# CRINICAL TRIAL PROTOCOL: CEN 1512

**CONTROLLED, RANDOMIZED CLINICAL TRIAL OF THE CIRCAID® COMPRESSION SLEEVE VERSUS SHORT-STRETCHING BANDAGE AT THE REDUCTION PHASE OF UPPER LIMB LYMPHATIC EDEMA AND VERSUS COMPRESSION SLEEVE AND SHORT-STRETCHING BANDAGES AT THE INITIAL MAINTENANCE PHASE.**

**Biomedical research**

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**Studied product: Circaid® compression sleeve**


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# SUMMARY

# 1. INTRODUCTION AND STUDY RATIONAL

## 1.1. INTRODUCTION

According to the INVS (National Institute of Health Surveillance), 54,000 women develop breast cancer each year [1] and their survival rate at 5 years is today of 86% [2]. One of the most common complications of breast cancer treatment is lymphedema, and despite progress made in surgery, 20% of them will progressively develop chronic lymphedema [3], corresponding to 10,800 new cases of arm lymphedema per year.
The impact of arm lymphedema on women is often important because it increases their anxiety, induces alterations of their body image and in their quality of life [4-6]. Over time, it can cause a real functional disability and pain [6,7].
Currently, there is no known surgical or pharmacological cure for lymphedema [8]. The treatment of lymphedema relies mainly on the physical treatments prescribed to reduce and maintain the size of the arm, restore the motor functions, improve its appearance and reduce pain [8]. It is based on decongestive therapy that combines an initial reduction phase with intensive decongestive treatment followed by a maintenance treatment [9,10]. According to the recommendations of French national health authority [11] and international consensus [12], the reduction must be done through relatively or totally non-elastic bandages and the maintenance phase by compression sleeves and / or the continuation of the bandages.
A prospective cohort study of 682 women with lymphedema in relation to breast cancers studied the maintenance of arm volume after the intensive reduction phase. It shows a gradual reappearance of lymphedema in the first year in 38.1% of women and demonstrates that women who wore a compression sleeve and compression bandages at night have a significantly reduced risk of relapse of 50% [hazard ratio, 0.53, (0.34-0.82), P = 0.004] [13].

## 1.2. RATIONAL

One of the difficulties encountered in the treatment of lymphedema, both in the active reduction phase and in the maintenance phase, is the appliance of the short-length compression bandages which requires good technicality and experience to exert the pressure required to remove liquids from tissue spaces and reduce the volume of the arm or prevent it from increasing again.

During the intensive decongestive treatment phase, which usually takes place in specialized lymphedema treatment departments, the staff are properly trained and have the required experience, but the appliance of these short-length compression bandages requires a lot of time. During the maintenance phase, the appliance of short stretch bandages gives way during the day to the wearing of a compression sleeve which can be put on fairly easily. But during the night, in the absence of a nurse or a spouse with the technical skills required to put them in place, few patients can benefit from the wearing of short stretching bandages. During the maintenance phase, many patients quickly give up these nocturnal bandages, thus losing the gain obtained during the reduction phase [10]. This situation is all the more regrettable that, as shown in the studies, this nocturnal wearing contributes to a very significant reduction in the rate of reappearance of lymphedema and avoids the recurrent need of intensive reduction sessions in hospitals, which are costly for health insurance. and uncomfortable for the patients.

To improve this situation, medi has developed a device called circaid®, consisting of non-elastic bands adjustable and repositionable with "Velcro" systems, which can be used both for the intensive reduction phase but also during the maintenance phase by the patients themselves because of its ease of placement.
It is composed of several inelastic strips or removable straps, parallel and overlapping slightly to leave no crease and no space between them. Velcro tabs or fasteners help ensure proper initial positioning and readjustment as the arm volume is reduced. This gives a given pressure by tightening or loosening each band while limiting friction and discomfort. In the intensive reduction phase, its ease of use reduces the time devoted by nurses to the use of short stretching tapes which, in addition to the need for good technique, requires a significant amount of time. In the maintenance phase, this original and comfortable compression device allows the patient to become autonomous after minimal learning. The simplicity of the introduction of the system on the limb and the calibration of the delivered pressure allows to develop the self management of the treatment, because it is possible to reposition the bands as and when the decrease of the edema, which makes it possible to optimize the effectiveness of the treatment. The ability to instantly readjust the circaid®Juxtafit system allows to constantly apply the right level of pressure delivered, to reduce the volume of the limb. This is not possible with a traditional multilayer bandage if the different layers are not completely remove. A visual calibrator ensures the right level of pressure delivered at all times.

In addition to efficiency, patients' quality of life is improved by being able to remove and return it on their own, making it easier to wash or dress. Similarly, less rigid while being just as compressive, it allows a better comfort in the daily gestures and in particular to have a normal range of arm flexion movements more compatible with driving than the wearing of tapes.
The product is currently marketed in many countries and is reimbursed in the following countries: United States, Quebec, the Netherlands, United Kingdom, Austria in the indication of the treatment of lymphedema.
In view of its admission to reimbursement in France, a meeting was held with HAS experts in the context of the so-called early meeting procedure in order to define the study that should be done. A detailed synopsis which is the one of the present protocol has been validated by the methodological experts of the HAS as being able to bring the arguments of effectiveness required by being as close as possible to the usual practice and by covering at the same time the phase of intensive reduction and the maintenance phase. It aims to compare the current protocol of care considered optimal for the reduction of lymphedema and the maintenance of this reduction with the protocol of care which would integrate the device circaid® in substitution to the laying of bands with short extension as it is now in other countries.

## 2. STUDY OBJECTIVES

### 2.1. PRIMARY OBJECTIVE

The main objective of the study is to compare, at the 30th day of the initial maintenance phase, the reduction in the volume of lymphatic edema of the upper limb obtained under the effect of the wearing of a compression sleeve on the day associated with the night wearing of the system of contention circaid® versus the wearing of a compression sleeve during the day associated with a possible treatment with it during the night, according to the recommendations of the HAS.

### 2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To compare, on the 5th day of the reduction phase, the reduction in the volume of lymphatic edema of the upper limb obtained under the effect of the night and day wearing of the circaid® compression system and the night and day wearing of short lengthening bands such as recommanded by the HAS.
- To compare, at the 90th day of the maintenance phase, the reduction in the volume of lymphatic edema maintained by the wearing of a compression sleeve during the day associated with the circaid® compression system at night and the wearing of a compression sleeve during the day associated with a possible wearing at night.
- To compare, at the 5th day of the reduction phase, at the 30th day of the initial maintenance phase and at the 90th day of the maintenance phase:
    - the physicians' opinions on lymphedema-induced discomfort improvement through the CGII (Clinical Global Improvement Impression);
    - the patients' opinions on lymphedema-induced discomfort improvement through the PGII (Patient Global Improvement Impression).
- To compare, at the 30th day of the initial maintenance phase and at the 90th day of the maintenance phase:
    - the adherence of patients to the wearing of their maintenance treatment;
    - the satisfaction and the wearing comfort experienced by the patients;
    - the patients' opinions on the ease of use of the product: the need for a third party, applications of pressure, the need for nurses or caregivers.
- To compare the tolerance of the different products at different phases of reduction and maintenance.

## 3. ETHICAL GUARANTEES OF THE TRIAL

This trial, carried out in accordance with Good Clinical Practice, received a favorable opinion from the Committee for the Protection of Persons (CPP) "IDF 11" (see Annex 3 §16.3).

After receiving complete information about the circaid® compression system, the other products used as comparators and the conditions for carrying out the study, each patient will give their written consent on a form in 3 copies: the original for the patient, a first copy for the investigator, a second copy for the sponsor (submission in a sealed envelope) (see Annex 4 §16.4). The patient is free at any time to stop her participation in the study.

## 4. NATURE OF THE TRIAL

Controlled randomized open label clinical trial on two parallel groups.

# 5. PATIENTS SELECTION

All patients meeting all inclusion criteria and none of the non-inclusion criteria will be eligible for the study.

## 5.1. INCLUSION CRITERIA

To be included in the trial, patients will:

- be women over the age of 18;
- presenting a unilateral lymphedema of the upper limb of stage II or III according to the International Society of Lymphology, secondary to the curative ganglion treatment of a cancer, whatever its nature, and requiring a decongestive treatment by contention / compression;
- presenting an increase in the volume of the arm affected by lymphedema of at least 10% when compared to the contralateral arm;
- benefiting of the French health insurance coverage;
- duly informed of the benefits, constraints and risks of the study;
- medically and legally able to understand the methods of carrying out the study and to give written informed consent to participate in the study;
- having given their free written informed consent to their participation in the study.

## 5.2. NON-INCLUSION CRITERIA

Not be included in the study:

- from a medical point of view, the patients:
    - with stage I lymphedema;
    - with lymphedema of multiple locations;
    - having had intensive decongestive treatment in the last 6 months;
    - having a recurrence of cancer or a peripheral arterial disease contraindicating or restraining compression.
- from a legal point of view, the patients:
    - not in a position to give free and informed consent because of an administrative or judicial decision or a pathology that may affect their judgment or a difficulty of linguistic comprehension;
    - currently participating in another clinical trial or in an exclusion period from another clinical trial;
    - who may not adhere to the terms of the protocole.

## 5.3. SAMPLE SIZE

The calculation performed with Nquery (see 13.1) shows that 136 patients are required (68 per group), which is increased to a total of 140 patients to take account patients lost of follow-up.

### 5.4. PATIENTS IDENTIFICATION

The included patients will be identified by the patient code consisting of:

- First two letters of the name;
- First letter of the first name.

## 6. STUDIED PRODUCT

### 6.1. CIRCAID DESCRIPTION

- Composition: circaid® is a medical device of class 1 risk (CE marking 93/42).

It is composed of non-elastic bands adjustable and repositionable thanks to "Velcro" systems. It can be placed on a bandage, on the skin or on an arm or leg sub-sleeve. In order to make the port more discreet, a sock cover or sleeve cover is provided.
The product is made of "breathe-o-prene", a patented derivative of neoprene; breathable, flexible, anti-odor, antimicrobial. The sleeve is composed of: Nylon, Polyurethane, Lycra and Silver for antibacterial effectiveness. The label is made of satin acetate. It does not contain latex.

This orthosis is intended to accommodate a 5% increase or a 10% decrease in limb circumference.

- Mode of action: it is a system of contention composed of several inelastic strips or straps removable, parallel and overlapping slightly to leave no crease and no space between them. "Velcro" tabs or hook-and-loop fasteners ensure proper initial positioning and readjustment of the system as the limb volume is reduced (arm sleeve). This gives a given pressure by tightening or loosening each band while limiting friction and discomfort.

- Comparative: short stretch strips. These are elastic compression belts with low resting pressure, high working pressure, and staying in place day and night. Extensible, they are 100% cotton, guaranteeing a high skin tolerance. They do not contain latex, phthalates and rosin.

### 6.2. DESCRIPTION OF THE USE OF THE PRODUCTS

The instructions for use of the product are attached in Annex 9 §16.9.

### 6.3. PACKAGING AND LABELING OF PRODUCTS UNDER STUDY

#### 6.3.1. Primary conditioning

The devices under study are packaged in cardboard boxes by medi France. Depending on the randomization, patients will receive or not at inclusion a box containing a device circaid®, in addition to other materials of the study.

#### 6.3.2. Labeling

Labeling will comply with European regulations, in French.
On the boxes:

- Name and address of the promoter;
- Protocol number "Study Code";
- Lot No XX;
- Content;
- Expiration date: exp.;
- Legal notice: "Product for clinical trial only" "Use under strict medical supervision (Article R5123 of the Public Health Code)" and "Do not leave within the reach of children".

The labels of the boxes containing the products under study will have a repositionable part to stick on the first sheet of the observation book, mentioning the protocol number and the treatment number.
A label model is presented in Annex 1 §16.1 of the protocol.

### 6.4. ALLOCATION OF PRODUCTS

The products will be provided to the investigator and handed over to the patients.
The investigator will only dispense products to patients included in this trial.

### 6.5. EXPEDITION AND STORAGE

#### 6.5.1. Expedition

CEN Gestion will provide the circaid® compression devices and all the materials needed for the study to the investigator.

#### 6.5.2. Storage

The products supplied by the promoter will be kept under the responsibility of the investigator under conditions ensuring their good conservation, at room temperature, in a locked room to which only the authorized personnel will have access.

### 6.6. PRODUCTS NOT USED

Unused products will not be redistributed by the investigator to other patients. They will be kept under the same conditions as the others and will be subject to on-site accounting.

### 6.7. ACCOUNTING AND RETURN OF PRODUCTS

The circaid® compression devices will be recovered from patients and will be replaced without charge if the doctor deems it necessary and if the patient wishes.
Unused products and empty packaging will be counted at the end of the study by the investigator and by the clinical research assistant who will proceed to their collection.
In case of recall of the products related to the study (decided by the Health Authorities or the sponsor), the investigator will be immediately informed by the sponsor.

The investigator, in collaboration with the representatives of the sponsor (monitors, ARCs) will then urgently:

- stop delivering the products concerned to the patients;
- inform the patients concerned that they must immediately stop using these products and bring them back.

## 7. CONCOMITENT TREATMENTS

All drug treatments taken by patients and any modifications during the study are allowed but must be documented. All physical treatments for lymphedema other than those prescribed in the protocol are prohibited and will result in exclusion from the study.

## 8. EVALUATION CRITERIA

### 8.1. MAIN EVALUATION CRITERION

The main criterion is the frequency of obtaining a 20% reduction in the volume of lymphedema. The volume of lymphedema is defined as the difference between the volume of the limb with lymphedema and the volume of the contralateral healthy limb. The volumes of the arms are calculated by the formula of the truncated cones from the measurements of the perimeters of the arms staged 5 cm in 5 cm from the wrist to the armpit. This method has shown excellent inter- and intra- observer reproducibility compared to the water displacement method. The main criterion is judged at the end of the initial maintenance phase at the 30th day (JS + 30).

### 8.2. SECONDARY EVALUATION CRITERIA

The secondary evaluation criteria are:

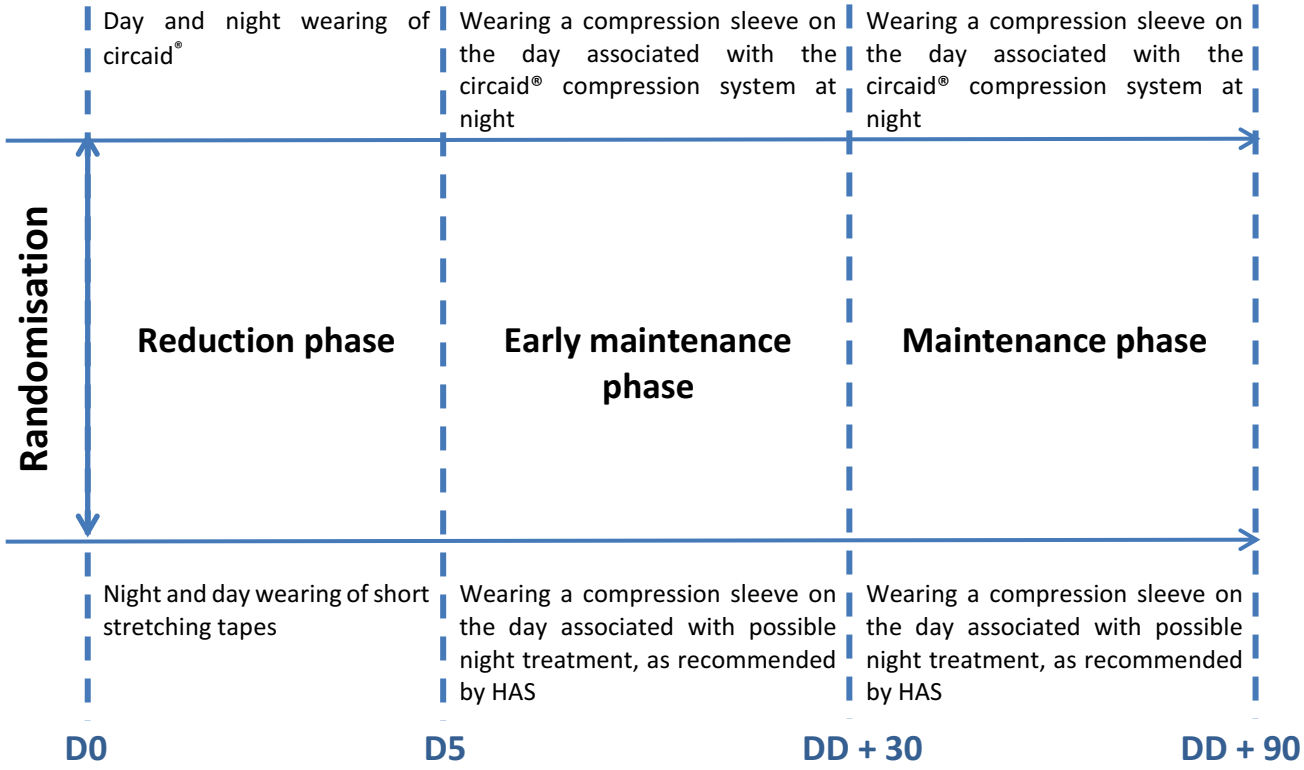
- the socio-demographic characteristics: age, occupation;
- the characteristics of lymphedema: origin, date of onset, stage of edema according to the classification of the international society of lymphology, laterality of edema, volume of the arm with lymphedema, and volume of lymphedema compared to the contralateral arm;
- the PGII and CGII;
- the adherence of patients to the wearing of their maintenance treatment by the adapted Morisky score;
- the patient satisfaction in terms of efficiency and wearing comfort measured on Likert scales in 5 classes;
- the occurrence of adverse events and their imputability to the products under study according to the materiovigilance;
- the quality of life of the patients measured by the IFC Lymph specific questionnaire;
- the opinion of the person on the ease of use of the product during the maintenance phase: need of a third person, applications of pressure, continued use, advice to third parties, comparison with possible previous treatments, ease of use employment;
- the need of nurses or caregivers for the setting up of the decongestive device during the maintenance phase.

## 9. STUDY COURSE

Following the meeting with CNEDIMTS (HAS), three observation periods were defined with the following products:

- D1 to D5: intensive hospital treatment performed by the night and day wearing of the circaid® compression system versus the night and day wearing of short stretching tapes.
- B. DD (Day of discharge from the hospital) to DD +30: ambulatory initial maintenance phase carried out by the wearing of a compression sleeve on the day associated with the nighttime compression system circaid® versus wearing a compression sleeve on the day associated with a possible treatment at night, as recommended by HAS.
- C. DD + 31 to DD + 90: ambulatory maintenance phase carried out by the wearing of a compression sleeve on the day associated with the nighttime circaid® compression system versus the wearing of a compression sleeve on the day associated with possible treatment at night.

Study design:




The study therefore includes four medical follow-up visits on day 0 (D0), day 5 (D5) (+/- 1 day), day of discharge (DD) + 30 days (+/- 5 days) and DD + 90 days (+/- 10 days), followed by self-questionnaire during the maintenance phase between DD and DD + 90, DD designating the day of discharge from the hospital at the end of the intensive reduction phase.

**At D0**, the doctor**:**

- collects the informed written consent of the patient after having duly informed her;
- collects its socio-demographic characteristics: age, occupation;
- collects the characteristics of its lymphedema: origin, date of onset, stage of edema according to the classification of the international society of lymphology, laterality of edema, volume of the arm with lymphedema, and volume of lymphedema compared to contralateral arm;

- collects the quality of life measured by the Lymph IFC specific questionnaire;
- implements decongestive treatment with the product defined by randomization.

**At D5** (+/- 1 day), the doctor:

- collects the characteristics of lymphedema: stage of edema according to the classification of the international society of lymphology, volume of the arm with lymphedema, and volume of lymphedema compared to the contralateral arm;
- completes the PGII and CGII;
- records patient satisfaction in terms of efficiency and comfort of wearing measured on Likert scales in 5 classes;
- collects the occurrence of adverse events and their imputability to the products under study according to the materiovigilance;
- collects the quality of life measured by the Lymph IFC specific questionnaire;
- gives the patient a self-questionnaire on which she reports each week who has placed the contention device (herself, spouse, nurse), and the existence of an intolerance to the wearing of it;
- gives the patient, according to the randomization list, the products under study during the maintenance phase;
- provides a nursing prescription for the application of a possible treatment to the patients concerned.

**At DD + 30 days** (+/- 5 days), the doctor:

- collects the characteristics of lymphedema: stage of edema according to the classification of the international society of lymphology, volume of the arm with lymphedema, and volume of lymphedema compared to the contralateral arm;
- collects the PGII and CGII;
- collects the quality of life measured by the Lymph IFC specific questionnaire;
- records patient satisfaction in terms of efficiency and wearing comfort measured on Likert scales in 5 classes;
- collects the observance of the port during the initial maintenance phase by the adapted Morisky score;
- collects the occurrence of adverse events and their imputability to the products under study according to the materiovigilance;
- retrieves the self-questionnaire from the early maintenance period and gives the patient a self-questionnaire for the maintenance period where she reports on each week who apply the compression device (herself, spouse, nurse ), and the existence of an intolerance to the wearing of it;
- provides a nursing prescription for the application of a possible treatment to the patients concerned;
- gives the patient, according to the randomization list, the products under study during the maintenance phase.

**At DD + 90 days** (+/- 10 days), the doctor:

- collects the characteristics of lymphedema: stage of edema according to the classification of the international society of lymphology, volume of the arm with lymphedema, and volume of lymphedema compared to the contralateral arm;
- collects the PGII and CGII;
- collects the quality of life measured by the Lymph IFC specific questionnaire;

- records patient satisfaction in terms of efficiency and wearing comfort measured on Likert scales in 5 classes;
- collects the observance of the port during the long-term maintenance phase by the adapted Morisky score;
- collects the occurrence of adverse events and their imputability to the products under study according to the materiovigilance;
- collects the need for the use of nurses or carers for the application of the decongestive device;
- collects the opinion of the person on the user-friendliness of the product: need of a third party, applications of pressure, continued use, advice to third parties, comparison with possible previous treatments, ease of use;
- retrieves the self-questionnaire of the maintenance period and the products under study;
- writes a prescription of the products that he thinks necessary for the lymphedema.

# 10. ADVERSE EVENTS

## 10.1. ADVERSE EVENTS

### 10.1.1. Definition

An adverse event is defined by any untoward medical occurrence occurring in a patient biomedical research, that does not necessarily have a causal relationship to the research nor the treatment of this. This also includes the signs, symptoms and intercurrent diseases, that may occur during the study period, whether they are related or not with the test product.
In all cases, the etiology should be sought and identified as soon as possible, and the sponsor of the study warned.

### 10.1.2. Gradation of adverse events

The medical assessment of intensity of adverse event or intercurrent diseases must be determined by using the following definitions:

- Mild: perception of the sign or symptom, but easily tolerated;
- Moderate: sufficiently annoying to interferes with usual activities of daily living;
- Severe: disability with inability to work or usual activities of daily living interruption.

### 10.1.3. Collection of adverse events

All adverse events will be actively sought from spontaneous statements of patients as well as in the clinical examinations and interrogations by the investigator at each visit.
All adverse events must be documented on CRF including nature, the date of onset, duration, end date, gravity, the therapeutic consequences and evolutions, and the relationship with test product (in the opinion of the investigator). The investigator will specify if it is or not a serious adverse event.
If the adverse event results in the interruption of the study, the 'End of the study' page at the end of the CRF will be completed by the investigator.

## 10.2. SERIOUS ADVERSE EVENTS

### 10.2.1. Definition

A serious adverse event (SAE) is defined as follows: any event or adverse reaction which results in death, is e life-threatening, requires patient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, regardless of the dose given.

Will also be considered as serious adverse events, other events such as: cancer, overdose, pregnancy and any adverse event or biological abnormality appeared during the study period defined as serious by the study protocol or considered by the investigator as sufficiently important or suggestive of a significant risk, contraindications, adverse reactions or precautions for use.

### 10.2.2. Notification of serious adverse events

All serious adverse events, as defined according to the above criteria, whatever the relationship of cause and effect in relation to the test product, must be recorded by the investigator as soon as he was informed of the adverse event.

The investigator must notify the sponsor this event by sending the form 'Notification of a serious adverse event' within 24 hours (initial notification) (cf. Annex 10 §16.10), providing all the available information on the adverse event to the representative of the sponsor:

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The sponsor representative will inform immediately by phone, fax or e-mail the sponsor medical director:

| | |
|---|---|
| Name: | Mr Eric Martin |
| Adress: | medi France |
| | 25 Rue Henri Farman, |
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| Phone: | 06 32 66 30 41 |
| Fax: | 01 48 61 76 27 |
| Email: | e.martin@medi-france.com |

The sponsor medical director will immediately inform the manager of the materiovigilance for circaid® who will manage the case according to the medi France procedure:

| | |
|---|---|
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#### 10.2.3. Serious adverse event follow-up

The investigator must provide a specific medical report or complete the form 'Notification of a serious adverse event' (follow-up) and collect all the results of the performed tests and records of hospitalization.
Serious adverse events must be followed and documented until disease stabilization or normalization.

#### 10.2.4. Serious adverse events occurring after the study

Any serious adverse event occurring in a patient, within 30 days after the end of the study, should be reported to the sponsor.
The sponsor must also be notified of any event occurring at any time after the end of the study for the patient likely to be linked to the study treatment, according to the investigator.

## 11. DATA COLLECTION AND MONITORING

### 11.1. DATA COLLECTION

All data required by the protocol and collected by the investigator must be present in the observation book.
A copy of the results of the examinations will be inserted in the observation book after validation by the investigator.
The notebooks will consist of triplicate document (NCR paper):

- the white sheet (original) is intended for the promoter;
- the green sheet is a working document;
- the yellow sheet (strain) is kept by the investigator.

*** Source data**

The investigator is asked to note all the data in the patient's medical record, including:

- the patient's participation in the study with the study code;
- demographic data (date of birth, name);
- medical and surgical history;
- vital parameters;
- concomitant treatments;
- the side effects;
- the information that the patient benefits from a social security scheme.

These data will be noted in a specific file different from the observation book, which will constitute the source data available at any time by the promoter.

## 11.2. DATA CONTROL

### 11.2.1. Direct access to source data

By his participation agreement, the investigator is committed to a strict compliance with the experimental protocol, the "Good Clinical Practices" and the amended law of 20 December 1988. It vouches for the authenticity of the data collected within the framework of the study and accepts the legal provisions authorizing the promoter of the study to set up a control of the quality.
In accordance with Good Clinical Practices, the data will be checked on the investigation site by the Clinical Research Assistant.
The investigator is committed to have the necessary availability to receive the Clinical Research Assistant and to keep at his disposal all the source documents for comparison with the observation booklet.

### 11.2.2. Monitoring visits

#### 11.2.2.1. Pre-selection / implementation visit

The pre-selection procedure will be carried out in the investigative center, through a contact between the Clinical Research Assistant and the investigator to present the protocol and the material, financial, administrative and regulatory aspects of the study.
The aim of this pre-selection is to present, under confidentiality, the protocol to the investigator and his collaborators, to evaluate the adequacy of the human and material resources necessary for the realization of the study and the experiences of the investigator and his collaborators.
During the implementation visit, the Clinical Research Assistant will ensure the presence in the investigating center of all the material required for the study conduct:

- file of the investigator with:
  - experimental protocol and its annexes:
    . information and consent form for the patient;
    . curriculum vitae of the coordinator;
    . insurance certificate;
    . favorable opinion of the CPP;
  - signed research agreement;
  - regulatory documents (administrative ...);
- observation books;
- products under study;
- study material.

#### 11.2.2.2. Follow-up / closure visits

The study follow-up visit will enable the Clinical Research Assistant to ensure that consent forms are signed by patients or their legal representatives before inclusion in the study, adherence to the protocol and the conformity of the collected data to data source.
The necessary corrections will be made by the investigator, then will be dated and initialed. The original of the CRF thus validated will be recovered by the Clinical Research Assistant.
The closing visit (done at the end of the study) will allow the recovery of the used products not retained by the patients and not used, the CRF and copies of the consent forms, as well as the verification of the conservation conditions of the data of the study (archiving). If necessary, the sponsor may request deferred corrections from the investigator who will sign them.

# 12. DATA MANAGEMENT

## 12.1. DATA ENTRY

A double data entry will be performed using a software meeting the standards enacted by the Good Clinical Practices (Capture System). The "computer notebooks" will be the exact image of the CRF. Computer data files as well as any modifications that will be made to them will be saved and retrievable on demand (audit trail).

## 12.2. DATA CONTROL

A verification of the data will be done by the Clinical Research Assistant and / or the monitor and / or the data manager on the CRF before entry or on the data listings after entry. This verification of the data will be completed by automated logic checks previously programmed. Requests for data corrections will be edited after comparing the double entry files and performing the consistency tests.

## 12.3. CODING DATA

The data corresponding to the medical history, intercurrent events and associated treatments will be coded according to the MedDRA and ATC dictionaries. The codings will be validated by a doctor.

## 12.4. DATA FREEZING

The freezing of the database will take place after integration of the requested corrections to the investigating physician and after the Validation Committee composed of the study methodologist, the coordinating investigator and the representative of the sponsor of the study.
It will be signed by the data manager before the database is transmitted to the Biometrics department.

# 13. STATISTICAL ANALYSIS

Statistical analyzes will be performed in accordance with international procedures (Statistical Principles for Clinical Trials: ICH Step 4, 5 Feb 1998) and using SAS software (version 9.4).

## 13.1. SAMPLE SIZE

The sample size is based on the assumption that at the end of the maintenance period, 3 out of 4 patients will have at least a 20% decrease in the volume of their lymphedema in the circaid® group versus 1 in 2 in the control group. At risk alpha = 0.05, in a two-sided Chi2 test with a power of 80%, the calculation performed with Nquery (see table below) shows that the number of patients required to highlight this difference is 58 patients per group. This number is increased by 15% to account for patients lost to follow-up or unusable records, i.e. 68 per group. These patients will be recruited by 5 centers on the basis of 28 patients per center.
Two group $\chi^2$ test of equal proportions (odds ratio = 1) (equal n's)

| | |
|---|---|
| Test significance level, $\alpha$ | 0,050 |
| 1 or 2 sided test? | 2 |
| Group 1 proportion, $\pi_1$ | 0,250 |
| Group 2 proportion, $\pi_2$ | 0,500 |
| Odds ratio, $\psi = \pi_2 (1 - \pi_1) / [\pi_1 (1 - \pi_2)]$ | 3,000 |
| Power ( % ) | 80 |
| n per group | 58 |

## 13.2. PROTOCOL DEVIATIONS AND ANALYSIS PLAN

All cases of deviations from the protocol will be managed according to CEN Biotech's Standard Operating Procedures.
A detailed statistical analysis plan, based mainly on this paragraph of the study protocol, and in accordance with CEN Biotech statistical procedures, will be developed. This analysis plan will be validated by the Medical Director of medi France.
A data validation plan will first focus on defining a position when considering protocol deviations and thus define the analysis populations (Intent to Treat and Per Protocol). The analysis plan will specifically identify the statistical tests, analysis procedures, treatment of missing data considered, and the primary and secondary endpoints that will be used.
Will be considered as major deviations (patient excluded from per protocol analysis) wrong inclusions (non-compliance with the inclusion criteria and non-inclusion) and the absence of data concerning the main criterion of analysis. All other cases will be considered *a priori* as minor deviations.

## 13.3. ANALYZED POPULATIONS

The populations analyzed are defined as follows:

- The "Intention to treat" population (ITT) will include all patients who have applied at least once the products under study subject of this research;
- The population "per protocol" (PP) will include all patients with no major deviation from the protocol.

## 13.4. STATISTICAL METHODS

### 13.4.1. Description of the population and comparability of groups at inclusion

The sociodemographic characteristics and the characteristics of their lymphedema (origin, date of onset, stage of edema according to the classification of the international society of lymphology, laterality of the edema, volume of the arm with lymphedema, and volume of lymphedema compared to contralateral arm) will be compared between groups by Chi2 tests for qualitative variables and by Student's t-tests for quantitative variables, or their non-parametric equivalents if the characteristics of distributions require it.

### 13.4.2. Study of the main objective

The frequency of patients whose lymphedema volume reduction is at least 20% of the initial volume is described by numbers, frequencies, 95% confidence intervals and compared between groups by a Chi2 test at DD + 30.

### 13.4.3. Studies of secondary objectives

- The evolution of the volume of lymphedema will be compared between the groups by repeated-time analysis of variance with two time factors and treatment with interaction on D5, DD + 30 and DD + 90.
- The frequency of patients whose lymphedema volume reduction is at least of 20% of the initial volume is described by numbers, frequencies, 95% confidence intervals and compared between groups by a Chi2 test at D5 and DD + 90.
- The percentage of patients for whom 70% of the initial benefit of the reduction of lymphedema obtained on day 5 is kept at DD + 90 at the end of the maintenance phase is described by number, frequency, 95% confidence interval and compared between groups by a Chi2 test at DD + 90.
- The improvement of the discomfort will be described through the CGII and the PGII (Patient Global Improvement Impression) by numbers, percentages and 95% confidence intervals and compared between groups by Wilcoxon rank tests. The evolutions within each group will be compared by Wilcoxon tests on repeated series.
- The improvement of the quality of life will be described through the IFC-specific Lymph Questionnaire by means of means, standard deviations and 95% confidence intervals and compared between the groups by a two-factor repeated time analysis of variance with interaction measurement. A Student's t-test will compare their variations between the two groups. The evolutions within each group will be compared by t-tests on repeated series.
- Their compliance with the Morisky score, the satisfaction of the patients in terms of efficiency and wearing comfort, their opinion on the ease of use of the product (need of a third person, applications of pressure, continuation of his use, advice to third parties, comparison with possible previous treatments, ease of use) will be compared between groups by Chi2 test or by a Fisher test if the characteristics of the distributions require it.
- The frequency and nature of adverse events will be described in terms of numbers and frequencies and compared between groups by Chi2 tests or Fisher tests if required by distribution conditions.
- The evolution of the quality of life of the patients will be described by numbers, percentages and 95% confidence interval and compared between groups by Wilcoxon rank tests. The evolutions within each group will be compared by Wilcoxon tests on repeated series.
- The frequency of those who use nurses or caregivers will be described by numbers, percentages, and 95% confidence intervals and will be compared between groups by Chi2 tests or Fisher tests if the characteristics of the distributions required it. The average number of nurse visits and its standard deviation will be calculated and compared between groups by Student's t tests. Its economic impact will be quantified by mean and standard deviation and compared by Student t tests on repeated series.
- The sociodemographic and clinical factors of patients likely to influence their adhesion, their satisfaction and the maintenance of the effect on lymphedema will be studied by logistic regression analyzes in order to identify those having a significant action after adjustments on the socio-demographic and clinics characteristic of the patients.

### 13.4.4. Intermediate analysis

Considering that the study is an open label study, an interim analysis may be conducted during the study when at least 50% of the initial enrollment has completed the study.

#### 13.4.5. Analysis software

Data record will be done on capture system and the analyzes will be conducted using the SAS software version 9.4. The significance level is set to alpha = 0.05.

## 14. REGULATORY OBLIGATIONS AND ADMINISTRATIVE PROCEDURES

In accordance with the principles of the Declaration of Helsinki (1964), reviewed in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996) and Edinburgh (2000), this trial should be conducted according to the rules of Good Clinical Practices, and according to the procedures applicable to biomedical research defined by the European directive 2001/20 / EC transposed by the decree n ° 2005-477 of April 26, 2006. This can moreover include an audit on site, by the sponsor, the Scientific Committee and / or an inspection by representatives of the health authorities, at any time. The investigator must accept the control of the source documents of the trial by the monitor, the representative of the health authorities, the representative of the sponsor and / or the scientific committee.

### 14.1. SCIENTIFIC COMMITTEE

Prior to the study, a scientific committee was appointed specifically to advise medi France and validate the entire project, namely:

- the scientific relevance of the study and its objectives;
- data collection documents;
- the quality control procedures of the data under study.

The scientific committee will be consulted by medi France for any medical or scientific questions arising during the study. He will advise medi France on the exploitation of the data, the writing of the study report and the publication of the results.

This scientific committee is composed as follows:

- Professor Isabelle QUERE, Head of the Department of Vascular Medicine at the University Hospital of Montpellier,
- Dr. Stéphane VIGNES, Unit Head of Lymphology Department at the Cognacq-Jay Hospital in Paris,
- Professor François-André ALLAERT, Ceren Medical Assessment Chair ESC & DIM CHU of Dijon.

### 14.2. COMMITTEE FOR THE PROTECTION OF PERSONS (ETHIC COMMITTEE)

This protocol, the patient information form and the Patient Consent Form have been submitted to the "IDF 11" CPP.

Any amendment to the protocol must be reported to the CPP "IDF 11", and its favorable opinion will have to be obtained if the amendment is likely to significantly modify the safety conditions of the patients participating to the research.

### 14.3. PATIENT INFORMATION AND INFORMED WRITTEN CONSENT

In accordance with the European Directive 2001/20 / EC transposed by Decree No. 2005-477 of 26 April 2006, the patient must give her free and informed consent.

#### 14.3.1. Patient information

Each patient meeting the selection criteria must be informed by the investigator of the purpose of the research, its methodology and duration, foreseeable constraints and risks, including if the research is terminated before completion, as well as the benefits he is entitled to expect from his participation.
The main points of information provided to the patient must appear on the information document that the investigator gives to the patient before the start of the trial.

The patient must know:

- she may refuse to participate in the research;
- that the inclusion visit and the follow-up visits are borne by the study sponsor and that she will not have to bear any additional direct or indirect financial burden due to its participation in the trial.

The investigator must answer any additional questions from the patient on the trial at the time of selection and throughout the duration of the research.
At her request, the patient will be informed by the investigator of the results of the trial in which she has participated.

#### 14.3.2. Consent of the patient

Prior to its inclusion in the trial, the written, free, express, informed consent of the patient must be collected (European Directive 2001/20 / EC transposed by Decree No. 2005-477 of 26 April 2006) in a triplicate form.
The original is returned to the patient, a copy is kept by the investigator and the third copy is placed in a sealed envelope containing only the code of the test, the name of the investigator, the number of written consents that it contains and the date. This envelope is for the Medical Director of CEN Biotech who keeps it under his responsibility.

### 14.4. INFORMATION RETENTION, ARCHIVING

According to European regulations, all correspondence on the patients, ie the source documents, the observation books, the CPP's opinion and the correspondence relating to the trial, must be filed and kept in the archiving file for 15 years by the investigator.

### 14.5. DECLARATION TO THE CNIL

Patient notebooks are identified by the patient number, the first two letters of the name, and the first letter of the first name. In these circumstances, the trial falls under the simplified procedure related to clinical research. This procedure will be followed up before the beginning of the test. Patients participating in the trial will be informed of the indirect nature of the data collected on them in the trial newsletter, and will consent in writing to the trial consent form. They will also be informed that they have a right of information concerning them which will be exercised with CEN Gestion.

### 14.6. DECLARATION TO ANSM

This protocol, in accordance with the French law, is the subject of a declaration to the ANSM.

## 14.7. INSURANCE CERTIFICATE

The conduct of this trial is covered by an insurance policy contracted with HDI Global SE under the number 01005344514058 170036. A copy of the insurance certificate will be given to the investigator and kept in the investigator file. This document is presented in Annex 2 §16.2 of the protocol.

## 14.8. CONFIDENTIALITY

This document, its annexes, the investigator's brochure are given to him in confidence and must be given or communicated only to the persons specifically named in the trial with the agreement or at the request of the monitor.
The collected data will be anonymised by any appropriate means. The notes of the notebooks of observation will only carry the initials of the patient (first two letters of the name and first letter of the first name) and the patient's number.
By Article L1121-3 of the Public Health Code, the promoter and his representatives are subject to the same obligations of professional secrecy than the investigator.

## 14.9. DISPENSATION OF PRODUCTS

medi France entrusts the investigating center with the mission of dispensing the study products, respecting the order of attribution of the products. Each patient will be allocated a batch of product consisting of all materials required for the study.

## 14.10. RETURN OF PRODUCTS

The circaid® devices used will be examined and recovered upon return to the final visit. Patients wishing to continue wearing them will be able to benefit from a new free delivery.

## 14.11. CONDITIONS OF PUBLICATION

The documents provided by medi France to the investigator, as well as the notebooks that he completes and the results are the property of medi France and their communication falls within the specific rules relating to studies defined by Article R 5121-13 of the Public Health Code.
The study may be published or communicated subject to the prior written consent of the sponsor, the coordinator and the principal investigator.
At the end of the trial, the patients will be able to have their overall results communicated on request to the investigator.

## 14.12. DATA SOURCES - ARCHIVING DOCUMENTS

The source documents, the observation books, the original consent forms, the signed protocol and all documents related to this trial must be legally retained by the investigator for a minimum of 15 years from the trial report. Archiving will be done in a closed room provided for this purpose.

The promoter organizes the storage of the test documentation in appropriate premises for at least the product's lifetime (European Directive 91/507 / EEC):

- protocol with annexes, amendments;
- notebooks with accompanying documents;
- follow-up document of the clinical study;
- all administrative documents and correspondence related to the study;
- statistical analysis report and study report (product life + 5 years);
- non-rewritable media copy of the "frozen" database of clinical data.

## 14.13. STOPPING OF THE STUDY

### 14.13.1.Study discontinuation by the sponsor

The sponsor may stop the study at any time for the following reasons:

- inability of the investigator to include patients according to schedule;
- lack of signed consent;
- major violations of the protocol;
- incomplete or incorrect data.

### 14.13.2.Study stopped by the investigator

In the event of an adverse event deemed to be severe by the investigating physician and possibly involving the health of the patients, the latter may stop the study in agreement with the sponsor.

### 14.13.3.Stopping the study by the patient

Any patient wishing to leave the study for any reason can do so at any time.
In all cases, the investigator should seek to review the patient as soon as possible for a complete final evaluation in order to:

- know the motivation of the decision and mention it on the observation notebook;
- evaluate the clinical condition of the patient;
- if necessary, take the appropriate therapeutic measures: management of a side effect or an intercurrent pathology, prescription of another treatment.

Patients will stop treatment before the end of the study in the case of the occurrence of a serious pathology justifying the prescription of treatments not authorized by the protocol, or incompatible with the continuation of the study, and will come out prematurely of the trial.
The study monitor will be notified by telephone or fax, and a letter or report explaining this study discontinuation will be sent to him as soon as possible.

### 14.13.4. Non inclusion

All documents relating to the selected patients (consent, test results) but not included will be retained by the investigator and managed in the same manner than the patient documents included in the study.

### 14.13.5.Wrong inclusion

Any wrong inclusion will be discussed with the study monitor. The patient should be out of the study and replaced by another patient. All available data will be retained for tolerance analysis.

### 14.14. QUALITY INSURANCE

The study will be performed in accordance with Good Clinical Practices and Standard Operating Procedures of CEN Gestion.

### 14.15. AUDIT AND INSPECTION

The investigator and the promoter agree to be audited by the Clinical Quality Insurance department of the promoter or of any person mandated by it and, if necessary, eventually being inspected by ANSM.
In all cases, the investigator accepts direct access to all data source to ensure the authenticity of the data.

### 14.16. CLINICAL REPORT

The clinical trial report, including a reminder of the objectives and methods, a presentation of the results and their discussion, will be written according to the ICH3 recommendations and submitted for approval, before signature, to the coordinator-investigator and the statistician who carried out the study analysis.

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