Protocol

Open-trial on the prevention of chronic migraines with the CEFALY device

Investigators

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1. Rationale

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

Last March, thanks to these clinical data FDA approved the Cefaly device for the prophylactic treatment of episodic migraine in patients 18 years of age or older having frequent attacks.

Clinical data and FDA approval limit the intended use to episodic migraine patients; therefore chronic migraine patients (having ≥15 headache days per month) cannot benefit from this treatment.

Yet patients with more than 6 migraine attacks per month were observed to benefit more from using the device than subjects with fewer than 6 attacks per month. This suggests that Cefaly device could be more appropriate for chronic migraine than for episodic migraine. In addition most chronic migraineurs are subject to medication overuse that worsen their health situation while Cefaly device reduces in average acute medication intake by 37% in all patients and by 75% for responder patients. These elements indicate the probable interest of the Cefaly device for the treatment of chronic migraine but clinical studies are needed to demonstrate the efficacy not only in episodic migraine but in chronic migraine as well.

The purpose of this pilot study is to assess the efficacy of the Cefaly device in the treatment of chronic migraine prior to implement a control trial where the size and final protocol will be specified thanks to the outcomes of this pilot trial.

2. Study objective and outcome measures

2.1. Study objective

The goal of this trial is to evaluate the efficacy of Cefaly supraorbital transcutaneous neurostimulation device as a preventive treatment in adult patients suffering from chronic migraines.

2.2. Outcome measures

Several measures will be established thanks to the migraine diary: headache episodes, headache days, moderate/severe headache days, migraine days, acute medication intake, cumulative headache hours, and headache intensity.

All efficacy analyses are also based on the mean change from baseline to the 28 days ending with week 12.

2.2.1. The primary outcomes measures:

- Mean change from baseline in frequency of headache days (defined as a calendar day with at least one headache episode) for the 28-day period ending with week 12
- Overall acute headache pain medication use (all categories) mean change from baseline to the 28 days ending with week 12

2.2.2. The secondary outcomes measures:

- Mean change in frequency of migraine days (defined as a calendar day of headache meeting ICHD-III beta criteria for migraine 1.1, 1.2, or 1.5)
- Mean change in frequency of moderate/severe headache days (defined as a headache day with at least one headache episode with intensity = 2 or 3)
- Mean change in monthly cumulative headache hours on headache days
- Mean change in frequency of headache episodes (defined as patient-reported headache with pain)
- 50% responder rate for migraine days
- Mean change in the average headache intensity

3. Study Design

3.1. General description

This study is a clinical study with the following characteristics:

- monocentric
- prospective
- open

3.2. Experimental protocol

The patients will have to fill in a migraine diary both in the run-in period and in the treatment period. After 28 days baseline, the patients still fulfilling the inclusion criteria will receive the Cefaly device for 12 weeks. Established medication of the patients should not be modified during the full protocol. A final visit will be organized after the 12 weeks of treatment to collect migraine diary, possible side effects and adverse events reported regardless possible relationship to the device.

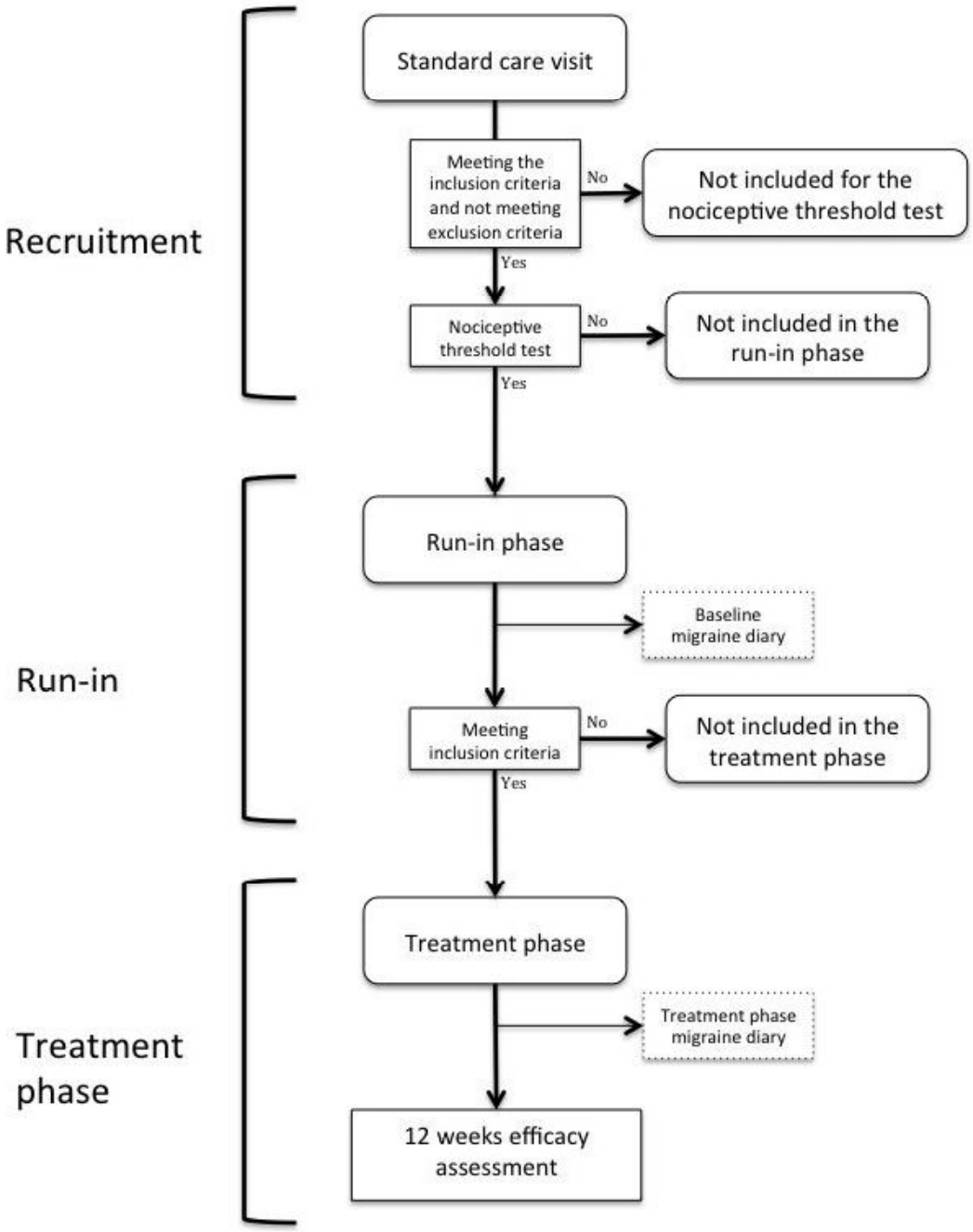

Figure 1: Study flow

3.2.1. Recruitment

The patients will be proposed to participate in the study during the standard care visits to the investigators. They will receive the information and consent documents and have to sign it if they wish to participate. 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 will be tested for tolerance to the neurostimulation (nociceptive threshold test). If the patient passes this test, he/she will be included in the run-in period.

3.2.2. Run-in period

After inclusion in the trial, patients will fill in during 4 weeks (28 days) a migraine diary in order to get baseline information on the different measures. At the end of this period a visit is foreseen, to verify the patient meets the criteria for number of days of headaches, and to deliver the device to the patient for the treatment period.

3.2.3. Treatment period

The patients who still fulfil the inclusion criteria after the run-in period will receive a Cefaly device for daily supra-orbital neurostimulation application for 12 weeks (84 days). They will activate the device at least for a 20 minute session a day, but preferably 2 sessions of 20 minutes a day, at the moment of the day that suits them best, but as much as possible at the same time of the day everyday. They can use as well the device during any headache or migraine to reduce the pain with two to six 20 minutes sessions. The final trial visit will be scheduled 12 weeks after the beginning of the treatment period to collect the diaries, monitor adverse events, collect devices for compliance measurement.

4. Subjects

4.1. Inclusion criteria:

At least 50 men or women aged 18 to 65 years with a history of chronic migraine meeting the diagnostic criteria listed in ICHD-III beta (2013) section 1, migraine (1), with the exception of ''complicated migraine'' (i.e., hemiplegic migraine, migraine with brainstem aura, ophthalmoplegic migraine-recurrent painful ophthalmoplegic neuropathy, migrainous infarction) will be enrolled. They are required during baseline to have ≥15 headache days and ≥ 8 migraine days.

Both patients with or without acute medication overuse (medication overuse headache – MOH) will be recruited: there should be an equal number of each (at least 25 patients with MOH and 25 without MOH).

4.2. Exclusion criteria:

The following exclusion criteria apply:

1. Women: Pregnant, lactating or <6 months post partum
2. For patients already on treatment with medications in the following classes: antihypertensives, antidepressants, antiepileptics, no dose change of those medications is allowed for at least 3 months before start of baseline and during the entire study period.
3. For patients treated with Botox, no injection within 4 months before start of baseline or during the study.
4. Diagnosis of other primary or secondary headache disorders, except of Medication Overuse Headache
5. A Beck Depression Inventory score of >24 at baseline
6. Psychiatric disorders that could have interfered with study participation
7. Intolerance to supraorbital neurostimulation that makes the treatment not applicable (test of nociceptive threshold with specific Cefaly program)

5. Medical device description and treatment

5.1. Medical 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 fibres. The device acts by stimulation of the upper branch of the trigeminal nerve in order to reduce the frequency of the migraine attacks.

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 1) is comprised of the following specifications:

- Dimensions: 163 mm x 170 mm x 40 mm
- Weight: 30 g.

Figure 1: CEFALY Device

The device is connected to the body via a self-adhesive electrode (Figure 2) applied on the forehead. The patient may use the device through sessions of 20 minutes. The CEFALY electrode is 94 mm long and 30 mm high. It makes the interface between the device and the skin. It's a multiuse electrode designed to be used 20 times.

Figure 2: CEFALY electrode

5.1.1. 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.

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 6 minutes). The pulse frequency is 60Hz. The pulse width is 250µs.

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 3)

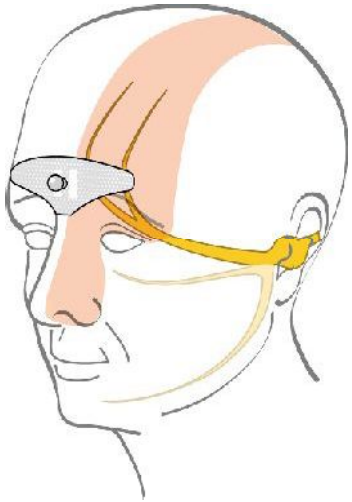

Figure 3: The electrode placed on the forehead covers the supratrochlearis and supraorbitalis nerves.

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.

5.1.2. Mechanism of action

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.

5.1.3. Usage during the trial

The CEFALY will be used daily by the patient in order to reduce the frequency of their headaches. The patients should have at least one session of stimulation per day, preferably 2 sessions, if possible roughly at the same time of the day every day. A session lasts 20 minutes. The patient can as well use the device during any headache or migraine to reduce the pain with two to six 20 minutes sessions.

The device contains a system that records the usage statistics (compliance). For each patient it will be possible to know how much time the device has been activated and at what intensity on average the patient has been stimulated.

5.2. Medication allowed and forbidden

We have to distinguish medication related with acute treatment from the one intended for prophylactic treatment.

For acute medication, all medications currently used by the patient will be allowed

Prophylactic treatment with Botox and any change in the doses of other prophylactic medications are not allowed as per Exclusion criteria 2 and 3 above.

5.3. Devices provisioning

The promoter will deliver the devices directly to the investigators.

The patient will receive the device at the medical visit. He/she will return it at the end of the 12 weeks treatment period.

6. Practical study modalities

6.1. Measurement

***Migraine Diary*.** During the run-in phase and the treatment phase, the patients will fill in a migraine diary. For each day, this diary contains:

- Intensity of pain (on a scale of 1 to 3)
- Time when the pain started
- Time when the pain stopped
- Accompanying symptoms: nausea, vomiting, photophobia, phonophobia
- Acute anti-migraine medication intake
- How many Cefaly sessions (treatment phase only)
- For women, indicate days of menstruation

With this diary, the different measures can be computed:

- Frequency of headaches days
- Acute medication intake
- 50% responders rate, computed as the number of patients having a reduction of at least 50% of their migraine days
- Frequency of migraine days (a headache day is a migraine day except if the intensity is 1 and there is no acute anti-migraine medication intake)
- Frequency of moderate/severe headaches
- Cumulative hours of headache
- Frequency of headache episodes
- Average headache intensity

6.2. Calendar

The study is foreseen to start beginning of 2015 and to be finished by the end of September 2015.

7. Data Management and Statistics

7.1. Data Management

The diaries will be provided to the sponsor anonymously, using a numbering system within UC Denver.

7.2. Statistical Methods

7.2.1. Sample size

The number of subjects to recruit in the study (50 patients, 25 with MOH and 25 without MOH) should be enough for statistical power, given that the CEFALY will provide a 25% reduction in the number of headache days.

7.2.2. 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 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.

These analyses will be conducted on an intent-to-treat (ITT) basis, i.e including all subjects who used the study device at least once. For each patient, the average outcome will be calculated for the run-in and for the treatment on all data available during each period, without any imputation of missing data.

8. Adverse Events Management

8.1. Definitions

8.1.1. 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.

8.1.2. 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 promoter is responsible of transmission of the SAE declaration to the authorities.

8.2. 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.

8.3. 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 aetiology, that could explain the AE.
- existence of similar published or known AE ….

8.4. Expected AE

The expected AE 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

8.5. AE collection

The patients are instructed to report all AE to the investigator. AE will be registered daily by the subject in the corresponding form. This form will be returned by the subject at the end of the study and will be analyzed by the investigator who will notify it in the CRF.

All AE 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.

8.6. Investigator's responsibility with respect to a SAE

8.6.1. SAE Notification

Each SAE will be described on the specific form with as much details as possible. The information 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 hospitalisation 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.

8.6.2. 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 : the specific form

8.6.3. 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.

8.6.4. 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).

8.7. Notification of pregnancy to the promoter

The CEFALY device is perfectly safe for pregnant women. However, pregnancy might have an influence on the migraine attacks.

If a pregnancy is suspected during the study, the subject should notify the result of the pregnancy test. If the pregnancy is confirmed, the subject's data are excluded from the analysis.

8.8. 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 Investigational Review Board (UC Denver).

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 7 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.

9. List of Annexes

Migraine diary template
CRF
AE reporting form
Informed consent

10. 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.
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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.