

A Phase III randomized, double-blind, sham-controlled **I**trial  
of **e**-TNS for the **A**cute treatment of **M**igraine  
(The **TEAM** Study)

## PROTOCOL

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## 1. Rationale

After having demonstrated a sedative effect (1), a multicenter, randomized, double-blind, 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.

More recently technical improvements with electrical parameters protocols and treatment protocols have allowed the development of an acute treatment of migraine attacks. Based on these innovations, and after a few pilot tests (4) (5), a Cefaly® Acute program has been tested in clinical trials for the acute treatment of migraine with or without aura.

- 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 ( $-3.22 \pm 2.40$ ;  $p<0.001$ ) and by 52.84% at 2-hour time point ( $-2.98 \pm 2.31$ ;  $p<0.001$ ). No patients took anti-migraine rescue medication 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 randomized, double-blind, 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 anti-migraine rescue medication.
- Dr. Denise Chou conducted a multicenter, randomized, double-blind, sham-controlled trial on the acute treatment of migraine with the Cefaly® Acute device (9). 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 ( $-3.46 \pm 2.32$  versus  $-1.78 \pm 1.89$ ,  $p < 0.001$ ; 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 ( $-3.83 \pm 2.13$  versus  $-1.85 \pm 1.89$ ,  $p < 0.001$ ; 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.

Based on these trials providing safety and efficacy evidences for e-TNS with the Cefaly® device in the acute treatment of migraine, the Cefaly® Acute device was cleared by the FDA in September 2017 for the acute treatment of migraine with or without aura in patients 18 years and older.

Nevertheless, these safety and efficacy evidences were mainly reported for migraine patients treated in the clinic and for migraine lasting already for several hours. In order to get data with identical protocol design as usually carried out for abortive migraine medication triptans (i.e. treatment at home, on a migraine attack at an early stage of its development), a pilot trial has been implemented by Dr. Mann at Rochester Clinical Research, Inc., Rochester, New York, USA (10). The efficacy outcomes were very encouraging: 35.4% of patients were pain-free at 2 hours and 60.4% free from their most bothersome migraine-associated symptom, 70.8% had pain relief at 2 hours, sustained pain freedom and sustained pain relief at 24 hours were respectively 25% and 50%.

Consequently, there are enough evidences, pilot and Phase II data, to go for a Phase III multicenter, randomized, double-blind, sham-controlled trial on the acute treatment of migraine at home with e-TNS using a Cefaly® Abortive Program device.

## 2. Study objective

The main objective of this study is to have Phase III evidences 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 randomized, double-blind, sham-controlled data of the efficacy and safety 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 anti-migraine rescue 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 anti-migraine rescue medication and no relapse of headache pain within the 24 hours after the beginning of the e-TNS session.
5. Sustained pain relief at 24 hours, defined as the percentage of patients having mild or no headache (Grade 1 or 0) at 2 hours, with no use of anti-migraine 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

Device safety will be assessed by the number of reported adverse events (AE) and their severity.

## 4. Study design

### 4.1. General description

This study is a multicenter, prospective, randomized, double-blind, sham-controlled Phase III trial, 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 or during a standard care visit at the headache clinic/research site or at an on-demand appointment. They will be screened during a visit at the investigation site (headache clinic or research site).

Inclusion and exclusion criteria will be reviewed, and the eligible patients will be randomized and then 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 e-TNS training test session with a verum or a sham training test device to control their ability to use the device appropriately and bear the feeling of the stimulation.

Included patients (who meet all of the study criteria) will be provided with study material (a Cefaly® Abortive Program (treatment) device with accessories and paper 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 flowchart is illustrated in Figure 1. During the different phases the investigator will monitor adverse events (AE).

#### 4.2.1. Recruitment phase

Patients contacted during a standard care visit at the headache clinic/research site or from research site database and advertising will be screened during a visit at the investigation site.

Patient will receive the information and consent documents and have to sign these documents before study procedures are initiated. The patient will be given a unique patient identification (screening) number (mentioned in the header of the patient's CRF). Then, the investigator will verify that the patient meets all the inclusion criteria and none of the 13 first exclusion criteria. If this is the case, the patient will be randomized to either the verum or the sham group and a unique randomization number will be allocated to him/her. This randomization number is mentioned on the sealed kit of investigational devices picked by the investigator and is reported in the patient's CRF. Then, the patient will be trained about the practical use of the Cefaly® Abortive Program device (verum or sham) thanks to an oral explanation, a video and an Instruction sheet. The patient will then perform him/herself a first 20-minute e-TNS training test session with a verum or sham training test device (according to the randomization) to check his/her

ability to use the device appropriately and to bear the sensation of neurostimulation, and therefore that the last exclusion criteria is not met.

Screened patient meeting all inclusion criteria and none of the exclusion criteria are included in the trial and will receive a verum or sham 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 reporting form). The investigator will explain to the patient how to fill in these documents.

The patient will complete a paper practice diary (Example diary) 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 this Example diary in details with the patient.

#### 4.2.2. Acute treatment phase

Included patient will be instructed to treat a single qualifying migraine headache within a 2-month period following the screening visit. A migraine headache is a qualifying migraine when all the following criteria 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<sup>1</sup>.
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 anti-migraine rescue 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 (verum or sham) 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 paper diary, the patient will have to report the following data just before the start of the e-TNS treatment session (baseline data):

- if there is any aura with the qualifying migraine attack
- the headache pain severity on the following scale: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain

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<sup>1</sup> if the patient woke up with a migraine, the starting time of the migraine is considered to be at the time of wake-up.

- the migraine-associated symptoms (photophobia, phonophobia, nausea, vomiting) and will specify which associated symptom is the most bothersome symptom (MBS).

Two hours after the beginning of the treatment session, whatever its duration (normally just after removing the device and the electrode if the session ran correctly for 2 hours), the patient will have to report the following data (2-hour data) in his/her diary:

- the headache pain severity on the following scale: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain
- the migraine-associated symptoms (photophobia, phonophobia, nausea, vomiting)

Patients will be instructed NOT to take any anti-migraine rescue medication during the 2-hour treatment session. Medication intake during the 2-hour treatment phase will be considered as a protocol violation.

Devices (verum and sham) are programmed for a unique 2-hour treatment session to be performed at home to treat a qualifying migraine. If the Cefaly® Abortive Program device (verum or sham) stopped during the 2-hour treatment session, 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, as mentioned before, the patient will have to report 2-hour data (headache pain severity and migraine-associated symptoms) 2 hours after the beginning of the treatment session, whatever the duration of the stimulation session.

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

The investigator will perform a follow-up phone call during the 2-month period during which the acute treatment phase has to take place.

#### 4.2.3. Post-treatment phase

Starting two hours after the beginning of the treatment session, the patient is allowed to take anti-migraine rescue medication if and only if the migraine headache pain is moderate or severe, either because there has not been pain relief or because after initial pain relief (no headache or mild headache pain) a moderate or severe headache is resuming.

The patient will have to report the following data in his/her diary at 24 hours after the beginning of the treatment session (24-hour data):

- the rescue medication intake, if any, between 2 hours and 24 hours after the beginning of the treatment session, and, if applicable, the time when the medication was taken
- the headache pain severity on the following scale: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain

- the migraine-associated symptoms (photophobia, phonophobia, nausea, vomiting)

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

#### 4.2.4. Final visit

The patient will be instructed to return to the investigation site within approximately 4 days after the treatment session to return the study material, i.e. the Cefaly® Abortive Program device as well as completed paper diary and AE reporting form. The investigator will review the diary in details to ensure data completeness and 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 identification (screening) number and the date (no initials).

All adverse events reported on the AE reporting form will be reviewed by the investigator to assess severity. The investigator will also ask the patient if he/she has experienced any adverse effects not reported on the form. Additionally, the investigator will ask the patient if he/she has experienced any device defects.

If a patient has not treated a migraine attack within two months following the screening visit, the study material (Cefaly® Abortive Program device with accessories) will have to be returned to the study site. This will be considered as a protocol violation.

#### 4.2.5. Discontinuation

##### Premature withdrawal of the trial

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. Patient withdrawal may be due to AE and/or SAE or upon patient request.

##### 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.

##### 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.

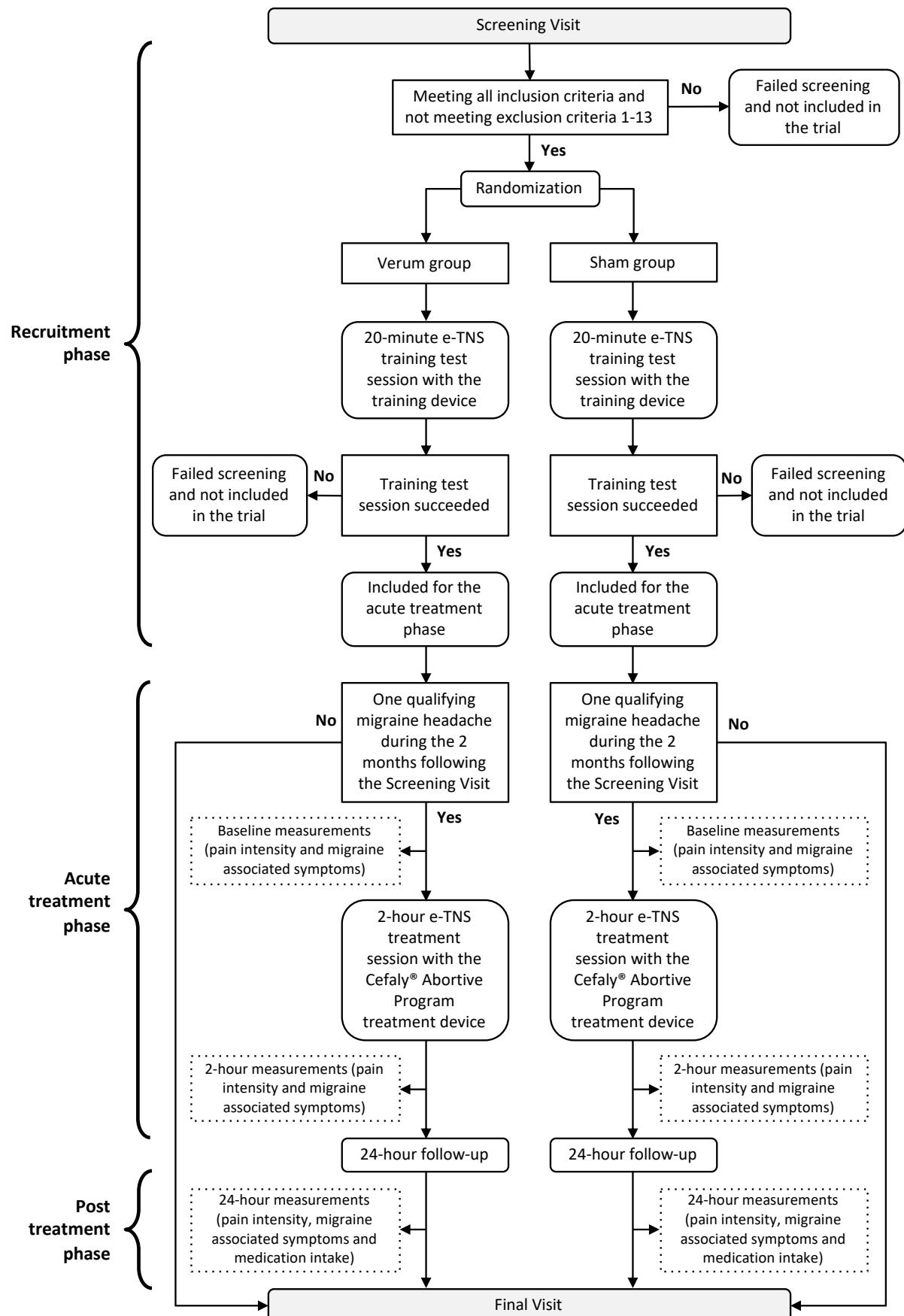


Figure 1 - Study flowchart

## 5. Subjects

The study will randomize at least 600 patients, men or women<sup>2</sup>, in a 1:1 ratio into each group (verum or sham).

### 5.1. Inclusion criteria

The following inclusion criteria apply:

- 1) Age from 18 to 65 on the day of signing the informed consent form
- 2)  $\geq$  1-year history of migraine with or without aura according to 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
- 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 reporting 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

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<sup>2</sup> Pregnant women can be enrolled. The device is perfectly safe for pregnant women.

- 7) Diagnosis of secondary headache disorders including Medication Overuse Headache
- 8) Patient abusing opioids or user of recreational or illicit drugs or having 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 in the last 30 days before the screening visit (Visit 1)
- 14) Patient not having the ability to use appropriately the device and/or to perform himself/herself or bear the first 20-minute stimulation session during the training test session at the study site

## 6. Medical device and treatment

### 6.1. Description of the device under investigation

The device under investigation is the Cefaly® Abortive Program device. It 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® Abortive Program device. The device acts by external stimulation of the upper branch of the trigeminal nerve (e-TNS). The Cefaly® Abortive Program device generates very precise electrical impulses to trigger action potentials on supraorbitalis and supratrochlearis nerve fibers.

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

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



Figure 2 - Cefaly® Abortive Program device

The Cefaly® Abortive Program device is connected to the body via a self-adhesive electrode (Figure 3) applied on the forehead. The Cefaly® electrode is 94 mm long and 30 mm high. It makes the interface between the Cefaly® Abortive Program device and the skin. This electrode has been approved by the FDA.



Figure 3 - Cefaly® electrode

According to the randomization, the patients will use a specific verum or sham Cefaly® Abortive Program device, that is programed to perform a unique 2-hour treatment session.

#### 6.1.1. Verum device

The Cefaly® Abortive Program verum device will be programed with the following parameters: rectangular biphasic pulse current (100 Hz, 250  $\mu$ s) 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).

#### 6.1.2. Sham device

The Cefaly® Abortive Program sham device will be programed with the following parameters: rectangular biphasic pulse current, with similar pulse width (250  $\mu$ s), at a linearly increasing intensity sufficient for the patient to feel strong paraesthesia similar to that produced by the verum device, but with a different frequency that will not induce a sedative effect to the central nervous system (1).

#### 6.1.3. Blinding

The sham device is identical in shape and color as the verum device. Also, the sham device will beep and flash identically to the verum device. No differences will exist between the sham and verum devices and it won't be possible for the patient as for the investigator to know which device is verum or sham. The only difference will be in the stimulation parameters.

Blinding between verum and sham stimulations has been validated by a test at Spincontrol Laboratory (Tours, France) on 128 subjects (62 received verum and 66 received sham) who were unable to distinguish between the verum and the sham stimulation.

## 6.2. Device technology

The Cefaly® Abortive Program device 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), that causes headache pain relief during migraine attacks.

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

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

The device is a constant current generator for a maximum skin impedance of 2.2 k $\Omega$  that delivers rectangular biphasic symmetrical pulses with a zero electrical mean. The impulses and generator characteristics allow insignificant overshoot and mismatch. The pulse width corresponds to the chronaxie of targeted supraorbitalis and supratrochlearis nerves. The frequency used in the current study for the

verum device is 100 Hz. The sham device has a different frequency that will not induce a sedative effect to the central nervous system (1).

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® Abortive Program 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 (e-TNS).

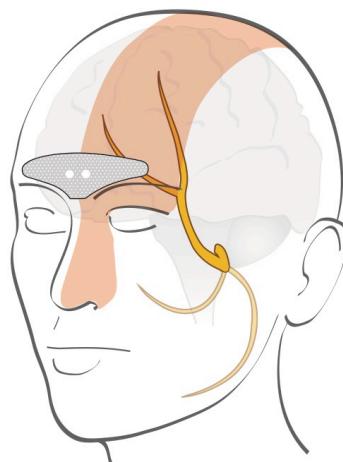


Figure 4 - The Cefaly® electrode placed on the forehead covers the supratrochlearis and supraorbitalis nerves

### 6.3. Mechanism of action

The Cefaly® Abortive Program 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® Abortive Program 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® Abortive Program device 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 with high frequencies of the trigeminal system induces a sedative effect on the central nervous system and a trigeminal nociceptive threshold modification, that causes headache pain relief during migraine attacks.

## 6.4. Training test devices

During the recruitment phase, the patient will have to perform him/herself a 20-minute training test session to check his/her ability to use the device appropriately. This training test session will be performed using a specific training test device.

Compared to the treatment device (Cefaly® Abortive Program device), the training test device has a shorter session duration (20 minutes instead of 120 minutes). The ramp-up and ramp-down times are the same and the stimulations parameters are identical. The training test device has a grey button (Figure 5) while the treatment device has a dark pink button. This prevented confusion in device handling.



Figure 5: Training test (left) and treatment (right) device used during the trial.

According to the randomization, the patients will use a specific verum or sham training test device, that is programed to perform a unique 20-minute training test session.

## 6.5. 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 training test device (verum or sham) for a first 20-minute training test session to check his/her ability to bear the paresthesia feeling (absence of forehead skin allodynia) and to use the device appropriately. Then, at home, the patient will apply the Cefaly® Abortive Program device (verum or sham) for a 120-minute treatment 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.

## 6.6. Medication during the trial

Patients will be instructed NOT to take any anti-migraine rescue medication during the 2-hour treatment phase. Medication intake during the 2-hour treatment phase will be considered as a protocol violation. After the 2-hour treatment phase, if and only 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 rescue

medication will be recorded by the patient in the diary for the 24 hours following the beginning of the treatment.

If the patient has a migraine prophylactic treatment, any modification of this migraine prophylaxis treatment is NOT allowed. Change in prophylactic treatment will be considered as a protocol violation.

## 6.7. Device provisioning

The sponsor will deliver all the investigational devices and related accessories directly to the investigators. A unique randomization number will be allocated to each patient. Each unique randomization number corresponds to either the verum or the sham group and is associated with one kit of two devices: a training test device and a Cefaly® Abortive Program (treatment) device. Consequently, for a given patient, the training test and Cefaly® Abortive Program devices are both verum or both sham, according to the randomization. A single sealed kit containing the training test device and the Cefaly® Abortive Program device, both with the same allocated randomization number, will be delivered to each patient, so that they cannot be reused on different patients. For each patient, the unique randomization number indicated on the kit has to be reported in the patient's CRF and will allow to identify, at the end of the study, which devices were used by each patient, and thus whether the patient used verum or sham devices.

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 sponsor, 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) at baseline.
- **Rescue medication intake.** The patient will also record whether he/she took ANY anti-migraine rescue medication during the 24 hours following the beginning of the e-TNS treatment 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	•	•	•
Identification of the most bothersome migraine-associated symptom (MBS)	•		
Rescue medication intake			•

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

### 7.2. Blinding

The investigator and patient will be blinded from whether the allocated devices are verum or sham.

The treatment allocation will be concealed using the following procedure. Verum and sham devices will be programmed by the manufacturer CEFALY Technology. They will be sent to each investigator by blocks with equal number of verum and sham kits of devices. The only indication on the kit of devices will be a unique randomization number. The list of correspondence between allocation (verum or sham) and randomization number (also named as randomization code) will be provided in a sealed envelope to the coordinating investigator. This procedure ensures a blinding from the enrolling investigator as well.

In case of an emergency, identification of a specific blinded investigational device can be revealed without breaking the blind for the remaining devices. In this case, the investigator should contact CEFALY Technology that will provide the required identification details.

## 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 identification number (i.e. patient screening number) for identification purposes. Each patient should be assigned only one number. Should the patient fail to qualify for the study, his/her identification (screening) number must not be re-used for any other patient in the study.

CRF and paper documents provided to the patient (i.e. diary and AE reporting form) will include the unique patient identification (screening) number in the header.

The collected data will be included in the following source documents: patient's case report form (CRF) and diary. These completed documents will be provided by the investigator to the sponsor. In practice, the investigator records these completed documents in an appropriate binder and sends the scan of the documents by email to the sponsor. 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 randomization 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 Form is sent to the investigator. The completed and signed form is sent back to the sponsor. 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 and investigators will report SAE and AE to the sponsor using the specific collecting forms annexed to the CRF. These SAE and AE collecting forms will be reviewed and analysed by the sponsor when received. The device defects are also collected and investigators will report device defects to the sponsor using the CRF.

### 8.2. Statistics

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

#### 8.2.1. Sample size

The sample size was computed based on the primary outcome, i.e. pain freedom at 2 hours. The sample size should allow detecting a statistically significant difference between the treatment (verum) and control (sham) outcome value with a power of at least 90% and a 5% level of significance.

In the pilot clinical trial, the pain freedom at 2 hours associated with the Cefaly® Abortive Program treatment was 35.4%. Results from previous randomized, sham-controlled trial using a stimulation device (transcranial magnetic stimulator) as acute treatment of migraine reported 22.0% of pain freedom at 2 hours in the sham group (11).

A power analysis showed that a sample of 239 patients per group allows detecting a statistically significant difference between the treatment (35.4%) and control (22.0%) pain freedom at 2 hours with a power of at least 90% and a 5% level of significance.

Taking into account a rate of 20% of patient loss during the study (based on the pilot clinical trial), at least 299 patients should be included in each group. Consequently, 600 patients will be included in the present clinical investigation.

NOTE: The sample size meets the FDA definition of Phase III clinical investigation (according to the FDA, a clinical investigation can be considered as a Phase III clinical study when the number of participants ranges from 300 to 3,000 volunteers who have the disease or condition).

#### 8.2.2. Study hypotheses

The general hypothesis is that the Cefaly® Abortive Program device is safe and effective for the abortive treatment of migraine.

In particular, for the abortive treatment of migraine:

- 2 hours of e-TNS with the Cefaly® Abortive Program device is better than 2 hours of sham e-TNS to achieve pain freedom, as measured by the pain freedom at 2 hours and the sustained pain freedom at 24 hours.
- 2 hours of e-TNS with the Cefaly® Abortive Program device is better than 2 hours of sham e-TNS to achieve symptoms freedom, as measured by the MBS freedom at 2 hours and the absence of migraine-associated symptoms at 2 hours.
- 2 hours of e-TNS with the Cefaly® Abortive Program device is better than 2 hours of sham e-TNS to achieve pain relief, as measured by the pain relief at 2 hours and the sustained pain relief at 24 hours.
- Anti-migraine rescue medication intake is lower after 2 hours of e-TNS with the Cefaly® Abortive Program device than after 2 hours of sham e-TNS.
- No serious adverse events (SAE) due to the 2-hour e-TNS session with the Cefaly® Abortive Program device within the 24 hours following the beginning of the treatment.

### 8.2.3. 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, when appropriate.
- 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  $\alpha=0.05$  (2-sided) level.
- Comparison between two independent samples (verum and sham group) will be performed using either the Mann-Whitney U test (also called the Mann-Whitney-Wilcoxon (MWW), Wilcoxon rank-sum test, or Wilcoxon-Mann-Whitney test), the Fisher test or the Anova test.

### 8.2.4. Statistical analysis

#### Efficacy analysis

The efficacy analysis will be executed on a modified intention-to-treat (mITT) basis.

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 (verum or sham) during at least 30 minutes\*.
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.

\*If the patient stopped the 2-hour treatment session after 30 minutes but 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 anti-migraine rescue medication between 2 hours and 24 hours after the beginning of the e-TNS treatment session, the headache pain intensity and migraine-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 comparing both groups (verum versus sham). The safety analysis will be performed on all randomized patients, i.e. patients who underwent at least the e-TNS training test session.

## 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 sponsor and the sponsor 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® Abortive Program device are:

- Reversible skin irritation at the place of electrode
- Allergic reaction to the gel of the electrode (1 out of 1000)
- Pain during the session
- Sleepiness
- Neck pain
- Nausea
- Tooth pain

Paraesthesia, tingling/itching and burning sensation are normal effects of the device and should therefore NOT be considered as AEs, unless this sensation leads to treatment discontinuation.

## 9.5. AE collection

The patients are instructed to report all AEs to the investigator. AEs will be analyzed by the investigator who will document it in the specific collecting forms annexed to the CRF.

All AEs will be collected in the specific collecting forms annexed to 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 sponsor 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 information to be communicated to the sponsor are:

- Patient identification (screening) number

- 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 (screening) number of the subject.

#### 9.6.2. Modalities of notification to the sponsor

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

- To sponsor (represented by the CEO)
- As fast as possible
- By e-mail: see the specific form annexed to 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 sponsor.

#### 9.6.4. Notification period

It is the investigator responsibility to notify the sponsor 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 sponsor to the authorities

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

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 sponsor takes the appropriate emergency measures. The sponsor 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.

NOTE: In case of findings that could affect adversely the safety of subjects or impact the conduct of the trial, the sponsor has to notify all concerned investigator(s).

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