A single center, pilot, open trial of the CEFALY® device in the treatment of patients with fibromyalgia

PROTOCOL

INVESTIGATOR

Lesley M. Arnold, M.D.

University of Cincinnati College of Medicine
260 Stetson Street, Suite 3200
Cincinnati, Ohio 45219
USA

PROMOTER

Pierre Rigaux, M.D.

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

Study Number: 50212

Signature

Investigator

Name	Date	Signature
Lesley M. Arnold		

Promoter

Name	Date	Signature
Pierre Rigaux		

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1. Rationale

Fibromyalgia (FM) is a chronic pain syndrome with characteristic symptoms of fatigue, sleep disturbance, mood problems and cognitive complaints. Recent research suggests that the central nervous system (CNS) plays a major role in these symptoms in part through central sensitization [1,2]. Current medications for the treatment of FM have limited efficacy and are associated with side effects for most patients. Furthermore, polypharmacy is common in patients with FM, which potentially increases the side effect burden of treatment. e-TNS (external trigeminal nerve stimulation) with the CEFALY® device produces a sedative effect [3] and has proven its efficacy as a prophylactic treatment for episodic migraine [4,5]. The device is FDA-approved for the prevention of frequent episodic migraine and is very safe, with less than 5% of reported adverse events that are all minor and fully reversible. Besides its indication for migraine, e-TNS CEFALY® device shows several actions on the CNS that could support its use in FM: it produces a sedative effect during the session, pilot trials reported improvement in depression [6], and migraine patients frequently report improved sleep and less fatigue. Therefore e-TNS with CEFALY® might help to improve symptoms of FM and make available a new valuable therapeutic treatment for FM.

Prior to conducting a randomized sham controlled clinical trial to investigate the efficacy and safety of e-TNS with the CEFALY® device in FM, a pilot open trial is needed to collect preliminary data on efficacy and safety and to establish the group sizes for the subsequent controlled trials.

2. Study objective

The main objective of this clinical pilot trial is to evaluate the use of the CEFALY® neurostimulator as a therapeutic treatment for FM.

3. Study outcomes

Primary outcomes:

- Mean pain intensity between baseline and 12 weeks endpoint
- Fibromyalgia Impact Questionnaire-revised (FIQR) total score between baseline and 12 weeks endpoint

Secondary outcomes:

- Mean pain intensity between baseline and 4 weeks visit
- FIQR total score between baseline and 4 weeks visit
- Patient Global Impression of Change (PGIC) at 4 weeks visit and at 12 weeks endpoint
- EQ-5D-3L between baseline and 4 weeks visit; and between baseline and 12 weeks endpoint
- Patient Reported Outcomes Measurement Information System (PROMIS) measures for depression, fatigue and sleep between baseline and 4 weeks visit; and between baseline and 12 weeks endpoint
- Multiple Ability Self-report Questionnaire (MASQ) between baseline and 4 weeks visit; and between baseline and 12 weeks endpoint

Exploratory outcomes:

- FM30 (≥30% responder rate) i.e. meeting the following criteria:
  - ≥30% reduction in pain (FIQR)
  - ≥10% improvement in physical function
  - ≥30% improvement in 2 of the following symptoms: (with FIQR) fatigue, sleep, depression, anxiety, (with MASQ) cognition
- FM20 (≥20% responder rate)
  - ≥20% reduction is pain (FIQR)
  - ≥10% improvement in physical function
  - ≥20% improvement in 2 of the following symptoms: (with FIQ) fatigue, sleep, depression, anxiety, (with MASQ) cognition

4. Study design

4.1. General description

This study is a clinical study with the following characteristics:

- Single center
- Prospective
- Open

4.2. Experimental protocol

Patient diagnosed with FM will be screened for study eligibility. Eligible patients will be scheduled for the baseline visit (enrollment visit) that will take place within a maximum of 4 weeks after the screening visit. At the baseline visit, the patients will be given a CEFALY® device together with the necessary accessories for a 12-week treatment period. Outcome measures will be administered at the baseline visit, after 4 weeks of treatment and at the end of the 12-week treatment period. The overall study flow is illustrated in Figure 1.

4.2.1. Screening visit

The patients will be evaluated for study eligibility at the screening visit (Visit 1). They will receive study information and consent documents, and they 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 will be tested for tolerance to the neurostimulation (nociceptive threshold test). If the patient passes this test, he/she will continue in the study.

4.2.2. Baseline visit (enrollment visit)

The baseline visit (Visit 2) is scheduled within 4 weeks following the screening visit. If the patient still meets the inclusion criteria regarding the pain intensity, he/she will complete the baseline questionnaires. The patient will receive a CEFALY® device together with the necessary accessories for a 12-week treatment period.

4.2.3. Treatment period – intermediate and final visits

During 12 weeks, patients will apply the CEFALY® twice a day, roughly at the same time of the day everyday (morning and evening) for a complete treatment session of 20 minutes. Compliance will be analyzed afterwards using a built-in recording system. An intermediate visit will be scheduled after 4 weeks of treatment (between minimum 4 weeks and maximum 6 weeks) (Visit 3). The patient will complete the visit questionnaires to assess efficacy of the treatment, and report possible side effects and adverse events regardless of possible relationship to the device. A final visit will occur after the 12 weeks of treatment (between minimum 12 weeks and maximum 14 weeks) (Visit 4) to collect the

CEFALY® device and complete visit questionnaires to assess efficacy as well as possible side effects and adverse events reported regardless of possible relationship to the CEFALY® device.

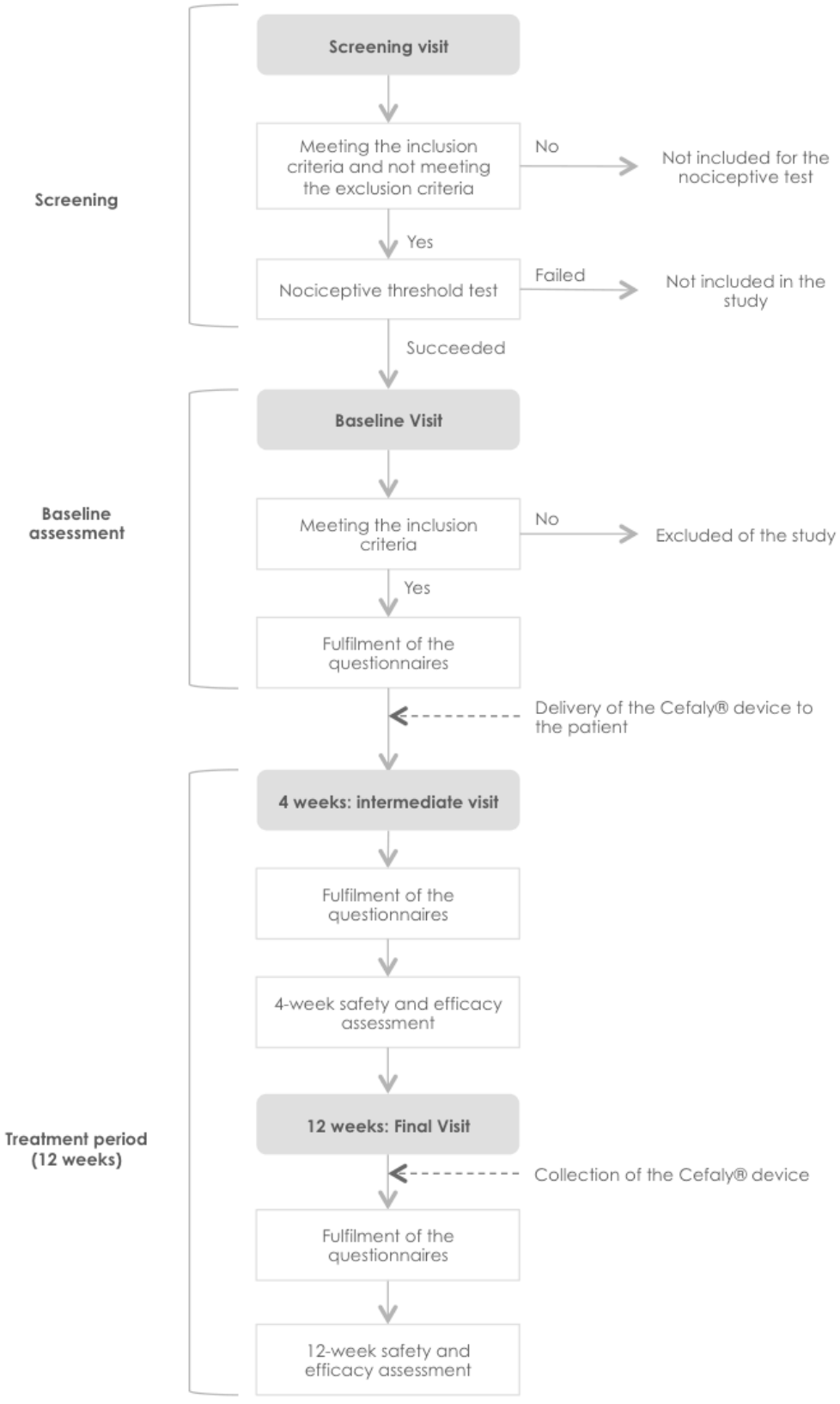

Figure 1 - Study flowchart

5. Subjects

The study will include 50 men or women.

5.1. Inclusion criteria

The following inclusion criteria apply:

1. Aged from18 to 65 years
2. Diagnosed with FM according to the 2010 ACR Preliminary Diagnostic Criteria for Fibromyalgia [7]
3. Having a minimum pain score of at least 4 on the 0-10 FIQR pain scale at screening and baseline.

5.2. Exclusion criteria

The following exclusion criteria apply:

1. Women: Pregnant, lactating or <6 months post partum
2. Episodic or Chronic Migraine according to the diagnostic criteria listed in ICHD-III beta (2013) section 1, migraine 1, having two or more attacks per month.
3. Change in any medication acting on the central nervous system (CNS) within 28 days before start of the study or during the study
4. Severe depression i.e. having a Beck Depression Inventory-Fast Screen (BDI-FS) score >12
5. Botox injection within 4 months before baseline or during the study.
6. Psychiatric disorders that could interfere with study participation: bipolar disorder, psychotic disorders and dementia.
7. Suicidal behavior and/or ideation i.e. having a Columbia Suicide Severity Rating Scale (C-SSRS) score ≥ 4 during the preceding 2 years
8. Patients currently taking any opioid medication
9. Patients currently taking medically prescribed marijuana
10. Current or history during the preceding year of alcohol or substance abuse including marijuana
11. Intolerance to supraorbital neurostimulation that makes the treatment not applicable (test of nociceptive threshold with specific Cefaly program)
12. Widespread rheumatic diseases (other than FM), evidence of inflammatory rheumatic disease
13. Any unstable medical condition in the judgment of the investigator that would interfere with study participation or study assessments.
14. Implanted active metal or electrical devices in the head
15. Cardiac pacemaker or implanted or wearable defibrillator

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 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 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.

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 60 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.

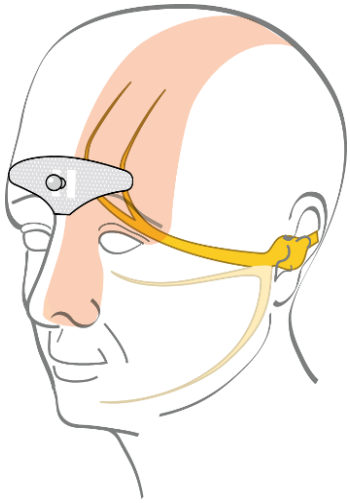

Figure 4 - The electrode placed on the forehead covers the supratrochlearis and supraorbitalis nerves

6.3. Mechanism of action

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 CEFALY® will be used twice a day by the patient. The patients should have at least two sessions of stimulation per day, roughly at the same time of the day everyday (morning and evening). A complete treatment session lasts 20 minutes. The patient should therefore use the device 40 minutes a day.

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.

6.5. Medication during the trial

- Medication acting on the CNS: cannot be changed within 28 days before start of the study or during the study.
- Botox injection: no injection within 4 months before start of the study or during the study

- Opioid medication: forbidden
- Marijuana: forbidden

6.6. Device provisioning

The promoter will deliver the devices directly to the investigators.

The patient will receive the device at the baseline visit and will return it at the end of the 12-week treatment period during the final visit.

7. Practical study modalities

7.1. Measures

The outcome measures taken in the study are all based on self-assessment questionnaires. The following will be used:

- FIQR: evaluation of the impact and the severity of FM symptoms.
- EQ-5D-3L: evaluation of the general quality of life.
- PROMIS for depression, fatigue, and sleep.
- MASQ: assessment of the self-perception of cognitive difficulties.
- PGIC: assessment of the patient perception of change induced by the treatment.

In order to evaluate the modification of pain level from baseline to 4-week treatment and to 12-week treatment, the item of the FIQR related to pain will be used, i.e. numeric rating scale (NRS) scoring the pain between 0 and 10.

During the screening visit, the following tests will be performed to evaluate the exclusion criteria 4 and 7, respectively:

- Beck Depression Inventory-Fast Screen (BDI-FS);
- Columbia Suicide Severity Rating Scale (C-SSRS).

The following table depicts at which visit the various questionnaires are completed.

	Visit 1 **Screening**	**Visit 2** **Baseline**	**Visit 3** **Intermediate assessment** **(4-week treatment)**	**Visit 4** **Final assessment** **(12-week treatment)**
FIQR	●(*)	●	●	●
EQ-5D-3L		●	●	●
PROMIS		●	●	●
MASQ		●	●	●
PGIC			●	●
BDI-FS	●			
C-SSRS	●			

(*) Only the item of the FIQR related to pain.

7.2. Calendar

The study is foreseen to start in September / October 2015 and to be finished by May 31 2016.

8. Data management and statistics

8.1. Data management

The data will be included in the case report form (CRF) that will be provided to the promoter anonymously, using a numbering system.

8.2. Statistics

8.2.1. Sample size

The number of subjects to recruit in the study (50 patients) is estimated to be sufficient for analysis.

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.
- Results analysis will be carry out on a per protocol basis, i.e. on ≥50% compliant patients; sub-analysis will be performed as well on an intention to treat basis, i.e. including all subjects who used the study device at least once. For each patient, the average outcome will be calculated before and after the treatment period on all data available, without any imputation of missing data.

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. AEs will be registered daily by the subject in the corresponding form. This form will be returned by the subject at the intermediate visit and at the end of the study and 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 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 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: the specific form

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 of pregnancy to the promoter

The CEFALY® device is perfectly safe for pregnant women. However, pregnancy causes many physiologic changes that can interfere with the FM assessment.

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

9.8. 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.

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.

10. List of Annexes

CRF

AE reporting form

Informed consent

Instruction sheet for the nociceptive threshold test

Patient questionnaires (FIQR, EQ-5D-3L, PROMIS depression, fatigue and sleep, MASQ and PGIC)

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