DE NOVO CLASSIFICATION REQUEST FOR NERIVIO MIGRA

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Trunk and limb electrical stimulator to treat headache. A trunk and limb electrical stimulator to treat headache is a device intended to treat headache through the application of electrical stimulation anywhere on the body of the patient apart from the patient's head or neck through electrodes placed on the skin. The stimulation may be provided transcutaneously or percutaneously.

NEW REGULATION NUMBER: 21 CFR 882.5899

CLASSIFICATION: Class II

PRODUCT CODE: QGT

BACKGROUND

DEVICE NAME: Nerivio Migra

SUBMISSION NUMBER: DEN180059

DATE OF DE NOVO: November 6, 2018

CONTACT: Theranica Bio-Electronics LTD.
45 Ha-Melakha St.
Netanya, Israel 4250574

INDICATIONS FOR USE

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

LIMITATIONS

The sale, distribution, and use of the Nerivio Migra are restricted to prescription use in accordance with 21 CFR 801.109.

The safety and effectiveness of the device has not been demonstrated for subjects with chronic migraine.

The safety and effectiveness of the device has not been demonstrated for the preventive treatment of migraine headache.

The device should not be used by people with congenital heart failure (severe cardiac or cerebrovascular disease.

The device should not be used by people with uncontrolled epilepsy.

The device should not be used by people with active implantable medical device, such as a pacemaker, hearing aid implant, or any implanted electronic device. Such use could cause electric shock, electrical interference or serious injuries or medical conditions.

The device has not been evaluated for use in pregnant women and people less than 18 years of age.

Please refer to the labeling for a more complete list of contraindications, warnings, and precautions.

DEVICE DESCRIPTION

The Nerivio Migra is a wearable, battery-powered device that is controlled by a mobile application. The system delivers low energy electrical pulses to the upper arm for 45 minutes per treatment, after which the device turns off automatically.

The device hardware consists of an armband intended to be worn on a user's upper arm. The armband contains the electronic circuitry and the battery in a plastic storage case as well as two electrodes that are attached to the interior of the armband and placed against the user's skin.

The device is operated and controlled via software that is installed and run on a user's personal mobile device such as a mobile phone or tablet. The device hardware communicates with the mobile application through a Bluetooth protocol. This mobile application software allows the user to control the stimulation intensity from 0 to 100% (representing intensity levels of 0-40mA), to start or stop the stimulation program, and to view device status such as the device's connection state, a progress bar for stimulation duration, battery level, and user notifications.

The patient is instructed to adjust the intensity to the strongest stimulation level below the perceived pain level. Treatments with Nerivio Migra are intended to be self-administered by the user immediately after the onset of migraine headache or aura.

The basic pulse structure is biphasic, with symmetrical interleaving phases and rectangular shape. The amplitude shift signal alternates between a nominal maximum and a nominal minimum of the amplitude signal. The maximal output current is 40mA. The assumed impedance is 1K ohm +/- 500 ohms.

Output parameters and other electrical specifications of the Nerivio Migra are presented below in Table 1.

Parameter	Specification
Number of channels	1
Waveform	Biphasic rectangular, modulated
Net Charge (µC per pulse)	0 (charge is balanced using a symmetrical, biphasic pulse)
Max output voltage 500Ω 2KΩ 10KΩ	 20V (measured) 60V (measured) 60V (measured)
Max output current 500Ω 2KΩ 10KΩ	 40mA 30mA 6mA
Maximum phase charge (500Ω)	8µC
Maximum average current (500Ω)	1.76mA
Maximum current density (peak) (500Ω)	1.6mA/cm^2
Maximum current density (r.m.s) (500Ω)	0.34mA/cm
Maximum average current density (abs value) (500Ω)	0.07mA/cm^2
Maximum average power density (500Ω)	1.41mW/cm^2
Frequency	100-120Hz, average 110Hz (measured)
Primary phase duration [µSec]	200
Pulse Duration [µSec]	400
Burst mode	No
Program duration [min]	45
Electrode Area	25cm^2

Electrode compliance with 21 CFR 898	Yes	
Electrode cable	No	
Indication Display	Device LED, on/off switch	Mobile Application
- On/off status - Wireless connection - Low battery - Current level - Output mode - Time to cut-off	- Yes (LED, switch position) - Yes - No - No - Yes - No	- No - Yes - Yes - Yes (stimulation intensity) - Yes (stimulation time bar) - Yes (stimulation time bar)
Power Source	Lithium ion battery Operating time: 360 minutes (8 treatments of 45 min)	
Processor control	Yes	
Wireless control	Yes	
Automatic overload trip	Yes, limiter for max current and voltage	
Automatic no load trip	Yes, out-of-range load detection	
Automatic shut off	Yes, timer	
Stimulation intensity control	Yes, current amplitude is adjusted by the user	

Table 1: Nerivio Migra output parameters

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The Nerivio Migra is connected to the patient's intact skin for a treatment period of 45 minutes. The skin-contacting components of the Nerivio Migra are the following:

- Electrodes with hydrogel that have been FDA cleared through K130987

(b) (4)

The Nerivio Migra has demonstrated biocompatibility by design because these off-the-shelf devices have been previously evaluated for cytotoxicity, irritation and sensitization, per ISO 10993-1 "Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process" and per recommendations in FDA's guidance document entitled, "Use of International Standard ISO 10993-1, "Biological evaluation of

medical devices - Part 1: Evaluation and testing within a risk management process." All results demonstrated acceptable performance.

SHELF LIFE AND STERILITY

The Nerivio Migra has a shelf life of 9 months.

There are no sterilization requirements for the marketed device and the user does not sterilize the device before first or repeat uses. The electrodes are non-sterile and designed for multiple usages. The electrode cover is reusable. Cleaning and maintenance instructions for the device are included in the labeling.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The Nerivio Migra was tested according to the following FDA-recognized consensus standards:

- IEC 60601-1-2, Issue: 2014/02/25 Ed:4.0 (Equivalent to AAMl/ANSI/IEC 60601-1-2:2014) "Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance -Collateral Standard: Electromagnetic disturbances - Requirements and Tests." Results demonstrated that the device is compliant to this standard.
- AAMl/ANSI ES60601-1:2005/(R)2012 and C1:2009/(R)2012 and, A2:2010/(R)2012 "Medical Electrical Equipment; Part 1: General requirements for basic safety and essential performance."
- IEC 60601-1-11:2015 “Medical electrical equipment: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment.”
- IEC 60601-2-10: 2012 and A1:2016 “Medical Electrical Equipment Part 2-10: Particular requirements for the basic safety and essential performance of nerve and muscle stimulators.”

SOFTWARE

A failure in the software of the Nerivio Migra could indirectly result in patient injury; therefore, the software of this device is considered to have a “Moderate” level of concern.

The submission contained all the elements of software documentation corresponding to a “Moderate” level of concern, as outlined in the FDA guidance document “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.” Adequate documentation describing the software, firmware, software specifications, architecture design, software development environment, traceability, revision level history, unresolved anomalies and cybersecurity provides the foundation that the software will operate in a manner as described in the specifications. A hazard analysis was performed to characterize software risks including device malfunction and measurement related errors. The submission included verification and validation (V&V) testing to address the potential hazards with satisfactory results.

ADDITIONAL PERFORMANCE TESTING

The following additional testing was performed:

- **Wireless Coexistence Testing**

  The device hardware communicates with the mobile application through a Bluetooth protocol and it is intended to be used in the home environment. Thus, a wireless Quality of Service and corresponding wireless coexistence testing was provided per with the FDA Guidance: Radio Frequency Wireless Technology in Medical Devices. Results demonstrated that the system meets specifications.

- **Lithium-Ion Battery Testing**

  The Nerivio Migra is powered by a Lithium-Ion battery AE503759P6H, 3.7V, 1.2 Ah. The battery is internal, integrated inside an enclosure, and cannot be charged or accessed by the user. The battery is charged outside of the device at the time of the device's manufacturing, then placed inside the enclosure of the device, which is sealed. The battery complies with the UL-1642 (Standard for Lithium batteries), IEC 62133-2 (Standard for lithium batteries), and IEC 60601-1 (Basic Safety).

- **Electrical Stimulation Output Characterization:**

  Testing was performed to characterize the stimulation output waveform, the functionality of the Nerivio Migra as a system, and the requirements of the output stimulation parameters. Results demonstrated that the system meets specifications.

- **Electrode Bench Testing:**

  Testing was performed to assess the mechanical measurements, the design of the electrodes (and tolerances) and the electrical characteristics (impedance and current distribution) of the electrodes under the expected worst-case conditions of normal operation. Results demonstrated that the electrodes passed all testing.

SUMMARY OF CLINICAL INFORMATION

Study Overview

The 252-subject pivotal study was a prospective, one-to-one randomized, double-blind, sham controlled multi-center study to evaluate the effectiveness and safety of Nerivio Migra. The neurostimulation amplitude for the treatment group was based on each subject's stimulation threshold. The sham group received different, "no-activation pseudo-amplitude" stimulation, which reached the subject's stimulation threshold. The study site personnel and investigator were blinded to the subject's therapy allocation. Subjects recorded migraine severity before treatment, 2 hours and 48 hours following the treatment using various metrics. Safety was assessed using adverse event data collected during the study.

Inclusion Criteria

1. Subjects age 18 through 75 years of age
2. Subjects meet the ICHD-3 diagnostic criteria for migraine with or without aura
3. Subjects report 2-8 migraine attacks per month.
4. No change in usage or dosage of migraine preventive medications for two months prior to study entry.
5. Subjects must be able and willing to comply with the protocol.
6. Subjects must be able and willing to provide written informed consent.

Exclusion Criteria

1. Subject has other significant pain, medical or psychologic problems that in the opinion of the investigator may confound the study assessments
2. Subject has an implanted electrical or neurostimulation device. These devices include a 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. Subject has known uncontrolled epilepsy.
4. Any use of Cannabis including medical use
5. Subject has more than 12 headache days per month.
6. Subject has undergone nerve block (occipital or other) in the head or neck within the last 2 weeks.
7. Participant is participating in any other clinical study.
8. The participant does not have the basic cognitive and motor skills needed to operate a smartphone.
9. Pregnant, or trying to get pregnant or lactating women.
10. Female subject experiencing only menstrual related migraine (migraines during menstrual period only).
11. Received any botulinum toxin injections for migraine within the previous month.
12. Received parenteral infusions for migraine within the previous 2 weeks.
13. Participant participated in a previous study with the Nerivio Migra device.

Study Endpoints

Safety:

Adverse event types and rates for all enrolled subjects.

Effectiveness:

The primary outcome measure was the percentage of participants reporting a reduction in their pain level without use of medication from severe or moderate to mild or no pain or from mild to no pain within 2 hours in the "test treatment" excluding the run-in treatment which was the first in-study migraine attack.

The secondary effectiveness outcome measures are the proportion of participants who did not take medications and reported:

1. A reduction in their most bothersome symptom (MBS) at 2 hours post-treatment. MBS may be nausea, photophobia, or phonophobia– as defined by each participant at the beginning of the treatment.
2. A reduction in pain and their MBS at 2 hours post-treatment
3. Freedom from pain at 2 hours post-treatment
4. Freedom from their MBS at 2 hours post-treatment.

Protocol (study design)

The 252-subject study included three phases: Phase One – Roll In, Phase Two – Parallel arm, double-blind treatment phase, and Phase Three – Optional Open-label extended treatment.

In the first ("roll-in") phase, participants were asked to keep a headache diary for one month in which all migraines were documented. Eligible participants were trained to use the smartphone migraine diary application for up to one month. Only participants who properly reported at least 2 and no more than 8 migraine attacks continued to the next phase.

The second phase was a double-blind treatment phase, in which eligible participants were randomly allocated in a 1:1 ratio to either active stimulation (treatment group) or sham pseudo-stimulation (sham group). All participants underwent training on how to use the device and how to use the diary and feedback application. During this training, an optimal individual stimulation intensity level ("well perceived but not painful") was identified for each participant (treatment and sham). Participants in both groups were then asked to treat their migraines for 6 weeks, or up to 4 qualified migraine attacks, using the device with the identified stimulation intensity (±5%). Participants were asked to treat each migraine within 60 minutes of symptom onset. The participants used the application to record pain scores at baseline, 2 hours post-treatment and 48 hours post-treatment, to record the presence/absence of associated migraine symptoms (nausea, photophobia, phonophobia), to define their Most Bothersome Symptom (MBS) prior to each treatment and to record if there is a relief in their MBS following the treatment. The first reported treatment was considered a "run-in test" treatment, aimed to verify the participants use the device properly, and was only included in the safety analysis. The effectiveness evaluation was performed on the first fully treated (30-45 minutes) attack with 2 hours post-treatment assessment following the "run-in test" treatment (hereby termed test treatment).

Phase Three was an optional, open-label extension phase. Following the completion of double-blind treatment phase of the study, all participants were offered to participate in a 2-month open-label period using an active device.

Sham Design

The sham device produced a perceptible signal, in which the sponsor implemented pseudo-random pulses, which have a relatively long duration in order to generate an "electrical sensation" for the participant and enable him/her to adjust the intensity as done in the active program.

Overall, both the active and the sham devices generated a similar sensation. Participants did not distinguish between the treatment and sham device.

The first time participants were introduced to the device was in the randomization visit, which occurred after the "roll-in" phase. During the "roll-in" phase, the participants only used the mobile application (without the device) to report their migraine attacks.

Statistical Analysis Plan (SAP)

- Analysis sets

1. **Intent to treat analysis set (ITT)**
   The ITT analysis set included all participants who were randomized. In accordance with the ITT principle, all participants randomized were kept in their originally assigned group.
2. **Modified intend to treat analysis set (mITT)**
   The mITT analysis set included all participants who were randomized and treated at least one attack (excluding the run-in test attack) within 1 hour from the attack onset.
3. **Per-protocol analysis set (PP)**
   The PP analysis set included participants who were randomized and for whom the first qualified attack (excluding the "run-in" test attack) conformed with the protocol instructions:
   - The treatment starts within one hour from attack onset.
   - No rescue medication (or pain medication) is consumed within 2 hours after start of treatment.
   - The treatment was not stopped early (i.e., before the first 30 minutes).
   - No pain medication consumption 24 hours prior to the onset of the migraine

- Statistical analysis of the analysis sets:

1. The ITT analysis set served as the main set for safety assessments
2. The mITT analysis set was used for all effectiveness assessments.
3. The primary and secondary effectiveness assessments were performed on the mITT analysis set and also on the PP and ITT analysis sets as a sensitivity analysis to assess the effect of protocol deviation and discontinuations

- Safety Analysis

  Adverse event (AE) rates were presented on all enrolled subjects, overall as well as by treatment group. The rates of events and type were presented and compared between groups using the Fisher's Exact test.

- Blinding Assessment

  The success of the blinding of subjects was assessed at the end of the study visit using a blinding assessment questionnaire. Subjects were asked whether they thought they were in the active or sham group or if they did not know using a three-point scale (active, sham or I don't know).

- Effectiveness analysis

Primary effectiveness analyses:

The primary outcome measure was the proportion of participants with a decrease in headache pain from severe or moderate to none or mild or from mild to no pain within 2 hours in the test treatment. The percentage of participants reporting such headache pain reduction without rescue medications was assessed in both study groups and was compared using a chi-squared test and a Fisher's exact test.

Secondary effectiveness analyses:

The secondary effectiveness variables were compared with a chi-squared test and a Fisher's exact test.

Study Results

- Subject Disposition

A total of 296 participants were recruited to the study, 252 participants were randomized at the end of the roll-in phase. Of these, 126 eligible participants were randomly assigned to receive active Nerivio Migra device (active group) and 126 were randomly assigned to receive sham Nerivio Migra device (sham group). Among the 252 randomized participants, 7 participants withdrew from the study (4 in the active group and 3 in the sham group); 3 participants (1 from the sham group and 2 from the active group) withdrew from the study due to intolerance to the sensation of the stimulation (two participants withdrew during the randomization visit after the training, so the devices were never used at home), and 4 participants (2 in the active group and 2 in the sham group) were lost to follow up. A total of 237 participants completed at least one treatment (the run-in treatment) and 202 participants completed the test treatment within one hour from symptom onset and reported a pain level at 2 hours (Figure 1). A modified intent to treat (mITT) group was defined as all randomized subjects who treated at least one attack (excluding the "run-in test" attack) within 1 hour from the attack onset.

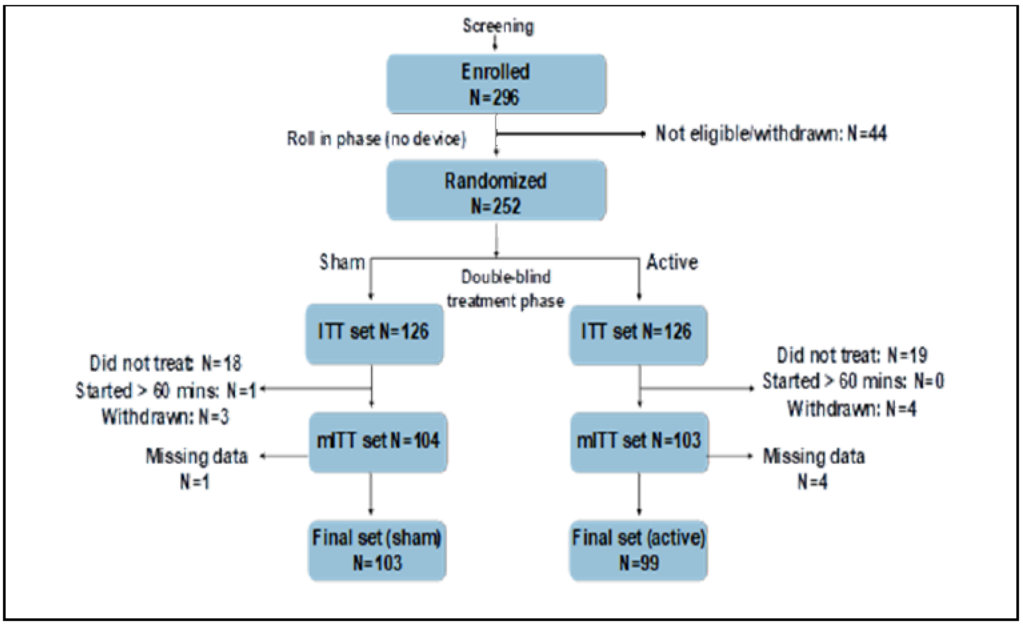

Figure 1: Participant disposition

- Subject Demographics

  The majority of participants were female (80.7%), and the mean age was 42.7±12.06 years. The demographic characteristics were generally similar among treatment groups (Table 2) and comparable to those reported in previous migraine studies. Migraine history and characteristics of the active and sham groups were comparable (Table 3).

		All	Active	Sham	Nominal P value
Gender	**Male**	19.4% (49/252)	19.8% (25/126)	19.0% (24/126)	0.9753
	Female	80.6% (203/252)	80.2% (101/126)	81.0% (102/126)	
Race	**Caucasian****	87.7% (221/252)	86.5% (109/126)	88.9% (112/126)	0.6595
	American Indian or Alaskan	0%	0%	0%	
	Asian	0.8% (2/252)	1.6% (2/126)	0%	
	African-American	7.1% (18/252)	8.1% (10/124)	6.3% (8/126)	
	Native Hawaiian	0.8% (2/252)	0.8% (1/126)	0.8% (1/126)	
	African Arab or Eastern Arabs	1.2% (3/252)	1.6% (2/126)	0.8% (1/126)	
	Other	2.4% (6/252)	1.6% (2/126)	3.2% (4/126)	
Age	**N**	252	126	126	0.1462
	Mean (SD)	42.7 (12.06)	43.8 (12.25)	41.6 (11.81)	
	Median [range]	41.8 [18.5; 70.1]	43.5 [18.5; 70.1]	40.8 [19.3; 66.9]	
Height	**N**	250	124	126	0.9730
	Mean (SD)	166.4 (9.00)	166.4 (9.46)	166.4 (8.56)	
	Median [range]	165.1 [130; 190]	165.1 [130; 190]	165.6 [147; 185]	
Weight	**N**	252	126	126	0.8182
	Mean (SD)	75.4 (18.79)	75.1 (20.47)	75.6 (17.03)	
	Median [range]	72.2 [39.0; 160.0]	71.7 [39.0; 160.0]	[46.0; 142.0]	

Table 2: Demographic characteristics (ITT)

		All	Active	Sham	Nominal P value
Average Number of Attacks per Month	**N**	251	126	125	0.8505
	Mean (SD)	5.3 (1.92)	5.2 (1.95)	5.3 (1.90)	
	Median [range]	5.0 [2.0; 9.0]	5.0 [2.0; 8.0]	5.0 [2.0; 9.0]	
Average number of migraine days per month	**N**	251	126	125	0.9559
	Mean (SD)	6.6 (2.40)	6.6 (2.43)	6.6 (2.41)	
	Median (range)	7.0 [2.0;12.0]	7.0 [2.0; 12.0]	7.0 [2.0; 12.0]	
Use of preventive medication		32.8% (82/250)	28.6% (36/126)	37.1% (46/124)	0.1511
aura preceding a migraine attack	**None**	50.2% (125/249)	49.6% (62/125)	50.8% (63/124)	0.6639
	Rarely	22.5% (56/249)	20.8% (26/125)	24.2% (30/124)	
	Often	27.3% (68/249)	29.6% (37/125)	25.0% (31/124)	
Average attack duration without medication	**0-2h**	2.4% (6/250)	3.2% (4/125)	1.6% (2/125)	0.3665
	2-6h	8.8% (22/250)	9.6% (12/125)	8.0% (10/125)	
	6-12h	14.8% (37/250)	10.4% (13/125)	19.2% (24/125)	
	12-24h	18.8% (47/250)	21.6% (27/125)	16.0% (20/125)	
	24-48	28.4% (71/250)	29.6% (37/125)	27.2% (34/125)	
	>48h	26.8% (67/250)	25.6% (32/125)	28.0% (35/125)	
Use of acute medication	**Always**	71.3% (179/251)	72.2% (91/126)	70.4% (88/125)	0.9767
	Sometimes	24.3% (61/251)	23.8% (30/126)	24.8% (31/125)	
	Rarely	2.8% (7/251)	2.4% (3/126)	3.2% (4/125)	
	Never	1.6% (4/251)	1.6% (2/126)	1.6% (2/125)	
Average attack duration with medication	**0-2h**	36.4% (90/247)	36.3% (45/124)	36.6% (45/123)	0.7547
	2-6h	36.4% (90/247)	35.5% (44/124)	37.4% (46/123)	
	6-12h	8.5% (21/247)	8.9% (11/124)	8.1% (10/123)	
	12-24h	7.3% (18/247)	8.1% (10/124)	6.5% (8/123)	
	24-48	6.5% (16/247)	4.8% (6/124)	8.1% (10/123)	
	>48h	4.9% (12/247)	6.5% (8/124)	3.3% (4/123)	
Most bothersome migraine symptom beyond pain	**None**	2.0% (5/250)	3.2% (4/125)	0.8% (1/125)	0.0617
	Nausea	27.2% (68/250)	29.6% (37/125)	24.8% (31/125)	
	Light	50.0% (125/250)	43.2% (54/125)	56.8% (71/125)	
	Sound	19.2% (48/250)	20.8% (26/125)	17.6% (22/125)	
	Skin Sensitivity	1.6% (4/250)	3.2% (4/125)	0% (0/125)	

Table 3: Migraine history

- Safety endpoint

  Safety analyses were performed on all 252 participants from the ITT population. 773 treatments were performed during the study (including the run-in treatment). The percentage of participants with at least 1 adverse event (regardless of its suspected cause) was 13.5% (34/252) and was comparable across treatment groups (15.1% (19/126) in the active group and 11.9% (15/126) in the sham group, $p_{Fisher's}$=0.5807). The incidence of device-related adverse events was low (3.6%), and similar between treatment groups (active group: 6/126 [4.8%]; sham group: 3/126 [2.4%]; $p_{Fisher's}$=0.4998). Notably, there were no unanticipated adverse device effects.

  23 device-related adverse events were reported during 773 treatments (2.7%), 14 in the active group and 9 in the sham group. All device-related adverse events reported were mild in severity, did not require treatment and were resolved. No serious adverse events related to the device were reported. No statistically significant differences were found between treatment groups in either the type or rate of adverse events during the double-blind treatment phase (Table 4).

	All	Active	Sham
Sensation of warmth	9/773 (1.2%)	6/385 (1.6%)	3/388 (0.8%)
Numbness of the arm/hand	2/773 (0.2%)	2/385 (0.5%)	0/388 (0%)
Redness	3/773 (0.4%)	2/385 (0.5%)	1/388 (0.3%)
Itching	1/773 (0.1%)	1/385 (0.2%)	0/388 (0%)
Neck and shoulder pain	2/773 (0.2%)	0/385 (0%)	2/388 (0.8%)
Pain in the arm	2/773 (0.2%)	2/385 (0.5%)	0/388 (0%)
Tingling	3/773 (0.4%)	0/385 (0%)	3/388 (0.8%)
Muscle spasm	1/773 (0.1%)	1/385 (0.2%)	0/388 (0%)

Table 4: TCH-003 Device-related adverse events

- Primary effectiveness outcome

  In the mITT analysis set (i.e., all participants who were randomized and treated at least one attack [excluding the run-in test attack] within 1 hour from the attack onset), the proportion of participants achieving a pain-reduction response 2 hours after treatment in the test treatment was 66.7% (66/99) in the active group compared with 38.8% (40/103) in the sham group (therapeutic gain 27.9%; $p_{chi\text{-}squared}<0.0001$. $p_{Fisher's}<0.0001$; Table 5). Similar results were obtained in the per-protocol analysis and in the ITT analysis (Table 5). The active treatment was also superior to the sham for the reduction of pain for each one of the possible baseline pain levels (severe, moderate, and mild).

Analysis set	All	Active	Sham	P value (Chi-squared test)	P value (Fisher's exact test)
mITT	**52.5% (106/202)**	**66.7% (66/99)**	**38.8% (40/103)**	**p<0.0001**	**p<0.0001**
PP	**53.8% (106/197)**	**67.3% (66/98)**	**40.4% (40/99)**	**p<0.0001**	**p<0.0002**
ITT	**52.7% (107/203)**	**66.7% (66/99)**	**39.4% (41/104)**	**p<0.0001**	**p<0.0002**

Table 5: TCH-003 Primary endpoints results for the mITT, PP and ITT sets

The percentage of participants who took rescue medication within 2 hours post-treatment was small in both groups (4/103=3.9% in the sham group and 1/99=1.0% in the active group). For the analysis of this endpoint, patients who used rescue medication before or within the 2 hours post-treatment were considered failures.

- Secondary effectiveness endpoints

  In the mITT dataset, the active stimulation treatment was more effective than the sham treatment for the proportion of participants achieving 2 hours of MBS relief (46.3% vs. 22.2%; p=0.0.0008) and for the proportion of participants who achieved both headache pain reduction and MBS relief at 2 hours post-treatment (40.0% vs. 15.2%; p=0.0004. For pain-free 2 hours post-treatment, the active device was superior to the sham device, with statistical significance (37.4% vs. 18.4%; p=0.0036). There was no significant difference between active and sham treatment for MBS-free 2 hours post-treatment (40.7% vs. 36.4%; p=0.0.55) (Table 6).

Secondary endpoint	Analysis Set	All	Active	Sham	P value (Chi-squared test)	P value (Fisher's exact test)
Secondary EP # 1: MBS relief 2 hours post-treatment	**mITT**	34.0% (66/194)	46.3% (44/95)	22.2% (22/99)	0.0008	0.001
	PP	34.6% (66/191)	46.8% (44/94)	22.7% (22/97)	0.0009	0.0010
	ITT	33.8% (66/195)	46.3% (44/95)	22.0% (22/100)	0.0007	0.0009
Secondary EP #2: headache relief and MBS relief 2 hours post-treatment	**mITT**	27.3% (53/194	40.0% (38/95)	15.2% (15/99)	0.0004	0,0004
	PP	27.7% (53/191)	40.4% (38/94)	15.5% (15/97)	0.0005	0.0007
	ITT	27.2% (53/195)	40.0% (38/95)	15.0% (15/100)	0.0004	0.0004
Secondary EP#3: MBS disappearance 2 hours post-treatment	**mITT**	38.5% (65/169	40.7% (33/81)	36.4% (32/88)	0.5590	0.6355
	PP	39.2% (65/166)	40.7% (33/81)	37.6% (32/85)	0.6831	0.7511
	ITT	38.8% (66/170)	40.7% (33/81)	37.1% (33/89)	0.6246	0.6399
Secondary EP #4: headache disappearance 2 hours post-treatment	**mITT**	27.7% (56/202)	37.4% (37/99)	18.4% (19/103)	0.0036	0.0039
	PP	28.4% (56/197)	37.8% (37/98)	19.2% (19/99)	0.0052	0.0060
	ITT	27.6% (56/203)	37.4% (37/99)	18.3% (19/104)	0.0031	0.0037

Table 6: Secondary endpoints results for the mITT, PP and ITT sets

- Aura – subgroup analysis

  To evaluate the effectiveness of the treatment as a function of presence/absence of aura, the pain reduction and pain free responses at 2 hours post-treatment were evaluated in the mITT set for attacks with aura and attacks without aura.

  The proportion of participants with aura achieving a pain-reduction response 2 hours after treatment was 63.2% and 35.9% in the active and sham groups, respectively. The proportion of participants without aura achieving a pain-reduction response 2 hours after treatment in the aura group was 67.5% and 39.8% in the active and sham groups, respectively. The proportion of participants with aura achieving pain-free response 2 hours after treatment was 36.8% and 20.0% in the active and sham groups, respectively. The proportion of participants without aura achieving pain-free response 2 hours after treatment in the aura group was 37.5% and 18.1% in the active and sham groups, respectively

- Blinding assessment

  At the end of the double-blind treatment phase, participants were asked to indicate to which group they thought they were assigned to (active, sham, do not know).

  The results indicate that a significant percentage of the population did not know to which group they were assigned (44.6% [50/112] in the active group and 41.9% [49/117] in the sham group). In the active group, 23.2% (26/112) of the participants believed they had received the active device and 32.1% (36/112) believed they had received the sham device. In the sham group, 50.4% (59/117) believed they had received the sham device and 7.7% (9/117) believed they had received the active device. Furthermore, after adjusting the primary endpoint for the participants' responses, the difference between the groups was still highly statistically significant (p=0.0039, mITT analysis set). The p-value of the

Breslow-Day test for homogeneity of the odds ratios across the "responses" groups (i.e., active, sham, do not know) was 0.9114, confirming that the treatment assigned response by the participants did not meaningfully impact the primary endpoint results.

- Study limitations

  1. Study population did not include chronic migraineurs. Chronic migraineurs may respond different to the Nerivio Migra
  2. Study population did not have any other implanted electrical devices.
  3. Effectiveness of the Nerivio Migra was evaluated only when used within one hour from migraine symptoms onset.

Labeling

The labeling consists of a User Manual (separate Android and iOS Versions) and information on the website (www.theranica.com).

The labeling is sufficient and meets the requirements of 21 CFR 801.109. It contains the indications for use, contraindications, warnings, precautions, device description, instructions for use and typical sensations experienced during treatment, a summary of the electrical stimulation output and device technical parameters, instructions on care and cleaning of the device, summary of clinical trials (website only), information related to electromagnetic compatibility and wireless specifications, expected service life, shelf-life, reuse, and disposal information, environmental operating conditions, and symbols & markings.

RISKS TO HEALTH

Table 7 below identifies the risks to health that may be associated with use of the trunk and limb electrical stimulator to treat headache and the measures necessary to mitigate these risks.

Table 7: Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Adverse tissue reaction	Biocompatibility evaluation
Electrical, mechanical, or thermal hazards that may result in user discomfort or injury (e.g., electrical shock or burn)	Non-clinical performance testing Electrical, mechanical, and thermal safety testing Electromagnetic compatibility (EMC) testing Software verification, verification, and hazard analysis Labeling
Interference with other devices	Electromagnetic compatibility (EMC) testing Labeling
Software malfunction leading to injury or discomfort (e.g., tissue damage due to over-stimulation)	Software verification, validation, and hazard analysis
Hardware malfunction leading to injury or discomfort	Non-clinical performance testing Shelf life testing Labeling
Use error that may result in user discomfort, injury, or delay treatment for headaches	Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the trunk and limb electrical stimulator to treat headache is subject to the following special controls:

1) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. This testing must include:
    a) Characterization of the electrical stimulation, including the following: waveforms; output modes; maximum output voltage and maximum output current (at 500Ω , 2kΩ, and 10kΩ loads); pulse duration; frequency; net charge per pulse; and maximum phase charge, maximum current density, maximum average current, and maximum average power density (at 500Ω);
    b) Characterization of the impedance monitoring system; and
    c) Characterization of the electrode performance including the electrical performance, adhesive integrity, shelf-life, reusability, and current distribution of the electrode surface area.
2) The patient-contacting components of the device must be demonstrated to be biocompatible.
3) Performance testing must demonstrate electromagnetic compatibility and electrical, mechanical and thermal safety in the intended use environment.
4) Software verification, validation, and hazard analysis must be performed.
5) Labeling must include the following:

a) Instructions for use, including the typical sensations experienced during treatment;

b) A detailed summary of the electrical stimulation output, and the device technical parameters, including any wireless specifications;

c) A shelf life for the electrodes and reuse information; and

d) Instructions on care and cleaning of the device.

BENEFIT/RISK DETERMINATION

The risks of the device are based on nonclinical studies (e.g., biocompatibility, electrical safety, EMC, and software testing) as well as data collected in the clinical study described above. The results of the nonclinical testing demonstrated that the device performed as per specifications and the results did not raise concerns regarding risks to the patients.

The safety analyses of the clinical study were performed on all 252 participants from the ITT population. 773 treatments were performed during the study (including the run-in treatment). The percentage of participants with at least 1 adverse event (regardless of its suspected cause) was 13.5% (34/252) and was comparable across treatment groups (15.1% (19/126) in the active group and 11.9% (15/126) in the sham group, pFisher's=0.5807). The incidence of device-related adverse events was low (3.6%), and similar between treatment groups (active group: 6/126 [4.8%]; sham group: 3/126 [2.4%]; pFisher's=0.4998). All adverse events were mild, anticipated, and resolved within 24 hours without any intervention or sequelae. Specifically reported were sensation of warmth, numbness of arm, redness, itching, tingling, pain and muscle spasm

Should any adverse reactions occur, the Nerivio Migra therapy level can be reduced (e.g., turning down stimulation level or shut down the device). In addition, the device is easily removed from the patient's upper arm.

The probable benefits of the device are based on data collected in the clinical study. There are statistically and clinically meaningful probable benefits of the device. All endpoints reached a statistically significance difference in favor of active over sham except Secondary Endpoint 3 (MBS disappearance at 2 hours post-treatment). The summary of results presented below uses the ITT analysis population.

- Primary endpoint: The study showed that active stimulation with Nerivio Migra is more effective than sham stimulation for the treatment of migraine with or without aura. 66.7% of participants in the active group showed pain reduction at 2 hours post-treatment compared to 39.4% in the sham group (pFisher's<0.0002); thus, the therapeutic gain in the active group of pain reduction at 2 hours post-treatment was 27.3%.
- Secondary endpoints: The active treatment was favored in the following secondary endpoints.
    - At Secondary Endpoint 1, most bothersome symptom (MBS) relief at 2 hours post -treatment, the therapeutic gain between groups was 24.3% in favor of active (pFishers=0.0009). This change may be of clinical significance.

- At Secondary Endpoint 2, pain reduction and MBS relief at 2 hours post-treatment, the therapeutic gain between groups was 25% in favor of active (pFishers=0.0005). This change may be of clinical significance.
- At Secondary Endpoint 3, MBS disappearance at 2 hours post-treatment, the therapeutic gain of 3.6% in favor of active did not reach statistical significance (pFishers=0.6399). This change is not of clinical significance.
- At Secondary Endpoint 4, pain freedom at 2 hours post-treatment, the therapeutic gain was 19.1% in favor of active (pFishers=0.0037). This change is not of clinical significance.

Thus, Nerivio Migra provides clinically meaningful relief from migraine pain and associated symptoms.

Patient Perspectives

Patient perspectives considered for the Nerivio Migra included an assessment of patients' impression. At the end of the study, participants received a post-study questionnaire to assess their satisfaction with the device. Favorable responses to device ease of use were obtained in 91.3% of the participants.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support that for acute treatment of migraine with or without aura in patients 18 years of age or older who do not have chronic migraine, the probable benefits outweigh the probable risks for the Nerivio Migra. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Nerivio Migra is granted and the device is classified under the following:

Product Code: QGT
Device Type: Trunk and limb electrical stimulator to treat headache
Class: II
Regulation: 21 CFR 882.5899