Abortive treatment of migraine with the Cefaly® Abortive Program device: Pilot trial

PROTOCOL

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Study Number: 50803

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1. Rationale

After having demonstrated a sedative effect (1), a multi-center, double-blind, randomized, sham-controlled trial has shown the efficacy and safety of external trigeminal nerve stimulation (e-TNS) with the Cefaly® device as preventive treatment of episodic migraine (2). Safety and patient satisfaction have been confirmed by a prospective study on 2,313 patients (3). The Cefaly® device was FDA-approved for migraine prevention in 2014.

Post-marketing data and survey (7) showed that many patients in Europe use the Cefaly® device not only for migraine prevention but as well during migraine attack to reduce the headache pain intensity. Several studies have been recently performed on the Cefaly® device as an acute treatment of migraine with specific electrical neurostimulation parameters.

- A pilot trial on migraine patients was performed at the University of Liège (Liege, Belgium) (4). Patients were asked to apply the Cefaly® device for a 20-minute session as an acute treatment for 3 migraine attacks. e-TNS completely relieved the patients in 13% of attacks, allowed to postpone the intake of anti-migraine drugs by more than 30 minutes in 20%. Results were inconclusive. But the protocol was not designed appropriately regarding the efficient use of the device and the duration of the stimulation. In particular, using the device without training may have resulted in stimulation under the minimum threshold of efficacy. In addition, the stimulation session duration was only 20 minutes, which we know from migraineurs is not long enough to get pain relief during migraine attacks.

- Kozminsky (5) assessed whether the Cefaly® device was effective and well tolerated as rescue therapy for migraine symptoms lasting 72 hours or longer, and concluded that e-TNS therapy with the Cefaly® device brought about a reduction of migraine-related pain (average minus 46%) as rescue therapy in these patients. e-TNS therapy via the Cefaly® device was well tolerated, and most patients would consider home therapy if it was affordable.

- Dr. Denise Chou, at Columbia University, implemented an open-label pilot trial on the acute treatment of migraine with the Cefaly® e-TNS device (6). Thirty (30) patients having a migraine attack with or without aura were included in the modified intention-to-treat (mITT) analysis. In terms of safety, no adverse events or side effects were reported. In terms of efficacy, mean pain intensity was significantly reduced by 57.10% after the 1-hour e-TNS treatment (-3.22 ± 2.40; $p<0.001$) and by 52.84% at 2-hour time point (-2.98 ± 2.31; $p<0.001$). No patients took rescue medications within the 2-hour observation phase. Within the 24-hour follow-up, 34.62% of patients used a rescue medication. The findings from this open-label study suggest that e-TNS with the Cefaly® device is a safe and effective acute treatment for migraine, and merits further study with a double-blind, randomized, sham-controlled trial.

- University of Liege in Belgium (Prof. J Schoenen) did a post-marketing survey on more than 800 regular users of the Cefaly® device in France, Switzerland and Belgium (7). 89.2% of responders to the questionnaire had been diagnosed by a physician as suffering from migraine. 88.6% of these patients reported to use the Cefaly® device during migraine attacks and that in 42.6% of these attacks, the use of the Cefaly® device prevented the intake of acute anti-migraine medication.

- Dr. Denise Chou conducted a multicenter, double-blind, randomized, sham controlled trial on the acute treatment of migraine with the Cefaly® device. One hundred and six (106) patients having a migraine attack with or without aura were randomized and included in the intention-to-treat (ITT) analysis. Among them, ninety-nine (99) were eligible for the modified intention-to-treat (mITT) analysis i.e. randomized patients having had the 1-hour stimulation treatment and having given their headache pain intensity measurement at baseline and at 1-hour time points. The last value carried-forward method was used when needed. In terms of safety, one adverse event (nausea) occurred but this event was minor and totally reversible (nausea resolved by itself after 20 minutes). There was no serious adverse events (SAE), nor were any subjective complaints or side effects reported in either group within the 24 hours after the beginning of the treatment. In terms of efficacy, in the ITT analysis, the primary outcome, mean migraine pain intensity after the 1-hour e-TNS session compared to baseline, was very significantly more reduced in the verum group than in the sham group (-3.46±2.32 versus -1.78±1.89, $p<0.001$; or -59% versus -30%, $p<0.001$). This pain relief percentage was as well significantly reduced in the verum group compared to the sham group at 2 hours and 24 hours. In the mITT analysis, mean migraine pain intensity was as well very significantly more reduced in the verum group than in the sham group at 1-hour (-3.83±2.13 versus -1.85±1.89, $p<0.001$; or -65% versus -32%, $p<0.001$) and at 2-hour and 24-hour time points. In addition, the percentage of pain free patients at 24-hour time point was significantly higher in the verum group compared with the sham group (32% versus 13%, $p<0.05$), and 30% sustained pain relief for 24 hours was significantly higher in the verum group compared to the sham group (43% versus 21%, $p<0.05$). Anti-migraine rescue medication intake within the 24 hours after the beginning of the treatment was not significantly lower in the verum group.

All these clinical data provide safety and efficacy evidence for e-TNS with the Cefaly® device in the acute treatment of migraine. Nevertheless, the evidences of efficacy were mainly reported for migraine patients treated in the clinic and for migraine lasting already for several hours. No data is available for patients using the device by themselves, at home, on a migraine attack at an early stage of its development. Such clinical data is therefore needed to assess the efficacy of the Cefaly® de vice as an acute migraine treatment at home, especially since migraine experts recommend patients to apply acute treatment of migraine at the beginning of the attack. An open pilot trial will allow to assess feasibility of the study design and provide data to prepare a phase 3 multicenter, randomized, controlled trial on the acute treatment of migraine at home by e-TNS with the Cefaly® device.

2. Study objective

The main objective of this study is to have a pilot assessment of the efficacy of the Cefaly® Abortive Program device used at home for 2 hours to treat a migraine attack, as triptans are generally used. That is to say having pilot data to assess the efficacy of the Cefaly® Abortive Program device in the abortive treatment of acute migraine as measured by 2-hour pain freedom, pain relief and migraine associated symptoms freedom, plus evolution of these measurements for 24 hours after the beginning of the treatment session.

3. Study outcomes

3.1. Efficacy outcomes

Primary outcomes:

1. Pain Freedom (PF) at 2 hours, defined as the percentage of patients having a reduction of a moderate or severe migraine headache (Grade 2 or 3) at baseline to no headache (Grade 0) at 2 hours after the beginning of the e-TNS session.

2. Most bothersome migraine-associated symptom (MBS) freedom at 2 hours, defined as the percentage of patients with absence, at 2 hours after the beginning of the e-TNS session, of the most bothersome migraine-associated symptom identified at baseline.

Secondary outcomes:

1. Pain Relief (PR) at 2 hours, defined as the percentage of patients having a reduction of a moderate or severe migraine headache (Grade 2 or 3) at baseline to a mild headache or to no headache (Grade 1 or 0) at 2 hours after the beginning of the e-TNS session.

2. Percentage of patients with absence of photophobia, phonophobia, nausea, vomiting at 2 hours after the beginning of the e-TNS session.

3. Use of rescue medication between 2 and 24 hours, defined as the percentage of patients who took acute anti-migraine medication between 2 and 24 hours after the beginning of the e-TNS session.

4. Sustained pain freedom at 24 hours, defined as the percentage of patients having no headache (Grade 0) at 2 hours, with no use of rescue medication and no relapse of headache pain within the 24 hours after the beginning of the e-TNS session.

Note: The baseline corresponds to the beginning of the e-TNS session.

3.2. Safety outcomes

A safety analysis will be performed on the reported adverse events, if any.

4. Study design

4.1. General description

This study is a mono-center, prospective, open-label phase 1 study, consisting of the treatment of a single moderate or severe migraine attack (Grade 2 or 3) at home.

4.2. Experimental protocol

Patients will be recruited from the research site database and advertising and will be enrolled during a visit at the research site.

Inclusion and exclusion criteria will be reviewed, and the eligible patients will be trained about the practical use of the Cefaly® Abortive Program device (device handling, electrode placement, etc.). Following that training, they will perform themselves a first 20-minute stimulation session to control their ability to use appropriately the device and bear the feeling of the stimulation.

Recruited patients (who meet all of the study entry criteria) will be provided with study material and documents for 2 months to be used on an outpatient basis as soon as they experience a moderate or severe migraine headache (Grade 2 or 3).

The overall study flow is illustrated in Figure 1. During the different phases the investigator will monitor adverse events (AE).

4.2.1. Recruitment phase

Patients contacted from the research site database and advertising will be screened during a visit at the research site.

Patient will receive the information and consent documents and have to sign these documents before study procedures are initiated. Then, the investigator will verify that the patient meets all the 6 inclusion criteria and none of the 13 first exclusion criteria. If this is the case, the patient will be trained about the practical use of the Cefaly® Abortive Program device (oral explanation, video and instruction sheet) and will perform him/herself a first 20-minute training session to check his/her ability to use the device appropriately and therefore that the last exclusion criteria is not met.

Screened patients meeting all inclusion criteria and none of the exclusion criteria are enrolled in the trial and will receive the study material (Cefaly® Abortive Program device with accessories) to be used at home to treat a single migraine attack and the related paper documents (diary and AE collecting form). The investigator will explain to the patient how to fill in these documents.

The patient will complete a practice diary (paper) for a simulated migraine during the screening visit, to ensure that he/she fully comprehends the procedure. The investigator or study coordinator will then review the diary in detail with the patient.

4.2.2. Acute treatment phase

During the 2 months following the screening visit, the patient will be instructed to treat a single qualifying migraine headache. A migraine headache is a qualifying migraine if all the following conditions are met:

1. The migraine headache severity is moderate or severe (Grade 2 or 3).
2. The migraine headache is associated with at least one of these migraine-associated symptoms: photophobia, phonophobia, nausea, vomiting.
3. The migraine headache started less than four hours ago or the patient woke up with migraine.
4. No other migraine headache or headache has occurred in the previous 48 hours.
5. The migraine headache is not already resolving on its own i.e. the pain is not already diminishing.
6. No acute anti-migraine medication has been taken since the beginning of the migraine headache.

In case of qualifying migraine, patient will have to apply the Cefaly® Abortive Program device for a complete treatment session of 2 hours as soon as the migraine headache is moderate or severe (Grade 2 or 3).

In his/her diary, the patient will note the headache pain severity on the following scale: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain. The patient will note as well the migraine associated symptoms (photophobia, phonophobia, nausea, vomiting) and will specify which associated symptom is the most bothersome symptom (MBS). The patient will note this data just before the start of the Cefaly® Abortive Program (baseline data) and 2 hours after the beginning of the treatment session (normally just after removing the device and the electrode if the session ran correctly) (2-hour data), whatever the duration of the stimulation session. The patient will also have to record if any aura was associated with the qualifying migraine attack.

Devices will be programed for only 1 treatment session to be performed at home to treat the qualifying migraine.

The Cefaly® device will be programed with the following parameters (Abortive Program): square pulse current (100 Hz, 250 µs) at a linearly increasing intensity starting at 0 mA up to a maximum of 16 mA after 14 minutes, then remaining stable for the rest of the session (106 minutes).

Patients will be instructed to not take any acute anti-migraine medication during the acute treatment phase.

During the acute treatment phase, when the Cefaly® Abortive Program device stopped, it may not be restarted. Duration, intensity and/or interruption will be recorded for each patient thanks to a built-in electronic system in the device.

In any case, the patient will have to note the headache pain severity in his/her diary at 2 hours after the beginning of the treatment session (2-hour data), whatever the duration of the stimulation session. The patient will note as well the migraine associated symptoms.

In his/her AE collecting form, the patient will record any adverse event occurring during the treatment phase and is instructed to notify the investigator immediately for any serious or severe adverse experience with the stimulation.

A follow-up phone call can be performed by the investigator.

4.2.3. Post-treatment phase

Two hours after the beginning of the treatment session, the patient is allowed to take rescue medication if the migraine headache pain is still moderate or severe, or if after initial pain relief (no headache or mild headache pain) a moderate or severe headache is resuming.

The patient will have to note the headache pain severity in his/her diary at 24 hours after the beginning of the treatment session (24-hour data), as well as the migraine associated symptoms. Patients will also be instructed to record in their diary the rescue medication intake, if any, during the 24 hours following the beginning of the treatment session.

In his/her AE collecting form, the patient will record any adverse event occurring during the 24 hours following the beginning of the treatment and is instructed to notify the investigator immediately for any serious or severe adverse experience with the stimulation.

4.2.4. Final visit

The patient will be instructed to return to the study site within approximately 4 days after the treatment session to return the study material as well as completed diary and AE collecting form. The investigator will review the paper diary in detail to ensure data accuracy (to avoid any missing data, unclear data or discrepancies). If necessary, the investigator will instruct the patient to make him/herself corrections and to sign the corrections with his/her screening number and the date (no initials).

All adverse events reported on the AE collecting form will be reviewed by the investigator to assess severity. Additionally, the investigator will ask the patient if he/she has experienced any adverse effect not reported on the form.

4.2.5. Discontinuation

Withdrawal

Patients may withdraw their consent at anytime during the study. If a patient wishes to discontinue from the study but no discontinuation visit is performed (e.g., patient refuses to return to the study site), then the patient should be formally discontinued from the study on the day the decision to discontinue is made.

Lost to follow-up

All attempts must be made to contact a patient who is lost to follow-up. Patients who are lost to follow-up should be formally discontinued from the study on the day of the last unsuccessful attempt at contact.

Absence of qualifying migraine

If a patient has not treated a qualifying migraine attack within two months of the screening visit, he/she will be discontinued from the study and study material will have to be returned to the study site.

Notification and practical modalities

At a minimum, for any patient who discontinues the study, the patient status must be completed in the CRF. When a patient discontinues prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. In particular, patients are required to return the Cefaly® Abortive Program device.

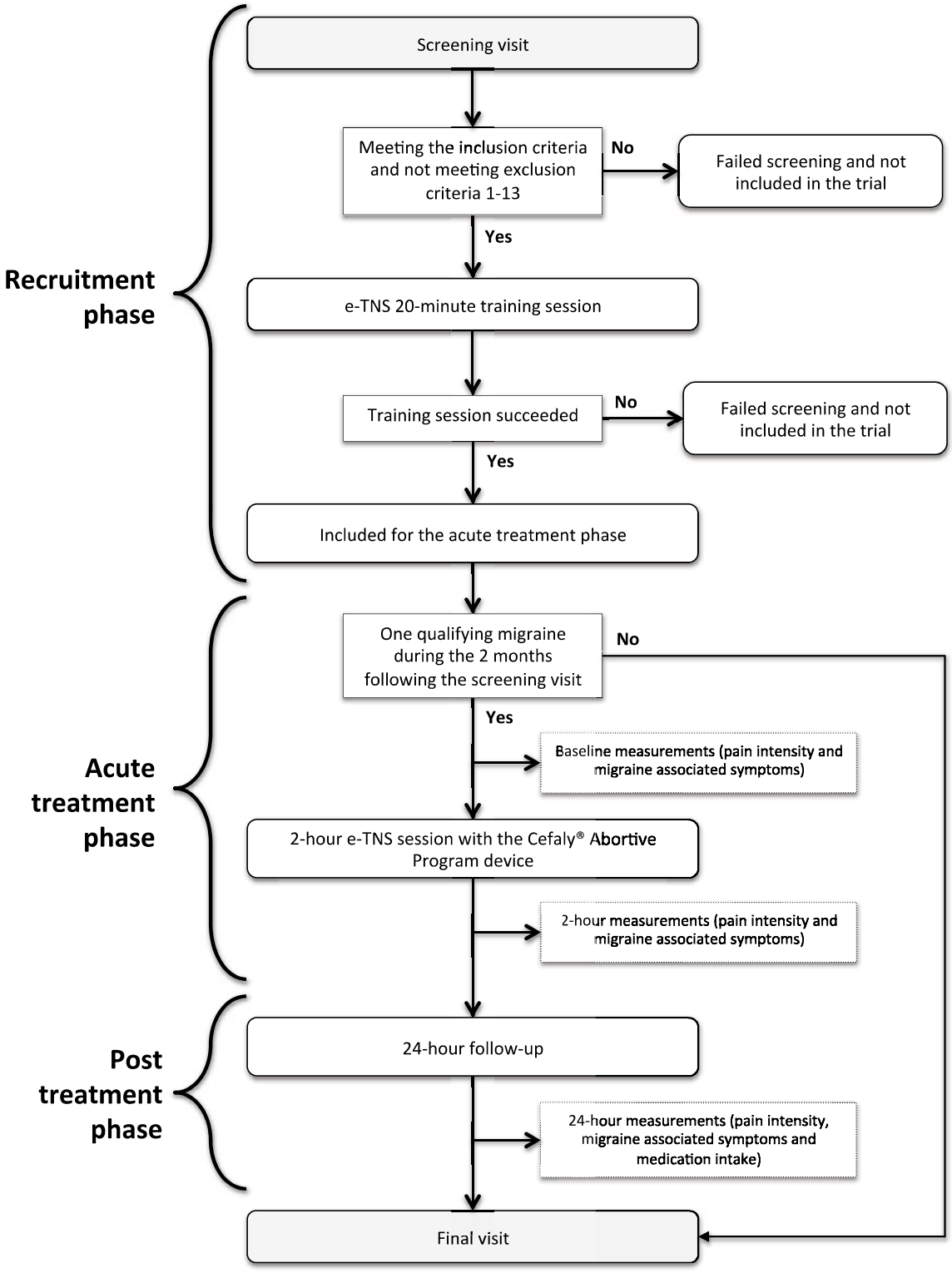

Figure 1 - Study flowchart

5. Subjects

The study will include at least 60 men or women.

5.1. Inclusion criteria

The following inclusion criteria apply:

1) Age from 18 to 65 years on the day of signing the informed consent form

2) ≥ 1-year history of migraine with or without aura according the diagnostic criteria listed in ICHD-III beta (2013) section 1, migraine (8), with the exception of aura without headache, hemiplegic migraine and brainstem aura migraine

3) Migraine onset before the age of 50 years

4) Having between 2 and 8 moderate or severe migraine attacks (Grade 2 or 3) per month in each of the two months prior to screening

5) Patient understands the study procedures, alternative treatments available, and voluntarily agrees to participate in the study by giving written informed consent

6) Patient is able to read and understand the written information (instruction sheet, paper diary and AE collecting form)

5.2. Exclusion criteria

The following exclusion criteria apply:

1) Patient has difficulty distinguishing his/her migraine attacks from tension-type headaches

2) Patient has more than 15 headache days per month

3) Patient having received supraorbital nerve blocks in the prior 4 months

4) Patient having received Botox treatment in the prior 4 months

5) Modification of a migraine prophylaxis treatment in the previous 3 months

6) Diagnosis of other primary headache disorders, except rare (< 4) tension-type headaches per month

7) Diagnosis of secondary headache disorders included Medication Overuse Headache

8) Patients abusing opioids or user of recreational or illicit drugs or has had a recent history (within the last year) of drug or alcohol abuse or dependence

9) Implanted metallic or electronic device in the head

10) Cardiac pacemaker or implanted or wearable defibrillator

11) Patient having had a previous experience with the Cefaly® device

12) Migraine Aura without headache

13) Patient is currently participating or has participated in a study with an investigational compound or device within 30 days of screening visit (Visit 1)

14) Patients not having the ability to use appropriately the device and/or to perform themselves or bear the first 20-minute stimulation session during the training session at the study site

6. Medical device and treatment

6.1. Device description

The Cefaly® device is a small, portable product, which is meant to be worn on the forehead by attachment to a self-adhesive electrode. A rechargeable battery provides power to the Cefaly® device. The Cefaly® generates very precise electrical impulses that permit stimulation of the nerve fibers. The device acts by stimulation of the upper branch of the trigeminal nerve.

The device has been approved by the FDA as a class II therapeutic device, indicated for the prophylactic treatment of episodic migraine in patients 18 years of age or older.

The Cefaly® device (Figure 2) is comprised of the following specifications:

- Dimensions: 55 mm x 40 mm x 15 mm
- Weight: 12 g.

Figure 2 - Cefaly® device

The Cefaly® device is connected to the body via a self-adhesive electrode (Figure 3) applied on the forehead. The device specific for the trial will run one "training session" of 20 minutes and one treatment session of 120 minutes. The Cefaly® electrode is 94 mm long and 30 mm high. It makes the interface between the Cefaly® device and the skin. This electrode has been approved by the FDA together with the Cefaly® device.

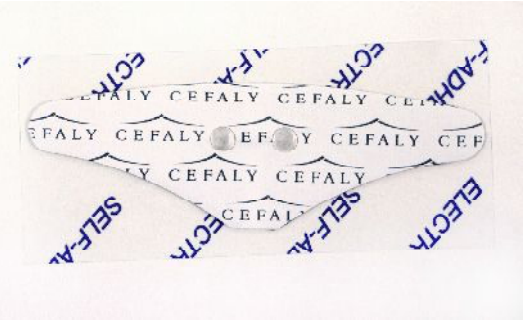

Figure 3 - Cefaly® electrode

6.2. Device technology

The Cefaly® is an external cranial neurostimulator designed for supraorbital neurostimulation (also known as external trigeminal nerve stimulation: e-TNS). Trigeminal nerve stimulation induces a sedative effect on the central nervous system (1).

The Cefaly® generates electrical impulses that are transmitted transcutaneously via a bipolar self-adhesive electrode placed on the forehead.

The Cefaly® operates on direct electrical energy, which is output from one rechargeable battery.

The Cefaly® Abortive Program delivers electrical energy in the form of rectangular biphasic pulses. The intensity is increasing linearly to reach a maximum of 16 mA after 14 minutes (and then stays constant for 106 minutes). The pulse frequency is 100 Hz. The pulse width is 250 µs.

The supraorbital electrode is designed in order to cover both sides of the supratrochlearis and supraorbitalis nerves, which are branches of the trigeminal nerve (Figure 4).

The electrical impulses generated by the Cefaly® device are transmitted transcutaneously via the supraorbital electrode to excite (trigger action potentials) the supratrochlearis and supraorbitalis nerves. Supratrochlearis and supraorbitalis (or supratrochlear and supraorbital) nerves belong to the upper branch of the trigeminal nerve (V1). Therefore, the supraorbital neurostimulation is also known as external trigeminal nerve stimulation.

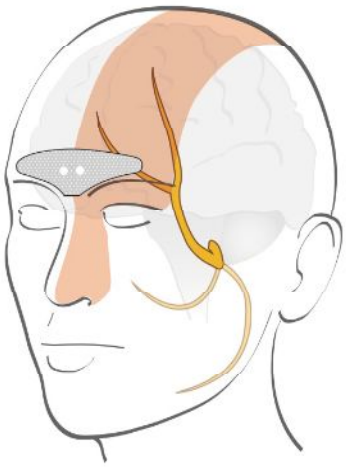

Figure 4 - The Cefaly® electrode placed on the forehead covers the supratrochlearis and supraorbitalis nerves

6.3. Mechanism of action

The Cefaly® device generates electrical impulses. Electrical impulses get out of the device via 2 metallic contacts. Contacts are in connection with 2 conductive areas on the self-adhesive electrode. The self-adhesive electrode is applied on the forehead. Therefore, electrical impulses generated by the Cefaly® device are running through the metallic contacts then through the electrode in order to carry out excitation on the nerve fibers just located under the forehead skin i.e. supratrochlearis and supraorbitalis (or supratrochlear and supraorbital) nerves which belong to the trigeminal nerve. Consequently, electrical impulses generated by the Cefaly® trigger signals (action potentials) on supratrochlear and supraorbital nerves or trigeminal nerve. Repetitive excitation of trigeminal nerve is a neuromodulation of the trigeminal system. Neuromodulation of the trigeminal system induces a sedative effect on the central nervous system and a trigeminal nociceptive threshold modification.

6.4. Use during the trial

Indications for use: abortive treatment of migraine with or without aura in patients 18 years of age or older.

The patient will apply the Cefaly® Abortive Program device for a first 20-minute training session to check his/her ability to use the device appropriately. Then, at home, the patient will apply the Cefaly® Abortive Program device for a 120-minute session during a qualifying migraine attack. Duration, intensity and/or interruption will be recorded for each patient thanks to a built-in electronic system in the device.

6.5. Medication during the trial

Patients will be instructed to not take any acute anti-migraine medication during the acute treatment phase. After the 2 hours acute treatment phase, if the patient has moderate or severe migraine

headache pain (Grade 2 or 3), he/she is allowed to take his/her own anti-migraine rescue medication. Use of acute medication will be recorded by the patient on the diary for the 24 hours following the beginning of the treatment.

6.6. Device provisioning

The promoter will deliver the specific Cefaly® Abortive Program devices and related accessories directly to the investigators. A single device will be delivered to each patient that cannot be reused on different patients. Each Cefaly® Abortive Program device will bear a unique number that has to be reported in the patient's CRF and will allow to identify, at the end of the study, which device was used by each patient.

Investigational clinical devices are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the promoter, the amount dispensed and returned, and the amount remaining at the conclusion of the study.

7. Practical study modalities

7.1. Efficacy outcome measures

The treatment efficacy outcomes will be assessed based on the following clinical data.

- **Headache pain severity.** In order to evaluate the modification of pain severity from baseline to 2-hour and 24-hour time points, patients will be asked to note their headache pain intensity on the following scale: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain.

- **Migraine associated symptoms**. The patient will also note the presence of migraine associated symptoms (photophobia, phonophobia, nausea, vomiting) and will specify which associated symptom is the most bothersome symptom (MBS).

- **Rescue medication intake**. The patient will also record whether he/she took ANY acute rescue medication during the 24 hours following the beginning of the e-TNS session.

The following table depicts when the different measures will be made:

	At baseline, i.e. just before the beginning of the e-TNS session	2 hours after the beginning of the e-TNS session	24 hours after the beginning of the e-TNS session
Headache pain severity	•	•	•
Migraine associated symptoms	•	•	•
Most bothersome migraine associated symptom (MBS)	•		
Rescue medication intake		•	

All clinical data will be collected on a paper diary and AE collecting form.

7.2. Calendar

The study is foreseen to start in June 2017 and to be finished by December 2017.

8. Data management and statistics

8.1. Data management

Each patient who signs a consent form to participate in the study will be assigned a unique number for identification purposes. Each patient should be assigned only one number. Should the patient fail to qualify for the study, his/her baseline number must not be re-used for any other patient in the study.

CRF and documents provided to the patient (diary and AE collecting form) will include the unique patient number in the header.

The collected data will be included in the case report form (CRF) and in patient diary. These completed documents will be provided by the investigator to the promoter. In practice, the investigator records these completed documents in an appropriate binder and sends the scan of the documents by email to the promoter. Tracking of completed source documents is performed: when a patient completed the clinical investigation but the related source documents have not been received, an email is sent to the investigator/study coordinator to request missing documents.

Duration, intensity and/or interruption of the treatment are recorded for each patient thanks to a built-in electronic system in the device. Each device will bear a unique number that has to be reported in the patient's CRF and will allow to identify which device was used by each patient.

In case of lack of data accuracy (missing data, unclear data, discrepancies), a data clarification query is sent to the investigator. The completed and signed form is sent back to the promoter. Tracking of data clarification forms is performed to ensure that all data clarification forms are completed by the investigator/study coordinator.

AE and SAE are collected on the paper CRF. Investigators will report SAE and AE on the specific forms annexed to the CRF. These SAE and AE forms will be reviewed and analysed by the promoter when received.

8.2. Statistics

The statistical analysis of the data obtained from this study will be the responsibility of the promoter.

8.2.1. Sample size

The sample size was computed based on the primary outcome, i.e. pain freedom at 2 hours. Results from previous sham-controlled trial using the Cefaly® device as acute treatment of migraine reported 7,7% of pain freedom at 2 hours in the placebo group. In the current study, the pain freedom at 2 hours

associated with the Cefaly® Abortive Program treatment is expected to be similar to the results related to triptans, in particular to Lasmiditan that presented 32,2%[1] of pain freedom at 2 hours.

A power analysis showed that a sample of 42 patients allows detecting a statistically significant difference between the expected (32,2%) and placebo (7,7%) pain freedom at 2 hours with a power of at least 80% and a 5% level of significance.

Taken into account a rate of 30% of patient loss during the study (based on the Lasmiditan study), at least 60 patients should be included in the study.

8.2.2. Statistical methods

- All relevant general, safety and efficacy data will be descriptively summarized at each time point.
- Continuous data will be summarized by the number of subjects (N), the arithmetic mean, the standard deviation, the coefficient of variation as a percentage (CV%), the median, the inter-quartile range, the minimum and the maximum value.
- Categorical data will be summarized by absolute (N) and relative (%) frequency tables.
- Where considered as relevant, the study data will also be graphically depicted.
- For each patient, the outcomes will be calculated according to all data available, and if necessary, imputation of missing data will be performed according to the last value carried forward method.
- Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

8.2.3. Statistical analysis

Modified intention-to-treat (mITT) analysis

Patient data will be included in the mITT analysis if all the four following conditions are met:

1. The patient treated a qualifying migraine.
2. The patient applied the Cefaly® Abortive Program treatment during at least one minute*.
3. The headache pain severity score **AND** the migraine associated symptom(s) at baseline were reported in the diary.
4. The headache pain severity score **OR** the migraine associated symptom(s) at 2 hours were reported in the diary.

[1] Data provided by Colucid Pharmaceuticals, Inc. and available on the following website: https://globenewswire.com/news-release/2016/09/06/869611/0/en/CoLucid-Pharmaceuticals-Announces-Achievement-of-Both-Primary-and-Key-Secondary-Endpoints-in-the-SAMURAI-Phase-3-Pivotal-Trial-of-Lasmiditan-in-Migraine.html (consulted in May 2017).

*If the patient stopped the 2-hour treatment session before its end for any reason, he/she is kept in the modified intention-to-treat (mITT) analysis if all the other conditions are met.

If the patient takes rescue medication between 2 hours and 24 hours after the beginning of the e-TNS session, the headache pain intensity and associated symptoms presence can be affected by the medication and the last value carried forward method (2-hour value carried forward method in this case) will be applied for the 24-hour time point headache pain severity and migraine associated symptoms.

Safety analysis

A safety analysis will be performed in case of reported adverse events.

9. Management of adverse events

9.1. Definition

Adverse Event (AE)

An adverse event (AE) is defined as any unfavorable and unintended sign, symptom or disease, regardless of whether it is considered related to the medical device or procedure that occurs during the course of the study.

In all cases, etiology will have to be researched and identified as soon as possible.

Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The investigator is responsible of transmission of SAE to the promoter and the promoter is responsible of transmission of the SAE declaration to the authorities.

9.2. Gradation

Adverse events should be categorized by the investigator according to severity:

- **Mild:** perception of sign or symptom, but **easily tolerated**.
- **Moderate: cumbersome** enough to impact subject activities.
- **Severe:** modifying **considerably** patient activities, or **impairing**, or constituting a **threat for the life** of the patient.

9.3. Causality

Main factors to take into account to determine the causality are:

- Events chronology,
- AE evolution when the product is not used anymore or used again,
- Existence of another etiology that could explain the AE,
- Existence of similar published or known AE.

9.4. Expected AE

The expected AEs of the Cefaly® are:

- Reversible skin irritation at the place of electrode
- Allergic reaction to the gel of the electrode (1 out of 1000)
- Headache after the session (0.52%)
- Feeling of fatigue

9.5. AE collection

The patients are instructed to report all AEs to the investigator during the 2 hours of the protocol. AEs will be analyzed by the investigator who will document it in the CRF.

All AEs will be collected in the CRF, specifying:

- Their nature
- Start date and duration
- Causality (according to investigator's opinion)
- Countermeasures and results

If the AE is a SAE, the promoter should be notified as soon as possible.

9.6. Investigator's responsibility with respect to a SAE.

9.6.1. SAE Notification

Each SAE will be described on the specific form with as much detail as possible. The informations to be communicated to the promoter are:

- Patient identification
- AE severity
- Start and end date
- Detailed description
- AE evolution
- Current diseases and relevant medical history of the patient

- Patient received treatments
- Causality link with the device under test

The investigator should also join to the AE report, each time it is possible:

- A copy of the hospitalization report
- A copy of all complementary exam results performed, including relevant negative results and joining the laboratory reference values
- Or any other document that he/she found useful and relevant
- Possibly, a copy of the autopsy report

All documents will be made anonymous and will bear the identification number of the subject.

9.6.2. Modalities of notification to the promoter

All SAE, no matter its causality relationship with the device under test, should be declared by the investigator:

- To promoter (represented by the CEO)
- As fast as possible
- By e-mail: see the specific form in the CRF

9.6.3. Monitoring

The monitoring is ensured until total recovery, stabilization or death of the patient, on common decision of the monitor and the investigator. Related costs are covered by the promoter.

9.6.4. Notification period

It is the investigator responsibility to notify the promoter about any SAE occurring:

- During the whole study period
- At any time, after the end of the study if the investigator thinks this could be related to the device under test during the study (if no other cause than the research could reasonably explain it).

9.7. Notification by the promoter to the authorities

In case the promoter is notified of an unexpected AE, he will report it directly to the national competent authority (FDA) and to the relevant central Investigational Review Board (Columbia University IRB).

Similarly, if a new fact relevant to the study or to the device appears that could impact the safety of the subjects participating to the study, the promoter takes the appropriate emergency measures. The promoter also notifies both the FDA and the IRB of this new fact and of the taken measures.

The delay to inform the authorities will be 2 days in case of death or life threatening AE, and 15 days in case of other unexpected AE or new fact. An extra delay of 8 days is foreseen to provide a follow-up report.

If necessary, the investigator will ask the subjects participating to the study to confirm their consent based on the updated information.

References

1. **BMC Neurol. 2011 Oct 28;11:135.** doi: 10.1186/1471-2377-11-135. Supraorbital transcutaneous neurostimulation has sedative effects in healthy subjects. Piquet M1, Balestra C, Sava SL, Schoenen JE.

2. **Neurology. 2013 Feb 19;80(8):697-704.** doi: 10.1212/WNL.0b013e3182825055. Epub 2013 Feb 6. Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Schoenen J1, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gérard P, Magis D.

3. **J Headache Pain. 2013 Dec 1;14:95.** doi: 10.1186/1129-2377-14-95. Safety and patients' satisfaction of transcutaneous supraorbital neurostimulation (tSNS) with the Cefaly® device in headache treatment: a survey of 2,313 headache sufferers in the general population. Magis D1, Sava S, d'Elia TS, Baschi R, Schoenen J.

4. **Cephalalgia. 2009 Jan 29:1101-172** doi: 10.1111/j.1468-2982.2008.01798_1.x Poster Abstracts. A pilot study on supra-orbital surface electrotherapy in migraine. Gérardy PY, Fabry D, Fumal A, Schoenen J.

5. **Headache. 2014;54(S1):12** doi: 10.1111/head.12405. Poster Abstract. Transcutaneous supraorbital nerve stimulation as a rescue therapy. Kozminski M.

6. **Neuromodulation.** Accepted Paper. External trigeminal nerve stimulation for the acute treatment of migraine: open-label trial on safety and efficacy. Chou DE, Gross GJ, Casadei C, Yugrakh MS.

7. **Acta Neurologica Belgica. 2017 Jan 27;** doi: 10.1007/s13760-017-0757-z. A survey on migraine attack treatment with the Cefaly® device in regular users. Penning S, Schoenen J.

8. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013, vol. 33, 9: pp. 629-808