## CLINICAL INVESTIGATION PLAN

## STUDY TITLE:

# A prospective, single arm, open label study of the safety and efficacy of Nerivio™ for the acute treatment of New Daily Headache Persistence (NDHP) in adolescents

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| **PROTOCOL NUMBER:** | **00016835** |
| **REVISION:** | 1.0 |
| **RELEASE DATE:** | 01/Feb/2022 |
| **DEVICE:** | Nerivio, a Neuromodulator device for the acute treatment of migraine |
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| APPROVED BY: | POSITION: | DATE: (DD/MM/YY) | SIGNATURE: |
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The Principal investigator 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.

Investigator's Signature _____ Date _____

Investigator's Printed Name _____

**A prospective, single arm, open label study of the safety and efficacy of Nerivio™ for the acute treatment of New Daily Headache Persistence (NDHP) in adolescents**

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## 1. Synopsis

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| **Title** | A prospective, single arm, open label study of the safety and efficacy of Nerivio™ for the acute treatment of New Daily Headache Persistence (NDHP) in adolescents |
| Principal Investigator | Marc DiSabella, DO<br>Director, Pediatric Headache Program<br>Associate Professor of Pediatrics and Child Neurology, George Washington School of Medicine and Health Sciences<br>Children's National Hospital, Washington, DC |
| **Investigational Device** | Nerivio™ is an FDA-authorized Remote Electrical Neuromodulation (REN) device for the acute treatment of migraine with or without aura in patients 12years old or above. The device delivers transcutaneous electrical stimulation to the upper arm to induce conditioned pain modulation (CPM) that activates a descending endogenous analgesic mechanism. |
| **Objectives** | To evaluate the safety and efficacy of Nerivio™ in the acute treatment of New Daily Headache Persistence (NDHP) in adolescents (12 to 17 years of age). |
| **Participant Population** | Adolescents 12-17 years old meeting the International Headache Society criteria for New Daily Persistent Headache (NDPH) |
| **Sample size** | Up to 100 participants |
| **Inclusion Criteria** | 1. Participants age 12-17 years old at the time of informed consent, inclusive.<br>2. Participants have at least a 6-month history of headaches that meet the diagnostic criteria for New Daily Persistent Headache (NDPH)<br>3. Participants who are on stable dosing of prophylaxis agents for at least three months.<br>4. Participants have personal access to a smartphone (24/7)<br>5. Participants must be able and willing to comply with the protocol<br>6. Parents/Guardians must be able and willing to provide written informed consent<br>7. Participants must be able and willing to provide informed assent |
| **Exclusion Criteria** | 1. Participants with an implanted electrical and/or neurostimulator device (e.g. cardiac pacemaker, cochlear implant).<br>2. Participants with congestive heart failure (CHF), severe cardiac or cerebrovascular disease.<br>3. Participants with epilepsy.<br>4. Participants who have undergone nerve block (occipital or other) in the head or neck, or treatment with onabotulinum toxin A (Botox) to the head and/or neck in the prior four months.<br>5. Current participation in any other clinical interventional study<br>6. Participants without basic cognitive and motor skills required for operating a smartphone.<br>7. Pregnant or breastfeeding females<br>8. Participants who have previous experience with the device<br>9. Participants with arm circumference below 7.9 inches (20 cm) |
| **Study Design** | A prospective, single arm, open label trial.<br>The study will be conducted in two phases: |

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| | Phase I - Run-in:<br>Eligible participants will use a smartphone headache diary application for 28 days. Participants who report at least 22 entries (70%) AND a constant and unremitting headache will be included in the treatment phase.<br><br>The C-SSRS will be administered at the screening visit and a "since last visit" form which will be administered at each subsequent in-clinic study visit to assess possible suicidal ideation and behavior. The C-SSRS will be scored by the investigator or Study Coordinator who has C-SSRS certification. The survey will be scored immediately after taken by participant. If reports of suicidal ideation with intent to act (endorse item 4 or 5), reports of actual, aborted, or interrupted suicide attempts, or reports of behavior preparatory for an attempt are identified, the investigator" will refer the subject for further examination.<br><br>Phase II - Treatment phase:<br>Participants who meet the run-in requirements will receive an active Nerivio device. Participants will be instructed to use the device within 60 minutes of awakening with a headache or upon increasing headache severityduring a period of 4 week. A treatment session is of 45 minutes<br>The participants will use the app to record pain intensity levels at baseline and 2-hours post-treatment, and to record the presence/absence of associated symptoms (nausea, photophobia, phonophobia) at baseline and 2 hours post-treatment. |
| **Qualifying NDHP attack** | A qualifying NDPH attack is defined as a headache that:<br>1. is at an intensity above their baseline pain<br>2. is present upon awakening |
| **Primary endpoint** | Pain relief at 2 hours post-treatment:<br>The proportion of participants achieving pain relief at 2 hours post-treatment in the test treatment, with no use of rescue/abortive medication (Pain relief defined as a reduction from severe to moderate, mild or none, moderate to mild or none, or mild to none) |

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| | Within-patient consistency<br>The repeatability of headache reduction, as described in the primary endpoint definition, in subsequent treated attacks. Thus, this endpoint measures the % of patient responding to the primary endpoint in at least 50% of their treated attacks<br><br>Disappearance of associated symptoms at 2 hours post-treatment<br>Disappearance of nausea, photophobia and phonophobia at 2 hours post-treatment<br><br>Functional disability at 2 hours post-treatment<br>The proportion of participants achieving improvement of at least one grade in functional disability in the test treatment at 2 hours post-treatment with no use of rescue medication<br><br>Improve of quality of life<br>Reduction in average headache disability as measured by PedsMIDAS before and at 1 month after initiation of treatment with REN. |

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| **Exploratory endpoints** | 1. Reduction in average headache intensity at 1 month after initiation of treatment with REN<br>2. Reduction in perceived stress as it relates to headache, and adverse reactions experienced as measured by HIT-6. |
| **Safety endpoints** | 1. <u>The safety of Nerivio</u><br>The incidence of adverse events in general and by seriousness, severity and association to the device.<br>2. <u>Treatment tolerability</u><br>The percent of subjects who fail to complete the study because of adverse events |
| **Datasets** | 1. Intent to treat analysis set (ITT)<br>The ITT analysis set includes all participants undergoing the treatment phase.<br>2. Modified intent to treat analysis set (mITT)<br>The mITT analysis set includes all participants undergoing the treatment phase who treat a test treatment within 60 minutes of attack onset. |
| **Data Analysis** | The ITT analysis set will be used for the primary endpoints of safety and tolerability assessments. Safety assessments will include spontaneously reported adverse events. The mITT analysis set will be used for the efficacy assessments. |

## 2. Background

REN is a novel treatment option which has successfully been shown to reduce migraine headaches in the adult population (Yarnitsky et al, 2020). There is now data to support its use in pediatrics and the device was recently FDA approved for use in pediatric migraine patients ages 12 years and older (Hershey et al, 2021). New daily persistent headache is a constant, unremitting headache disorder with clinical symptoms of migraine and/or tension-type headache and is seen in as many as 14% of pediatric and adolescents patients (Strong et al, 2021). Pediatric patients with a diagnosis of new daily persistent headache are typically resistant to standard pharmacologic treatments and often experience systemic side effects related to medications; thus, REN offers the potential for an exciting new treatment option for patients with refractory headache disorders.

## 3. Identification and description of the device information

### 3.1. Intended use

Current indication for use of the device:

The Nerivio™ is indicated for acute treatment of migraine with or without aura in patients 12 years of age or older. It is a prescription use, self-administered device for use in the home environment at the onset of migraine headache or aura.

This study aims to evaluate the effect of the Nerivio treatment in subjects with New Daily Persistent Headache (NDPH) in adolescents (12-17 years of age).

### 3.2. Device description

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

The Nerivio™ (Figure 1) includes several main components:

- A pair of electrodes covered with hydrogel and a removeable protective film
- An electronic circuitry and a battery
- A software that includes firmware and a software application for mobile platforms
- An armband to secure the attachment of the device and enable a discreet treatment

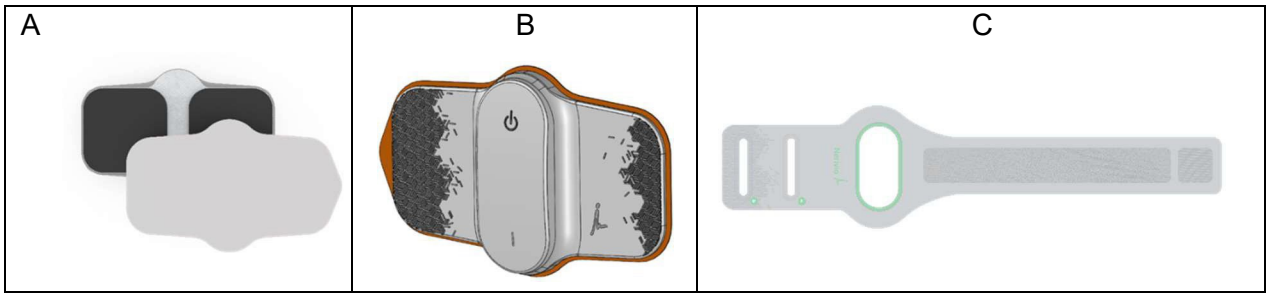


**Figure 1 - Nerivio™ device.** (A) Internal side, (B) External side, and (C) The armband

### 3.3. The application

Activation, control over stimulation intensity and termination of stimulation are performed via a dedicated smartphone application and installed on the user's cell phone. The application has a graphical user interface (GUI)ץ

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

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

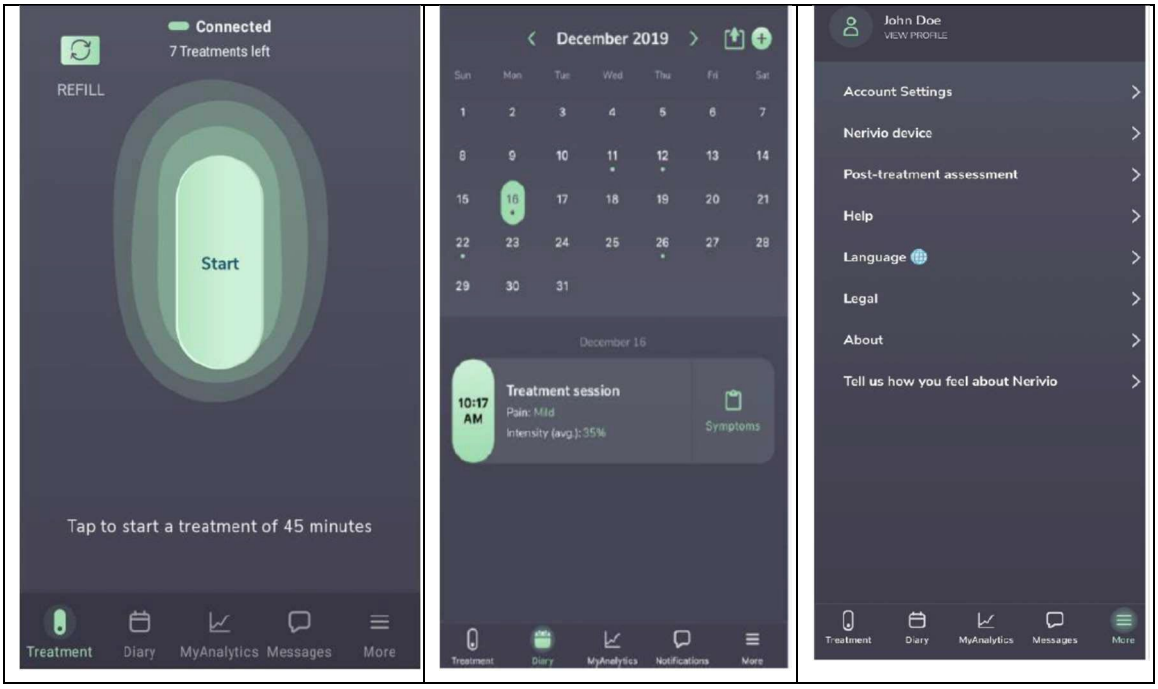

**Figure 2: The app main screens**

# 4. Objectives & hypotheses

## 4.1. Study objectives

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

## 4.2. Study hypothesis

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

# 5. Study design

## 5.1. Participants

This study will be conducted on up to 100 eligible participants.

### 5.1.1. Inclusion criteria

- Participants age 12-17 years old at the time of informed consent, inclusive.
- Participants have at least a 6-month history of headaches that meet the diagnostic criteria for New Daily Persistent Headache (NDPH)
- Participants who are on stable dosing of prophylaxis agents for at least three months.
- Participants have personal access to a smartphone (24/7)
- Participants must be able and willing to comply with the protocol
- Parents/Guardians must be able and willing to provide written informed consent
- Participants must be able and willing to provide informed assent

### 5.1.2. Exclusion criteria

- Participants with an implanted electrical and/or neurostimulator device (e.g. cardiac pacemaker, cochlear implant).
- Participants with congestive heart failure (CHF), severe cardiac or cerebrovascular disease.
- Participants with epilepsy.
- Participants who have undergone nerve block (occipital or other) in the head or neck, or treatment with onabotulinum toxin A (Botox) to the head and/or neck in the prior four months.
- Current participation in any other clinical study that includes treatment

- Participants without basic cognitive and motor skills required for operating a smartphone.
- Pregnant or breastfeeding females
- Participants who have previous experience with the device
- Participants with arm circumference below 7.9 inches (20 cm)
- Patient has, in the judgement of the investigator, a psychiatric disorder as defined by the ***Diagnostic and Statistical Manual of Mental Disorders, 5th Edition***, that would interfere with adherence to study requirements or safe participation in the trial. This includes a current or historical diagnosis of a substance use disorder.
- Patient is, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
- At Screening patient has answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) or has answered " yes " to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS, and the ideation or behavior occurred within the past month. If reports of suicidal ideation with intent to act (endorse item 4 or 5), reports of actual, aborted, or interrupted suicide attempts, or reports of behavior preparatory for an attempt are identified, the investigator is to appropriately manage the subject in accordance with standard of care.

#### 5.1.3. Withdrawal/discontinuation

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

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

- Participant is lost to follow-up
- Refusal of the participant to continue treatment and/or follow-up observations
- Serious adverse event
- Participants encountering difficulties with the investigational product (IP) (e.g. cannot tolerate the treatment, unable to operate the application)

- Significant protocol deviation/violation or noncompliance, either by the patient or the investigator
- Decision made by the investigator that termination is in the patient's best medical interest
- Device malfunction
- Other ethical or clinical considerations upon investigator discretion

### 5.2. Procedures

This open label study includes 2 phases and up to 3 visits. All visits will be conducted in the presence of a parent/guardian.

***First visit – enrollment:*** The first visit will include screening, enrollment and training on operating the headache diary within the smartphone application. The screening process will include an eligibility assessment and a urine pregnancy test (if required). Following successful screening, enrollment interview and signing an informed consent by the parent/guardian and an informed assent by the participant. The participants will be trained to use the electronic diary application, installed on their own smartphones. During this visit, participants will complete baseline questionnaires that included information on the headaches (frequency, severity, etc…), typical associated symptoms, use of preventive and abortive medications/treatments, and the effect that their headaches on their daily routine and quality of lifeThe C-SSRS will be administered at the screening visit and a "since last visit" form which will be administered at each subsequent in-clinic study visit to assess possible suicidal ideation and behavior. The C- SSRS will be scored by the investigator or Study Coordinator who has C- SSRS certification. The survey will be scored immediately after taken by participant. If reports of suicidal ideation with intent to act (endorse item 4 or 5), reports of actual, aborted, or interrupted suicide attempts, or reports of behavior preparatory for an attempt are identified, the investigator" will refer the subject for further examination.

***Phase 1 – run-in phase:*** After the enrollment visit, participants will undergo a 4-week diary phase aimed to collect baseline NDPH characteristics. Participants will be asked to report in the application each headache attack. These reports will be collected and analyzed.

***Second visit – Device training visit:*** During this visit, participants and their parent/guardian will be trained to use the device, including finding the optimal individual stimulation intensity level (perceptible but not painful).

Participants will be asked to treat their NDPH with the device using the identified optimal intensity. If the research staff recognizes that the participant cannot tolerate the feeling of the electrical stimulation, the participant may be withdrawn from the study.

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

- Treatments of headache with Nerivio™ should be performed within 60 minutes of awakening with a headache or upon increasing headache severity and always within one hour of symptoms onset. Treatments of mild headaches are accepted.
- Avoid taking rescue medications within two hours post-treatment (2 hours from start of treatment), if possible.

- The treatment should be performed for 45 minutes.

In addition, participants will complete study questionnaires, as required.

***Phase 2 –Treatment phase:*** Participants will be instructed to use the device within 60 minutes of awakening with a headache or upon increasing headache severity during a period of 4 week. Participants will be instructed to use the device with the intensity level identified during the device training visit (with a range of ±5 units) and make sure the stimulation is perceptible but not painful. Participants will be instructed to avoid taking rescue medications within 2 hours post-treatment. If medications are used, participants will be instructed to record in the app when and which medication was taken. The participants will use the app to record pain intensity levels (none, mild, moderate, or severe) at baseline and 2 hours post-treatment, and to record the presence/absence of associated symptoms (nausea, photophobia, phonophobia) at baseline and 2 hours post-treatment.

Participants who do not achieve satisfactory relief at 2 hours post-treatment may treat again with the Nerivio™ device or may treat with usual care at that time or any time thereafter if the headache does not resolve.

***Third (final) visit – End of study:*** Participants will return to the clinic following the end of the 4-week treatment phase, at which time they will return the device and complete the required questionnaires

#### 5.2.1. Study duration

The duration of the study for each participant is expected to be ~ 8 weeks.

### 5.3. Study endpoints

#### 5.3.1. Primary endpoints

1. Pain relief at 2 hours post-treatment:
   The proportion of participants achieving pain relief at 2 hours post-treatment in the test treatment, with no use of rescue/abortive medication (Pain relief defined as a reduction in pain scale from severe to moderate, mild, or none)from moderate or severe to mild or none.

#### 5.3.2. Secondary endpoints

1. Within-patient consistency
   The repeatability of headache reduction, as described in the primary endpoint definition, in subsequent treated attacks. Thus, this endpoint measures the %

of patient responding to the primary endpoint in at least 50% of their treated attacks.

2. Disappearance of associated symptoms at 2 hours post-treatment
   Disappearance of nausea, photophobia and phonophobia at 2 hours post-treatment.

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

4. Improve of quality of life
   Reduction in average headache disability as measured by PedsMIDAS before and at 1 month after initiation of treatment with REN.

#### 5.3.3. Exploratory endpoints

1. Reduction in average headache intensity at 1 month
2. Reduction in perceived stress

#### 5.3.4. Safety endpoints

1. The safety of Nerivio
   The incidence of adverse events in general and by seriousness, severity and association to the device.
2. Treatment tolerability
   The percent of subjects who fail to complete the study because of adverse events.

## 6. Statistical Considerations

### 6.1. Study design and aim

The study is designed as a prospective, open label study. This study aims to evaluate the safety and efficacy of Nerivio™ for the acute treatment of NDPH in adolescents (ages 12-17 years).

### 6.2. Sample size

100 participants

### 6.3. Analysis sets

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

***Modified intend to treat analysis set (mITT)***
The mITT analysis set includes all patients undergoing the treatment phase and treat at least one (1) treatment within 60 minutes of headache onset. Subjects with no valid post baseline assessment will not be included in the relevant analysis.

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

- has started within 60 minutes of awakening with headache or increased intensity from baseline
- was administered for 45 minutes
- includes data on headache intensity at 2 hours post-treatment
- rescue medication was not used before or within 2 hours post-treatment

***Statistical analysis of the analysis sets***

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

### 6.4. Statistical analysis

#### 6.4.1. General considerations

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

#### 6.4.2. Demographic and other baseline variables

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

#### 6.4.3. Safety analysis

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

#### 6.4.4. Efficacy analysis

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

Use of rescue medication before the 2-hours assessment will be considered a treatment failure for the 2-hours endpoints, and before the 24 hours assessment for the sustained 24-hours endpoints. The percentage of participants achieving each of the efficacy outcomes will be presented in a tabular form along with two-sided 95% exact confidence intervals.

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

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

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

## 7. Data management

### 7.1. Data capture

Data capture will be performed using electronic patient reported outcome (PRO) collection tools implemented in the smartphone application.

PRO data collected from the smartphone application will be saved in dedicated log files on the smartphones for backup purposes.

### 7.2. Records and data retention

A copy of all records (e.g., informed consent documents, source data, safety reports, study device dispensing records, etc.) which support case report forms for this study, will be retained in the files of the responsible investigator for a minimum of five (5) years.

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.

## 8. Device accountability

The devices will be provided by Theranica Bioelectronics (Netanya, ISRAEL). The device serial number will be documented when provided to the participant.

The devices will only be used in the clinical investigation and according to the study protocol.

The investigator will be responsible for providing device training to the participants according to the instructions for use. If the participant damages or loses the device, we can replace up to one device per participant, if needed. We will not request any compensation for that or hold any claims for that.

## 9. Informed consent processrescue

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

## 10. Adverse events

Adverse event (AE) is defined as any unfavorable and unintended medical change, temporally associated with the use of the Nerivio, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the device, is also an adverse experience. An adverse device effect (ADE) is an adverse event related to the use of the Nerivio device. In this study the ADE refers to side effect and complications.

A serious adverse event (SAE) is defined as an adverse event that leads to

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

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

### 10.1. Characteristics of AEs

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

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

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

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

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

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

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

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

### 10.2. Reporting of AEs and SAEs

All adverse events will be recorded in appropriate adverse events case report form. The adverse events will be used for the safety assessment.

### 10.3. Anticipated device-related AEs

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

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

All anticipated devoice-related AEs, if present, are temporary and should disappear shortly after the treatment.
The following migraine symptoms are foreseeable and will not be considered as device related: headache, nausea, light sensitivity, sensitivity to noise, allodynia, abdominal pain, loss of appetite, cold or heat sensation, paleness, fatigue, dizziness, anxious mood, fever (rare), blurred vision, vision symptoms such as bright flashing dots or lights, blind spots, wavy or jagged lines (aura).

## 11. Patient confidentiality & data protection

The privacy of the participants and the confidentiality of all personal data will be maintained in reports and publications and will not be otherwise published in any way.
The privacy will be maintained according to prevailing national data protection, privacy and secrecy laws. Each patient will be identified by a unique patient identification number.

## 12. Guidelines and applicable documents

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

## 13. Reference