SPONSOR:	***CHD VENDEE*** ***LA ROCHE SUR YON***
CLINICAL TRIAL PROTOCOL ***RHIZ'ART***	
TEST CODE	CHD 046-17
EudraCT no.	2017-002298-20
PRODUCT/MOLECULE	Hyaluronic acid (Sinovial®) and corticoids (Diprostene®)
FULL TITLE	Effects of infiltration with hyaluronic acid and corticosteroids on pain versus corticosteroids alone in rhizarthrosis
CLINICAL PHASE	Phase IV
INDICATION(S) (TARGET)	Patients suffering from rhizarthrosis
PRINCIPAL INVESTIGATOR	Dr. Cormier Grégoire CHD Vendée Rheumatology Department
PROTOCOL VERSION NO.	*4.0*
PROTOCOL DATE	*24/05/2018*
ETHICS COMMITTEE	*CPP (EC) Ile de France III* *Initial favorable opinion on: 09/12/2017*
FRENCH AGENCY FOR DRUG SAFETY	*Initial authorization on 01/23/2018*
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Contents

SIGNATURES

SIGNATURE OF THE COORDINATING INVESTIGATOR

I have read all the pages of the protocol for the clinical trial sponsored by the CHD Vendée in La Roche sur Yon. I confirm that it contains all the information necessary for the conduct of the trial. I undertake to carry out the trial in compliance with the protocol and the terms and conditions defined therein. I undertake to carry out the trial in compliance with:

- the principles of the "Declaration of Helsinki",
- international (ICH-E6) and French rules and recommendations of good clinical practice (guidelines for good clinical practice for biomedical research involving medicinal products for human use - decisions of November 24, 2006)
- national legislation and regulations governing clinical trials,
- compliance with the EU Clinical Trials Directive [2001/20/EC], a copy of each of which I received from the sponsor.

I also undertake to ensure that the investigators and other qualified members of my team have access to copies of this protocol and documents relating to the conduct of the trial to enable them to work in compliance with the provisions set out in these documents.

NOM: Dr. Grégoire CORMIER, Rhumatologie, CHD Vendée

Signature : .....

Date : 27.11.2019

SIGNATURES

Promoteur :

NOM : M. Francis SAINT-HILBERT, Directeur Général CHD Vendée

Signature : .....

Date : 2/12/19

Investigateur principal : *(en cas d'étude multicentrique)*

NOM : _____ Date : _____

CENTRE : _____ Signature: .....

AMENDMENTS TO THE INITIAL PROTOCOL

Modification	Pattern	Protocol version
Amendment 1	Pharmacy chapter clarification	2.0 of 02/22/2018
Amendment 2	Co-investigator update	2.0 of 02/22/2018
Amendment 3	Blind box allocation and co-investigator update	3.0 of 05/24/2018
Amendment 4	Co-investigator update	3.0 of 05/24/2018
Amendment 5	NIFC update	3.0 of 05/24/2018
Amendment 6	Addition of a center + extension of the inclusion period (18 months)	4.0 of 07/25/2019

Summary

Title	*RHIZ'ART* – The effects of infiltration with hyaluronic acid and corticosteroids on pain versus corticosteroids alone in rhizarthrosis.
Developer	*CHD Vendée La Roche sur Yon*
Coordinating Investigator	*Dr. Grégoire CORMIER, CHD Vendée*
Protocol version	4.0 du 25/07/2019
Justification / context	Rhizarthrosis, or arthrosis of the trapeziometacarpal joint, is a common form of osteoarthritis that affects 10-25% of women, particularly after menopause. It affects unstable joints that are subject to significant pressure. It progresses over several years and can lead to a Z-shaped deformity of the thumb column, which is functionally disabling. Treatment consists of a combination of non-pharmacological measures such as relative resting of the joint, resting orthoses and icing, with pharmacological measures such as analgesics, oral or local non-steroidal anti-inflammatory drugs, or even cortisone or hyaluronic acid infiltrations. To date, no study has tested the benefit of combining cortisone and hyaluronic acid in rhizarthrosis. In view of the current literature, we propose conducting a two-arm study, with corticosteroids as the reference arm and hyaluronic acid combined with cortisone as the experimental arm.
Main objective	To compare the efficacy of corticosteroid infiltration alone to corticosteroid infiltration combined with hyaluronic acid in patients with rhizarthrosis at 3 months.
Secondary Objectives	- Comparison of the changes in pain with activity at M1, M6 and M12; and of the most intense pain. - Comparison of pain between M0 and M3, by weekly recordings of VAS (in a notebook given to the patient). - Comparison of the changes in pain at rest at M0, M1, M3, M6 and M12; and of the most intense pain. - Comparison of the changes in function with the Cochin hand scale at M1, M3, M6 and M12. - Comparison of grip and opposition strength changes at M1, M3, M6 and M12. - Description of ultrasound changes. - Comparison of injection pain. - Comparison of the patient's perception of changes in pain at 3 months. - Comparison of new infiltrations. - Description of adverse effects and events. - Description of analgesic and NSAID use.

	- Comparison of the after-effects of infiltration.
Primary endpoint	The primary endpoint for evaluating the efficacy of rhizarthrosis infiltration was the intensity of pain at the base of the thumb (as defined by the patient, i.e., during activity) on the Visual Analogue Scale (VAS) of pain at baseline and at 3 months in the 2 groups.
Secondary endpoint	- Recording VAS during activity - VAS for pain perceived at the base of the thumb at rest - The worst pain score - Cochin score - Grip and opposition strength - Ultrasound evaluation at inclusion and M3 - VAS during infiltration - Verbal score for overall change at 3 months. - Number of corticosteroid infiltrations - Recording adverse effects and events - Recording data on analgesic and NSAID use - Number of days off work from the start of orthosis use - Possible progression to a surgical procedure
Methodology / Study diagram	- Phase IV drug trial - Regional multicenter study (CHU Nantes, CHD Vendée, CHG Le Mans) - Comparative, Randomized, Controlled, Superiority - Control group: reference drug (Diprostene®) - Double-blind (patient and primary endpoint assessor) - With 2 groups compared: one receiving corticosteroids (CTC) and 0.9% NaCl; the other receiving a combination of Hyaluronic Acid (HA) and CTC - In 2 parallel groups
Inclusion Criteria	- Adults, ≥ 40 years - Pain at the base of the thumb (near the wrist) triggered by direct pressure and movement - Pain resistant to well-conducted medical treatment, with analgesics, NSAIDs and icing, with a VAS ≥ 4 for more than 3 months. - Radiological lesions (Kapandji view; anterior + profile) typical of rhizarthrosis, Eaton and Litter stage II or III, with at least 2 of the following 5 radiological features observed on the trapeziometacarpal joint: -marginal osteophyte -pinching of the joint space -subchondral sclerosis -subchondral geode -absence of osteopenia - Patient capable of understanding the protocol and having signed an informed consent form - Patient with social security coverage

Non-Inclusion Criteria	- Known allergy to one of the products (Diprostene® or Sinovial®) including the excipients (methyl parahydroxybenzoate, propyl parahydroxybenzoate, benzyl alcohol). - Change in analgesic treatment in the 4 weeks prior to inclusion. - Patients with symptomatic bilateral rhizarthrosis - Scaphoidotrapezial osteoarthritis - Local or general infection -Severe coagulation disorders, ongoing anticoagulant therapy - Severe and/or uncontrolled hypertension - Previous local surgery - Associated inflammatory rheumatism - De Quervain's tendinopathy, thumb with associated protrusion - Previous infiltrations less than 6 months old - Uncontrolled diabetes - Live vaccines -Severe cases of water and/or sodium retention (hypernatremia), particularly in heart failure, decompensated liver disease (edema and ascites) - Pregnant or breast-feeding women - Immunocompromised or hemodialysis patients - Patients under guardianship or deprived of their liberty - Patients participating in another clinical research protocol involving a drug or medical device - Patients unable to follow the protocol, as judged by investigator
Treatments / Strategies / Procedures	HA + CTC arm: 0.5ml Diprostene® and 0.5ml Sinovial mini®. CTC + Na Cl 0.9% arm: 0.5 ml Diprostene® and 0.5 ml NaCl 0.9%.
Number of patients	A total of 150 patients
Search duration	Length of inclusion period: 36 months Duration of participation for each patient: 12 months Total study duration: 48 months
Expected benefits	Optimization of the management of patients suffering from rhizarthrosis

List of abbreviations

CMC OA	Carpometacarpal (base of the thumb) Osteoarthritis
HA	Hyaluronic Acid
MA	Marketing Authorization
CRA	Clinical Research Associate
GCP	Good Clinical Practice
EC	Ethics Committee
CNIL	Commission Nationale de l'Informatique et des Libertés (French Data Protection Authority)
CRF	Case Report Form (observation booklet)
CTC	Corticosteroids
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Unexpected Serious Adverse Reaction
IDE	State-qualified nurse
SmPC	Summary of Product Characteristics

1. General information

1.1. Title

The effects of infiltration with hyaluronic acid and corticosteroids on pain versus corticosteroids and saline in rhizarthrosis. **RHIZ'ART**.

1.2. Sponsor

1.2.1. Identity

CHD Vendée - La Roche sur Yon
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1.2.2. Protocol signed on behalf of the Sponsor

Mr. Francis SAINT HUBERT
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1.3. Study coordination and follow-up

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Dr. Anne CHIFFOLEAU
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1.8. Methodologist - Biostatistician

Mrs. Lucie PLANCHE
Statistician, CHD Vendée

1.9. Supervisory Board

Dr Yannick Poirier, Head of the Pharmacy Department, CHD Vendée
Dr Nicolas Fraquet, PH, Orthopedic Surgery, CHD Vendée
Dr Nathalie DEROUET, Head of the Federative Center, Le Mans Hospital

2. Scientific rationale and general description of the research project

2.1. Name and description of investigational drug(s)

We will be using two commonly used products: the drug Diprostene® (Betamethasone) and the medical device Sinovial mini®.
These are described in detail in Chapter 6.

2.2. Summary of the results of available non-clinical trials and clinical trials relevant to the biomedical research in question

Rhizarthrosis, or arthrosis of the trapeziometacarpal joint, is a common form of osteoarthritis that affects 10-25% of women, particularly after menopause. It affects unstable joints that are subject to high pressure. It is often bilateral, with frequent asymmetry of clinical and radiological involvement. Pain is located at the anatomical snuffbox, with fluctuating progression and no correlation between radiological and clinical severity. It progresses over several years and can lead to a Z-shaped deformity of the thumb column, which is functionally disabling.
Treatment combines non-pharmacological measures, such as relative resting of the joint, rest orthoses, icing, etc., with pharmacological measures such as analgesics, oral or local non-steroidal anti-inflammatories, or even cortisone or hyaluronic acid infiltrations. The European League Against Rheumatism's (EULAR) recommendations for digital osteoarthritis state that "intra-articular delayed corticosteroid infiltration is effective in painful flare-ups of digital osteoarthritis, particularly of the trapeziometacarpal joint". Both products have been granted marketing authorization, but only corticoids are eligible for reimbursement.
However, no methodologically rigorous studies have tested these infiltrations versus placebo. Only Meenagh has conducted this type of study, but on a small number of patients (2 groups of 20 patients) with small volumes injected (0.25 ml); with no difference noted between the placebo and corticosteroid groups. [1]

On the other hand, these two types of infiltration have been compared, with both showing efficacy on pain and function.
In 2005, Stahl[2] conducted a randomized study to compare the efficacy of corticosteroid infiltration (CTC) versus hyaluronic acid (HA) and found a reduction in pain in both groups at one month, which was maintained at 6 months. On the other hand, hyaluronic acid infiltration improved functional capacity as early as 3 months and the improvement lasted longer than with corticosteroids.
In 2006, Fuchs[3] reported similar results, with improvement in pain and function for both types of infiltration in a randomized study of 56 patients. Pain improvement was faster with corticosteroids (significant at 2 weeks) but slightly better with HA at 26 weeks, with a clearer functional gain for HA mainly at 6 months.
In 2008, in a 3-arm study, one of which was placebo, Heyworth[4] made the same findings but with no significant difference with placebo. He noted an improvement in pain and function in

all 3 groups (18 to 22 patients in each), with a clearer improvement in pain for the HA group at 6 months and in function at 3 and 6 months.
Moreover, the latest study in 2015 by Montfort[5], concludes that "HA was more effective over time and improved functional status more markedly in patients with severe symptoms".
Concerning the number of HA infiltrations to be administered in rhizarthrosis, a French team led by Roux C[6] showed that there was no difference between groups receiving one, two or three infiltrations at one-week intervals, in terms of neither pain nor function.

Therefore, the 2 types of infiltration appear to be effective, but with different response profiles: corticoids have a rapid analgesic and anti-inflammatory action, whereas HA has a more delayed and sustained action over time. Consequently, it seems appealing to combine these 2 treatments to obtain a synergistic effect. One study demonstrated the benefits of this combination in gonarthrosis, which was more effective on pain than hyaluronic acid alone and there was no difference in functional improvement between the two groups[7].
Some authors have questioned the potential clinical or histological risks of combining these two drugs, given the risk of reduced chondrocyte proliferation and increased apoptosis which could lead to chondral degradation. However, no increased risks have been reported with this combination, neither clinically[8] nor histologically[9].

To date, no study has tested the benefit of combining cortisone and hyaluronic acid in rhizarthrosis. In view of the current literature, and following a meta-analysis published in May 2016, which echoed these results and concluded that "the synergy of these two drugs should be explored further [...]. Further comparative trials involving a larger number of patients would be useful"[10], we propose answering this question by conducting a two-arm study, one reference arm with cortisone and placebo and the other with a combination of hyaluronic acid and cortisone.

2.3. Summary of the benefits, if any, and of foreseeable and known risks to persons undergoing research

2.3.1. Benefits

2.3.1.1. Individual benefits

The research participants can expect to benefit individually from the analgesic action of the product(s) proposed for this pathology, as well as a limitation of the disability.
This benefit will be objectively assessed both directly by the participant and by an external medical assessment based on a pain scale.

2.3.1.2. Collective benefit

A collective benefit of rhizarthrosis management optimization can also be envisaged from this research, with a reduction in work stoppages.

2.3.2. Risks

2.3.2.1. Individual risk

Risks and physical constraints

Risks associated with protocol treatments:

Betamethasone (Diprostene®) has a marketing authorization for this indication, and the risks associated with its administration are listed in the SmPC: these are mainly local reactions but flushing and anaphylactic or anaphylactoid reactions are also possible.

Systemic complications of corticosteroid therapy are unlikely, given the dose administered and the low systemic uptake.

Hyaluronic acid (Sinovial mini®) is a CE-marked medical device for which the complications are listed in the instructions for use. Hyaluronic acid AEs are mainly local reactions (pain, inflammation, etc.).

The injection of 0.9% NaCL presents no particular risk in terms of salt intake, given the small quantity injected.

Intra-articular administration entails a risk of pain during injection, minimal bleeding or local hematoma following injection, and a risk of infection, but these can be prevented by aseptic measures/good practice during preparation and administration. Intravascular injection is prevented by adherence to good injection practices.

A local reaction to the ultrasound gel is possible. A reaction to the latex used for the sterile ultrasound protector is also possible.

Adverse events are detailed in section 8-Safety assessment. Reference documents (SmPC-notice) are appended to the protocol.

Other constraints directly related to research include:

- Recording pain and any adverse effects in a patient diary on a weekly basis for the first 3 months after the procedure.
- Answering a questionnaire to obtain the Cochin score and the verbal global evaluation scale.
- Follow-up visits scheduled as part of the protocol at 1, 3, 6 and 12 months.

Psychological risks and constraints

Patients may not participate in any other clinical research protocol involving a drug or medical device during their participation in the RHIZ'ART study.

Socio-economic risks and constraints

Not applicable

2.3.2.2. Collective risk

Not applicable

2.3.3. Benefit/risk balance

Relatively significant pain relief benefits expected with minimal risks.

2.4. Description and justification of the route of administration, dosage, administration schedule and duration of treatment

Drug administration is detailed in Chapter 6.

2.5. Declaration that the research will be carried out in accordance with the protocol, good clinical practice and applicable laws and regulations

The sponsor and the investigator agree that this research will be conducted:
- in accordance with the protocol,
- in accordance with current French and international good clinical practice,
- in accordance with the laws and regulations currently in force in France and internationally

2.6. Description of the study population

The target population for this study is patients over 40 years of age who consult the rheumatology departments of the participating centers, and who experience pain that is resistant to standard medical treatment with NSAIDs, ice application or analgesics, and with a VAS greater than or equal to 4 with activity.
Selection procedures are described in Chapter 5.

Patients who participate in the RHIZ'ART study may not simultaneously participate in any other interventional research (except interventional research with minimal risks and constraints) for the duration of their participation in the study (i.e., 12 months).

2.7. References to scientific literature and relevant data for research purposes

See Appendix 1

3. Objective(s) of the research

3.1. Primary objective

To compare the efficacy of corticosteroid infiltration alone with corticosteroid infiltration combined with hyaluronic acid in patients with rhizarthrosis at 3 months.

3.2. Secondary objectives

- Comparison of the changes in pain with activity at M1, M6 and M12 and of the most intense pain.
- Comparison of pain between M0 and M3, by weekly recording of a VAS score.
- Comparison of the changes in pain at rest at M0, M1, M3, M6 and M12 and of the most intense pain.
- Comparison of the changes in function with the Cochin hand scale at M1, M3, M6 and M12.
- Comparison of grip and opposition strength changes at M1, M3, M6 and M12.
- Description of ultrasound changes.
- Comparison of injection pain.
- Comparison of the patient's perception of the changes in pain at 3 months.
- Comparison of new infiltrations.
- Description of adverse effects and events.
- Description of analgesic and NSAID use.
- Comparison of the after-effects of infiltration.

4. Research design

4.1. Precise statement of primary and, if applicable, secondary evaluation criteria

4.1.1. Primary endpoint

The primary endpoint for evaluating the efficacy of thumb infiltration is the intensity of pain at the base of the thumb (as defined by the patient, i.e., during activity) on the Visual Analogue Scale (VAS) at baseline and at 3 months in the 2 groups.

The pain intensity of osteoarthritis of the base of the thumb (CMC OA) will be estimated by the patient using a non-graduated 10 cm **line**, presented horizontally to the patient with the extreme position of the vertical border on the left (0mm) representing the absence of perceived pain and the extreme position on the right (10 cm), the perception of the maximum pain that the patient can imagine. The information obtained is measured and translated into a score between 0 and 10.
The patient will be asked: "How would you rate the intensity of pain caused by osteoarthritis in your thumb during activity?
This scale has been used as a criterion of therapeutic efficacy in several studies of osteoarthritis of the hand. [11] The reliability, validity, and sensitivity to change in hand osteoarthritis have been evaluated. Reducing pain at the base of the thumb is one of the major objectives of infiltration in rhizarthrosis. [12]

Activity pain:
The activity will be defined by a forced pincer grasp (example to be given to the patient: lifting a saucepan, a stack of plates, opening a jar, peeling potatoes, etc.).

4.1.2. Secondary endpoints

- VAS recorded at inclusion, M1, M6 and M12 post-infiltration.

- Recording of VAS between 0 and 3 months.
- This will be done by means of weekly VAS measurements taken by the patient himself/herself, recorded in a notebook given to the patient.
- A VAS of perceived pain at the base of the thumb will be recorded at rest at inclusion, and at 1, 3, 6 and 12 months.
- The worst Pain Score at M0, M1, M3, M6 and M12.
- Cochin score at inclusion, M1, M3, M6 and M12.

This score incorporates the inability to cook, get dressed, wash, work and perform other activities reported by the patient. It ranges from 0 to 90: the higher the score, the greater the impact of the rheumatological pathology on hand function. This index has been validated for its reliability, validity, and sensitivity to change in the arthritic hand.[11] The questionnaire takes an average of 3 minutes to complete, has an inter-observer correlation of 0.96 and good construct validity. Another advantage of this scale is the capacity to discriminate between improving and deteriorating patients.

- Grip and opposition strength.

Measurements will be carried out using two different JAMAR dynamometers according to a standardized methodology;[13]

The first allows measurement of opposition strength, expressed in kilograms. The thumb-index grip of the dominant and non-dominant hands is measured 3 times. A one-minute rest period is observed between each test. The highest values will be used.

The second measures grip strength in kilograms.

These two strengths will be assessed at inclusion, and at 1, 3, 6 and 12 months.

- Ultrasound evaluation at inclusion and M3.

Initial ultrasound data will be collected at M0 in B and Doppler modes, and at 3 months. The appearance of lesions on ultrasound will be graded as stage I, II or III according to the OMERACT grading principle (Cf appendix 4).

- A VAS recorded during infiltration.
- Verbal score for overall change at 3 months.

The verbal progression scale is a dynamic criterion for assessing disease progression in relation to a given reference. The use of this type of scale is suggested by treatises on the measures to be used in research projects in osteoarthritis, and the scale has proved its effectiveness in a large number of trials. [14]

At the 3-month follow-up visit, the patient will be asked to answer the following question: "Today, compared to the start of treatment (M0), I consider that my thumb:"

  - has worsened
  - has stabilized or had zero improvement
  - has improved slightly
  - has improved moderately
  - has improved significantly
  - is healing

- The number of corticosteroid infiltrations over the 12 months of follow-up.

- Recording of adverse effects and events over the 12 months of follow-up.

- Recording of analgesic and NSAID use (number of days taken and cumulative dosage over the week preceding each follow-up visit).
- The number of days off work from the start of orthosis use over the 12 months of follow-up.
- Possible progression to a surgical procedure over the 12 months of follow-up.

4.2. Description of the research methodology, including a schematic diagram with details of planned visits and examinations

4.2.1. Experimental design

- Phase IV drug trial
- Regional multicenter study (La Roche sur Yon, Le Mans, Nantes)
- Comparative
- Randomized
- Controlled
- Control group: reference arm (Diprostene®) and 0.9% NaCl
- Of superiority
- Double-blind (patient and evaluator)
- In 2 parallel groups: one with injection of CTC and 0.9% NaCl; the second with injection of HA and CTC

4.2.2. Course of the study

4.2.2.1. Inclusion

Inclusion and non-inclusion criteria will be verified in a pre-inclusion visit.
On this occasion, the study will be presented to the patient, together with oral and written information and the informed consent form.
During the inclusion visit, the informed consent form and data for the various parameters mentioned above will be collected by means of a clinical examination; an initial ultrasound scan in B mode and Doppler mode, a pain VAS (at rest and during activity), the Cochin scale, grip and opposition strength and a pain VAS during the infiltration procedure.
Two (2) doctors at each center will be investigators and will manage the iterative evaluations.
One (1) to two (2) doctors per center will perform the infiltrations; these doctors will not be evaluating doctors.

4.2.2.2. Ultrasound-guided infiltration technique

Infiltrations will be performed on each site in a standardized manner.
The patient is placed in a supine position with arms extended at the side of the body, hands resting on a hard surface, and the palm of the hand to be infiltrated facing upwards.

The reference section is the longitudinal section of the palmar aspect of the joint. The trapeziometacarpal joint is identified as the hypoechoic zone between the 2 bones.
The joint is approached perpendicularly to the probe: the approach is generally lateral to medial but can be easily performed in the other direction depending on the patient's position and the operator's experience. In this technique, the needle appears as a hyperechoic point with a comet-tail artefact. The needle is introduced perpendicularly to the probe at an angle of 30° to 45° until the hyperechoic spot appears. A 25 G subcutaneous needle is used, with local anesthesia using Xylocaine for the subcutaneous planes and passage of the capsule.
The criterion for success is that the infiltration is performed without resistance, with distension of the capsule observed on ultrasound.
This technique was chosen because it allows intra-articular verification as shown by Di Sante who administered intra-articular injections of hyaluronic acid using a perpendicular approach to the probe, and in 100% of the patients obtained a bulging appearance of the capsule after injection, indicating the intra-articular localization of the product. [15]
Similarly, in an anatomical study, Umphrey et al demonstrated the intra-articular localization of the infiltration product by arthrography in 17 cadavers, with 16 (94%) actually having had an intra-articular injection. [16]

Depending on the randomization arm, either 0.5 ml of CTC and 0.5 ml of 0.9% NaCl; or 0.5 ml of CTC and 0.5 ml of HA will be injected.
During these infiltrations, a sterile drape will be placed vertically on an infusion stand, to ensure patient "blinding".
Therefore, the operator will not be blinded; but this doctor will not be the evaluating doctor, who will be effectively blinded to the product(s) injected.
Each infiltration will be followed, if necessary, by a 48-hour work stoppage in accordance with standard practice.
Each patient will be fitted with a resting orthosis for use at night.

4.2.2.3. Patient follow-up

The patient will have a follow-up appointment in 1 month and 6 months post-infiltration with a clinical research nurse or a clinical research technician who will collect pain VAS, Cochin scale, grip and opposition strength, adverse events, and new infiltration data (with the time interval since the initial infiltration). Specific questions will be asked concerning the occurrence of the following adverse events: arthralgia, joint stiffness, joint swelling, and back pain.
The patient will have a follow-up appointment in 3 months and 12 months post-infiltration with the evaluating physician who will perform a clinical examination and collect the pain VAS, Cochin scale, grip and opposition strength, adverse events, and new infiltration data (with the time interval since the initial infiltration). Specific questions will be asked concerning the occurrence of the following adverse events: arthralgia, joint stiffness, joint swelling, and back pain. An ultrasound scan will also be performed at 3 months post-infiltration by the evaluating physician.

The patient's use of treatments (analgesics, NSAIDs) will be recorded in a patient diary for the first 3 months. The use of treatments (analgesics, NSAIDs) will then be recorded in the week preceding the M6 and M12 visits.

If the patient's condition so requires, a further CTC infiltration may be administered at the discretion of the investigator in charge of the patient.
This information will be recorded in the observation book.
If the new infiltration takes place within 3 months of randomization (infiltration according to randomization arm), the patient will be considered a treatment failure (primary endpoint assessed at 3 months).

Study schedule:

Actions	M-1 (Pre-inclusion visit)	M0 (**Inclusion visit)**	M1	M3	M6	M12
Checking inclusion/non-inclusion criteria	X					
Signing the informed consent		X				
History	X					
Clinical examination		X	X	X	X	X
Randomization		X				
VAS at rest		X	X	X	X	X
VAS for thumb-index grip (during activity)		X	X	X	X	X
VAS for infiltration		X				
Worst Pain Score		X	X	X	X	X
Cochin scale		X	X	X	X	X
Verbal score for overall change			X	X	X	X
Dynamometer (2x3 measurements)		X	X	X	X	X
B-mode and Doppler ultrasound		X		X		
Concomitant treatments (analgesics, NSAIDs)		X	X	X	X	X
Adverse events		X	X	X	X	X

* Weekly VAS for the first 3 months will be recorded in the patient's diary.
The use of new infiltrations, the number of days off work and any progression to a surgical procedure will be recorded during the 12 months of follow-up.

The time allowed for visits at M1 and M3 (primary endpoint) is +/-3 days.
The time allowed for the other follow-up visits (M6 and M12) is +/- 1 week.

4.3. Description of measures taken to reduce and avoid bias

4.3.1. Drawing of lots

Randomization will be blinded to patient and evaluator, with 2 groups of patients: one group receiving an injection of hyaluronic acid combined with corticosteroids, and the other receiving an injection of corticosteroids and 0.9% NaCl. Randomization will be stratified by center. It will be carried out in a 1:1 ratio and in blocks.

Capture System software will be used for randomization by connecting to the website: https://www.dirc-hugo-online.org/csonline/. A login, password and study number will be issued by a data manager in the Research Promotion Department of La Roche sur Yon Hospital. The following information must be provided:

- First initial of the last name,
- First initial of the first name,
- Month and year of birth,
- Compliance with inclusion and non-inclusion criteria (yes/no),
- Signing of the informed consent (yes/no).

Randomization will be carried out by the investigator once the possibility of inclusion in the study has been confirmed and the patient's informed consent has been signed.
The inclusion number will be assigned automatically during randomization. A confirmation e-mail will be sent to the person who carried out the randomization, as well as to all those concerned.

The randomization list will be drawn up by a statistician from the Research Promotion Department of La Roche sur Yon Hospital. An explanatory guide to randomization will be available online in Capture System.

4.3.2. Blinding methods

The patient will be blinded to the injected product by the use of a sterile drape placed vertically on an infusion stand during the procedure. The infiltrating physician will not be blinded to the injected product (syringes used are recognizable), but he/she will not be the evaluating physician, who will be blinded to the injected product.

The randomization list will be drawn up by the study biostatistician before the start of enrollment. This list will be kept by the research promotion team, made up of the biostatistician, the data manager, and the research promotion unit.
The procedure for lifting the blind is described in chapter 4.8.

4.4. Description of the dosage and administration of investigational drug(s). Description of the unit form, packaging and labeling of the investigational drug(s)

Product descriptions are given in chapter 6.1.

4.4.1. Dosage and administration

See chapter 6.1 for details of dosage and administration.

4.4.2. Unit forms, packaging, and labeling

The unit form, packaging and labeling are described in chapter 6.

4.5. Planned duration of participation and description of the chronology and duration of all trial periods, including follow-up, if applicable

The study duration is estimated at 4 years (including 36 months of inclusion).
As of the first inclusion, the sponsor will inform the competent authority and the EC without delay of the effective start date of the study, which will correspond to the date on which the consent form is signed by the first person to participate in the research.
The sponsor will inform the ANSM and the EC of the study end date within 90 days.
Total duration of patient participation in the study: 1 year

4.6. Description of permanent or temporary interruption rules

4.6.1. Participant withdrawal from research

Subjects may withdraw their consent and ask to leave the study at any time, for any reason. In the event of premature withdrawal, the investigator must document the reasons as fully as possible.
If consent is withdrawn, data already collected may be analyzed unless the patient objects.
The investigator may temporarily or permanently discontinue a patient's participation in the study for any reason that is in the patient's best interest, particularly in the event of serious adverse events.
If a patient is lost to follow-up, the investigator will make every effort to renew contact with the patient.
Premature study withdrawals and the reason for them will be noted on the patient's CRF.

4.6.2. Partial or total discontinuation of the research

The study may be prematurely terminated in the event of unexpected, serious adverse events requiring a review of the product's safety profile. Similarly, unforeseen events or new product information, which make it unlikely that the objectives of the study or clinical program will be achieved, may lead the sponsor to prematurely terminate the study.
The study may also be interrupted by decision of the health authorities, particularly in the event of modification or withdrawal of the marketing authorization or CE mark.

The sponsor reserves the right to discontinue the study at any time if the inclusion objectives are not met.

In the event of premature study termination, the sponsor will inform the ANSM and the EC within 15 days.

4.7. Investigational drug(s) accountability process

The accountability process is detailed in chapter 6.3.

4.8. Measures implemented to maintain blinding and procedures for removing blinding, if applicable

There are two possible procedures for removing the blind:

- in working days and hours, requests made by e-mail specifying the patient's inclusion number and the reason for unblinding, the randomization arm will be e-mailed the same day by a member of the promotion team.
- in emergency situations or during non-business hours, the blind release procedure is carried out directly via e-CRF, with the randomization arm transmitted within 5 minutes by automatic e-mail.

Unblinding is permissible in case of an adverse event. It will be restricted to cases where:

- knowledge of the product received could influence patient management of the adverse event observed (e.g., allergic-type reaction, use of an antidote or specific immunoglobulins, etc.). If this is not the case, unblinding would be pointless.
- the pharmacovigilance unit suspects a SUSAR and must notify the competent authorities.

  Since the drug is administered by injection only, with no re-administration, the need for unblinding will be limited.

The unblinding procedure must remain exceptional and should only be initiated by the investigator if necessary.

Unblinding is definitive when the investigator is informed by the research promotion team (the biostatistician, data manager and sponsor) of the treatment arm to which the patient has been allocated (experimental or standard treatment arm).
Unblinding does not result in the patient being withdrawn from the study, but data concerning him/her will be excluded from the per protocol analysis.

The occurrence of an effective unblinding will be mentioned in the corresponding patient's CRF (so that it can be analyzed accordingly), without the randomization arm being apparent.

4.9. Identification of all data to be recorded directly in the observation notebooks, which will be considered as source data

VAS

Grip strength and opposition score
Cochin score
Verbal score for overall change

5. Selecting and excluding participants

5.1. Inclusion criteria

- Adults, ≥ 40 years
- Pain at the base of the thumb (near the wrist) triggered by direct pressure and movement
- Pain resistant to well-conducted medical treatment with analgesics, NSAIDs and ice application, with a VAS ≥ 4 for more than 3 months.
- Radiological lesions (Kapandji view - anterior + profile) typical of rhizarthrosis, Eaton and Litter stage II or III, with at least 2 of the following 5 radiological features observed at the trapeziometacarpal joint:
    - marginal osteophyte
    - pinching of the joint space
    - subchondral sclerosis
    - subchondral geode
    - absence of osteopenia
- Patient capable of understanding the protocol and having signed an informed consent form
- Patient with social security coverage

5.2. Non-inclusion criteria

- Known allergy to one of the products (Diprostene® or Sinovial mini®) including the excipients (methyl parahydroxybenzoate, propyl parahydroxybenzoate, benzyl alcohol).
- Change in analgesic treatment within 4 weeks prior to inclusion (change of product and/or dosage).
- Patients with symptomatic bilateral rhizarthrosis
- Scaphoidotrapezial osteoarthritis
- Local or general infection
- Severe coagulation disorders, ongoing anticoagulant therapy
- Severe and/or uncontrolled hypertension
- Previous local surgery
- Associated inflammatory rheumatism
- De Quervain's tendinopathy, thumb with associated protrusion
- Previous infiltrations less than 6 months before
- Uncontrolled diabetes
- Live vaccines

- Severe cases of water and/or sodium retention (hypernatremia), particularly in heart failure, decompensated liver disease (edema and ascites)
- Pregnant women * or nursing mothers
- Immunocompromised or hemodialysis patients
- Patients under guardianship or deprived of their liberty
- Patients participating in another clinical research protocol involving a drug or medical device
- Patients unable to follow protocol, as judged by the investigator

** For non-menopausal women: pregnancy test and effective contraception*
Women of childbearing age will be required to use effective contraception. These include oral contraceptives (the pill), monthly vaginal rings, weekly transdermal patches, subcutaneous implants, intrauterine devices (IUDs) or sterilization.
The women concerned must have used an effective contraceptive method in the month prior to inclusion and must continue to do so for 15 days following infiltration.

5.3. Recruitment procedures

Any patient seen or referred to rheumatology departments for management of rheumatoid arthritis and who meet the inclusion criteria will be offered the protocol. This recruitment corresponds to the standard recruitment of these patients, referred by their attending rheumatologist or general practitioner.

5.4. Procedure for premature discontinuation of treatment corresponding to discontinuation of treatment with the experimental drug, and procedure for exclusion from research corresponding to discontinuation of treatment and monitoring of the person within the framework of the research.

5.4.1. Criteria and procedures for premature discontinuation of treatment or exclusion of a person from research

The study products are administered in a single dose with two syringes on the day of the initial infiltration (regardless of the randomization arm).

Therefore, in principle, there is no reason to discontinue treatment prematurely, except in the event of a reaction (such as an allergic reaction) during the injection, in which case the treatment should be stopped.
If it has not been possible to administer all the products in the patient's randomization arm, this information will be recorded in the CRF. Protocol visits will nevertheless continue.

5.4.2. Arrangements for replacing these participants, if necessary

No replacements will be made.

6. Treatments administered to research participants

6.1. Description of the treatment(s) required to conduct the research

6.1.1. Investigational drug(s)

Treatment identification

1/ Diprostene®:

- INN: Betamethasone
- MA holder: MSD FRANCE
- Dosage form: 1 mL colorless type I glass pre-filled syringe with bromobutyl rubber plunger seal and styrene-butadiene copolymer tip.
- Contains the following excipients: benzyl alcohol, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216) and sodium.

QUALITATIVE AND QUANTITATIVE COMPOSITION
Betamethasone dipropionate .....6.43 mg
Corresponding amount of betamethasone .....5.00 mg
Betamethasone disodium phosphate ..... 2.63 mg
Corresponding amount of betamethasone ..... 2.00 mg

MARKETING AUTHORIZATION NUMBER(S)
320 050-9: 1 ml pre-filled syringe (colorless glass) + 1 sterile needle, 50 mm long and 8/10 mm in diameter + 1 sterile needle 25 mm long and 5/10 mm in diameter

Indications:
Systemic use:
Seasonal allergic rhinitis after failure of other therapies (systemic antihistamines, intranasal corticosteroids, or short courses of oral corticosteroids).

Local use
These are local corticosteroid therapies when the condition justifies a high local concentration, such as for:

- Rheumatology:
- intra-articular injections: inflammatory arthritis, osteoarthritis flare-up;
- periarticular injections: tendonitis, bursitis;
- soft tissue injections: talalgia, carpal tunnel syndrome, Dupuytren's disease.

2/ Sinovial mini®:

- INN: Sodium hyaluronate
- MA holder: Génévrier
- Galenic form: 1 ml pre-filled syringe containing 8 mg HA
- Indication: for infiltration of small joints

- Containing sodium chloride, sodium phosphate and water for injection

Packaging and labelling

Study products will be packaged and labeled in accordance with current clinical trial regulations, by the Hôtel-Dieu pharmacy at Nantes University Hospital.

Treatment kits will be produced by the Hôtel-Dieu pharmacy at Nantes University Hospital as follows:

- 1st kit: 1 pre-filled syringe of Diprostene (1ml) and 1 pre-filled syringe of Sinovial mini (1ml)
- 2nd kit: 1 syringe of Diprostene (1 ml) and 1 ampoule of 0.9% NaCl (10 ml)

Each kit will be accompanied by instructions for preparation by the IDE.

For the CTC + HA arm: the IDE should keep only 0.5ml of Diprostene from the 1ml syringe and only 0.5ml of Sinovial from the 1ml syringe.

For the CTC and 0.9% NaCl arm: the IDE should keep only 0.5 ml of Diprostene and prepare 0.5 ml of 0.9% NaCl in another syringe.

The nurse preparing the syringes and the doctor performing the procedure will not be blinded.

Syringes will be prepared by the rheumatology department IDE in the operating room.

Labeling

The treatments under study will be labeled in accordance with good clinical practice and current regulations.

Model label for treatment kits:

Sponsor: CHD Vendée - Bd Stéphane Moreau - 85925 La Roche-sur-Yon - Tel.: 02 51 44 65 72
RHIZ'ART study *(CHD046-17)*
Diprostene®7mg + Sinovial mini® 8mg KIT
Diprostene®7mg + 0.9% NaCl KIT

Route of administration for injection: intra-articular (refer to protocol)

KIT - center n° - treatment n°

Dispensing date: ...../...../.....
Patient number:.....Patient name:.....
Batch no.: .....Expiry date: .../..../.....

Store between +4°C and +25°C. Do not refrigerate. Do not freeze.
Drugs for biomedical research only
Use under strict medical supervision

Treatment manufacturing and distribution:
The CHU Nantes pharmacy will act as the coordinating pharmacy, helping to label and distribute products to pharmacies in the various investigation centers. They will be in charge of supplying study products and will prepare kits (the contents of which are described in paragraph 6.1.1.2) during the preparation campaign.
Regular shipments of these kits will be made to the center pharmacies when the centers open, and during the course of the study, according to the rate of inclusion.

The treatments provided by the sponsor will be made available to the rheumatology department as supplies.

Treatments used in research will be traceable (batch number, expiration date, etc.).
Pharmacists at each investigation center will be responsible for:

- Receiving treatment kits
- Storing treatment kits
- Managing and monitoring the provision of treatment kits in the department according to the rate of inclusion

The kits (including preparation instructions) will be given to the designated person in the investigating department. It will be this person's responsibility to prepare the syringes to be administered extemporaneously ("unblinded"), under conditions which ensure that the patient remains blinded, and then to hand them over to the investigating physician, who will administer them under sterile conditions.
A nominative prescription referencing the allocated (blind) treatment number will be written for each patient.

At the end of the study, expired, quarantined or unused syringes may be destroyed with the agreement of the sponsor.

Administration
1/ Diprostene®:

- infiltration according to GCP of 0.5 ml under ultrasound control
- preparation by the IDE in charge of the study

2/ Sinovial® mini:

-Infiltration according to GCP of 0.5 ml under ultrasound control
- preparation by the IDE in charge of the study

Dosage adjustment
No dosage adjustment is planned since the products are administered in a single infiltration.

Reference documents, leaflets and SmPCs include precautions for use and administration:
Sinovial mini®:
Intra-articular injections should only be administered by a doctor. Do not use disinfectants such as quaternary ammonium salts or benzalkonium chloride, as they are known to be incompatible with hyaluronic acid. The possible presence of an air bubble does not compromise the product's

characteristics. The injection site must be located on healthy skin. Inject only into the joint space. Do not inject intravascularly. Do not inject outside the joint line into synovial tissue or the joint capsule. Extra-articular infiltration of Sinovial may cause local adverse effects. Do not use Sinovial in the presence of significant joint effusion. Do not re-sterilize. Syringe and needles are for single use only. To avoid any risk of contamination do not reuse. As with any invasive joint procedure, patients are advised to refrain from physical exertion after the joint injection, and to resume normal activities only after a few days.

Diprostene®:
Rigorous asepsis is essential.
Local injection of corticosteroids can destabilize diabetes and trigger psychosis and severe hypertension.
Caution should be exercised when administering to patients at high risk of infection, particularly hemodialysis patients or prosthesis wearers.
The risk of vasomotor reactions, particularly chest pain, must be taken account of in patients with underlying progressive cardiovascular disease.
Do not inject intratendinously due to a risk of rupture.
Not for I.V. or I.M. administration.
This product is not suitable for inhalation by nebulizer.

6.1.2. Non-experimental drug(s)

6.1.2.1. Treatment identification

NA

6.1.2.2. Packaging and labeling

NA

6.1.2.3. Treatment manufacturing and distribution

NA

6.1.2.4. Administration

NA

6.1.2.5. Dosage adjustment

NA

6.2. Drugs and treatments authorized and prohibited under the protocol, including rescue medication

6.2.1. Authorized treatments

All treatments useful for the therapeutic management of the patient are authorized.
They must be recorded in the CRF.

6.2.2. Unauthorized treatments

Potential interactions with study products.
The risk of interaction between glucocorticoids and other drugs is considered exceptional for local injections in normal circumstances of use. However, anticoagulants/antiplatelets likely to increase the risk of bleeding, and drugs with immunosuppressive potential that increase the risk of infection should be avoided.
(see Diprostene® SmPC and Sinovial® leaflet (Appendices 5 and 6).

6.2.3. Emergency treatment

NA

6.3. Method for monitoring treatment compliance

The complete dose contained in each syringe must be administered in a single injection. If this is not the case, it will be noted along with the reason in the observation book.

6.4. Storage conditions for experimental drugs

6.4.1. Description of pharmacy storage

A specific procedure describing the contents of the kits and their storage conditions will be drawn up by the CHD Vendée pharmacy and sent to the pharmacies of the investigating centers when the first shipment of study products is made. The kits must be stored at a temperature of 4 to 25°C and the products they contain must be protected from light and any source of heat. The storage area should have restricted and secure access. Storage conditions at room temperature must be guaranteed by a temperature monitoring and recording system.

6.4.2. Service storage description if applicable

Therapeutic units should not be stored above 25°C.
Any deviation in temperature must be reported to the Clinical Research Associates within 24 hours.

The treatment kits will be made available by each hospital pharmacy of the participating centers as supplies to the department (Rheumatology) so that they are available within the timeframe stipulated by the research. This supply will be traceable by the pharmacy and the department, in line with biomedical research requirements.
The storage area must have restricted, secure access.

Products must be administered immediately after preparation. This is why, in the event of non-immediate use, storage times and conditions before use are the sole responsibility of the user.

6.4.3. Description of patient storage, if applicable

NA

6.5. Inventory management, restocking and dispensing treatments

Stocks are managed by the CHD Vendée pharmacy. CHD Vendée will receive notification of inclusion and randomization via an automatic eCRF transmission.
Regular supplies will be stored in the rheumatology departments of participating centers.
Follow-up of randomization notifications, together with the traceability of dispensing within the trial, will enable replenishment to be triggered.

7. Efficiency assessment

7.1. Description of the efficacy evaluation parameters

The evaluation parameters are described in chapter 4.1.

7.2. Methods and timetable for measuring, collecting and analyzing effectiveness evaluation parameters

The evaluation parameters are described in chapter 4.2.2.3.

8. Safety assessment

8.1. Definitions

Vigilance	This is the monitoring of drugs, medical devices, and other healthcare products. It also involves preventing the risk of adverse effects resulting from their use, whether this risk is potential or proven,
Adverse events (AE)	Any untoward occurrence in a patient or clinical trial participant that is not necessarily related to the clinical trial treatment.
Intensity of adverse events (AE)	It will be graded according to the criteria set when the protocol was drawn up. For any event not noted in the set classification, the rating will be as follows: 1 = mild 2 = moderate 3 = severe

	4 = life-threatening
Adverse reactions (AR)	Any untoward response for which a causal link, whatever its importance (doubtful, plausible, possible, certain), can be envisaged either with the treatment under study or with the comparator or protocol, and, for an investigational drug, whatever the dose. For medical devices, any noxious and unintended response to a medical device, or any incident that could have resulted in such a response had an appropriate action not been taken, in a person undergoing research or in the user of the medical device, or any effect related to a failure or alteration of an *in vitro* diagnostic medical device that is harmful to the health of a person undergoing research.
Serious adverse events (SAE)	Any adverse effect/event that: * results in death, * is life-threatening, * results in temporary or permanent disability, * requires or prolongs the patient's hospital stay, * causes a congenital or neonatal anomaly, * is medically important (the list of medically important effects/events is defined by the EMA).
Unexpected adverse events (SUSAR)	An effect whose nature, severity, frequency, or course are not consistent with the product information as listed in the investigator's brochure, the Summary of Product Characteristics or as defined in the protocol. Article R1123-46 (8°) For research involving a medicinal product, an unexpected adverse effect is any adverse effect of the product whose nature, severity, frequency, or course are not consistent with the reference safety information given in the summary of product characteristics or in the investigator's brochure when the product is not authorized. For other research involving the human body, an unexpected adverse reaction is any adverse reaction whose nature, severity or course is not consistent with information about the products, procedures and methods used in the research.
Overdose	Actual = Administration of a greater quantity of the drug (in a single or cumulative administration) than that authorized in the Summary of Product Characteristics, the investigator's brochure. Relative = Administration of the drug at the recommended dosage, but not adapted to the individual (undernutrition, dehydration, renal failure, etc.).
Misuse	Inappropriate use in relation to relevant reference data, occurring during the care chain, exposing a given patient to a proven or potential risk, without correlative benefit
Medication error (ME)	Corresponds to the omission or unintentional performance of an act during the care process involving a medicinal

	product, which may result in a risk or adverse event for the patient.
New fact	"Any new data that may lead to a reassessment of the benefit/risk ratio of the research or of the product that is the subject of the research, to modifications in the use of this product, in the conduct of the research, or of the documents relating to the research, or to suspending or interrupting or modifying the protocol of the research or similar research."

8.2. Expected adverse events (AE or SAR)

An expected adverse reaction (AR) is a reaction that has already been mentioned in the most recent version of the investigator's brochure or package insert or in the current version of the summary of product characteristics (SmPC) for medicines that already have marketing authorization.

In the context of this protocol, the expected AEs are:

- Diprostene®: The systemic adverse effects of glucocorticoids have a low risk of occurrence after local administration, given the low blood levels, but the risk of hypercorticism (fluid retention, destabilization of diabetes and arterial hypertension, etc.) and of slowing down the thalamic-pituitary-adrenal system increases with the dose and frequency of injections.
Adverse reactions common to all routes of administration:

- Risk of local infection (depending on injection site): arthritis, meningitis, epiduritis.
- Localized atrophy of muscular, subcutaneous, and cutaneous tissues.
- A few exceptional cases of tendon rupture have been reported, particularly when co-prescribed with fluoroquinolones.
- Acute microcrystalline arthritis (with microcrystalline suspension) of early onset.
- Local calcifications.
- Allergic reactions: cutaneous, localized, or generalized urticaria, angioedema, anaphylactic shock.
- Flushing: headaches and flushing may occur. These usually disappear within a day or two.
- Lumbar pain, more rarely chest pain and/or hypotension occurring within minutes of injection and spontaneously reversible.
- Blood pressure surges.
- Pain at injection site

- Sinovial mini®: Associated symptoms such as pain, warmth, redness, or swelling may occur at the injection site after using Sinovial. Applying ice to the treated joint can relieve such associated symptoms. These usually subside within a short period.

- The protocol:
  - Anxiety about randomization (not having the "effective" drug),
  - Constraints related to protocol monitoring (questionnaires)

- Preparation and administration:

- Risk of error during drug preparation (content, dose, sterility, etc.)
- Risk of pain during infiltration
- Risk of subcutaneous hematoma
- Risk of hemarthrosis
- Risk of septic arthritis or local infection
- Risk of painful flare-ups in the days following infiltration

- The pathology: if infiltrations (of CTC and/or HA) are ineffective, the progression of pain may lead to surgical treatment (arthrodesis, trapezectomy, prosthesis, etc.).

- Auxiliary treatments: particularly analgesics and NSAIDs:
It is impossible to list co-medications precisely as patients continue to receive their usual treatments. Nevertheless, the expected AEs correspond to those listed in the respective SmPCs of the products used in their MA indication.

- Effects expected from other associated pathologies and medical history prior to the study: related to the natural progression of pre-existing concomitant diseases.

The sponsor must be notified of pregnancies, as well as errors, risks of error, misuse, overdoses, defects, and new facts, even when there are no consequences for the patient or seriousness criteria.

8.3. Non-reportable serious adverse events

Certain circumstances requiring hospitalization do not fall under the "hospitalization/extension of hospitalization" severity criterion and should not be reported as an SAE. These include:
- hospitalization for a procedure, event or treatment predefined by the protocol,
- admission/extension of stay for social or administrative reasons,
- day hospital consultation,
- hospitalization for medical or surgical treatment scheduled before the start of the research or for a previously known pathology unrelated to the research and not associated with a deterioration in the patient's condition

Complications arising from the pathology

8.4. The investigator's role

8.4.1. Reporting serious adverse events

Information to be sent to the Sponsor

Each event is described on the appropriate form ("Initial Report of a Serious Adverse Event" or "Follow-up Report of Serious Adverse Event"), as exhaustively as possible. The information to be transmitted is as follows:

- patient identification (number, code, date of birth (MM/YYYY), date of inclusion, gender, weight, height),
- intensity (severity) of EvI
- EvI severity criteria,
- EvI start and end dates,

- clear, detailed description of the AE (diagnosis, symptoms, intensity, chronology, actions taken and results) without abbreviations,
- evolution of AE,
- current illnesses or relevant patient history,
- treatments received by the patient,
- causal relationship of the AE with the investigational drug(s), comparator(s), any associated treatments, research, or other criteria.

Whenever possible, the investigator must also attach to the SAE report:

- a copy of the hospitalization or extended hospitalization report,
- if applicable, a copy of the autopsy report,
- a copy of all additional test results, including relevant negative results, together with the laboratory's normal values,
- any other document deemed to be useful and relevant.

These documents will be anonymized and bear the patient's identification number.

8.4.2. Procedures for notifying the sponsor

Any SAE, regardless of the causal relationship with the trial or research treatment(s) (with the exception of those identified in the protocol as not requiring immediate reporting), must be reported:

- by fax to the sponsor: 02 51 08 05 91

Pharmacovigilance analysis is entrusted to the CHU Nantes vigilance unit (Pharmacovigilance physician Dr. Anne Chiffoleau, anne.chiffoleau@chu-nantes.fr, or vigilance officer Ms. Alexandre Jobert, alexandra.jobert@chu-nantes.fr).

All correspondence between the investigator and the vigilance unit must be copied to the sponsor at the same time.

8.4.3. Time limit for notifying the sponsor (Article R1123-49)

As soon as the investigating physician becomes aware of any SAE, it must be reported to the study sponsor.

The investigator notifies the sponsor of all serious adverse events, adverse reactions, and serious incidents without delay after becoming aware of them. This notification is the subject of a written report and is followed by further detailed written reports, to be sent to the sponsor without delay on the day the investigator becomes aware of them.

8.4.4. Notification period to the sponsor

It is the investigator's responsibility to record and report all SAEs that occur during the entire study:

- from the date of infiltration (randomization in the study),
- and until the patient's M12 visit.

In addition, regardless of how soon after the end of the study they occur, all SAEs likely to be due to the research must be reported to the sponsor if no cause other than the research can be reasonably attributed to them (for example, serious effects that may appear long after exposure to the drug, such as cancers or congenital anomalies).

Notification of non-serious adverse events:
All other AEs will be reported on the "adverse event" form in the observation book, specifying the date of occurrence, description, intensity, duration, method of resolution, etiology, imputability and decisions taken.

8.5. The role of the sponsor

8.5.1. Analysis of serious adverse events

The sponsor must evaluate:

- the cause of SAEs (all adverse events, for which the investigator or sponsor considers that a causal relationship with the investigational drug(s) can be reasonably envisaged, are considered as suspected serious adverse events. In the event of a different assessment by the sponsor and the investigator, both opinions are mentioned on the report sent to the competent authority if such a report is necessary),
- and whether they are expected or unexpected, with the help of the reference document (investigator's brochure, package insert or SmPC) in force.

8.5.2. Transmission of annual safety reports

On the anniversary date of the trial authorization issued by the Health Authorities, the sponsor draws up a safety report that complies with the specifications, including in particular:
- a list of serious adverse events likely to be associated with the investigational drug(s), including unexpected and expected serious adverse events,
- a concise, critical analysis of patient safety for research purposes.
It is sent to the competent authorities (ANSM) and the EC within the regulatory deadlines.

8.5.3. Supervisory Board

The mission of the Independent Monitoring Committee is to monitor the clinical and biological safety of the study treatments. It is responsible for providing information to help the sponsor to make decisions whether to amend or discontinue the trial. It is set up at the start of the study and comprises at least 3 members not directly involved in the trial.
The Supervisory Board transmits its recommendations to the sponsor who decides whether or not to stop the study. A decision may be made to stop the study earlier if it appears contrary to the rules to continue (occurrence of serious adverse events, publication of the results of a trial providing the answer to the question asked, etc.).

8.5.4. Methods and duration of follow-up of participants following the occurrence of undesirable events

Each adverse event will be monitored until its complete resolution (stabilization at a level deemed acceptable by the investigator, or return to the previous state), even if the patient is withdrawn from the trial.

9. Statistics

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9.1. Description of planned statistical methods, including schedule of planned interim analyses

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

Primary endpoint:

The VAS on activity at 3 months will be compared between groups using a mixed model, taking account of the initial VAS as a fixed effect and the center as a random effect.

Secondary endpoints:

- Changes in pain at rest and during activity over time will be compared between groups, using random-effects models to account for inter-individual variability modeled via random effects (based on the idea that patients represent a random sample from a larger population), as well as intra-individual variability modeled via measurement error; the group effect (HA + CTC vs. CTC alone), time (M0, M1, M3, M6, M12) and their possible interaction will be estimated and tested.

- Changes in **Cochin scale** parameters, **grip strength** and **opposition strength over** time will be compared between groups using random-effects models. The effect of group (HA + CTC vs. CTC alone), time (M0, M1, M3, M6, M12) and their possible interaction will be estimated and tested.

- The proportion of patients with a change in **ultrasound score** between D0 and M3 will be compared between groups using a Chi2 test.

- The VAS of pain at the time of injection will be compared between the two groups using a Student's t test.

- The number of **new infiltrations** during the follow-up year will be compared between groups using a Student's t test.

- Adverse events will be described for each group in terms of numbers and percentages.

- Changes in **analgesic use** will be compared between groups using random-effects models. The group effect (HA + CTC vs. CTC alone), time (M0, M1, M3, M6, M12) and their possible interaction will be estimated and tested.

- The number of days **off work** during the follow-up year will be compared between groups using a Student's t test.

- The rate of patients undergoing **surgery** will be compared between groups using a Chi2 test.

9.2. Expected number of participants to be included in the research and expected number of participants in each research location with statistical justification.

The study is a superiority trial that focuses on pain reduction at 3 months. This is assessed on the basis of the difference between the two groups in scores measured between 3 months and baseline. Based on data in the literature, we estimate a mean score of 6.4 +/- 1.3 at baseline (Montfort, 2014).
According to the same reference, we assume a 25% reduction in pain in the "corticosteroid alone" group, and a 35% reduction in the "corticosteroid and hyaluronic acid combination" group.
To demonstrate this difference with 80% power and 5% alpha risk, 132 patients will be required.
To ensure sufficient power, 18 additional patients will be included in the study, for a total of 150 patients.

9.3. Expected statistical significance

The level of statistical significance is 5%.

9.4. Statistical criteria for discontinuing research

NA

9.5. Missing, unused or invalid data accountability process

The number of missing data and the reason for the missing data will be described for each treatment group.
For patients who do not have an available endpoint at inclusion or at M3, the mean VAS of the randomization group will be imputed in order to analyze the entire randomized population in the intention-to-treat analysis.

9.6. Managing changes to the initial strategy analysis plan

NA

9.7. Choosing the people to include in analyses

The analysis will focus on the Intention-to-treat population.
A sensitivity analysis on the "Per protocol" population will be performed: exclusion of patients with major protocol deviations (non-administration of all products in the randomization arm, new infiltration less than 3 months after the initial infiltration, possible progression to a surgical procedure less than 3 months after the initial infiltration).

10. Right of access to source data and documents

10.1. Data access

In accordance with GCP:
- the sponsor is responsible for obtaining the agreement of all parties involved in the research to guarantee direct access to all research sites, source data, source documents and reports for quality control and audit purposes by the sponsor,
- investigators will make the documents and individual data strictly necessary for controls available to those responsible for monitoring, quality control or auditing biomedical research, in accordance with the legislative and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

10.2. Source documents

Source documents, defined as any original document or object used to prove the existence or accuracy of data or facts recorded during the clinical study, will be kept for 15 years by the investigator, or by the hospital in the case of hospital medical records.

10.3. Data confidentiality

In accordance with the provisions concerning the confidentiality of data to which those responsible for the quality control of biomedical research have access (article L.1121-3 of the French Public Health Code), and in accordance with the provisions concerning the confidentiality of information relating in particular to the nature of the investigational medicinal products, the trials, the persons involved and the results obtained (article R. 5121-13 of the French Public Health Code), persons with direct access will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the trials, the persons involved and in particular their identity, as well as the results obtained.
These people, like the investigators themselves, are bound by professional secrecy (under the conditions defined by articles 226-13 and 226-14 of the French Penal Code).
During or at the end of biomedical research, data collected on subjects and transmitted to the sponsor by the investigators (or any other specialist) will be rendered anonymous.
Under no circumstances may the names or addresses of the persons concerned appear in plain text.
Only the first letter of the subject's last name and the first letter of his or her first name will be recorded, along with a coded number specific to the study, indicating the order of inclusion of subjects.
The sponsor will ensure that each participant in the research has given his or her written consent for access to individual data concerning him or her and strictly necessary for the quality control of the research.

11. Quality control and assurance

A Clinical Research Associate (CRA) appointed by the sponsor will ensure that the study is carried out properly, and that the data generated are documented, recorded, and reported in accordance with the Standard Operating Procedures implemented at the CHD Vendée and in compliance with Good Clinical Practice and current legislative and regulatory provisions.

The investigator and members of his team agree to make themselves available for Quality Control visits carried out at regular intervals by the Clinical Research Associate. During these visits, the following elements will be reviewed:

- informed consent
- compliance with the study protocol and procedures defined therein
- quality of data collected in the observation book: accuracy, missing data, consistency of data with "source" documents (medical records, appointment books, original laboratory results, etc.)
- management of any product.

The investigators also agree to quality assurance audits by the sponsor and inspections by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections, without prejudice to medical confidentiality.

12. Ethical considerations

12.1. Ethics committee

The study protocol, information form and consent form will be submitted to the Comité de Protection des Personnes Ile de France III (Ethics Committee) for approval.
Notification of the EC's positive opinion will be sent to the study sponsor and the competent authority.
A request for authorization will be sent by the Sponsor to the ANSM before the start of the study.

12.2. Substantial changes

Any substantial modification to the protocol made by the investigator must be approved by the sponsor. Prior to implementation, the sponsor must obtain a favorable opinion from the EC and authorization from the ANSM, within their respective areas of competence. If necessary, a new consent form must be obtained from the participants in the research.

12.3. Patient information and the written informed consent form

Patients will be fully and fairly informed, in comprehensible terms, of the objectives and constraints of the study, the possible risks involved, the necessary monitoring and safety measures, and their right to refuse to participate in the study or to withdraw at any time.

All this information appears on an information and consent form given to the patient. The patient's free, informed, and written consent will be obtained by the investigator, or a physician representing him/her, prior to final inclusion in the study. A copy of the information and consent form signed by both parties will be given to the patient, and the investigator will retain the original. At the end of the study, a copy will be placed in a sealed tamper-proof envelope containing all the consent forms, which will be archived by the sponsor.

13. Data processing and document and data storage

13.1. Observation notebook

All information required by the protocol must be recorded in the observation notebooks. Data should be collected as they are obtained and recorded explicitly in these notebooks. Any missing data should be coded.
This electronic case report form will be set up in each center, using an Internet data collection medium. Investigators will be provided with a document to help them use this tool.
If the investigator fills in the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all data entered. What's more, when data is entered, it is immediately checked for consistency. As such, he/she must validate any value modification in the CRF. These modifications are subject to an audit trail. A justification may be included as a comment.
Data will be archived at participating sites.

13.2. Data capture and processing

Data will be entered electronically via a web browser.
Data analysis will be carried out by Lucie Planche, biostatistician, CHD Vendée, La Roche sur Yon.

1.1. CNIL

This study falls within the scope of the "Reference Methodology" (MR-001) relating to data processing, files, and freedoms in application of the provisions of Article 54 Section 5 of the updated Law n°78-17 of January 6, 1978 **(Decision no. 2016-262 of July 21, 2016)**
CHD Vendée de La Roche sur Yon, the study sponsor, has signed a commitment to comply with this "Reference Methodology".

13.3. Archiving

At the end of the period of practical use, all documents to be archived, as defined in the standard operating procedures of the CHD Vendée de La Roche sur Yon, will be archived and placed under the responsibility of the Sponsor for 15 years after the end of the study, in accordance with institutional practices.

No removal or destruction may be carried out without the agreement of the Sponsor. At the end of the 15-year period, the Sponsor will be consulted for destruction. All data, documents and reports are subject to audit or inspection.

14. Financing and insurance

14.1. Study budget

The study budget was evaluated by the Clinical Research Unit of the CHD Vendée de la Roche sur Yon in agreement with the coordinating investigator.
The budget required to conduct the study was obtained through an internal call for tenders from the CHD Vendée in La Roche sur Yon.

14.2. Insurance

For the duration of the study, the Sponsor will subscribe to a civil liability insurance policy that also covers the physician involved in the study. The Sponsor will also ensure full compensation for any harmful consequences of the research for the participant and his or her beneficiaries, unless it can be proven that the damage is not attributable to the Sponsor or to any other party involved, without being able to invoke the act of a third party or the voluntary withdrawal of the person who had initially agreed to participate in the research.

15. Study feasibility

The teams involved in this study include rheumatologists trained in osteoarticular ultrasound, with several years' experience in ultrasound-guided infiltration procedures. Some of these doctors are instructors for a DIU (inter-university diploma) for guided osteoarticular procedures. In terms of recruitment, the CHD Vendée recruits approximately 100 patients with rhizarthrosis requiring infiltration per year, 60 at the CHU Nantes and approximately 40 at the CHG Le Mans, i.e., 200 patients per year (and 300 in 18 months). Taking into consideration non-participants (refusals, non-inclusion criteria, etc.), the number of 150 patients to be included seems realistic.

16. Publication rules

Scientific communications and reports relating to this study will be produced under the responsibility of the principal investigator coordinating the study, with the agreement of the responsible investigators. 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.

Publication rules will follow international recommendations (N Engl J Med, 1997; 336:309-315).
The study will be registered on an open-access website (Clinical trial) prior to the inclusion of the 1st patient in the study.

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