationship to study device, and an alternative etiology is equally or less likely compared to the potential relationship to study device.
Unrelated - The AE is clearly NOT related to the device.

14.2 Definitions of Adverse Event and Adverse Device Effect

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in study participants, whether

or not related to the investigational device. This should relate to baseline information whenever available.

An adverse device effect (ADE) is an adverse event related to the use of the investigational device. In this study the ADE is refers to "side effect" or “complications”.

14.3 Definition of Serious Adverse Event

A serious adverse event (SAE) is an adverse event, that
a) led to death,
b) led to 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 a body structure or a body function,
c) led to fetal distress, fetal death or a congenital abnormality or birth defect
It is responsibility of site PI to report any Serious Adverse Event or Serious Adverse Device Event to Theranica Bioelectronics, within 24 hours to:

Theranica Bioelectronics
Alon Ironi
Tel: +972.72.390.9758
Fax: + 972.72.390.9755
Email: aloni@theranica.com

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.

14.4 Device Deficiency

Device deficiency is an inadequacy with respect to the device’s identity, quality, durability, reliability, safety, or performance, such as a malfunction, failure, use error or inadequate labeling. Device deficiencies may or may not be associated with an adverse event.

All device deficiencies will be entered in the eCRF. Device deficiencies 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, the device(s) associated with a malfunction or failure should be retained until arrangements for its collection are made by Theranica.

Device deficiencies will be summarized and reported in the clinical study report and will be reported to the regulatory authorities per country’s applicable reporting requirements.

14.5 Time-frame for Investigator Reporting AE to Sponsor, EC, RA

Serious adverse events, whether or not related to the device, and whether anticipated or unanticipated, must be reported to the sponsor within 24 hours of learning of the event occurrence by the site staff. This requirement is in addition to, and does not replace, other investigator responsibilities for adverse event reporting. Notification on a SAE is forwarded to

Theranica designated contact person. Additionally, SAEs should be reported by the site to the involved IRB/EC and Regulatory Authorities as applicable.

Unanticipated device related adverse events shall be reported to the sponsor within 48 hours of learning of the event occurrence by the site staff.

In addition, device related side effects shall be reported to the sponsor and documented in monitoring visit/phone call summary.

Any AE that results in withdrawal from observation in the study must be reported to the sponsor within 24 hours after the decision to withdraw the patient is made.

Any death occurring during the study must be reported to the sponsor within 24 hours of discovery of the event. "Death" should not be reported as an AE, the cause of death should be reported as an AE. The only exception is "Sudden Death" when the cause is unknown. A copy of the death records, death certificate and an autopsy report (if performed) must be provided to the sponsor as soon as possible.

The sponsor is responsible for relaying adequate information on SAEs to the regulatory authorities per country's applicable reporting requirements.

14.6 Adverse Event Reporting Forms

The eCRFs for AE or SAE will include all relevant information of the AE or SAE with regards to onset and resolution time, grade, causality to device, treatment given etc.

14.7 Foreseeable Complications and Anticipated Adverse Device Related Effects.

Possible adverse events associated with Transcutaneous Electrical Nerve Stimulation include, but are not limited to the following:

- Likely
    - Minor skin irritation from wearing the device, which disappears shortly after the treatment is over.
- Less Likely
    - Red marks at the site of stimulation, that disappear shortly after the treatment is over.
    - Possible sensation of slight warmth where the device touches the skin. This disappears shortly after the treatment is over.
    - A sensation of itching or tingling or stinging at the site of stimulation, which disappears shortly after the treatment is over.
    - Slight muscle fatigue or weakness in arm where the device is applied, which disappears shortly after the treatment is over.
- Very unlikely
    - Slight muscle spasms in the arm where the device is applied, which disappears shortly after the treatment is over.

The following migraine symptoms are foreseeable and will not be considered as device related: headache, nausea, light sensitivity, sensitivity to noise or odors, stomach upset, abdominal pain, loss of appetite, cold or heat sensation, paleness, fatigue, dizziness, fever (rare), blurred vision, bright flashing dots or lights, blind spots, wavy or jagged lines (aura).

14.8 Safety Monitoring and Adjudication of Adverse Events

The sponsor will review submitted AE information and may request supplemental information if needed. For SAE, USADE and ADE (as classified by the investigator) a narrative will be prepared and adjudicated for assessing the relatedness, seriousness and possible action items required. The sponsor may ask for further information or clarification from the investigator. A summary of the adjudication results will be issued; if different than investigator's report, PI will be notified.

Adjudicated events will serve as a basis for reporting AE/SAE. Differences between site-reported events and adjudicated events will also be presented and discussed in the report.

15 VULNERABLE POPULATION

No vulnerable population will be enrolled to this study.

16 EARLY TERMINATION OF THE CLINICAL INVESTIGATION

16.1 Criteria and Arrangements

The study may be discontinued if:
- At any time, in the opinion of study PI, the study represents an unreasonable medical risk to patients.
- The sponsor decides to terminate the study due to company considerations (e.g. Data Monitoring Committee recommends study termination based on futility analysis of interim data)

In the event of clinical investigation premature termination or suspension, Theranica will send a report outlining the circumstances 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. In the event of clinical investigation premature termination or suspension, enrolled subjects will be followed up as per the institution's standard of care.

16.2 Requirements for Patient Follow-Up in case of Withdrawal

In case of patient withdrawal, all efforts will be made to collect and report the final visit observations as thoroughly and timely as possible.

17 PUBLICATION POLICY

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

18 PATIENT CONFIDENTIALITY & DATA PROTECTION

The privacy of participants and confidentiality of personal data will be maintained in reports and publications and will not be otherwise published in any way.

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 authenticity of data collected, as documented in informed consent form.

19 GUIDELINES AND APPLICABLE DOCUMENTS

1. EN ISO 14155; (2011): Clinical investigation of medical devices for human patients
2. EN ISO 14971; (2012): Medical devices – Application of risk management to medical devices.

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21 ACRONYM LIST

ADE - Adverse Device Effect

AE - Adverse Event

CA – Competent Authority

CE - Conformité Européenne [CE Mark]

CI – Confidence Interval

CIP - Clinical Investigation Plan

CRF - Case Report Form

CV - Curriculum Vitae

d – Day

DM - Data Management

DNIC - diffused noxious inhibitory control

EC - Ethical Committee

GCP - Good Clinical Practice

GMP- Good Manufacturing Practice

IB - Investigator Brochure

ICF - Informed Consent Form

ICH - International Conference on Harmonization

IFU – Instructions for Use

ISO - International Organization for Standardization

m - Month

MDD - Medical Device Directive

MoH – Ministry of Health

NPS – Numeric Pain Rating Scale

PI - Principal Investigator

PP - Per-Protocol analysis set

RA - Regulatory Authority

SADE - Serious Adverse Device Effect

SAE - Serious Adverse Event

SD - Standard Deviation

SDV - Source Data Verification

SOPs - Standard Operating Procedures

w - Week

APPENDIX A. STIMULATION PROGRAMS

- Waveform: Biphasic, rectangular, symmetrical
- Duration of primary phase (µsec): 200
- Pulse duration (µsec): 400
- Pulse frequency (Hz): 100-120*
- Max output current (mA): 60

* In order to avoid habituation (i.e., cease of response to the stimulus), Migra employs frequency drifting in the following manner – after each 5-minute section of the treatment, the frequency of the output will toggle between 100-110-120Hz.

APPENDIX B- SUBJECT QUESTIONNAIRES

Appendix B. Subjects' questionnaires**NM1 MCT – Start of Study Questionnaire**

The Migraine Disability Assessment questionnaire was put together to help you measure the impact that migraines (and headaches) on your life.

Please answer all the following questions regarding ALL the migraines you've had in the past 2 months. For each question, select one choice.

Part I – Migraine Disability Assessment

Establishing baseline

1. How many days per month, in the 2 months before the study, did you miss work or school because of your migraine?
    1. 0
    2. 1-3
    3. 4-8
    4. More than 8
2. In how many days per month, in the 2 months before the study, was your productivity at work or school significantly reduced because of your migraine (do not include days that you indicated in question #1)?
    1. 0
    2. 1-3
    3. 4-8
    4. More than 8
3. In how many days per month, in the 2 months before the study, did you not do household work because of your migraine (such as housework, home repairs or maintenance, shopping, caring for children, etc.)?
    1. 0
    2. 1-3
    3. 4-8
    4. More than 8
4. In how many days per month, in the 2 months before the study, was your productivity in household work significantly reduced because of your migraine (such as housework, home repairs or maintenance, shopping, caring for children, etc.)?
    1. 0
    2. 1-3
    3. 4-8
    4. More than 8
5. On how many days per month, in the 2 months before the study, did you miss family, social or leisure activities because of your migraine?
    1. 0
    2. 1-3
    3. 4-8
    4. More than 8
6. In general, how would you grade the degradation in your quality of life as a result of migraines?
    1. None
    2. Mild effect
    3. Moderate effect

4. Severe effect

7. How much do you typically spend on migraine medication, per month?
    1. Less than $10
    2. $11-$20
    3. $21-$50
    4. More than $50

NM1 MCT – End of Study Questionnaire

The Migraine Disability Assessment questionnaire was put together to help you measure the impact that migraines (and headaches) on your life.

Please answer all the following questions regarding ALL the headaches you've had in the past 2 months. For each question, select one choice.

1. How many days per month, in the last 2 months, did you miss work or school because of your migraine?
    1. 0
    2. 1-3
    3. 4-8
    4. More than 8
2. In how many days per month, in the last 2 months, was your productivity at work or school significantly reduced because of your migraine (do not include days that you indicated in question #1)?
    1. 0
    2. 1-3
    3. 4-8
    4. More than 8
3. In how many days per month, in the last 2 months, did you not do household work because of your migraine (such as housework, home repairs or maintenance, shopping, caring for children, etc.)?
    1. 0
    2. 1-3
    3. 4-8
    4. More than 8
4. In how many days per month, in the last 2 months, was your productivity in household work significantly reduced because of your migraine (such as housework, home repairs or maintenance, shopping, caring for children, etc.)?
    1. 0
    2. 1-3
    3. 4-8
    4. More than 8

5. On how many days per month, in the last 2 months, did you miss family, social or leisure activities because of your migraine?
    1. 0
    2. 1-3
    3. 4-8
    4. More than 8
6. In the past two months, how would you grade the degradation in your quality of life as a result of migraines?
    1. None
    2. Mild effect
    3. Moderate effect
    4. Severe effect
7. How much do you typically spend on migraine medication, per month, during the 3-months study?
    1. Less than $10
    2. $11-$20
    3. $21-$50
    4. More than $50

Part II – Device Usability and Pricing

1. If you could purchase the device now, how much would you be willing to pay for it, per month?
    1. Less than $10
    2. $11-$20
    3. $21-$50
    4. More than $50
2. If you had the device permanently in your possession, what would be your estimate for additional (extra) spending on medication?
    1. Less than $10
    2. $11-$20
    3. $21-$50
    4. More than $50
3. If you had the device permanently in your possession, what would be your estimate for additional (extra) spending on medication?
    1. Less than $10
    2. $11-$20
    3. $21-$50
    4. More than $50

4. How likely are you to recommend using NM1 device for a friend or family member that also suffer from migraines?
    1. Not likely
    2. Likely
    3. Very likely
    4. Extremely likely
5. How likely would you be willing to share the information about your migraine episodes with your physician or any other designated care-taker, via the device and its App?
    1. Not likely
    2. Likely
    3. Very likely
    4. Extremely likely

Did you experience any inconvenience during the treatment?

6. Itching at the location of the device?
    1. None
    2. Mild
    3. Moderate
    4. Severe
7. Skin redness at the location of the device?
    5. None
    6. Mild
    7. Moderate
    8. Severe
8. Sensation of heat at the location of the device?
    9. None
    10. Mild
    11. Moderate
    12. Severe
9. Overall, how would you rate the study and your experience with the device?
    1. Excellent
    2. Very good
    3. Good
    4. Fair
    5. Poor
10. How user friendly and intuitive was the App?
    1. Extremely friendly/intuitive

2. Very friendly/intuitive
3. Somewhat friendly/intuitive
4. Not so friendly/intuitive
5. Not friendly/intuitive at all

11. To what extent did you like using the device?
    a. Liked it a lot
    b. Liked it
    c. Did not like it so much
    d. Disliked it very much