Multi-center, double-blind, randomized, sham-controlled trial on the acute treatment of migraine with the Cefaly® device

PROTOCOL

PRINCIPAL INVESTIGATOR

Denise E. Chou, M.D.

Columbia University Medical Center
Department of Neurology
51 West 51st Street, Suite 380
New York, NY, 10019
USA

INVESTIGATORS

Deena Kuruvilla, MD

Assistant Professor

Department of Neurology

Yale School of Medicine

Peter McAllister, MD

The New England Institute for Clinical Research.

30 Buxton Farm Road

Stamford CT 06905

USA

Dana Winegarner, DO

Rowe Neurology Institute

8550 Marshall Drive, Suite 100

Lenexa, KS 66214-9836

USA

PROMOTER

CEFALY Technology
ZI des Hauts Sarts, 4ème Avenue 5
4040 Herstal (Liège), BELGIUM

Study Number: 50213

Signature

Investigators

Name	Date	Signature
Dr. Denise E. Chou		
Dr. Deena Kuruvilla		
Dr. Peter McAllister		
Dr. Dana Winegarner		

Promoter

Name	Date	Signature
CEFALY Technology Dr. Pierre Rigaux		

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1. Rationale

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

Many patients in Europe have reported benefit using the device only during attacks. In past few years, small studies have been performed using the Cefaly® device as an acute treatment:

- A medical lab in France ("Spincontrol") implemented an open clinical trial during 28 days on 32 patients suffering from frequent tension-type headache but not migraine. 66% reported pain relief using the device during an attack.

- University of Liege conducted a pilot trial on migraine patients (4). Ten patients were asked to apply the Cefaly® device as an acute treatment for 3 attacks. Electro-stimulation provided complete pain relief in 13% of attacks, delayed the need for acute medication use by more than 30 minutes in 20%, had no effect in 57% and increased the pain in 10%. However, there were flaws in the protocol design, including the short duration of the session (20 minutes), which is not sufficient to provide relief based on experiential feedback from migraineurs. In addition, the number of attacks treated was too small, as patients may require several sessions to adapt to and allow the intensity of stimulation to rise to a therapeutic level (otherwise it is under a minimum threshold of efficacy).

- Kozminsky (5) assessed whether the Cefaly® device was effective and well-tolerated as rescue therapy for migraine symptoms lasting 72 hours or longer. t-SNS (or 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 reported that they would consider home therapy if it were affordable.

- Since March 2015, an open-label pilot trial on the acute treatment of migraine using the Cefaly® device has been underway at Columbia University, NY. Patients experiencing a migraine attack for at least 3 hours (without use of acute medications during this time) and having stable pain intensity for at least 1 hour, are eligible to receive a 60-minute stimulation to treat their attack. Pain is assessed on a 10-point visual analogue scale (VAS) before, after the 1-hour treatment, and 2 hours after the beginning of the treatment. The study is still on-going, but the results to date confirm prior observations that e-TNS therapy via the Cefaly® device can significantly reduce pain intensity during an acute migraine attack, as measured via the VAS.

Based on the data from the above studies and preliminary findings from the open-label pilot trial at Columbia, it is reasonable to further investigate the efficacy of e-TNS with the Cefaly® device as an acute treatment for migraine via a double-blind, randomized, sham-controlled trial.

2. Study objective

The main objective of this study is to assess the efficacy of the Cefaly® device as an acute treatment of migraine attack in adult patients.

3. Study outcomes

Primary outcome:

- Mean change of pain score at 1 hour compared to baseline

Secondary outcomes:

- Proportion of patients not having required rescue medication at 2 hours
- Mean change of pain score at 2 hours compared to baseline (if rescue therapy was not used)
- Proportion of patients not having required rescue medication within 24 hours
- Mean change of pain score at 24 hours compared to baseline (if rescue therapy was not used)

4. Study design

4.1. General description

This study is a clinical study with the following characteristics:

- Multi-center (4 investigation sites)
- Prospective
- Double-blind
- Sham-controlled
- Randomized

4.2. Experimental protocol

Patients having a stabilized migraine attack will be recruited during a standard care visit or at an on-demand appointment. They will report their pain score before the treatment (recruitment phase), after 1 hour of treatment (acute treatment phase) and finally 2 hours after the beginning of the treatment (post-treatment phase). At that moment (2 hours after the beginning of the treatment), patients will receive rescue medication if necessary. Rescue medication intake will be reported during the 24 hours following the beginning of the treatment. Pain score at 24 hours after the treatment will be reported as well. The overall study flow is illustrated in Figure 1. During the different phases the investigator will monitor adverse events.

4.2.1. Recruitment phase

Two options are available to recruit patients:

- Eligible patients can be recruited during a standard care visit if they are experiencing a migraine attack having lasted at least 3 hours, with pain stabilized for at least 1 hour, and have not used acute migraine medication within the past 3 hours.

- Patients can also be screened beforehand (having been informed about the study at a standard visit or via advertisement), and arrange for an on-demand appointment when they are undergoing an attack for at least 3 hours, with pain stabilized for at least 1 hour.

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 inclusion criteria and none of the exclusion criteria. If this is the case, the patient has to give a value on an 11-point visual analog scale (VAS) (0 = no pain, 10 = maximum pain) of the current pain associated with the migraine attack.

The patient will then be randomized to either the verum or the sham group. To this end, a unique device will be allocated to him/her.

The investigator will then apply the device on the patient and start the stimulation. If the patient cannot bear the paresthesia of the neurostimulation (needs to stabilize intensity before 4 minutes i.e. nociceptive threshold < 5 mA for impulse width of 250 µs), the patient is considered meeting the exclusion criteria of allodynia (too low nociceptive threshold). The patient is in this case not included in the trial.

4.2.2. Acute treatment phase

When the patient bears more than 4 minutes of neurostimulation, he/she is included in the trial, and the neurostimulation continues for the 56 remaining minutes of the stimulation. The patient will be randomized to receive either:

- Verum stimulation, with 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 (46 minutes), OR
- Sham stimulation with felt paresthesia.

At the end of the one-hour treatment period the patient gives again an estimate of the pain on the same VAS.

During the treatment, the patient can stabilize the intensity by pressing the button or can stop the treatment. The device can also be stopped accidentally, what interrupts the treatment. When stopped, voluntarily or accidentally, the device 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 gives the estimate of the pain after 60 minutes.

4.2.3. Post-treatment phase

Two hours after the beginning of the treatment the patient will have to give a new estimate of the pain on the VAS, provided that the patient didn't take a recue medication before.

After the 2 hours, if needed usual rescue treatment can be administrated to the patient. If so, this is recorded by the investigator.

Patients will also be instructed to record the pain level 24 hours after the beginning of the treatment. They will be contacted to report this pain level and whether or not rescue medication was taken within the 24 hours following the beginning of the treatment. In case of rescue medication intake within the 24 hours following the treatment the pain level at 24 hours will not be taken into account.

4.2.4. Drop-outs, intention-to-treat and last value carried forward

a) During the treatment one-hour phase

If the patient takes rescue medication before 1 hour, it is a drop-out because the action of the medication affects the pain estimate at 1 hour.

If the patient stops the one-hour treatment and leaves the clinic, it is a drop-out because there is no pain estimate at 1 hour.

If the device stopped working accidentally, it is a drop-out because of technical reason.

On the other hand, if a patient does not get the full Cefaly acute treatment (does not want to complete the 1 hour stimulation), but stays available for the 2 hours of the protocol, this patient is kept in the trial and considered as an intention-to-treat patient (as opposed to per protocol patient).

b) During the post treatment phase

If the patient takes rescue medication before 2 hours, only the one-hour pain intensity estimate has been measured; the last value carried-forward method will be applied for 2 and 24 hours pain intensity estimate.

If the patient takes rescue medication at 2 hours or after 2 hours, the last value carried-forward will be applied for the 24 hours pain intensity estimate.

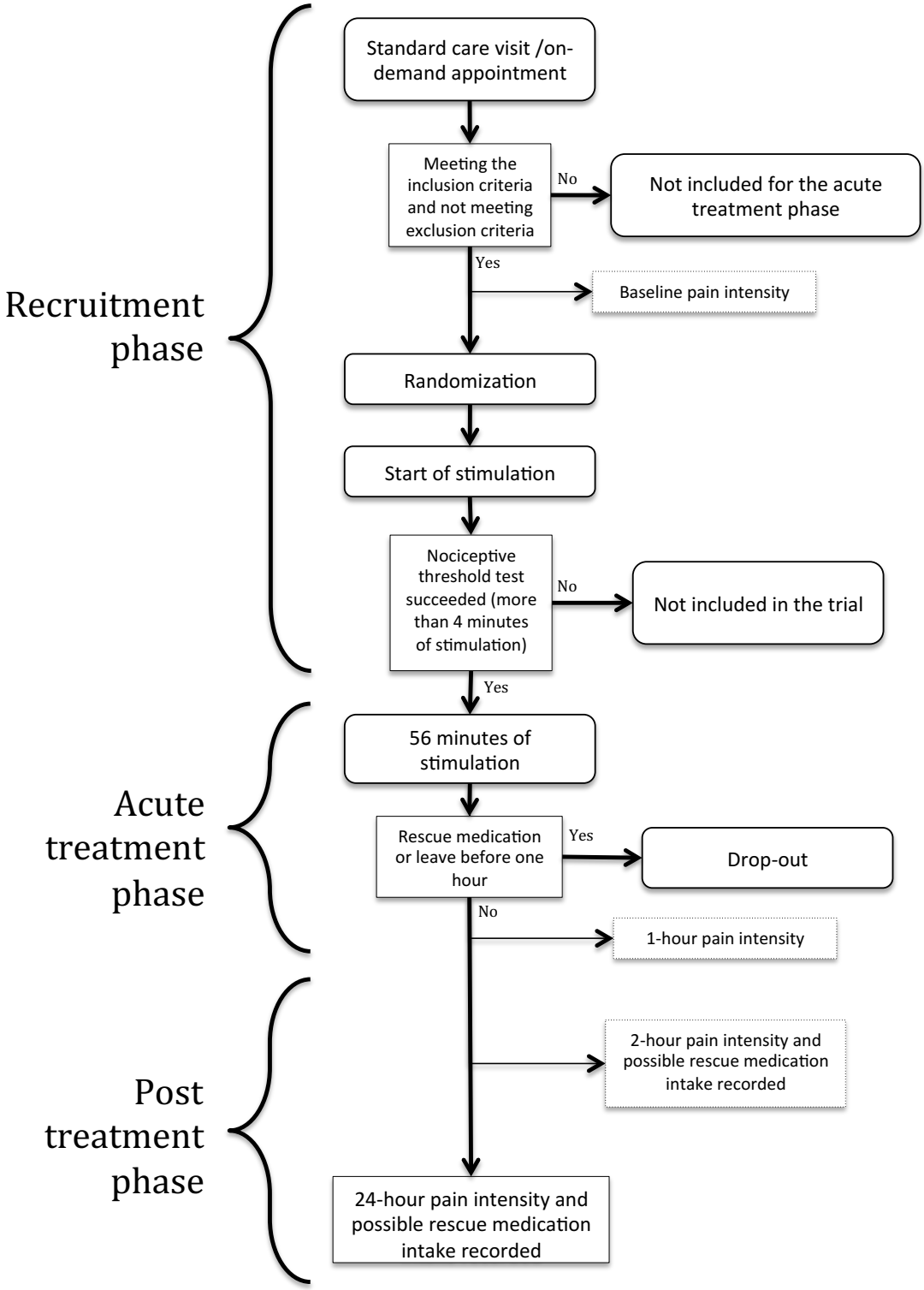

Figure 1 - Study flowchart

5. Subjects

The study will include 90 men or women.

5.1. Inclusion criteria

The following inclusion criteria apply:

1. Aged from 18 to 65 years
2. History of episodic or chronic migraine with or without aura meeting the diagnostic criteria listed in ICHD-III beta (2013) section 1, migraine, with the exception of ''complicated migraine'' (i.e., hemiplegic migraine, basilar-type migraine, ophthalmoplegic migraine, migrainous infarction)
3. Having a migraine attack lasting at least 3 hours
4. Migraine pain intensity stabilized for at least 1 hour
5. Frontal, retro-, or peri- orbital headache.

5.2. Exclusion criteria

The following exclusion criteria apply:

1. Pregnant women
2. Patients having received Botox treatment in the prior 4 months
3. Patients having received supraorbital nerve blocks in the prior 4 months
4. Diagnosis of other primary or secondary headache disorders, except of Medication Overuse Headache
5. Patients with only temporal or occipital headache
6. Patients using opioid medication
7. Patients having taken abortive migraine medication in the prior 3 hours
8. Allodynia: intolerance to supraorbital neurostimulation (allodynia) that makes the treatment not applicable (the patients will be excluded if they are unable to tolerate the first 5 minutes of neurostimulation).
9. Implanted metal or electrical devices in the head
10. Cardiac pacemaker or implanted or wearable defibrillator
11. Patient having had a previous experience with Cefaly®

6. Medical device and treatment

6.1. Device description

The Cefaly® is a small, portable product, which is meant to be worn on the forehead by attachment to a self-adhesive electrode. Two 1.5V AAA batteries provide 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: 163 mm x 170 mm x 40 mm.
- Weight: 30 g.

Figure 2 - Cefaly® device

The 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 sessions of 60 minutes. The Cefaly® electrode is 94 mm long and 30 mm high. It makes the interface between the device and the skin. This electrode has been approved by the FDA together with the 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 two 1.5V AAA batteries.

The Cefaly® 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 46 minutes). The pulse frequency is 100 Hz. The pulse width is 250 µs.

If the user feels that the intensity becomes too high, a simple pressure on the button will stabilize the intensity for the rest of the session.

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.

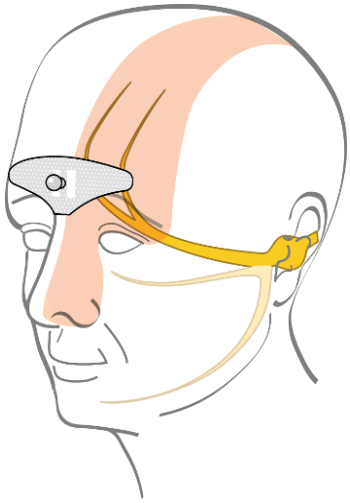

Figure 4 - The electrode placed on the forehead covers the supratrochlearis and supraorbitalis nerves

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

The investigator will apply the device on the patient's head. A session of 60 minutes will be applied. If the patient experiences discomfort during the stimulation, he or she can stabilize the intensity of stimulation at any time by pushing the "on" button of the device (the current intensity will then remain stable until the end of the session). The patient should at least let the device increases the intensity for 4 minutes in order to be included in the trial: before this point, the patient's nociceptive threshold is considered too low because of allodynia.

6.5. Sham device

As this study is sham-controlled, a sham neurostimulator has to be provided. The sham stimulator is identical in shape and colour as the verum Cefaly® device. Also, it will beep and flash identically to the verum Cefaly® device. No difference 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. The sham stimulator will contain a stimulation program with a low frequency, which will be sufficient for the patient to feel paresthesia similar to that produced by the verum, but will not induce a sedative effect to the central nervous system.

The sham device has been validated in a clinical trial on 128 subjects (62 verum and 66 sham). Following the trial, the patients were indeed unable to distinguish whether they received an active or a sham device.

6.6. Medication during the trial

No medication can be used during the 2 hours of the study (1 hour of Cefaly stimulation followed by 1 hour of observation). Any rescue medication can be used after these 2 hours and have to be recorded during the 24 hours following the beginning of the treatment.

If a patient wants a rescue medication during the one-hour treatment phase it is a drop-out, if the patient wants a rescue medication after the one-hour treatment phase but before the 2 hours of the study the last value carried-forward is applied.

6.7. Device provisioning

The promoter will deliver the specific devices directly to the investigators. The devices will be delivered by sets of even number of verum and sham devices, ensuring at least one device per patient. The investigator will not be able to distinguish both. A single device cannot be reused on different patients. Each 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, whether the patient used a sham or verum device. Electrodes will be delivered in enough quantity to ensure to have one per patient.

7. Practical study modalities

7.1. Measures

Pain score. In order to evaluate the modification of pain score from baseline to 1-hour treatment and to 2-hour treatment, patients will be asked to give an indication on the pain level using a visual analogue scale (VAS) counting eleven levels (0 = no pain, 10 = maximum pain) at the recruitment phase (before applying the treatment), right after the treatment phase (1 hour), 2 hours after the beginning of the treatment and at 24 hours after the beginning of the treatment.

Rescue medication after the treatment. The investigator will also record whether the patient uses another acute medication right after the 2 hours. Patients will also be contacted 24 hours after the beginning of the treatment to report whether or not rescue medication was taken within the 24 hours following the beginning of the treatment.

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

	Baseline	1 hour	2 hours	24 hours
Pain score	●	●	●	●
Rescue medication intake			●	●

7.2. Calendar

The study is foreseen to start in December 2016 and to be finished by July 2016.

7.3. Blinding

Blinding between verum and sham devices has been previously validated in a trial on 128 patients (62 verum and 66 sham). A new device will be used for each study patient. Sham and verum stimulators and electrodes will look alike. Verum will use a high frequency impulse and sham a low frequency. Both devices will generate paresthesia on the forehead to ensure blinding. Patients will therefore not be able to know if it is the active neurostimulation or the sham.

The investigator and research coordinator will be blinded from which device the patient has (sham or verum). A built-in electronic system will record the treatment delivered to each patient.

The treatment allocation will be concealed using the following procedure. Verum and sham stimulators will be programmed by the manufacturer Cefaly Technology. They will be sent to each investigator by blocks with equal number of verum and sham devices. The only indication on the device box will be a

number. The list of correspondence will be sent in a sealed envelope to the investigators. This procedure ensures a blinding from the enrolling investigator as well.

8. Data management and statistics

8.1. Data management

The data will be included in the case report form (CRF) that will be provided by the investigator to the promoter anonymously, using a numbering system. To trace to which group the patient belongs (sham or verum), the device number will be collected in the CRF as well.

8.2. Statistics

8.2.1. Sample size

Results from a randomized controlled trial on an acute migraine treatment (6) showed in the placebo group a reduction in mean pain score of 10% after 1 hour and 14% after 2 hours, compared to baseline. The results of the pilot trial on the acute treatment of migraine using the Cefaly® device showed a reduction in mean pain score of 59% after 1 hour and 55% after 2 hours. The standard deviation related to mean pain score was 2.42 after 1 hour and after 2 hours. Based on these results we could assume a difference in mean pain score of 2.83 after 1 hour and 2.40 after 2 hours between the active and placebo groups. A minimum of 17 patients in each group would be statistically required to detect a significant difference in mean pain score after 1 hour and after 2 hours, with a power of 80% and at two-sided alpha level of 5%, using a t-test for two independent samples.

A previous study reported 71% of patients from the placebo group using rescue medication compared to 41.33% for active groups on average (7). Considering these percentages, 43 patients in each group would have been statistically required to detect a significant difference in rescue medication use after 24 hours with a power of 80% and at two-sided alpha level of 5%, using a proportion test for two independent samples.

Overall, at least 43 patients in each group should allow to detect a significant difference between active and placebo groups in mean pain score after 1 hour and after 2 hours, and in rescue medication use. As the trial will be conducted in three different centres, the number of patients is rounded to 45 in each group (i.e. 15 patients per group and per centre). Consequently, 90 patients will be recruited.

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.

- Imputation of missing data will be performed according to the last value carried forward method.
- Analyses will be conducted on an intent-to-treat (ITT) basis, i.e. including all subjects who used the study device for more than 4 minutes (see in exclusion criteria 8. Allodynia), did not take rescue medication before the 1 hour and reported pain at 1 hour.
- A sub-analysis of the per-protocol patients (those receiving the complete 1-hour treatment) will be performed as well.

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.

10. List of Annexes

CRF

Informed consent

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