Neurolief

Abridged Clinical Investigation Plan

Clinical Investigation Plan/Study Title	The RIME study - Combined occipital and supraorbital transcutaneous nerve stimulation for treatment of migraine
Clinical Investigation Plan Identifier	SP-302-RIME
Study Product Name	Relivion™
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1. Glossary

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
CAPA	Corrective and Preventive Action
CFR	Code of Federal Regulation
CIP	Clinical Investigation Plan
CP	Conditional Power
CRF	Case Report Form
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
ePRO	electronic Patient Reported Outcome
FDA	Food and Drug Administration
HEENT	Head, Eye, Ear, Nose and Throat
ICHD	International Classification of Headache Disorders
IEC	International Electrotechnical Commission
IRB	Institutional Review Board
ISO	International Organization of Standardization
ITL	Israel Testing Laboratories
ITT	Intent to Treat
MBS	Most Bothersome migraine-related Symptom
mITT	modified Intent to Treat
NSR	Non-Significant Risk
ONS	Occipital Nerve Stimulation
OS-TNS	Occipital and Supraorbital Transcutaneous Nerve Stimulation
OUS	Outside United States
P/N	Part Number
PNS	Peripheral Nerve Stimulation
PRO	Patient Reported Outcome
RA	Return Authorization
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TENS	Transcutaneous Electrical Nerve Stimulation
UM	User Manual
US	United States
U(S)ADE	Unanticipated (Serious) Adverse Device Effect
VAS	Visual Analog Scale

2. Synopsis

Title	The RIME study - Combined occipital and supraorbital transcutaneous nerve stimulation for treatment of migraine
Clinical Study Type	Pivotal, Non-Significant Risk (NSR) Device Study
Product Name	Relivion™ (Device version RLV3; SW version 0.3.21 ; App Version 1.0)
Sponsor	Neurolief Ltd.
US Agent	Elaine J. Whitmore, Ph.D. SciVance Consulting 7113 River Club Blvd. Bradenton, Florida 34202
Indication under investigation	The Relivion™ is a non-invasive transcutaneous neuro-stimulator intended for treatment of headache and is indicated for the acute treatment of migraine with or without aura in subjects 18 years of age or older. The Relivion is intended to be a prescription device, self-used at home.
Investigation Purpose	The RIME Study will evaluate the safety and efficacy of a self-administered abortive treatment for migraine headache using combined occipital and supraorbital transcutaneous nerve stimulator (Relivion™). This pivotal clinical investigation is intended to support the clinical evaluation of Neurolief's Relivion device in the context of its initial FDA clearance under 21 CFR part 882.5891, Transcutaneous electrical nerve stimulator to treat headache.
Product Status	Pre-market
Patient Population	Male and Female subjects, 18 years of age and older suffering from migraine headache with and without aura.
Primary Objectives	To assess the headache pain relief from baseline to 2 hours post-treatment, without rescue medications, when using active combined occipital and supraorbital transcutaneous nerve stimulation (Relivion™) compared to sham stimulation, in subjects suffering from acute migraine headache. Pain score will be assessed on a 4-point scale whereas 0 =no pain, 1=Mild pain, 2=Moderate pain, 3= Severe pain

Secondary Objectives	1. To assess the proportion of subjects reporting improvement in their most bothersome migraine-associated symptom (MBS) other than a headache, without rescue medications, 2 hours from Relivion™ treatment initiation compared to sham stimulation, in subjects suffering from acute migraine headache. MBS may be nausea, photophobia or phonophobia. 2. To assess the proportion of subjects reporting headache relief at 1-hour without rescue medications, compared to sham stimulation. 3. To assess the proportion of subjects who are pain free at 2 hours from Relivion™ treatment initiation without rescue medications, compared to sham stimulation, in subjects suffering from acute migraine headache.
Safety Objective	To demonstrate safety in using the Relivion™ device.
Exploratory Objectives	1. To assess the proportion of subjects reporting freedom from their MBS other than a headache, without rescue medications, 2 hours from Relivion™ treatment initiation compared to sham stimulation, in subjects suffering from acute migraine headache. 2. To assess the proportion of subjects who are pain free at 1-hour post Relivion™ treatment initiation (if rescue therapy was not used), in their first treated migraine attack. 3. To assess the subjects positive Global Impression of Effect of study device at the end of the study, defined as satisfied or very satisfied using a simple Likert-type scale whereas 1 = Very dissatisfied, 2 = dissatisfied, 3 = unsure, 4 = satisfied, 5 = Very satisfied, in active versus sham stimulation. 4. To assess the proportion of subjects reporting headache relief without taking rescue medications within 2 and 24 hours from Relivion™ treatment initiation compared to sham stimulation, in subjects suffering from acute migraine headache.
Planned Study Duration	Each subject will participate in the study for up to 110 days (~16 weeks) including the run-in period. The overall enrollment period is expected to last approximately 12 months.
Study Design	Multi-center, prospective, 2-arms randomized, double-blind, parallel-group, sham controlled study. The study will include the following study periods: • Run-in Period (28+10 days) • Randomization to Relivion™ vs. Sham control (1:1 randomization) and Self-Practice Period (up to 14 days) • Treatment Period (up to 5 migraine attacks or 70±10 days from randomization visit, whichever comes first) After completion of the Treatment Period the subject's participation will be over.

	The study will be conducted at a maximum of 12 investigational sites in the United States (US) and Israel,; Sites in the US will enroll approximately 33% of total subjects. Each site will enroll a maximum of 60 subjects.
Randomization	Upon completion of the run-in period, eligible subjects 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 center: • Group A - active stimulation • Group B - sham stimulation The randomization scheme will be prepared by the study statistician using the SAS (version 9.4.) random number procedure. The block size will be random, and all study personnel will be therefore blinded to the randomization block size.
Sample Size	The planned sample size is up to 200 randomized subjects, to allow for 90 evaluable subjects per treatment group, anticipating 10% drop-out. One interim analysis is planned after 144 (80%) evaluable subjects have been accrued.
Inclusion Criteria	1. Subjects 18 years of age and older. 2. Subject meets the ICHD-3 (2018) diagnostic criteria for Migraine with or without aura. 3. Subject reports 1-6 Migraine attacks per month; other headaches no more than 6 days per month. 4. Subject is willing to and capable of complying with the specified study requirements, provided written Informed Consent, can complete the electronic diaries, and can be contacted by telephone.
Exclusion Criteria	1. Subject having received Botox treatment in the head region in the prior 3 months. 2. Subject having received supraorbital or occipital nerve blocks in the prior month. 3. Past 6 months of chronic migraine, New Daily Persistent Headache, and chronic tension-type headache per ICHD-3 (2018) diagnostic criteria. 4. Current medication overuse headache. 5. Use of opioid medications in the prior 1 month. 6. Use of barbiturates in the prior 1 month.

	7. Subject has >10 headache days per month 8. Implanted metal/shrapnel or electrical devices in the head (not including dental implants), a cardiac pacemaker or an implanted or wearable defibrillator. 9. Received parenteral infusions for migraine within the previous 2 weeks. 10. Subject has known uncontrolled epilepsy. 11. History of neurosurgical interventions 12. Subject with implanted neurostimulators, surgical clips (above the shoulder line) or any medical pumps. 13. Current drug abuse or alcoholism. 14. Subject is participating in any other clinical study. 15. Skin lesion or inflammation at the region of the stimulating electrodes. 16. Personality or somatoform disorder. 17. Pregnancy or Lactation. 18. Women with child bearing potential without medically acceptable method of contraception (NOTE: Females of child bearing potential must have a negative pregnancy test). 19. Documented history of cerebrovascular event. 20. Subject with recent brain or facial trauma (occurred less than 3 months prior to this study). 21. Subject participated in a previous study with the Relivion device. 22. The subject does not have the basic cognitive and motor skills needed to operate a smartphone. 23. Subject with head circumference smaller than 51 centimeters or head circumference larger than 60 centimeters 24. Subject with other significant pain problem that in the opinion of the investigator may confound the study assessments.
Primary Efficacy Endpoint	Proportion of subjects reporting reduction of migraine headache pain 2 hours post treatment initiation from severe or moderate to mild or no pain, or from mild to no pain, in their first eligible (per section 9.1.6) treated migraine attack, when using active combined occipital and supraorbital transcutaneous nerve stimulation compared to sham stimulation, in subjects suffering from acute migraine headache. Use of rescue medication prior to 2 hours post treatment initiation will be considered a failure for this end-point (i.e. patient will be assigned the status of no reduction).

Secondary Efficacy Endpoints	1. Proportion of subjects reporting improvement in their MBS other than a headache, 2 hours post-treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack. MBS may be nausea, photophobia, phonophobia as defined by each subject prior to beginning of the treatment. 2. Proportion of subjects reporting reduction of migraine headache pain 1-hour post treatment initiation (if rescue therapy was not used), from severe or moderate to mild or no pain, or from mild to no pain, in their first eligible treated migraine attack. 3. Proportion of subjects who are pain free at 2 hours post treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack.
Safety Endpoint	Safety of the study device following study treatment: Rate of Adverse events related or unrelated to the study device [Time Frame: 24 hours post treatment initiation].
Exploratory Endpoints	1. Proportion of subjects reporting freedom from their MBS other than a headache, 2 hours post-treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack. 2. Proportion of subjects who are pain free at 1-hour post treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack. 3. Proportion of subjects rating the subjects positive (score of 4 or 5) Global Impression of Effect of study device at the end of the study, defined as satisfied or very satisfied using a simple Likert-type scale whereas 1 = Very dissatisfied, 2 = dissatisfied, 3 = unsure, 4 = satisfied, 5 = Very satisfied. 4. Proportion of subjects reporting 2-24h headache relief, defined as headache relief at 2 hours without rescue medications, then no moderate to severe headache in the next 22 hours, and no use of rescue medication or additional stimulation, in their first eligible treated migraine attack.
Statistical Considerations	**Study Hypothesis:** H_0: $P_T = P_S$ H_A: $P_T \neq P_S$ Where P_T and P_S represent the proportion (%) of subjects reporting pain relief in the active treatment group and sham group respectively **Sample Size Estimation:** The sample size for this study was calculated to test the null hypothesis with a chi-squared test, even though the final analysis may employ a regression model and/or a Fisher's exact test. Sample sizes are calculated to test the null hypothesis with 80% power at a 5% level of significance.

	If we assume that 45% of the subjects in the active treatment arm will have successful pain relief versus 25% in the sham arm, 180 evaluable subjects are required, 90 per group. Allowing for a ~10% drop-out rate, a total of 200 (100 active vs. 100 sham) subjects should be enrolled in the study. **Interim Analysis:** One interim analysis is planned after 144 (80%) evaluable subjects have been accrued. 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 final result will exceed a critical value at the interim given the observed effect size $\widehat{\delta_1}$ = difference between pain reduction rates in the active versus control groups at the interim look. **Primary endpoint analysis:** The primary endpoint is the proportion of subjects reporting reduction of migraine headache pain 2 hours post treatment initiation from severe or moderate to mild or no pain, or from mild to no pain, in their first treated migraine attack, when using active combined occipital and supraorbital transcutaneous nerve stimulation compared to sham stimulation, in subjects suffering from acute migraine headache. Use of rescue medication will be considered a failure for this end-point (i.e. patient will be assigned the status of no reduction). A count and percentage of subjects reporting such headache pain reduction without rescue medications 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 and a Fisher's exact test. If the null hypothesis is rejected in favor of the alternative hypothesis and the proportion (%) of subjects reporting reduction of migraine in the treated group is greater than that of the sham group, the study will be deemed successful.

3. Introduction

3.1. Background

Migraine is a prevalent and debilitating primary headache disorder. In the U.S population the prevalence of migraine is approximately 18% in women and 6% in men [1]. The World Health Organization (WHO) estimates that half to three quarters of adults aged 18-65 years in the world have had headache in the last year and, among those individuals, 30% or more have reported migraine [2]. Migraine prevalence is highest in those aged 30 to 39 years [3]. Migraine patients suffer from disabling symptoms that usually consist of a moderate to severe headache lasting 4 to 72 hours, nausea and/or vomiting, phonophobia (noise sensitivity) and photophobia (light sensitivity). Seventy five percent (75%) have a reduced ability to function during the migraine episodes and 33% require bed rest during their attacks [3]. Patients with migraine are often refractory to medical treatment and some of the most effective anti-migraine drugs, such as Triptans, have substantial side effects [4].

Triptans are the first-line therapy for patients whose attacks do not reliably respond to simple or combination analgesics [4]. The Most common side effects of Triptans are dizziness, nausea, weakness, tiredness, drowsiness, paresthesias, flushing, neck tightness and chest pressure which occur in about 20% of patients. Triptans have also been associated with the development of headache caused by medication overuse. Therefore, most experts recommend a conservative limit on its use to about 2 days per week [2]. Serious cardiovascular events, some resulting in death, have been reported in association with the use of Triptans. Thus, Triptans are contraindicated in an estimated 4.7 million Americans with migraine [4]. These contraindications and side effects have left millions of patients without a proper solution for their pain. Therefore, these patients may benefit from other, non-pharmaceutical strategies to modulate their pain. One of the tools to achieve pain reduction is Peripheral Nerve Stimulation (PNS). PNS can be applied either invasively or non-invasively. Invasive PNS involves surgery that places a small electrical device next to one of the peripheral nerves. Invasive procedures of PNS for treatment of migraine include occipital nerve stimulation (ONS) which has been shown to provide relief for chronic migraine in numerous clinical trials [5-9]. Another more recent PNS procedure for treatment of migraine combines both occipital and supraorbital nerve stimulation [10,11]. Recent clinical studies support the expectation that applying peripheral nerve stimulation to a combination of the occipital and supraorbital nerves may result in a better outcome compared to stimulation of the occipital nerve alone [10,11]. Indeed, the response rate for patients with intractable head-wide pain who were treated with implanted PNS to the occipital and supraorbital nerve is reported to be better than 90% [10,11]. This is an improvement from using stimulation to the occipital nerves only which is reported to bring about just a 40% response rate [10]. However, implanted peripheral nerve stimulation remains an invasive and costly procedure with high rate of complications including infection, bleeding or fluid collection under the skin, as well as hardware-related malfunctions such as migration and breakage of the implanted leads and pulse generator failure [5]. Thus, these procedures are currently offered only for intractable severe cases of chronic migraine.

Transcutaneous nerve stimulation is a noninvasive technique that for decades was considered of potential benefit for patients with headache [12]. Supraorbital transcutaneous stimulation has been applied and found to be safe and effective as a prophylactic therapy for migraine. In a sham-controlled trial, therapeutic gain was found to be within the range of those reported for other preventive drug and non-drug antimigraine treatments [13]. In a safety and patients' satisfaction survey of 2,313 patients using transcutaneous supraorbital stimulation, no serious adverse events were reported [14]. In a recent trial [15] of supraorbital stimulation for acute treatment of migraine, a significant difference was shown in pain reduction between the sham and active treatment, with no significant adverse events.

Due to the challenge of transferring current through the hair, stimulation of the occipital nerve is mostly performed with implanted [5,6,8,16] and percutaneous [17] nerve stimulators. However, due to its superficial anatomic location at the level of the external occipital protuberance [18, 19] once the electrodes are placed under the hair and close enough to the scalp, it can be stimulated transcutaneously. It may thereby provide similar clinical benefits without the risks associated with an invasive procedure. A combined occipital and supraorbital stimulation by means of transcutaneous nerve stimulation may provide a safe, effective and fast acting treatment for reducing migraine related pain.

According to this rationale, Neurolief is developing the Relivion™ - a transcutaneous neuro-stimulator applying combined occipital and supraorbital transcutaneous nerve stimulation for treatment of migraine. Following completion of early clinical studies showing favorable results, Neurolief designed the proposed clinical trial to evaluate the safety and efficacy of the Relivion™ in a two-arms controlled, double blinded randomized study.

3.2. Purpose

The RIME Study will evaluate the safety and efficacy of a self-administered abortive treatment for migraine headache using combined occipital and supraorbital transcutaneous nerve stimulator (Relivion™).

This pivotal clinical investigation is intended to support the clinical evaluation of Neurolief's Relivion™ device in the context of its initial FDA clearance under 21 CFR part 882.5891, Transcutaneous electrical nerve stimulator to treat headache.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective

To assess the headache pain relief from baseline to 2 hours post-treatment, without rescue medications, when using active combined occipital and supraorbital transcutaneous nerve stimulation (Relivion™) compared to sham stimulation, in subjects suffering from acute migraine headache. Pain score will be assessed on a 4-point scale whereas 0 =no pain, 1=Mild pain, 2=Moderate pain, 3= Severe pain

4.1.2. Secondary Objectives

1. To assess the proportion of subjects reporting improvement in their most bothersome migraine-associated symptom (MBS) other than a headache, without rescue medications, 2 hours from Relivion™ treatment initiation compared to sham stimulation, in subjects suffering from acute migraine headache. MBS may be nausea, photophobia or phonophobia.
2. To assess the proportion of subjects reporting headache relief at 1-hour without rescue medications, compared to sham stimulation.
3. To assess the proportion of subjects who are pain free at 2 hours from Relivion™ treatment initiation without rescue medications, compared to sham stimulation, in subjects suffering from acute migraine headache.

4.1.3. Safety Objective

To demonstrate safety in using the Relivion™ device.

4.1.4. Exploratory Objectives

1. To assess the proportion of subjects reporting freedom from their MBS other than a headache, without rescue medications, 2 hours from Relivion™ treatment initiation compared to sham stimulation, in subjects suffering from acute migraine headache.
2. To assess the proportion of subjects who are pain free at 1-hour post Relivion™ treatment initiation (if rescue therapy was not used), in their first treated migraine attack.
3. To assess the subjects positive Global Impression of Effect of study device at the end of the study, defined as satisfied or very satisfied using a simple Likert-type scale whereas 1 = Very dissatisfied, 2 = dissatisfied, 3 = unsure, 4 = satisfied, 5 = Very satisfied, in active versus sham stimulation.
4. To assess the proportion of subjects reporting headache relief without taking rescue medications within 2 and 24 hours from Relivion™ treatment initiation compared to sham stimulation, in subjects suffering from acute migraine headache.

4.2. Endpoints

4.2.1. Primary Efficacy Endpoint

Proportion of subjects reporting reduction of migraine headache pain 2 hours post treatment initiation from severe or moderate to mild or no pain, or from mild to no pain, in their first eligible treated migraine attack, when using active combined occipital and supraorbital transcutaneous nerve stimulation compared to sham stimulation, in subjects suffering from acute migraine headache.

Use of rescue medication will be considered a failure for this end-point (*i.e.* patient will be assigned the status of no reduction).

4.2.2. Secondary Efficacy Endpoints

1. Proportion of subjects reporting improvement in their MBS other than a headache, 2 hours post-treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack. MBS may be nausea, photophobia, phonophobia as defined by each subject prior to beginning of the treatment.
2. Proportion of subjects reporting reduction of migraine headache pain 1-hour post treatment initiation (if rescue therapy was not used), from severe or moderate to mild or no pain, or from mild to no pain, in their first eligible treated migraine attack.
3. Proportion of subjects who are pain free at 2 hours post treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack.

4.2.3. Safety Endpoint

Safety of the study device following study treatment: Rate of Adverse events related or unrelated to the study device [Time Frame: 24 hours post treatment initiation].

4.2.4. Exploratory Endpoints

1. Proportion of subjects reporting freedom from their MBS other than a headache, 2 hours post-treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack.
2. Proportion of subjects who are pain free at 1-hour post treatment initiation (if rescue therapy was not used), in their first eligible treated migraine attack.
3. Proportion of subjects rating the subjects positive (score of 4 or 5) Global Impression of Effect of study device at the end of the study, defined as satisfied or very satisfied using a simple Likert-type scale whereas 1 = Very dissatisfied, 2 = dissatisfied, 3 = unsure, 4 = satisfied, 5 = Very satisfied.
4. Proportion of subjects reporting 2-24h headache relief, defined as headache relief at 2 hours without rescue medications, then no moderate to severe headache in the next 22 hours, and no use of rescue medication or additional stimulation.

5. Product Description

5.1. General

The Relivion™ is an external neurostimulator designed for transcutaneous electrical nerve stimulation. The headset integrates three pairs of output electrodes which come in contact with the subject scalp at the forehead (two pairs) and occiput (1 pair). The electrodes deliver the stimulation pulses produced by the stimulation unit to the subject's scalp. The frontal electrodes stimulate the trigeminal (supraorbital & supratrochlear) nerve branches and the posterior electrodes stimulate the occipital nerve branches (**Figures 1** and **2** below). Stimulation intensity can be adjusted by the user.

The Relivion™ is a prescription device that will be self-used in a home environment.

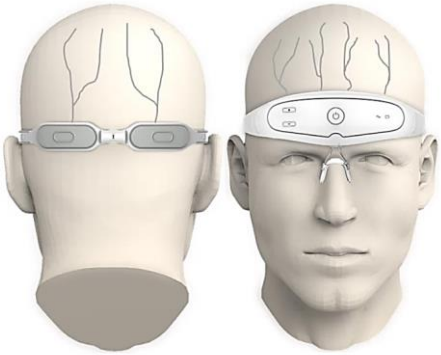

Figure 1: Relivion™ and its target nerves

Figure 2: Relivion™ on a user

The device is comprised of a headset with integrated electrodes, designed to enable stimulation of the target nerves. The on-board stimulation circuit is adapted to deliver stimulation patterns to enhance proper nerve activation. The headset adjusts to various head sizes and contours and can be worn

comfortably. Each time the headset is worn, the six electrodes are placed over the underlying nerves. Four anterior forehead electrodes are aligned with branches of the trigeminal nerve (supraorbital & supratrochlear) and two posterior electrodes are aligned with the greater occipital nerve branches. The headset includes two flexible arms that penetrate under the hair layers while the headset is donned. A size adjustment mechanism is located at both sides of the headset. It enables adjustment of the headset size to the head of the user before first use. The Relivion™ includes six replaceable electrode pads that are positioned above the headset electrodes. The pads consist of a water absorbing foam and should be wetted by the user before each use in order to provide proper conductivity between the electrodes and the scalp. Water releasing covers are located on the outer side of each occipital electrode. After positioning the headset on the head, the user press once on the water release covers to release moisture from the electrode pads onto the scalp, thereby maintaining conductivity between the electrodes and the scalp. The Relivion™ incorporates an on-board interface that enables the user to activate/deactivate the device and to adjust the stimulation intensity. It also provides visual and auditory indications such as whether the device is active/non-active and when there is a low battery.

The Relivion™ can communicate via a low energy Bluetooth link with a mobile application on the user's smartphone. The mobile application displays the device status and provides indications and alerts such as treatment intensity level, treatment duration, low battery, charging state, etc. The mobile application is optional as the Relivion™ can be fully operated without it. Furthermore, the device cannot be controlled (activate, adjust intensity, etc.) by the mobile application.

Further details, images and specifications are provided in the User Manual.

5.2. Mode of Action

As explained, the Relivion™ is an external neurostimulator designed for transcutaneous electrical nerve stimulation. The headset integrates three pairs of output electrodes which come in contact with the subject skin at the forehead and occiput. The electrodes deliver the stimulation pulses produced by the stimulation unit to the subject's scalp. The frontal electrodes stimulate the trigeminal (supraorbital and supratrochlear) nerve branches and the posterior electrodes stimulate the greater occipital nerve branches.

Overactive pain and symptom areas of the brain are believed to play a primary role in the onset of migraines [20]. The Relivion™ device treats migraine by stimulating the trigeminal and occipital nerve branches, thereby reducing the overactive pain-and-symptom areas and altering the activity in pain-associated central structures.

5.3. Dosage Form

For purposes of this study, the Relivion™ will be provided in therapeutic and non-therapeutic modes, to accommodate for the Active and Sham groups:

- Group A – Active Treatment: For the therapeutic mode the device will be preset to the following parameters: stimulation waveform- symmetrical biphasic, phase duration 330-400 microseconds, pulse frequency 80Hz, trigeminal stimulation intensity – up to 6mA, Occipital stimulation intensity– up to 12mA.
- Group B – Sham Control: For the non-therapeutic mode the device will be preset to the following parameters: Stimulation waveform- symmetrical biphasic, phase duration- 70-100 microseconds, pulse frequency 0.33 Hz, trigeminal stimulation intensity up to 5mA, occipital stimulation intensity up to 10mA.

Both Active and Sham stimulation devices are packaged and labeled identically to maintain blinding of both the subject and study staff.

Each Relivion treatment will last 60±30 minutes. The Relivion device programmed treatment duration will be 1 hour. In case an earlier substantial pain relief is achieved, subject may stop treatment earlier.

5.4. Intended Use & Intended Population

The Relivion™ transcutaneous electrical nerve stimulator is intended for the treatment of headache and is indicated for the acute treatment of migraine with or without aura in patients 18 years of age or older. It is a prescription device to be self-used at home.

6. Study Design

6.1. General

Multi-center, prospective, 2-arms randomized, double-blind, parallel-group, sham controlled study evaluating the safety and efficacy of the of the Relivion™ in subjects 18 years of age and older suffering from migraine headache with and without aura. The study will include the following periods:

1. Run-in Period (28 days)
2. Randomization to Active Relivion vs. Sham control treatment arm (1:1 randomization) and Self-Practice Period (Up to 14 days)
3. Treatment Period (up to 5 migraine attacks or 70±10 days from Randomization visit, whichever comes first)

After completion of the Treatment Period the subject's participation will be over.

Study flowchart is summarized in **Figure 4** and details of the assessments to be completed at each period / visit are provided is **Section 9**.

The planned number of subjects is 200. There are no procedures for the replacement of subjects.

The study will be conducted at a maximum of 1*2* investigational sites in the US and Israel,; Sites in the US will enroll approximately 33% of total subjects. Each site will enroll a maximum of 60 subjects.

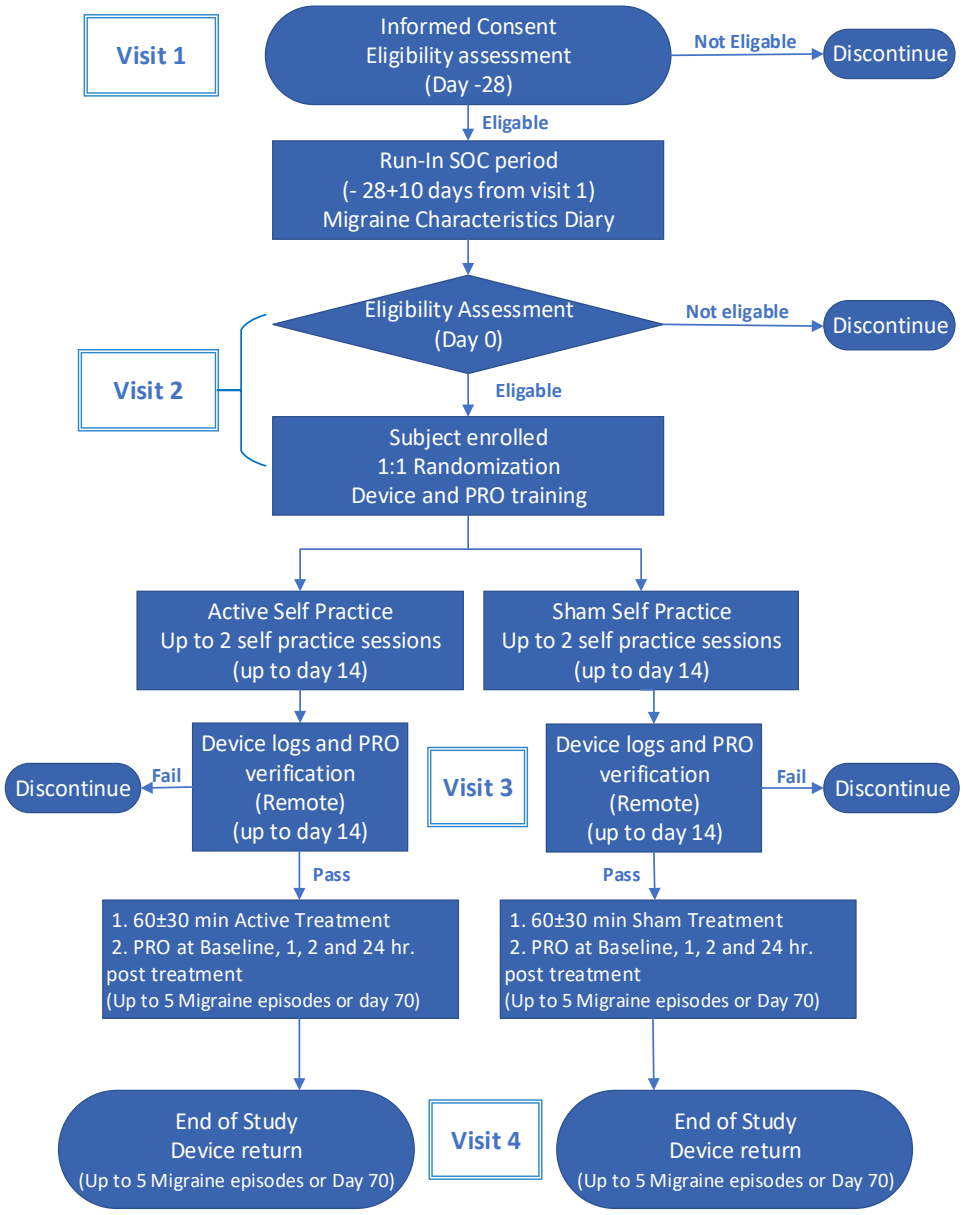

Figure 3: Study Flowchart

6.2. Randomization

Subjects will be prospectively randomized into the clinical study. Randomization will occur only after the subject provides informed consent, completes the Run-in Period and all required screening and baseline procedures, and satisfies the study eligibility criteria.

6.3. Measures to Minimize Bias

Several measures will be implemented to minimize systematic error/bias:

- Randomization to active treatment vs. sham control.
- Blinding of both subjects and study personnel.
- At the end of Visit 2, before starting the self-practice, subjects will be asked for their opinion concerning their group assignment. Their response will be documented in the CRF.
- Screening log will be completed by investigational sites listing all migraine patients consented to the RIME study. The log will include reasons for exclusion from the study.
- Pain assessment will be performed using a subject diary.
- Investigator's reported serious adverse events and device related adverse events will be reviewed and adjudicated, if required, by Neurolief and if needed forwarded to the company's medical advisor for further review and assessment. The adjudicated results will be updated in the study CRF and used in all cases for purposes of data analysis.
- Medical monitoring will take place in reviewing safety data and ensuring appropriate reporting of adverse events. The sponsor, the Medical advisor and Principal Investigator will oversee the overall safety of the study.
- Clinical monitors will verify patients' data and ensure compliance with good clinical practice (GCP), CIP and other study requirements.

7. Selection of Subjects

7.1. Study Population

The study will include male and female subjects, 18 years of age and older suffering from migraine headache with and without aura.

7.2. Subject Enrollment

A maximum of 200 subjects will be enrolled to the study. Subjects will be assessed, treated and followed as per the requirements listed in **Table 1**.

Adults known to the clinic as suffering from migraine, or subjects referred to the clinic, or subjects who approach the clinic due to study approved advertising may be recruited for inclusion in the study. After being informed of the nature of the study, the subject will sign a written informed consent form (ICF) that has been approved by the Sponsor and the appropriate IRB/ EC of the respective clinical site or the

central IRB/EC, during the screening visit. Written, informed consent will be obtained for all patients who are potential study candidates prior to applying any study specific assessment to the subject or any data collection. See **Section 9.4** for details on subject informed consent procedure.

Refer to **Figure 1** for a summary of the study schedule of assessment. Specifically, subjects will be evaluated at Visit 1 to assess whether they meet study eligibility criteria. Those meeting all of the inclusion and none of the exclusion criteria will initiate the Run-In Period for 28 days (+10 days). Subjects will return for Visit 2 (Day 0) for a repeat assessment of eligibility. Those found eligible will be enrolled and randomized. A subject is considered enrolled in the study when it is determined that all inclusion/exclusion criteria are met during visit 2 and after run-in period diary is assessed. At this point they will undergo device, device app and Patient Reported Outcome (PRO) training and will be asked to complete the blinding assessment. Subjects will be sent home with the device and the study dedicated smartphone for a 2 weeks Self-Practice Period. During these 2 weeks they will perform 2 self-training treatment sessions, not during a Migraine attack and complete the PRO. Device logs will be verified by the study team during Visit 3 (potentially remote verification). Subjects with at least 1 self-training session completed successfully will be approved by site team to initiate the Treatment Period and to treat at least 1 and up to 5 migraine episodes, within up to 70±10 days from visit 1, whichever comes first. Once completing the Treatment Period, they will return for end of study visit (Visit 4) during which the device will be returned, final data will be collected and the subjects will be exited from the study.

Subjects found ineligible by the procedures required at screening will be marked as 'screen failure' on the screening & enrollment log and will not take part in the study. Screen failure subjects will not be included in the intention-to-treat analysis, nor will they be counted as part of the target subject sample number.

7.3. Inclusion Criteria

In order to be included in the RIME study patients must fulfill all of the inclusion criteria.

1. Subjects 18 years of age and older.
2. Subject meets the ICHD-3 (2018) diagnostic criteria for Migraine with or without aura.
3. Subject reports 1-6 Migraine attacks per month; other headaches no more than 6 days per month.
4. Subject is willing to and capable of complying with the specified study requirements, provided written Informed Consent, can complete the electronic diaries, and can be contacted by telephone.

7.4. Exclusion Criteria

In order to be included in the RIME study patients must fulfill none of the exclusion criteria.

1. Subject having received Botox treatment in the head region in the prior 3 months.
2. Subject having received supraorbital or occipital nerve blocks in the prior month.

3. Past 6 months of chronic migraine, New Daily Persistent Headache, and chronic tension-type headache per ICHD-3 (2018) diagnostic criteria.
4. Subject has >10 headache days per month
5. Current medication overuse headache.
6. Use of opioid medications in the prior 1 month.
7. Use of barbiturates in the prior 1 month.
8. Implanted metal/shrapnel or electrical devices in the head (not including dental implants), a cardiac pacemaker or an implanted or wearable defibrillator.
9. Received parenteral infusions for migraine within the previous 2 weeks.
10. Subject has known uncontrolled epilepsy.
11. History of neurosurgical interventions
12. Subject with implanted neurostimulators, surgical clips (above the shoulder line) or any medical pumps.
13. Current drug abuse or alcoholism.
14. Subject is participating in any other clinical study.
15. Skin lesion or inflammation at the region of the stimulating electrodes.
16. Personality or somatoform disorder.
17. Pregnancy or Lactation.
18. Women with child bearing potential without medically acceptable method of contraception (NOTE: Females of child bearing potential must have a negative pregnancy test).
19. Documented history of cerebrovascular event.
20. Subject with recent brain or facial trauma (occurred less than 3 months prior to this study).
21. Subject participated in a previous study with the Relivion device.
22. The subject does not have the basic cognitive and motor skills needed to operate a smartphone.
23. Subject with head circumference smaller than 51 centimeters or head circumference larger than 60 centimeters
24. Subject with other significant pain problem that in the opinion of the investigator may confound the study assessments.

8. Study Procedures

8.1. Schedule of Events

The schedule of events is depicted in **Table 1** and **Figure 1**.

Table 1: Schedule of Events

Visit	Visit 1	Run-In Period	Visit 2	Self-Practice Period	Visit 3	Treatment Period	Visit 4
Event / Timeline	**Day -28**	**-28 +10 days from Visit 1**	**Day 0**	**up to Day 14**	**remote; Up to Day 14**	**Up to 5 episodes / Day 70±10**	**Up to 5 episodes / Day 70±10**
Written Informed Consent	X						
Eligibility assessment	X		X				
3-month migraine retrospective history questionnaire	X						
Medical history & Demography	X						
Prophylactic anti-migraine & rescue headache medication	X		X[1]				X[1]
Physical examination[2] & Vital signs	X						
Documented significant change in health status (*e.g.*, surgery, accident, MI)			X				
Pregnancy test[3]	X		X				
Run-in Diary		X					
Enrollment & Randomization			X				
Device and PRO[4] training			X				
Device and PRO Self-practice			X	X			
Blinding assessment questionnaire			X				
Device logs and PRO verification			X[5]		X		X
Active / sham treatment						X	
Diary PRO at baseline, 1, 2 & 24 hr post treatment						X	
Global Impression of Effect questionnaire							X
Adverse events			X				X
End of study							X

1 Document change in medications

2 Physical exam to include: Head, eyes, ears, nose, throat (HEENT), Lungs, Heart and Neurologic exam; Vital signs include blood pressure, pulse and respiratory rate

3 Pregnancy test for women of childbearing potential only

4 PRO: Patient Reported Outcome

5 Device logs only at Visit 2

8.1.1. Visit 1 - Run-in (day -28)

Written below are the assessments to be completed at Visit 1:

- Written informed consent.
- Eligibility assessment.
- 3-month migraine retrospective history questionnaire.
- Prophylactic anti-migraine & rescue headache medication (all medications, preventive, prescribed acute, and over the counter are to be recorded).
- Medical history & Demography.
- Physical exam, including Head, eyes, ears, nose, throat (HEENT), Lungs, Heart, Neurologic exam and Vital signs including blood pressure, pulse and respiratory rate.
- Pregnancy test (for women of childbearing potential).
- Run-in Period diary dispensing and training.

The research coordinator will review the study requirements with the subject to help ensure compliance. Telephone numbers must be obtained from the subject to ensure the ability to contact him/her.

8.1.2. Run-In Period (Day 0 -28+10 days)

- Completion of the Run-In Diary by the subject during the run-in period. A Subject who failed to complete the required information on the Run-In Diary will be considered a screen failure. The diary will capture information with respect to frequency, intensity and duration of migraine episodes, existence of aura and other symptoms, use of rescue medications, and other types of headaches. Two (2) different Migraine episodes will be defined by, at minimum, by 48 hours free of pain in between.
- Study team may contact the subject periodically to remind him/her to fill in the diary

8.1.3. Visit 2 - Randomization (28+10 days from Visit 1)

Written below are the assessments to be completed at Visit 2:

- Review of Run-in Diary.
- Change in prophylactic anti-migraine & rescue headache medication will be documented.
- Documented significant change in health status (*e.g.*, surgery, accident, MI)
- Pregnancy test (women of childbearing potential only).
- Verification of eligibility.
- Randomization to Group A (Active Treatment) and Group B (Sham Control).
- Subject will read the User manual and watch the instructional video and be trained on the device by the study team.
- Device size will be adjusted to subject head circumferences.

- Subject will self-practice the device along with the mobile application to become familiar with its use and with the stimulation.
- Blinding Assessment questionnaire.
- Subject will be trained on the Patient Reported Outcome (electronic/hard copy) diary for documenting the outcome measures and rescue medication intake.
- Mobile application/Device logs verification for stimulation intensity. Stimulation intensity to be above 2mA. In case subject fail to reach a minimum stimulation intensity of 2mA, subject will be withdrawn.
- Subject will be provided with the device, a dedicated smartphone, a subject's instruction form and Patient Reported Outcome diary (electronic/hard copy) for up to 14 days Self-Practice period at their home.
- Adverse events occurring during the visit will be documented.

8.1.4. Self-Practice Period (up to 14 days)

- Subject's self-practice of the device and Patient Reported Outcome diary twice, not during a migraine episode, for 30-60 minutes. Device Logs will be automatically uploaded by the mobile application to the study cloud-based database.
- Study team may contact the subject periodically to remind him/her to perform self-practice procedure.
- Subject will notify study team once completing 2 self-practice sessions.

8.1.5. Visit 3 (remotely or clinic visit; up to day 14)

Written below are the assessments to be completed at Visit 3:

- A visit is needed in case device logs were not download to the study cloud-based database, otherwise a remote contact is allowed.
- Upon subject notification of the completeness of 2 self-practice sessions:
  - Study team will confirm within device logs that the subject completed at least one self-practice session successfully. Device logs shall present Subject's study code, Device serial number, Date of stimulation session, stimulation session timeline bar presenting stimulation events such as "pass", "fail", Device failure events. A stimulation session marked as "Pass" if a minimal stimulation of 2 mA was delivered, or "Fail" if a minimal stimulation of 2 mA was not delivered. An eligible self-practice session will be defined by a recorded device log with a stimulation duration of at least 30 minutes of a "Pass" session in the device log.
  - Study team will verify correct reporting on PRO and inform/retrain subject on correct PRO reporting, if required.
  - If at least one self-practice session completed successfully, study team will contact the subject and guide him/her to use the device during up to 5 migraine episodes within up to day 70±10 from Visit 2.
  - Call will be documented and will be considered as remote study Visit 3.

- If both self-practice sessions are non-eligible, subject will be withdrawn from the study. Study team will call the subject and invite him/her to a study termination visit. Subject invitation will be considered as remote study Visit 3, termination visit will be documented.

8.1.6. Treatment period (up to 5 treated Migraine episodes or day 70±10 whichever comes first)

- Subjects will use the device for at least 1 and up to 5 migraine episodes within up to day 70±10 from visit 2, whichever comes first.
- Subjects will be instructed to differentiate between 2 different Migraine episodes which will be defined by, at minimum, 48 hours free of pain in between.
- Study team will contact the subject periodically to remind him/her to use the device during his/her next migraine episode.
- Study team will periodically verify device logs of treated attacks on the study cloud database and may contact the subject for re-training if required.
- Subject will use the device at home or surroundings immediately upon the initiation of the Migraine headache and no later than 30 minutes afterwards:
  - Subject will initiate the treatment procedure by turning on the device and the dedicated mobile application. The mobile application will guide the subject through the treatment procedure steps and will direct him/her to the study Patient Reported Outcome diary when required.
  - Prior to initiating the treatment, subject will report on the Patient Reported Outcome diary that:
    - He/she did not use analgesics or other pain relief drugs or cannabis within 4 hours period before the treatment.
    - Confirm no more than 30 minutes have passed since Migraine episode headache initiated.
    - Confirm that at least 48 pain free hours have passed since the subject previous Migraine episode.
    - Confirm he/she did not wake up with a Migraine headache.

      In case subject used analgesics or other pain relief drugs or cannabis within 4 hours period before the treatment initiation and/or more than 30 minutes passed from the start of the migraine episode and/or less than 48 pain free hours have passed since subject's previous Migraine episode and/or subject woke up with a Migraine headache, subject will be instructed to refrain from using the device and await his/her next migraine episode.
  - Prior to initiation of treatment and no later than 30 minutes from Migraine headache pain initiation, subject will document on the Patient Reported Outcome diary his/her baseline migraine pain level (whereas 1=Mild pain, 2=Moderate pain, 3=Severe pain) and the most bothersome migraine-associated symptom (nausea, photophobia, phonophobia or none).
  - Subject will then initiate the treatment along with the dedicated mobile application. The treatment will last 60±30 minutes. The Relivion™ device programmed treatment duration will be 1 hour. In case an earlier substantial pain relief is achieved, subject may stop treatment earlier but not less than 30 minutes from treatment start. If necessary, treatment can be paused by the

subject and then be resumed. Treatment with total stimulation time of at least 30 minutes of a "pass" session on the device log timeline, will count as a completed treatment.

- Subjects will be asked to refrain from consuming rescue medication/cannabis for at least 2 hours post treatment initiation. Subjects using rescue medication/cannabis prior to 2 hours post treatment initiation will be considered as failure (will be assigned the value of 0=no headache pain reduction) in the primary analysis.
- Subjects will document on the Patient Reported Outcome diary:
  - Pain according to a 4 points scale (0=no pain, 1=Mild pain, 2=Moderate pain, 3=Severe pain) at 1 and 2 hours ±30 minutes and at 24 hours ±6 hours post initiation of treatment.
  - Most Bothersome migraine-associated Symptom (MBS) other than a headache (chosen at baseline) improvement (yes/no) at 1 and 2 hours ±30 minutes post-treatment initiation.
  - Rescue medication intake.

8.1.7. Visit 4 - Termination visit (following 5 treated Migraine episodes or day 70±10, whichever comes first)

Written below are the assessments to be completed at Visit 4:

- After up to 5 migraine episodes within up to day 70±10, whichever comes first, subject will report to the clinic and return the device, Smartphone and hard copy subject diary, if applicable.
- Change in prophylactic anti-migraine & rescue headache medication will be documented.
- Subjects device Global Impression of Effect will be documented.
- Adverse events will be documented.
- Device logs, for each Migraine treated episode, will be downloaded by the study team (from study cloud database or from the device) to ascertain eligible treatments. An eligible treatment is defined as:
  - treatment meeting the basic criteria (*i.e.*, no analgesics or other pain relief drugs or cannabis within 4 hours period before the treatment initiation; no more than 30 minutes passed from the start of the migraine episode; more than 48 pain free hours have passed since subject's previous Migraine episode; and subject did not wake up with a Migraine headache); and
  - with total stimulation time of at least 30 minutes of a "pass" session on the device log timeline, where pass is defined as a minimal stimulation of 2mA delivered).

  The characteristics of each treatment will be indicated on the subject CRF.

At this point subject's participation in this study will be over. The subjects will continue receiving medical care as per local standard of care, but not within the clinical study. Adverse Events that are still ongoing will be followed per local standard of care, but not within the clinical study.

8.2. Prior and Concomitant Medications

During the Run-In and Self-Practice Periods, the subject will use prophylactic medications as prescribed and rescue medications as needed and will document their use in the Migraine Diary.

During the Treatment Period, the subject will continue his/her prophylactic medications and rescue medications as needed. While using the Relivion™ the subject will be asked to refrain from taking rescue medications/cannabis in the 4 hours prior to and 2 hours following each treatment.

8.3. Subject Consent

Informed consent will be obtained before any study-specific procedures are initiated or data collected. Principal Investigator or his/her authorized designee will conduct the informed consent process.

8.4. Randomization, Treatment Assignment and Blinding

Subjects will be prospectively randomized into the clinical study. Randomization will occur only after the subject provides informed consent, completes the Run-in Period and all required screening and baseline procedures, and satisfies the study eligibility criteria. Eligible subjects 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 center:

- Group A - active stimulation.
- Group B - sham stimulation.

The randomization scheme will be prepared by the study statistician using the SAS (version 9.4.) random number procedure. The block size will be random, and all study personnel will therefore be blinded to the randomization block size. Only the unblinded statistician /sponsor unblinding party and designates will be privy to the masked randomization scheme.

The Relivion™ Active and Sham devices will look the same and will be provided in the same packaging bearing the same labeling. Hence, both subjects and study personnel will remain blinded to the assigned treatment group.

8.5. Medication Compliance

While using the Relivion™ the subject will be asked to refrain from taking rescue medications/cannabis in the 4 hours prior to and 2 hours following each treatment. Subject will ascertain he/she did not consume any rescue medications/cannabis in the 4 hours prior to study treatment initiation. During each study treatment and up to 24 hours afterwards subjects will document any rescue medication/cannabis intake. PRO data of subjects who consumed rescue medications/cannabis will not be considered for the analysis of the related treatment time point.

8.6. Assessment of Efficacy

Efficacy parameters including Pain level, use of rescue medications/cannabis, presence and relief of most bothersome migraine-associated symptom other than headache will be documented during treatment at baseline, 1 hour, 2 hours and 24 hours.

These parameters will be documented by the subject using the diary (electronic or hard copy).

Treatment duration and intensity will be documented automatically in the device logs.

8.7. Assessment of Safety

Safety will be assessed by the collection of adverse events information from Enrollment (randomization) through study exit. Type, incidence, severity, duration, and procedure/device relationship of adverse events (AEs) will be collected throughout the study. Subjects with AEs at study exit will be followed for 14 days or until event resolves, whichever comes first. Adverse event data will be collected and reported on eCRFs.

9. Risks and Benefits

Risk management is performed as per ISO 14971, complete documentation is maintained on file (Neurolief document # QAD-022).

9.1. Risk Control and Mitigation

The following efforts will minimize risks to subjects 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 subjects for home use of the device.
- Clearly defining the inclusion and exclusion criteria such that only appropriate patients are enrolled in the study.

9.2. Risk-Benefit Rationale

Assessing the risks against the potential benefits of the use of the Relivion™ for alleviating migraine pain, Neurolief and the principal investigators have determined that there is a high likelihood that the expected benefit may outweigh the risk in patients fulfilling the study eligibility criteria.

10. Adverse Events and Device Deficiencies

Adverse event definitions used in this study are based on ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice).

Adverse Events will be collected for all enrolled subjects with the point of enrolment (Visit #2) and end at the study termination visit (visit #4). Subjects with AEs at termination visit will be followed for 14 days or until event resolves, whichever comes first.

During the course of the study, all AEs will be collected and reported on the eCRF including:

- All AEs related to Relivion device and/or procedure
- All AEs not related to Relivion device and/or procedure
- All device deficiencies that may lead to a SAE
- All Deaths

10.1. Relivion Anticipated Adverse Events

Possible risks and adverse events that may be associated with the Relivion™ device are based on adverse events reports of similarity devices include, but are not limited to the following:

- Unpleasant sensation during treatment
- Scalp Numbness sensation during and after treatment
- Persistent tingling sensation after the treatment ends
- Pain
- Skin reaction (for example, irritation, lesion, burn) beneath the stimulation electrodes In this case, treatment should be temporarily discontinued.
- Redness of the skin under or around the electrodes. Skin redness usually disappears within several hours after treatment
- Sleepiness, fatigue or sleep disorders
- Sedative effect during or after treatment
- Dizziness during or after treatment
- Tension type headache after treatment

10.1.1. Reporting of Adverse Events

Please refer to **Table 2** for a list of the minimum AE reporting requirements for Investigators. If local regulations or IRB/EC require faster reporting, then the Investigator will adhere to those requirements. Reporting of all safety events to the Sponsor will be completed through Investigator submission of the AE eCRF in the remote data capture (RDC) system. In case of emergency only for SAEs (ex. RDC system is

unavailable), the sponsor site representative may be contacted directly; this will not serve as a substitute for proper reporting on the appropriate eCRF.

Table 2: AE Reporting Requirements

Type	Report to	Reporting Timeframe (from time of learning of event)
Adverse Event (AE)	Sponsor	Within 10 working days
	IRB/EC	Per EC reporting requirements
Serious Adverse Event (SAE)	Sponsor	Within 24 hours
	IRB/EC	Per/IRB/ EC reporting requirements
Adverse Device Effect (ADE), Serious Adverse Device Effect (SADE) and Unanticipated Serious Adverse Device Effect (USADE/UADE)	Sponsor	Within 24 hours
	IRB/EC	Per EC reporting requirements
Device Deficiency	Sponsor	Within 48 hours
	IRB/EC	If SAE occurs due to the device deficiency, within 24 hours of learning of the event and per EC reporting requirements
	EC	Per EC reporting requirements

Events will be reviewed by the Sponsor to determine any reporting obligations to the FDA or Regulatory Authorities as well as IRB/EC. Reporting will occur within the timelines per local regulations and requirements. The Principle Investigator is responsible to report the events to the IRB/EC.

The sponsor shall immediately conduct an evaluation of any unanticipated events if determines that the events presents an unreasonable risk to subjects, report the results of such evaluation to the Regulatory authority and to reviewing IRB/EC and participating investigators within 10 working days after the sponsor first receives notice of the event.

10.1.2. Safety Monitoring and Adjudication of Adverse Events

The sponsor will review submitted AE information and may request supplemental information if needed. For SAE, U(SA)DE 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 and the information will be forwarded to Neurolief medical advisor for final adjudication.

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.

11. Statistical Considerations

11.1. Study Endpoint Variables

11.1.1. Primary endpoint variable

The primary endpoint, the proportion of subjects reporting reduction of migraine headache pain 2 hours post treatment initiation from severe or moderate to mild or no pain, or from mild to no pain, in their first treated migraine attack, when using active combined occipital and supraorbital transcutaneous nerve stimulation compared to sham stimulation, in subjects suffering from acute migraine headache, will be measured in the form of a binary variable which will be assigned the value of "1" if the subject reports such headache pain reduction without having used rescue medications, and "0" otherwise. Rescue medication use within the 2 hours post treatment initiation will result in the subject will be coded as "0" automatically.

11.1.2. Secondary endpoint variables

The three secondary endpoints will also be represented in the form of binary variables which will be assigned the value of "1" if the subject is a "responder" to each specific secondary endpoint, and "0" otherwise.

11.1.3. Exploratory endpoint variables

The exploratory endpoints will be measured in the form of a binary variables which will be assigned the value of "1" if the subject responds to each specific exploratory endpoint, and "0" otherwise.

Global Impression of Effect will also be measured via a 5-level Likert scale.

11.1.4. Safety endpoint variables

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

11.2. Study Hypothesis

Study Hypothesis:

H_0: $P_T = P_S$

H_A: $P_T \neq P_S$

Where PT and PS represent the proportions (%) of subjects reporting pain relief in the active treatment group and sham group respectively.

11.3. Sample Size Estimation

The sample size for this study was calculated to test the null hypothesis with a chi-squared test, even though the final analysis may employ a regression model and/or a Fisher's exact test.

The sample size is calculated to test the null hypothesis with 80% power at a 5% level of significance using the POWER procedure in SAS v9.4.

If we assume that 45% of the subjects in the active treatment arm will have successful pain relief versus 25% in the sham arm then 180 evaluable subjects are required, 90 per group. Allowing for a ~10% drop-out rate, a total of 200 (100 active vs. 100 sham) subjects should be enrolled in the study.

11.4. Interim Analysis

Planning one interim analysis that permits an increase in the sample size as described below does not additionally inflate the type I error [22-24]. In addition, the final analysis is performed using the conventional test as appropriate for the statistical hypothesis.

One interim analysis is planned once ~80% of the information is collected, i.e. the interim look will be performed after 144 evaluable subjects have been accrued. Based on the conditional power at the interim analysis, the study will either continue to the originally planned sample size if the result is "favorable", stop for futility if the result is "unfavorable", or we shall increase 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 final result will exceed a critical value at the interim given the observed effect size δ_1 = difference between pain reduction rates in the active versus control groups at the interim look. The following guidelines for sample size increase, depending on the zone into which CP falls at the interim, the calculated CPmin, the maximum sample size designated of 340 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.

The sponsor and the clinics will remain blinded throughout the study to the interim analysis results as well, only the decision made will be shared.

Notation:

n1= sample size at interim analysis

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

n_{max} = the highest sample size the company is willing to use/ can afford, n_{max} = 340 subjects and it is calculated based on a smaller effect size of 15% in the same manner as above in **Section 12.3**.

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

11.4.1. Procedure

After all the relevant data will be entered into the database, and the database cleaned, a soft lock to the database will be performed. An independent un-blinded statistician (not the study statistician) will perform the assessments described below. A designated data monitoring team will recommend whether to stop the study once the interim results are available.

At the interim analysis, the data of the evaluable subjects per ITT and mITT will be analyzed.

11.4.2. Blinding

Only the unblinded statistician and members of the interim decision team will be exposed to the interim report. The members of the data monitoring team may also have access to the unmasked information of the interim analysis. Investigators and company directors will only be informed of a decision to continue or to discontinue the trial, or to implement modifications in trial procedure. The un-blinded statistician who is responsible for conducting the interim analyses should ensure that the unmasked data is not available to any unauthorized person within or outside the company.

11.4.3. Decision Rules

The following are the decision rules for the interim analysis which will be performed upon accrual of 80% of the sample size, 144 evaluable subjects:

- If the result is “Unfavorable”, i.e. CP < CPmin = 32.91% (interim result is so disappointing that it is not worth increasing the sample size to retrieve conditional power) or if the difference between percentage of subjects reporting pain relief at the interim (Pt-Pc) is less than 0%, then stop the trial for futility.
- If the result is “Promising”, i.e. 32.91% ≤ CP < 80% the sample size is increased 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 340 subjects.
- If the result is “Favorable”, i.e. CP ≥ 80% the interim results are sufficiently favorable and trial continues to the original sample size planned 180 without the need to adaptively increase the sample size.

Note that the interim analysis will be conducted on all population (ITT, mITT and PP analysis sets, see **Section 12.6**), and the study will be stopped due to futility only if the interim effects in both populations fall below the threshold.

11.4.4. Controlling the Alpha Level for the Primary Endpoint

The overall alpha level for this study is 5%. According to [references 1-2-3], planning an interim analysis that permits an increase in the sample size as described above does not inflate the type I error.

11.5. Randomization

Upon completion of the run-in period, eligible subjects 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 center:

- Group A – active (Relivion™) stimulation
- Group B = sham stimulation

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

11.6. Analysis Populations

Intent-to-Treat (ITT) Population: The ITT population will include all randomized subjects, according to the ITT principle all subjects will be kept in a group as randomized.

Modified Intent-to-Treat (mITT) Population: The mITT population will include all randomized subjects who treat at least one eligible attack (excluding the "self-practice test"), with group assignment as treated.

Per-Protocol Population: The Per-Protocol population will include all subjects in the mITT population who completed the treatment period in compliance with the protocol and have no major protocol deviations, with group assignment as treated.

The ITT analysis set will serve as the main analysis set for all safety evaluations.

The efficacy analyses will be performed on the mITT analysis set.

The primary and secondary efficacy assessments will also be performed on the PP and the ITT analysis sets as a sensitivity analysis.

11.7. Statistical Analysis

11.7.1. General Considerations

Statistical analyses will be performed using SAS® v9.4 (SAS Institute, Cary NC, USA). Statistical analyses and reporting will be performed in compliance with FDA Guidance E6 GCP, 21 CFR part 812, E9 and ISO 14155.

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.

Deviations from the planned analysis will be described, with proper justification, in the clinical study report.

11.7.2. Significance Level and Handling of Type I Error

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%.

Hierarchy Approach for Secondary Endpoint 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 tested and only if $p<0.05$, will the secondary endpoints be tested. For the three secondary performance endpoints, the Benjamini–Hochberg step-up method will be used to adjust the p-values.

11.7.3. Demographic and Other Baseline Characteristics

Demographic and baseline condition related characteristics will be tabulated and compared between the study groups by data type, this data will also be compared between US and OUS sites for poolability confirmation. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum and categorical variables by a count and percentage.

These data will include:

- Demographic data

- Medical history
- Type of pain medications/treatments used for migraine as well as rescue
- Other concomitant medication
- Migraine attacks characteristics
- Physical examination

11.7.4. Disposition of Subjects

The number of subjects who entered the study and completed each stage of the study will be provided, 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 subjects excluded from the performance analysis will be provided as well.

11.7.5. Efficacy Analysis

Primary Efficacy Analyses

The primary endpoint is the proportion (%) of patients reporting reduction in their pain level 2 hours post-treatment without rescue medications from severe or moderate to mild or no pain, or from mild to no pain, in their first treated eligible (per **Section 9.1.6**) migraine attack (excluding the "self-practice" treatment). A count and percentage of subjects reporting such headache pain reduction without rescue medications 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 and a Fisher's exact test.

If the null hypothesis is rejected in favor of the alternative hypothesis and the proportion (%) of subjects responding to this endpoint in the active 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 Analyses of Primary Endpoint

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 will be performed and reported by adding the variables listed below to a logistic regression model:

- use of migraine medications
- blinding assessment
- US vs. OUS sites

Secondary Efficacy Analyses

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

Exploratory Analyses

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

Global Impression of Effect will also be summarized by descriptive statistics per treatment group and compared between the groups with a t-test.

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

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 Fisher's exact 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.

Handling of Missing Data

Multiple imputation for binary data will be used as the primary imputation method in the case of missing data for the primary efficacy end-point.

Additional 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:

Observed Data: Use only subjects with non-missing pain data and who did not withdraw early from study

Dropout/AE Imputation: A subject with no post baseline measurement of pain or a subject withdrawn due to an adverse event or treatment intolerability should be considered as a nonresponder for this analysis.

Best Case Scenario: Assume all visits with missing pain data in active group are successes. Assume all subjects in the sham group with missing pain data are failures.

Worst Case Scenario: Assume all visits with missing pain data in active group are failures. Assume all subjects in the sham group with missing data are successes.

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

Pooling

Subgroup analysis of the primary efficacy 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 subject and clinical characteristics, will be investigated and reported.

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