"Does the application of cold reduce the pain associated with the application of a high concentration capsaicin patch in patients with pain localized neuropathic pain?"

DIDOCAP study

PROTOCOL OF RESEARCH IN ROUTINE CARE

Nursing project

Internal reference: CHD 049-16

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Signing of a research protocol in routine care page

Internal reference: CHD 049-16
Title: "Does the application of cold reduce the pain associated with the application of a high concentration capsaicin patch in patients with localised neuropathic pain?" DIDOCAP study

The research will be conducted in accordance with the protocol and the legislative and regulatory provisions in force.

Head of Research : Dr. Yves-Marie PLUCHON CETD Service CHD Vendée 85925 La Roche sur Yon	Date: ...../...../..... Signature :
The promoter : Mr Francis SAINT-HUBERT General Management Vendee Departmental Hospital La Roche sur Yon	Date: ...../...../..... Signature :
Referent : Centre: ..... Name:	Date: ...../...../..... Signature :

The research received a favourable opinion from the CPP Ouest VI in Brest on 26/07/2016.

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SUMMARY

Title	"Does cold application decrease pain associated with high concentration capsaicin patching in patients with localised neuropathic pain?" **DIDOCAP study**
Manager	Departmental Hospital Centre (CHD) Vendée - La Roche Sur Yon
Head of Research	Dr. Yves-Marie PLUCHON, CHD Vendée - La Roche sur Yon
Responsible for the implementation of the research	Natacha TAILLIEZ, nurse, CHD Vendée - La Roche sur Yon
Population concerned	Patients treated for neuropathic pain
Nature of the care assessed	Treatment of neuropathic pain with high concentration capsaicin patch
Number of centres	4 centres/ 5 sites - CHD Vendée, La Roche sur Yon / Montaigu - Brétéché Clinic, Nantes - CH of Challans - Côte de Lumière Hospital, Les Sables D'Olonne
Expected number of patients	100 patients randomised
Main objective	To evaluate the effectiveness of cold application on pain reduction (burning sensation) after one hour of high concentration capsaicin patch (Qutenza®) in patients with localised neuropathic pain.
Secondary objectives	• To evaluate the efficacy of Qutenza® patch treatment on neuropathic pain in patients receiving cold application during placement. • Assess pain kinetics during the hour of application. • To evaluate the effectiveness of short-term cold application on the burning sensation. • To evaluate the reduction of the pain area 2 months after the • Quentza® patch in patients with localized neuropathic pain
Inclusion criteria	- Male, Female - Major - Not objecting to participation in the study - Follow-up for localized neuropathic pain - Diagnostic score DN4 ≥ 4 - Neuropathic pain in failure of conventional first-line treatment - To benefit from the first Qutenza® patch - Able to understand the proposed study

Non-inclusion criteria	- Patch application on feet, face, mucous membranes - Premedication with EMLA -Having already received a Qutenza® patch - Allergy to Qutenza® components - Known and poorly stabilised hypertension - known cryoglobulinemia - pregnant or breastfeeding woman - Patient benefiting from a legal protection measure (guardianship, curatorship...) - Patient deprived of liberty - Non-membership in a social security scheme. - Refusal to participate in the study
Evaluation criteria	*Primary endpoint* - Collection of VAS (burning sensation) after 1 hour of Qutenza® patch application. *Secondary evaluation criteria* - Collection of the EVA (burning sensation) at 30 minutes of exposure, - Collection of VAS (neuropathic pain) before and 2 months after insertion, - Collection of DN4 score before and at 2 months after placement - Collection of pain (burning and neuropathic pain) by EN within one week of insertion, - Duration of burning sensation after application - Cold application during the week following the installation, - Taking painkillers in the week following insertion - Taking painkillers while applying the Qutenza® patch - Measurement of the painful area before patching and 2 months after patching
Statistical methodology	Prospective, randomised, two-centre, open-label nursing study. Patients will be randomized into two groups at the time of their first Qutenza insertion® : - Patient receiving Qutenza® without cold pack - Patient receiving Qutenza® in combination with a cooling pad
Duration of a patient's participation	2 months after the first Qutenza® patch application (post-first application consultation) - in practice this consultation is sometimes carried out up to 3 months after the application depending on availability and the organisation of the service.
Timetable of the study	Inclusion period: 42 months Duration of patient follow-up: 2 months (maximum 3 months allowed) Total duration of the research: maximum 45 months

LIST OF ABBREVIATIONS

CCTIRS	Advisory Committee on Information Processing in Health Research
CETD	Pain Assessment and Treatment Centre
CHD Vendée	Vendée Departmental Hospital Centre
CNIL	Commission Nationale Informatique et Libertés
EMLA	Eutectic mixture of local anesthetics
EVA	Visual Analogue Scale
TRPV1	Transient Receptor Potential Vanilloide 1

I SCIENTIFIC JUSTIFICATION, GENERAL DESCRIPTION

1. NAME AND DESCRIPTION OF THE CONDITION UNDER STUDY

Since 1994, neuropathic pain has been defined by the International Association for the Study of Pain (IASP) as "pain initiated or caused by a primary injury or dysfunction of the nervous system". More recently, it has been proposed to define neuropathic pain as "pain associated with injury or disease affecting the somatosensory system", but this definition has not yet been officially accepted.
Neuropathic pain is often misunderstood, underestimated and under-treated. However, this pain is not rare, since, according to a recent epidemiological study in the general population, chronic pain with neuropathic characteristics affects 7% of the French adult population.

These pains are due to a lesion of the peripheral nervous system (lesion of a nerve, a plexus, a nerve root) or central (lesion of the spinal cord, the brain stem, the thalamus).
The causes can be traumatic, toxic, viral, tumoral or metabolic.
The factors that lead to chronic pain can be professional, medico-legal, socio-economic, psychological, functional, etc.

The diagnosis is based on a thorough interview and a well conducted clinical examination. The DN4 questionnaire, neuropathic pain in 4 questions, validated in French (5), is currently the reference tool for the diagnosis of neuropathic pain. (Appendix C).
The patient suffering from neuropathic pain may experience tingling, intense tingling, electric shocks, a burning pain background, a compression sensation with numbness in the affected area.
The repercussions of these pains are important on the quality of life: fatigue, anxiety, sleep disorders, depression.

Neuropathic pain is unresponsive or poorly responsive to Tier I analgesics such as paracetamol and non-steroidal anti-inflammatory drugs. Other therapeutic classes should be considered.
The first and most common treatment approach is to prescribe antidepressants or antiepileptics in moderate doses.
These drugs have different side effects for different people.

2 GENERAL DESCRIPTION OF THE RESEARCH

« Capsaicin », extracted from the red pepper plant, has long been used therapeutically in the form of a cream at a low concentration requiring repeated applications and most often in postherpetic neuropathic pain.

Since pain is transmitted by neurotransmitters, the application of a patch soaked in this substance releases the conductive nerve fibres inflamed by excessive histamine and serotonin secretions. As a result, the pain may be greatly reduced, but the application of the patch is associated with an initial, unsustainable burning sensation.

In the late 1990s, the improved knowledge of the TRPV1 (*Transient Receptor Potential Vanilloid 1)* receptors of the nociceptors, of which capsaicin is an agonist, and the specific work on neuropathic pain allowed the use of capsaicin to be reviewed.
The availability to the medical profession of a highly concentrated 8% "trans-dermal device" form has changed practice.

The long-term (3 months) efficacy of single applications of a high concentration (8%) capsaicin patch to the painful area (for 60 or 90 minutes) has been reported for postherpetic pain and painful HIV neuropathy(6,7,8)

The interest of this treatment lies in the low risk of systemic side effects and the prolonged duration of effectiveness. However, the initial application, which is often very painful, requires monitoring of the patient, preferably in hospital, during application and the use of analgesics.

At the CHD Vendée, QUTENZA®, capsaicin at 8%, has been used since 2012 in the treatment of peripheral neuropathic pain.
The application protocol is as follows:
The painful area must be determined by the doctor and marked on the skin. The patch should be applied to intact, non-irritated, dry skin. The Qutenza® patch is left in place for 60 minutes, and applications may be repeated every 60 to 90 days if pain persists or recurs. If necessary, the hair covering the area to be treated is trimmed short to promote adhesion of the Qutenza® patch (do not shave). The areas to be treated should be washed gently with soap and water. The patch of Qutenza® can be cut to the size and shape of the area to be treated, in this case it must be cut before removing the protective film.

The application of the Qutenza® patch may progressively cause a burning sensation which may become intense due to the local inflammatory action of capsaicin. Then, after a few hours to a few days, the desired analgesic effect usually appears through an inactivation of the Cfibres, which suppresses the transmission of the pain message.

Initially, it was recommended to prepare the area to be treated by applying a local anaesthetic, but the work of a German team (1) showed that this approach was of no interest as it had no real effect on the initial iatrogenicity of capsaicin.

To reduce the burning sensation, a cooling procedure can be applied immediately after the patch is applied.

According to the recommendations of the ASTELLAS laboratory, patients suffering from pain during and after the application of the patch may receive supportive treatment such as local cooling.

Furthermore, the application of cold during the application of the capsaicin device does not alter the pharmacokinetics of the product. (1)

At the Centre d'Evaluation et de Traitement de la Douleur (CETD) in La Roche sur Yon, we applied this procedure and found a reduction in the burning sensation felt by a group of 90 patients, half of whom did not have this cold application.
The application of cold during the application of the capsaicin patch is already done in current practice, but there is still no real consensus, nor any study on the reduction of pain (burning sensation) nor on the effectiveness.

Our hypothesis is that the application of cold during the application of the Qutenza patch® could decrease the patient's Visual Analogue Scale (VAS) (pain sensation) by 2 points.

3. SUMMARY OF BENEFITS, IF ANY, AND FORESEEABLE AND KNOWN RISKS TO INDIVIDUALS INVOLVED IN THE RESEARCH

There are no foreseeable risks associated with participation in the study. Patients will be managed according to standard practice.
For patients receiving cold application, it will be necessary to protect the areas not treated by the patch but in contact with the cold with compresses to avoid the risk of cold burns.

There was no direct predictable benefit for patients randomised to the no-cooling arm.

On the other hand, the patient having received cold during the application should be less painful, he will not keep in memory this unpleasant memory (knowing that it is an area already presenting multiple painful symptoms) and will be ready to come back for a 2nd application. The patient's experience will therefore be better.

4. STATEMENT THAT THE RESEARCH WILL BE CONDUCTED IN ACCORDANCE WITH THE PROTOCOL AND GOOD CLINICAL PRACTICE

The investigator also undertakes that this research will be conducted :

- in accordance with the protocol,
- in accordance with current French and international good clinical practice.

II OBJECTIVES

1. MAIN OBJECTIVE:

To evaluate the effectiveness of cold application on pain reduction (burning sensation) after one hour of Qutenza® patch application in patients with localized neuropathic pain.

Our hypothesis is that the application of cold during the application of the Qutenza patch® could decrease the patient's VAS (pain sensation) by 2 points.

2. SECONDARY OBJECTIVES:

- To evaluate the efficacy of Qutenza® patch treatment on neuropathic pain in patients receiving cold application during placement.
- Assess pain kinetics during the hour of application.
- To evaluate the effectiveness of short-term cold application on the burning sensation.
- To evaluate the reduction in pain area 2 months after Quentza® patching in patients with localised neuropathic pain

III DESIGN AND CONDUCT OF THE RESEARCH

1. CLEAR STATEMENT OF PRIMARY AND, WHERE APPROPRIATE, SECONDARY EVALUATION CRITERIA

Primary endpoint:

- Collection of VAS (burning sensation) after 1 hour of Qutenza patch application® .

In retrospective observations made at the CETD of the La Roche sur Yon Hospital, 70% of patients receiving a first Qutenza® patch reported more pain at 1 hour than at 30 minutes. For this reason, it was decided to evaluate the primary endpoint at 1 hour of application. Nevertheless, the pain at 30 minutes of application will be evaluated as a secondary endpoint.

Secondary evaluation criteria :

- Collection of VAS (neuropathic pain) before insertion and VAS (neuropathic pain) at 2 months after insertion,
- Collection of the DN4 score before and at 2 months after implantation.

The DN4 questionnaire is used to estimate the probability of neuropathic pain. It is a score out of 10, if the patient's score is equal to or higher than 4/10 the test is positive.
Although the DN4 questionnaire is a questionnaire for the diagnosis of neuropathic pain, it is also used in the participating centres for patient follow-up as it is a simple, easy-to-use scale that has become standard in all CETD consultations.
This scale does not assess the intensity of pain, but its type and characteristics; equally important for patients in improving their quality of life. The DN4 can be compared before insertion and at follow-up. Pain intensity will be assessed via VAS.

- Collection of the EVA (burning sensation) at 30 minutes of exposure.
- Taking painkillers while applying the Qutenza® patch
- Collection of pain (burning and neuropathic pain) by EN within one week of insertion,
- Duration of burning sensation after application
- Cold application during the week following the installation,
- Taking painkillers in the week following insertion
- Measurement of the painful area before patching and 2 months after patching

2. DESCRIPTION OF THE RESEARCH METHODOLOGY

Feasibility :

On retrospective observations carried out at the CETD of the CHD of La Roche sur Yon and at the CETD of the Clinique Brétéché in Nantes, the data of 124 patients were collected over a period of 16 months (non-exhaustive collection). Among these patients, 74 received a first Qutenza® patch (59.7%).

Extrapolating these results and adding the Challans and Sables d'Olonne centres, we expect to obtain a potential of 100 patients over a 42-month period.

Conduct of the study :

This is a multicentre study on 5 different geographical sites (La Roche sur Yon, Montaigu, Challans, Nantes, Les Sables D'Olonne). It is planned to randomise 100 patients in total. In order to compensate for possible patients who would be included (signed non-objection) but could not be randomised, a maximum of **110 patients will be included**. Enrolment will be completed once the study has reached 100 randomised patients.

Approximately two months before the first Qutenza® patch is applied, the patient is seen in an information consultation by a doctor as part of their treatment at the CETD. On this occasion, a nurse will complete the consultation by presenting the DIDOCAP study and by proposing to the patient to participate.

The patient will go home with the information leaflet. The patient's non-objection can be collected on the day of this consultation or at the latest on the day of the first patch of Qutenza®. The non-objection will be collected and signed by the doctor and/or the nurse.
If the patient refuses, he/she will receive the most appropriate treatment for his/her situation (Qutenza patch® with or without the application of cold, at the discretion of the medical team and according to the patient's choice in accordance with the standard practice of the centres).

If the patient accepts, a randomisation will be performed on the day of the Qutenza patch® (via the e-CRF). The two randomisation groups are :

- **Patient receiving Qutenza® without cold application or**
- **Patient receiving Qutenza® combined with cold application**

At each consultation (2 months before inclusion, on the day of inclusion (patching), at 1 month and at 2 months after patching) the patient will be seen by both a doctor and a nurse.

Doctor: The doctor prescribes the Qutenza® patch, and carries out the tracing with the nurse on the day of application in the day hospital. He also prescribes painkillers for the week following the application if necessary.
The doctor sees the patient again at 1 and 2 months.

Nurse: The nurse greets the patient, assesses the pain, performs a global evaluation, gives information about adverse events related to the procedure, applies the patch according to the doctor's instructions following the Qutenza® patch use procedure.

Cold application :

The patch is applied by a nurse.

For patients randomised to the Qutenza® patch with cold application, cold application will be in the form of Actipoche® pads (reusable) provided by the sponsor for all participating sites.

The Actipoche® cushion (placed in its cover) will be placed as soon as the application of the patch of Qutenza® directly on the patch. If necessary, two Actipoche® cushions will be used to cover the entire area treated by the Qutenza® patches.
Depending on the area treated, the cushions will be held in place either by a band (e.g. if the area treated is the knee) or by pressure (e.g. patient lying on his back for treatment of the scapula)

In order to ensure the optimal temperature of the Actipoche® cushion, the Actipoche® cushion(s) will be replaced after 30 minutes with a new Actipoche® cushion for all patients.

The Actipoche® cushion(s) will be removed at the same time as the Qutenza® patch after 1 hour of application.

The Actipoche® cushion can be used for both thermotherapy and cryotherapy.

In cryotherapy: According to the product leaflet, it is recommended to place the Actipoche® cushion, without its cover, in the freezer for at least 20 minutes or in the refrigerator for about 2 hours for optimal use.
In the participating centres, the cushions will be placed in the freezer before application (i.e. at a temperature of approximately -6°C).

To use: Insert the pouch into its cover and apply to the painful area for 20-30 minutes. Check the temperature of the cushion with the back of your hand before application.

Between uses, the cushion can be stored either in the refrigerator or at room temperature.

The leaflet states that analgesic or painkiller products can alter the perception of heat and cold in patients and that it is therefore not recommended to use the Actipoche® cushion in addition to this type of product.
This precaution is intended to prevent possible misuse of the Actipoche® cushion during personal use at home.
In the study, the Actipoche® cushion will be used in addition to the Qutenza® patch, which has a long-term analgesic action but is also associated with a strong burning sensation when applied.
The perception of heat and cold will certainly be modified in patients, but this application will be carried out under medical supervision during the entire period of application.

Criteria assessed :

The protocol consists of assessing the intensity of the burning sensation by means of a VAS at 30 minutes and 60 minutes of exposure.

It should be noted that the VAS evaluated before the Qutenza® patch, at 1 month and at 2 months after application concern the patient's neuropathic pain, whereas the VAS at 30 and 60 minutes are the pain related to the burning sensation.
Concomitant treatment(s) received by the patient prior to the application of Qutenza® and in particular those taken on the day of application of the Qutenza® patch will also be collected.

Patients will be reviewed in a medical consultation at 1 month and 2 months after insertion, according to standard practice. This last visit may be carried out at 2 months or at the latest at 3 months after insertion, depending on the organisation and availability of the department.

3. DESCRIPTION OF MEASURES TAKEN TO REDUCE AND AVOID BIAS

Randomisation will be performed in an open-label fashion, according to 2 groups of patients: one group with cold application and another group without cold application on the Qutenza patch® . The randomisation will be stratified on the centre. It will be carried out according to a 1:1 ratio and will be performed in blocks. Patients will be randomised on the day of application.

Randomisation will be carried out via the Capture System software by connecting to the website: https://nantes-lrsy.hugo-online.fr/CSOnline/.
The connection will be carried out thanks to a login, a password and a study number, delivered by the data manager of the CHD Vendée of La Roche sur Yon.
The following information should be filled in:

- First initial of the name,
- First initial of the first name,
- Month and year of birth,
- Compliance with inclusion and non-inclusion criteria (yes/no), - No opposition to the study collected (yes/no).

Randomisation will be carried out by the investigator after confirmation of the possibility of inclusion in the study and the collection of no objection.
The inclusion number will be assigned automatically during randomisation. An email confirmation will be sent to the person who performed the randomisation and to all the persons concerned at the centre.

The randomisation list will be drawn up by the study methodologist, Aurélie Le Thuaut, CHD Vendée before the start of the study. An explanatory guide to randomisation will be available online under Capture System.
The randomisation list will be protected by restricted access and accessible only by the study biostatistician.

4. DURATION OF PARTICIPATION FOR A SUBJECT IN THE RESEARCH AND A DESCRIPTION OF THE TIMING AND DURATION OF ALL TRIAL PERIODS, INCLUDING FOLLOW-UP WHERE APPLICABLE

The duration of a patient's participation will be 2 months from the day of the installation with a delay of up to 3 months depending on the availability and organisation of the service.

5. DESCRIPTION OF THE PERMANENT OR TEMPORARY CESSATION RULES

Subjects may withdraw their agreement to participate and request to be removed from the study at any time and for any reason. The investigator may temporarily or permanently discontinue a subject's participation in the study for any reason that is in the best interest of the subject.

6. DATA COLLECTED

See Annex A

IV SELECTION OF PEOPLE

All patients consulting the anti-pain centre of the CHD de Vendée, the Brétéché clinic, the Challans hospital, or the Côte de Lumière hospital in Les Sables d'Olonne for neuropathic pain requiring Qutenza® and meeting the inclusion criteria will be included in this study.

1. INCLUSION CRITERIA

- Male, Female
- Major
- Not objecting to participation in the study
- Follow-up for localized neuropathic pain
- Diagnostic score DN4 ≥ 4
  Neuropathic pain in failure of conventional first-line treatment
- Expected to benefit from a first patch of Qutenza ®
- Able to understand the proposed study

2. NON-INCLUSION CRITERIA

- Application of Qutenza® patches on the feet, face, mucous membranes

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- Premedication with EMLA
- Having already received a Qutenza patch®
- Allergy to the components of Qutenza®
- Known and poorly stabilised hypertension
- known cryoglobulinemia
- pregnant or breastfeeding woman
- Patient benefiting from a legal protection measure (guardianship, curatorship,...)
- Patient deprived of liberty
- Non-membership in a social security scheme.
- Refusal to participate in the study

V PRODUCTS ADMINISTERED TO RESEARCH SUBJECTS

1. INTERVENTION UNDER STUDY

Randomisation: application of cold or not during the application of the Qutenza patch® (transdermal anaesthetic device, active ingredient: capsaicin)

For patients randomly selected in the group receiving the Qutenza® patch with cold application:

- Actipoche® cushion (reusable) provided by the promoter for all participating sites

Ref : Laboratoire Cooper - Actipoche® Hot/Cold Large Size 20 x 30cm
This is the brand of cushion currently used by the various participating centres.

Composition : Gel based on : Propylene glycol - Sodium polyacrylate - Dye - Water. Plastic casing.

2. PERMITTED TREATMENTS

As this is a routine care study, the management of the patient remains similar to standard practice. There are no prohibited treatments. The analgesic treatments taken by the patient will be noted in his or her observation book so that they can be taken into account in the analysis of the study.

VI STATISTICS

1. DESCRIPTION OF THE PLANNED STATISTICAL METHODS, INCLUDING THE TIMING OF PLANNED INTERIM ANALYSES

A descriptive analysis will be performed for all patient data overall and by randomisation arm. Quantitative variables will be described by mean, standard deviation, median, quartiles, extreme values. Qualitative variables will be described by the number of patients and the proportions according to the defined modalities.

Main criterion

The primary endpoint was the VAS collected 1 hour after the start of the procedure.
The mean VAS between the 2 groups (with or without cold application) will be estimated and compared using a linear mixed model taking into account the stratification criterion on the centre. The "cold application" criterion will be taken into account as a fixed effect and the centre as a random effect.

The main analysis will be "intention to treat". It may be supplemented by a "per-protocol" analysis. No intermediate analysis is planned.

Secondary criteria

VAS (neuropathic pain) before and at 2 months after surgery
- The mean difference between the 2 groups (with or without cold application) will be estimated and compared using a linear mixed model taking into account the VAS score measured at baseline and the stratification criterion on the centre.

DN4 before installation and at 2 months
- The mean difference between the 2 groups (with or without cold application) will be estimated and compared using a linear mixed model taking into account the DN4 score measured at baseline and the stratification criterion on the centre.

EVA (burning sensation) after 30 minutes
- The mean VAS between the 2 groups (with or without cold application) will be estimated and compared using a linear mixed model taking into account the stratification criterion on the centre.

The evolution of the pain at 30 minutes and 1 hour will be represented graphically.

Short-term follow-up (7 days)
- The mean NE between the 2 groups (with or without cold application) will be estimated and compared using a linear mixed model taking into account the stratification criterion on the centre.
-The use of cold application during the week following the application will be compared between the 2 groups by a Chi2 test.

2. EXPECTED NUMBER OF PEOPLE TO BE INCLUDED IN THE RESEARCH, AND EXPECTED NUMBER OF PEOPLE IN EACH RESEARCH LOCATION WITH ITS STATISTICAL JUSTIFICATION

Based on retrospective observations carried out at the CETD of the La Roche sur Yon hospital, on average, patients present a VAS pain of 7/10 one hour after application. We would like to reduce this pain to 5/10 (a reduction of 2 clinically relevant points) by applying cold during the application of the Qutenza patch .®)

Assuming a decrease of 2 points between the initial VAS of the burn and the VAS at 1H, with a standard deviation of 2.8, an alpha risk of 5% and a power of 90%, 42 patients per group will be required. In order to compensate for possible dropouts, 50 patients per arm, i.e. 100 patients in total, will be randomised.
In addition, in order to also accommodate possible patients who would be included (signed non-objection) but could not be randomised, a maximum of **110 patients will be included**.
Enrolment will be completed once the study has reached 100 randomised patients.

3. EXPECTED LEVEL OF STATISTICAL SIGNIFICANCE

The significance level is set at 5%.

4.METHOD OF ACCOUNTING FOR MISSING DATA

The number of missing data and the reason for the missing data will be described in each of the treatment groups.
As the endpoint is collected one hour after patching, there will be no missing data on this endpoint.

VII RIGHT OF ACCESS TO SOURCE DATA AND DOCUMENTS

1. Access to data

The medical data of each patient will only be transmitted to the organisation of the person responsible for the research or any person duly authorised by the latter under conditions that guarantee their confidentiality.

2. Source documents

Where appropriate, the responsible person's home organization may request direct access to the medical file for verification of research procedures and/or data, without breaching confidentiality and within the limits permitted by laws and regulations.

3. Data privacy

Persons with direct access shall take all necessary precautions to ensure the confidentiality of information relating to the persons who have access, in particular as regards their identity and the results obtained.
These persons, as well as the investigators themselves, are subject to professional secrecy (according to the conditions defined by articles 226-13 and 226-14 of the penal code). During or after the research, the data collected on the subjects and transmitted by the participants will be made anonymous.
Under no circumstances should the names of the persons concerned or their addresses appear in clear text.
Only the first letter of the subject's name and the first letter of the subject's first name will be recorded, along with the month and year of birth and a coded study number indicating the order of inclusion of subjects.

VIII QUALITY ASSURANCE

The research will be conducted according to the standard operating procedures of the management centre. The care of individuals in the participating centres will be carried out in accordance with medical ethics and recommendations.

IX ETHICAL ASSESSMENTS OF THE SPECIFIC MONITORING ARRANGEMENTS IN THE PROTOCOL

As this is a routine care study, no therapeutic modifications will be made within the framework of the protocol. The occurrence of an adverse effect during the present protocol will give rise to a declaration in the appropriate vigilance system (pharmacovigilance, biovigilance, hemovigilance, materiovigilance, etc.).

1. Committee for the Protection of Individuals

The protocol and the information and no objection form for the study will be submitted to the CPP for advice.

2. Substantial changes

Any substantial modification to the study protocol must be notified to the Committee for the Protection of Individuals in order to verify that the proposed modifications do not alter at any time the guarantees provided to the persons who are to undergo the research. Information letter and no objection

Patients will be informed fully and fairly, in understandable terms, of the objectives of the study, their rights to refuse to participate in the study or to withdraw at any time. All this information will be included on an information and opt-out form given to the patient.

X DATA PROCESSING AND RETENTION OF DOCUMENTS AND DATA

1. Data entry

One case report form (CRF) will be created per patient. All information required by the protocol must be provided in the CRF. The CRF will include the different steps of the patient's management in the protocol. It should include the data necessary to confirm compliance with the protocol, identify major deviations from the protocol and all data necessary for analysis.
The anonymity of the subjects will be ensured according to the rules defined by the protocol. The data will be entered on a secure database and will only contain the patient's inclusion number as identity. The computer processing of the data is completely anonymous once the clinical collection has been completed.

Patients are informed and informed that the results are available to them at the end of the analysis of this study if they request them.

2. CNIL

This study falls within the scope of the "Reference Methodology" (MR-003) in application of the provisions of Article 54 paragraph 5 of Law No. 78-17 of 6 January 1978 on information technology, files and freedoms (updated and published in the official journal on 14 August 2016).

3. Archiving

Archiving of study documents will be done in accordance with Good Clinical Practice and the regulations in force.

XI INSURANCE

Insofar as the research is indeed qualified as Research in routine care by the CPP requested, which means that there is no additional risk linked to the study, the insurance will be that of the establishment responsible for the care (Article L. 1142-2).

XII RULES ON PUBLICATION

Scientific papers and reports related to this study will be produced under the responsibility of the principal investigator coordinating the study with the agreement of the responsible investigators. The co-authors of the report and publications will be the investigators and clinicians involved, in proportion to their contribution to the study, as well as the biostatistician and associated researchers.

The rules for publication will follow international recommendations (N Engl J Med, 1997; 336:309-315).

XIII REFERENCES TO THE SCIENTIFIC LITERATURE AND RELEVANT DATA USED AS A REFERENCE FOR THE RESEARCH

1. Comparison of cooling and EMLA to reduce the burning pain during capsaicin 8% patch application: a randomized, double-blind, placebo-controlled study. KnolleE, Zadrazil M,Kovacs GG, Medwed S, Scharbert G, Schemper M. Pain. 2013 Aug 7

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