Benefit of the use of honey dressings for healing after excision of pilonidal cysts

"Pilomiel"

IDRCB No. 2015-A00452-47

CHD018-15

Coordinating Investigator: Emeric ABET
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Sponsor : Departmental Hospital Center
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GENERAL INFORMATIONS :

- **Prospective, monocentric, randomized, controlled, open-label study**
- *IDRCB* ***number*** *:* **2015-A00452-47**
- *the* ***internal CHD number: CHD018-15***
- ***Sponsor: CHD Vendée, Bd Stéphane Moreau, represented by its Managing Director, Mr Francis SAINT-HUBERT***
- ***The study will be managed by the CHD Vendée Clinical Research Unit***
- ***The Coordinating Investigator is Dr Emeric ABET***

Signature page

SPONSOR'S SIGNATURE

The sponsor undertakes to carry out this study in accordance with all the legislative and regulatory provisions to which the research may be subject and according to the protocol.		
Name and function of the signatory representative: Mr. Francis SAINT-HUBERT, Managing Director of CHD Vendée	**Date :**	**Signature :**

SIGNATURE OF INVESTIGATORS

I have read all the pages of the clinical trial protocol of which the CHD Vendée is the sponsor. I confirm that it contains all the information necessary to conduct the trial. I undertake to carry out the trial in accordance with the protocol and the terms and conditions defined therein. I undertake to carry out the test respecting:

- the principles of the "Declaration of Helsinki",
- European regulations and/or national legislation relating to clinical trials,

I also undertake that the investigators and other qualified members of my team have access to this protocol as well as to the documents relating to the conduct of the trial to enable them to work in accordance with the provisions contained in these documents. .

Coordinating Investigator	**Last name :**	**Date :**	**Signature :**
Principal Investigator	**Name and establishment:**	**Date :**	**Signature :**

Summary

Study title	Pilomiel
Key words	Pilonidal sinus, sacrococcygeal cyst, wound, healing, honey
Study Sponsor	CHD Vendée La Roche sur Yon
Principal Investigator	Emeric Abet
Number of centers planned	Monocentric
Study schedule	Recruitment period: 6 years Duration of treatment per patient: 180 days maximum Duration of follow-up per patient: Until complete healing (180 days maximum)
Study design	- Monocentric - Controlled - Randomized
Study objectives	Primary : Evaluate wound healing time with honey dressings compared to conventional dressings Secondary : - Evaluate the cost generated by the dressings - Evaluate patients' quality of life and discomfort - Evaluate the duration of work stoppage - Assess the tolerance of dressings
Number of cases (sample size)	100 patients will be randomized
Calendar of the different visits and the different examinations	Inclusion - Daily dressings by an IDE at home - Consultation with a specialized IDE after 8 days then every 15 days if necessary on decision of the specialized IDE according to the evolution of the wound - Consultation with a surgeon every 4 weeks Patients will be followed until complete healing of the wound and up to a maximum of 180 days if they have not healed.

Main criteria for selection, inclusion, non-inclusion and exclusion	Inclusion criteria: • Cavity Wound to 6 weeks of a pilonidal cyst excision • Bloodless wound • Pilonidal cyst not recurred • Age : 18 years and older • Signature of informed consent • In the capacity to understand the study Non-inclusion criteria • Bleeding wound • Refused to participate in Protocol • Patient immunocompromised • Recurrent pilonidal cyst • Patients on long-term corticosteroid • Patient deprived of liberty, under guardianship • Patient unable to understand the study • Allergy or hypersensitivity to honey • Allergy Or hypersensitivity to hyaluronic acid • Allergy or hypersensitivity to guar gum • Allergy or hypersensitivity to pectin • Known allergy to propolis (potentially present in honey) • Sensitivity to zinc oxide • Sensitivity known dressings used in this trial or any component • Diabetes Non-insulin or insulin
Treatment, medical device, cell therapy product, interventional act under study	MELECTIS® G : sterile honey for wound care
Primary endpoint	Time to wound closure between randomisation (positioning of the first dressing) and complete closure of the wound (or end of follow-up if patient has not healed).
Secondary endpoints	- Number of dressings performed between randomization and healing - Assessment of quality of life by the VQ dermato score - Number of days off work

	- Number of intolerance, dressing discontinuation and/or need to change treatment
Statistical analysis	The time between the randomization of the patient and the complete healing of the wound will be compared between the two groups by a Student t-test.

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1. Scientific rationale and general description of the research

1.1 Name and description of the investigational drug(s).

MELECTIS® G : sterile honey for wound care .

1.2 Summary of the results of non-clinical trials and clinical trials available and relevant to the research concerned.

Healing of pilonidal cyst excision can be difficult with long healing times. This difficult healing is a source of discomfort for the patient but also of social handicap (prolonged absence from work) (1-3). Many pilonidal cyst excision techniques have been proposed (4-6). The excision technique with directed healing is the most practiced technique since it has the lowest recurrence rate (7.8). This healing technique requires frequent dressings that can be bothersome (painful, smelly, exudative, etc.). With this technique, variable healing times have been observed, however users always mention late closures, unfortunately the times have not been published. However, 2 preliminary studies were carried out at the University Hospital of Nantes and in our center showing healing times of approximately 68 days with significant standard deviations of 50 and 29 days respectively.
In recent years, the use of honey in chronic wounds has developed (9). Several virtues have been demonstrated: the antibacterial effect (10,11) and antibiofilm. Through these different activities, the use of honey in pilonidal cyst excision wounds could be of interest in accelerating healing.

1.3 Summary of the benefits, if any, and the foreseeable and known risks for the people participating in the research.

1.3.1 Benefits

1.3.1.1 Individual benefit

Acceleration of healing.
Reduction in the number of dressings .
Acceleration of return to work .

1.3.1.2Collective benefit

Decrease in the cost generated by the dressings and by the reduction in the duration of the work stoppage

1.3.2 Risks

The risks are related to cystic disease. Complications are wound infection and recurrence of the pilonidal cyst. With this excision and directed healing technique, the recurrence rate is estimated at 5%.
The main risks associated with the honey dressing are pain and discomfort due to the hyperosmolarity it creates.

1.3.3 Specify the expected AEs and SAEs related to the protocol's medical device (sterile honey)

Side effects can be:
- pain when applying the cream to the wound (hyperosmolar activity of the honey cream)
In some cases (less than 5% of patients), application of sterile honey to the wound may cause irritation, stinging or burning. These sensations can be temporary or permanent. If such a case occurs, it is advisable to renew the dressing using a damp compress. If symptoms persist, another treatment solution should be considered by the medical team.

- Bleeding from the wound (chemical cleansing mechanism)
- Allergic skin reactions related to the product but also to the dressing
- Hyperbudding healing that may require wound nitration
- A nauseating chronic suppuration

1.3.4 Benefit/risk balance

The benefit is greater since it is to reduce the duration of the dressings and consequently the patient's discomfort compared to a medical device whose adverse effects are relatively limited. The medical device is a local application treatment, therefore its systemic passage is relatively low.
The expected benefit is far greater than the risk, with an acceleration of healing with a reduction in the duration of dressings and their consequences in terms of pain and discomfort, an easier return to daily activities, compared to the use of a medical device whose adverse effects are limited, especially since its systemic passage is low.

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

The route of administration is cutaneous (local application). The duration of treatment will be until complete healing or at most up to 180 days if the wound is not healed.

1.5 Declaration indicating that the research will be carried out in accordance with the protocol, good clinical practices and the legislative and regulatory provisions in force.

The sponsor and any investigator undertake to carry out this study according to the recommendations of the Declaration of Helsinki and its revisions, the provisions of European Directive 2001/20-EC as transposed into French law by laws 2004-806 of 9 August 2004 relating to public health policy and 2004-800 of August 6, 2004 relating to bioethics and implementing decrees and orders, Regulation 2017/745 of April 5, 2017 relating to medical devices (MD), MDCG 2020 -10/1, standard NF ISO 14155 clinical investigation of medical devices and follow the recommendations of good clinical practice.

They undertake to comply with all legislative and regulatory provisions to which the research may be subject.

1.6 Description of the population to be studied.

Patients followed in the digestive surgery department following excision of a pilonidal cyst at the CHD and whose wound remains cavitated 6 weeks **postoperatively.**

1.6.1 Description of the population

1. Inclusion criteria:

- Cavity Wound to 6 weeks of a pilonidal cyst excision
- Bloodless wound
- Pilonidal cyst not recurred
- Age : 18 years and older
- Signature of informed consent
- In the capacity to understand the study

2. Non-inclusion criteria:

- Bleeding wound
- Refused to participate in Protocol
- Patient immunocompromised
- Recurrent pilonidal cyst
- Patients on long-term corticosteroid
- Patient deprived of liberty, under guardianship
- Patient unable to understand the study
- Allergy or hypersensitivity to honey
- Allergy Or hypersensitivity to hyaluronic acid
- Allergy or hypersensitivity to guar gum
- Allergy or hypersensitivity to pectin
- Known allergy to propolis (potentially present in honey)
- Sensitivity to zinc oxide
- Sensitivity known dressings used in this trial or any component
- Diabetes Non-insulin or insulin

1.6.2 Description and number of subjects planned for the sample:

The study plans to include 110 patients with the aim of obtaining 100 randomized patients. Inclusions will stop when the potential of randomized patients is reached.

1.7 References to scientific literature and relevant data serving as a reference for research.

1.Chintapatla S, Safarani N, Kumar S, Haboubi N. Sacrococcygeal pilonidal sinus: historical review, pathological insight and surgical options. Tech coloproctol. 2003, 7:3-8.
2.Nelson JM, Billingham RP. Pilonidal disease and hidradenitis suppurativa. The ASCRS Textbook of Colonand Rectal Surgery. 2007, 228-39.
3. Hull TL, Wu J. Pilonidal disease. Surg Clin N Am. 2002,82:1169-1185.
4. PetersonS, Koch R, Stelzner S, Wendlandt TP, Ludwig K. Primary closure techniques in chronic pilonidal sinus: a survey of the results of different surgical approaches. Say ColonRectum. 2002.45, 205:439-44
5. Acartürk TO, Parsak CK, Sakman G, Demicran O. Superior gluteal artery perforator flap in the reconstruction of the pilonidal sinus. Journal of Plastic, Reconstructive & Anesthetic Surgery. 2010, 63, 133-39.
6. Can MF, Sevinc MM, Yilmaz M. Comparison of Karydakis flap reconstruction versus primary midline closure in sacrococcygeal pilonidal disease: results of 200 military service members. Surg Today. 2009, 39:580-6

7. MacCallum IJD, King PM, Bruce J. Healing by primary closure versus open healing after surgery for pilonidal sinus: systematic review and meta-analysis. BMJ. 2008, 336:868
8.Sievert H, Evers T, Matevossian E, Hoenemann C, Hoffmann S, Doll D. The influence of lifestyle (smoking and body mass index) on wound healing and long-term recurrence rate in 534 primary pilonidal sinus patients. Int J Colorectal Dis. 2013.20.
9. Descottes B. Healing by honey, the experience of 25 years. Phytotherapy. 2009, 7:112-16
10. Natarajan et al. Healing of an MRSA-colonized, hydroxyurea-induced leg ulcer with honey. J Dermatolog Treat. 2001, Mar, 12(1):33-6.
11. Blaser et al. Effect of medical honey on wounds colonized or infected with MRSA. J Wound Care. 2007, Sep; 16(8):325-8

2 Research objectives:

2.1 Main objective

Evaluate the healing time of the wound with honey dressings compared to conventional dressings .

2.2 Secondary objectives

- Evaluate the cost generated by the dressings
- Evaluate patients' quality of life and discomfort
- Evaluate the duration of work stoppage
- Assess the tolerance of dressings

3 Research design:

3.1 Precise statement of the main evaluation criterion and, if applicable, of the secondary evaluation criteria.

3.1.1 Primary endpoint

Time to wound closure between randomization (positioning of the first dressing) and complete wound closure (or end of follow-up set at 180 days if the patient has not healed within this time).

The complete closure of the wound will be validated by the IDE in charge of the patient during a daily visit or a specialist consultation. The date of complete closure will be notified in the notebook given to the patient.

3.1.2 Secondary endpoints

- Number of dressings performed between randomisation and healing (or end of follow-up).
- Assessment of quality of life by the VQ dermato score one month after randomisation and at the time of healing (or at D180 if no healing)
- Number of days off work
- Number of intolerance, dressing discontinuation and/or need to change treatment

3.2 Description of the research methodology, accompanied by its schematic presentation specifying in particular the visits and examinations planned.

3.2.1 Experimental plan

This is a prospective, single-center, randomized, controlled, open-label study with 2 randomization arms:
_ Patients treated with alginate dressing (standard group)
_ Patients treated with alginate dressing + sterile honey (experimental group)

3.2.2 Course of the study

The Pilomiel study will be explained and proposed initially to the patient during the consultation 3 weeks after the excision of the cyst.
The patient's signed written consent must be obtained between this consultation and at the latest on the day of the consultation 6 weeks after excision.
In the case of a minor patient, the minor must be informed (information letter) and the signed consent of both parents must be collected (unless an exemption is authorized by the CPP).
During the consultation 6 weeks after the intervention, if the patient still presents with a cavitary wound, meets all of the inclusion criteria and the appropriate consent forms have been signed, he or she may be included and randomisation will be carried out.
The two randomization arms are:

_ alginate dressing
_ dressing with alginate wick + sterile honey

_Measurement of the wound in the 3 axes: Measurement of the depth, width and length of the wound. The objective is to obtain the volume of excision.
_ Realization of daily dressing by an IDE at home with care protocol sheet (Appendix 6)
_ Consultation after 8 days +/- 3 days with a specialized IDE for all patients then every 15 days if necessary on decision of the specialized IDE according to the evolution of the wound, the tolerance of the dressing and the proper realization of the dressing at home and this, until healing.
(If necessary, request medical advice during these consultations) .
The reason for continuing or stopping consultations with the specialized IDE will be recorded in the CRF.

The patient will be seen in consultation every 4 weeks by the surgeon until complete healing.

During the consultation 6 weeks after the excision, the patient will be given a notebook which he must complete daily. During each visit, he must notify his adverse events, his EVA following the application of the dressing, the stopping or not of the dressing due to intolerance, indicate whether he is on sick leave or not. The IDE must record the exact date of complete healing of the wound and therefore of stopping the dressings.

A quality of life questionnaire will also be completed by the patient:
- one month from randomisation
- and at the end of healing (or at D180 if the patient has not healed within this period).
The patient will be followed until the healing of the wound. This follow-up will be for a maximum of 180 days after randomization if it has not healed.

At the end of the 180 days, if the patient included in the experimental arm has not healed, he will be taken care of according to the usual practice of the center in the face of late healing, namely depending on the case:
- VAC therapy (negative pressure therapy, la V.A.C. Therapy, applies mechanical and biological forces to the wound to create an environment that promotes healing. These forces are known as macrostrain and microstrain.)
- eosin to dry out the wound (drying and antiseptic properties).
- revision surgery, new excision if necessary

STUDY TIMETABLE

Shares	D0 (inclusion visit) = 6 weeks post excision	D8	D15	D30	J45	J60	J75	J90	J105	J120	J135	J150	J165	J180
Patient information	x													
Signature of consent	x													
Randomization	x													
Background	x													
Medical clinical examination (digestive surgeon)	x			x		x		x		x		x		x
Paramedical consultation (Specialized IDE)**	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pharmacovigilance monitoring		x	x	x	x	x	x	x	x	x	x	x	x	x
VQ-dermato quality of life score*				X*										X*

IDE at home every day in the two randomization groups

*The VQ-dermato quality of life score will be assessed at one month from randomisation and at the time of healing or at the last follow-up visit for unhealed patients.

** Specialized IDE: Consultation after 8 days for all patients then every 15 days if necessary on decision of the specialized IDE according to the evolution of the wound and until healing.

All consultations can be carried out within +/- 3 days.

3.3 Description of the measures taken to reduce and avoid bias, including in particular:

3.3.1 The drawing of lots;

A randomisation list will be pre-established before the start of the study. This will be incremented at an interface of the CS Online software in order to be able to carry out an electronic randomization.

The randomization will be carried out on the day of the consultation at 6 weeks post-operative after obtaining the signed consent of the patient (or the parents of the minor if applicable).

The randomization arm will be transmitted to the investigator by automatic edition of an e-mail via CS Online.

3.3.2 Blinding methods.

There is no blinding of sterile honey.

3.4 Expected length of time individuals will be involved and description of the timing and duration of all periods of the trial, including follow-up, if applicable.

See Study schedule.

3.5 Description of permanent or temporary stoppage rules

3.5.1 Criteria for premature termination of a person's participation in research

A person's participation may be terminated prematurely for the following reasons:

- Withdrawal of consent by the patient (or parents if the patient is a minor), the latter will leave the study and the data concerning him will not be used if he opposes it, except for the vigilance data and their monitoring
- Death.

Withdrawals from studies can only be effective after confirmation by the investigator and the sponsor. These exits from studies are always final.

3.5.2 Procedures for premature termination of a person's participation in research

In the event of premature termination of the study, the patient's care will then be the standard care of the service.
For the terms and duration of follow-up of people who stopped the study prematurely, see the statistics section.

3.5.3 Criteria for definitive or temporary cessation of part or all of the research.

The study may be terminated prematurely in the event of the occurrence of serious, unexpected adverse events requiring a review of the product's safety profile.
Similarly, an abnormally high frequency of adverse reactions related to sterile honey, unforeseen events or new information relating to the product, in view of which the objectives of the study or the clinical program will not likely be achieved, may lead the sponsor to terminate the study prematurely.
The study may also be interrupted by decision of the health authorities and in particular in the event of withdrawal of the CE marking.
The CHD Vendée reserves the right to interrupt the study, at any time, if it turns out that the inclusion objectives have not been achieved. In the event of premature termination of the study, the information will be transmitted by the sponsor within 15 days to the ANSM and the CPP.

In the event of premature termination of the trial, a declaration must be made without delay to the competent authorities, then within a maximum period of 15 calendar days a request for authorization of substantial modification must be made if necessary.

3.6 Identification of all the data to be collected directly in the observation notebooks, which will be considered as source data

- Size of the wound during the various consultations: measurement of depth, width and length
- Collection of EVA (Visual Analogue Scale) during dressings
- Number of dressings performed at home and therefore the number of nursing visits
- Number of days off work.
- Quality of life score at one month from randomisation and at the time of healing (or at the end of follow-up, if the patient has not healed)
- EvI collected on the patient diary

4 Selection and exclusion of persons from research:

4.1 Criteria for inclusion of people who lend themselves to research.

- Cavity Wound to 6 weeks of a pilonidal cyst excision
- Bloodless wound
- Pilonidal cyst not recurred
- Age : 18 years and older
- Signature of informed consent
- In the capacity to understand the study

4.2 Criteria for non-inclusion of people who lend themselves to research.

- Bleeding wound
- Refused to participate in Protocol
- Patient immunocompromised
- Recurrent pilonidal cyst
- Patients on long-term corticosteroid
- Patient deprived of liberty, under guardianship
- Patient unable to understand the study
- Allergy or hypersensitivity to honey
- Allergy Or hypersensitivity to hyaluronic acid
- Allergy or hypersensitivity to guar gum
- Allergy or hypersensitivity to pectin
- Known allergy to propolis (potentially present in honey)
- Sensitivity to zinc oxide
- Sensitivity known dressings used in this trial or any component
- Diabetes Non-insulin or insulin

4.3 Procedure for premature cessation of treatment corresponding to the cessation of treatment with the experimental medicinal product, and procedure for exclusion from research corresponding to the cessation of treatment and monitoring of the person in the context of research:

4.3.1 Criteria and procedures for premature termination of treatment or exclusion of a person from research;

The treatment may be stopped if the patient's quality of life becomes too impaired by the dressings (including the occurrence of EvI) and/or requires a change of dressings and/or active procedure.

This will also be stopped if a recurrence of the pilonidal cyst occurs or in the event of poor progression of the healing according to the assessment of the investigator.

4.3.2 Collection methods and schedule for this data;

See study schedule .

4.3.3 Arrangements for replacing these people, if applicable;

No replacement of people who prematurely stopped the study treatment.

4.3.4 Follow-up methods for these people

See study schedule
Maximum duration of follow-up: 180 days

5 Treatment given to people who agree to research:

5.1 Description of the treatment(s) necessary to carry out the research and methods of administration.

5.1.1 Investigational medical device(s) / comparator

5.1.1.1 Identification of medical devices :

MELECTIS® G : sterile honey for wound care. GMDN code: 44787.

Melectis ® is a standardized medical device (class II B) based on honey, which was developed to promote the healing of acute and chronic wounds. It results from a blend of monofloral honeys selected according to their antibacterial, anti-inflammatory and pro-healing properties. To prevent any further contamination in wounds, this medical device has been sterilized to eliminate germs (>500 CFU - Colony Forming Units - per gram) naturally present in all food honeys. Sterilization with gamma rays nevertheless makes it possible to preserve the biological properties of the product.

Melectis ® is recommended for acute wounds (dermabrasions, surgical and traumatic wounds), first and second degree burns, chronic wounds (leg or foot ulcers, pressure sores, bedsores, etc.)

5.1.1.2 Administration

Local application

The device must be impregnated on a standard dressing (Algosteril, Aquacel, Mepilex border), and must fit well to the bottom of the wound.
Do not apply the honey patch if the wound is bleeding.

5.1.1.3 Dosage adjustment

It is preferable to renew the dressings made with **Melectis** ® once a day when the wounds are moderately exuding and/or infected. If the secondary dressing is soiled or if it leaks, it is even advisable to redo the dressings more frequently. On clean, low-exuding wounds in the budding phase, dressings can be changed every 48/72 hours.

5.1.1.4 Storage conditions for medical devices

Description of storage at the pharmacy

Stocks are managed by the CHD Vendée pharmacy.

Tubes of sterile honey (Melectis®) are provided and labeled "clinical research" by CHD Vendée.
Once the tubes have been labeled, they are stored in the specific "Clinical Trials" room in the temperature-controlled pharmacy.

The CHD Vendée pharmacy provides:
- Receipt of packages
- Storage of products at a temperature that must not exceed 30°C(air-conditioned room)
- Delivery of products to the digestive surgery department (consultations) and accounting

Description of storage in the service

Depending on the rate of inclusions, the digestive surgery department will be supplied with tubes of sterile honey by the CHD Vendée pharmacy.
The CHD Vendée digestive surgery department provides:
- Storage of products at room temperature (not to exceed 30°C)
- Delivery of products to patients in the "alginate wick dressing + sterile honey" randomization arm and accounting

The dispensation will be made at the end of the randomization via the electronic CRF.
Patients in the "alginate dressing + sterile honey" randomization arm will receive their first dressing with honey on the day of randomization and will leave with the tube used (a single tube can only be used by one patient).
Replenishments will be made during consultations with specialized IDEs every 8 or 15 days.

The capacity of a tube (30g) allows the realization of dressings on average over 15 days.
Uncapped Mélectis® G tubes can be used up to 90 days after opening.

Description of patient storage

In the patient, the storage of sterile honey tubes must be done at a temperature that must not exceed 30 °C.

5.1.2 Other drugs in the protocol

5.1.2.1 Identification of medical treatments/devices:

Standard dressings:
Alginate wick: Algosteril or Aquacel wick

As part of the standard treatment, dressings with wicking will be made either with Algosteril® or Aquacel ™ . In the immediate postoperative period, the packing will be done with Algosteril® during the first 3 weeks; its haemostatic activity to prevent bleeding. Secondarily, the dressings may vary depending on the wound (evolving wound) and the healing between the two types of locks.

Dressings with Aquacel® will be used preferably if the wound is very exudative. On the other hand, if the wound appears "in gills" the dressing with Algosteril® will be preferred.

The dressings with wicking above will be covered with absorbent hydrocolloid dressings of the Mepilex Border® or Aquacel™ Foam type without any particular differentiation in use.

The dressings delivered by the CHD Vendée will be round wick Algosteril type dressings. Patients will receive a prescription for the renewal of their daily dressings which may be issued by a town pharmacist, the specific type of which may therefore differ depending on the pharmacy.
In general, the dressings made are either of the type:

- Algostéril® (round or flat wick) + Mepilex® border
- Either Aquacel ™ Extra ™ + Aquacel ™ Foam

The instructions for the Algosteril®, Aquacel ™ and Mepilex® Border dressings are available in the appendix to the protocol.

Analgesic treatment:
_ Level I analgesic: paracetamol 1 gx 4/d
_ Level II analgesic: Ixprim 1 tab x 4/d

5.1.2.2 Administration

Standard dressings:
Local application

Analgesic treatment:
The administration will be per os

5.1.2.3 Dosage adjustment

Standard dressings:
None

Analgesic treatment:
Adaptation of the paracetamol dose to the weight 15mg/Kg x 4/D
In adults, the maximum dosage of paracetamol per os is 1g 4 times a day.

5.2 Medications and treatments authorized and prohibited under the protocol, including rescue medication.

5.2.1 Authorized treatments

All except those specified in the following paragraph.

5.2.2 Unauthorized processing

Immunosuppressants and corticosteroids (Except inhaled corticosteroids used occasionally for asthma, rhinitis, etc.)

6 Evaluation of efficacy / tolerance / bioavailability if pharmacokinetics / pharmacodynamics… (if applicable):

6.1 Description of evaluation parameters.

See Observation notebook

6.2 Planned methods and schedule for measuring, collecting and analyzing effectiveness metrics.

See collection calendar

7 Safety assessment:

7.1 Definitions

According to Regulation (EU) 2017/745 of the European Parliament and of the Council of April 5, 2017 relating to medical devices (RDM), MDCG 2020-10/1 and standard NF EN ISO 14155 Clinical investigation of medical devices for human subjects-Good clinical practice:

Adverse events MDR article 2 (57)	Any harmful manifestation, any unintentional illness or injury or any untoward clinical sign, including an abnormal laboratory finding, in participants, users or other persons, in the context of a clinical investigation, whether or not related to the device under clinical investigation.
Adverse Device Effect Standard NF EN ISO 14155 3.1 MCDG 2020-10/1	Adverse event linked to the use of the medical device under investigation. Note 1: This definition includes any adverse event resulting from deficiencies or inadequacies in the instructions for use, deployment, implantation, installation and operation, or any malfunction of the medical device under investigation. Note 2: This definition includes any event resulting from a user error or intentional misuse of the medical device under investigation. Note 3: This takes the comparator into account if it is a medical device.
User MDR article 2 (37-38)	Any healthcare professional or lay person who uses a device.
Serious adverse events MDR article 2 (58)	Any adverse event leading to: to death ; b) a serious deterioration in the participant's state of health, which is the cause of:

	- an illness or injury endangering the life of the patient; - a permanent deficiency of an anatomical structure or function; - hospitalization or extension of the patient's hospitalization; - a medical or surgical intervention intended to prevent any disease or injury endangering the life of the patient or any permanent impairment of an anatomical structure or function; - a chronic illness; (c) fetal distress, fetal death, congenital physical or mental impairment or birth defect. Note (Standard NF EN ISO 14155): Planned hospitalization due to a pre-existing condition or a procedure required by the clinical investigation plan, without serious deterioration in health, is not considered a serious adverse event.
Serious health risk Standard NF EN ISO 14155 3.46	Signaling an adverse event or device defect that indicates an imminent risk of death or serious deterioration in the health of subjects, users or other persons, and which requires immediate corrective action for other subjects, users or other people.
Serious Adverse Device Effect Standard NF EN ISO 14155 3.44 and MDCG 2020-10/1	An adverse device effect resulting in one of the consequences characteristic of a serious adverse event.
Unexpected/unexpected serious adverse reaction DM MDCG 2020-10/1 10.2.18- MDR (EU) 2017/745-ISO 14155 3.51 standard	A serious unexpected adverse device reaction is one that, by its nature, incidence, severity or outcome, was not identified in the current risk assessment. Procedures associated with the use of a device should be addressed in the risk assessment, which helps to determine whether or not procedure-related SAEs are serious unexpected adverse effects of the device. SAEs related to procedures imposed by the clinical investigation plan but not with the use of the device should not be considered as serious adverse effects of the device.
Intensity of Adverse Events	Grade 1 = **mild** (no interference on the patient's daily activity) Grade 2 = **moderate** (moderate interference on the patient's daily activity but still acceptable Grade 3 = **severe** (significant interference with the patient's daily activity and unacceptable) Grade 4 = **life-threatening**

	Grade 5 = **death**
Device Failure (DD) MDR article 2 (59)	Any defects in the identity, quality, durability, reliability, safety or performance of a device under investigation, including any malfunction, user error or fault in the Information provided by the manufacturer.
New fact (FN) Article R1123-46 of the public health code	Any new data that may lead to a reassessment of the report of the benefits and risks 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 in the documents relating to the research, or to suspend or discontinue or modify the protocol of the research or similar research. For trials involving the first administration or use of a health product in people without any medical condition: any serious adverse effects.
Causality MDCG 2020-10/1 9	**Unrelated** : the causal link with the MD, the comparator or the procedures can be excluded **Possible:** the causal link with the use of the MD, the comparator or with the trial procedures is weak but cannot be completely excluded. Other causes are also possible (underlying or concomitant disease/clinical condition/effect of another treatment). Cases where the relationship cannot be assessed or no information has been obtained should also be classified as possible. **Probable** : the causal link with the use of the MD or the comparator, or the relationship with the trial procedures, seems relevant and/or the event cannot reasonably be explained by another cause. **Certain:** the serious adverse event is linked to the use of the MD, the comparator, or the trial procedures beyond any reasonable doubt.
Unexpected adverse reaction experimental drug Article R1123-46 of the public health code	For research on a medicinal product, unexpected adverse reaction: any adverse reaction to the product whose nature, severity, frequency or course is not consistent with the reference safety information mentioned in the summary of product characteristics or in the investigator's brochure when the product is not authorised.
Adverse reaction to an investigational drug Article R1123-46 of the public health code	Any harmful and unwanted reaction to an investigational drug regardless of the dose administered.

Summary table of adverse event categories according to standard NF EN ISO 14155:

Adverse events	Not related to device	Related to the device or the investigation procedure	
Not Serious	Adverse event (AE)	Adverse Device Effects (ADRs)	
Severe	Serious adverse event (SAE)	Serious Adverse Device Reactions (SAREIs)	
		Expected	**Unexpected**
		Expected EIGD, EIGAD	Unexpected EIGD or EIGID

7.2 Expected serious adverse effects or events

An expected serious adverse event is an event already mentioned in the most recent version of the investigator's brochure / Instructions for use / instructions for use for MDs or in the most recent summary of product characteristics (SPC) for medicinal products already having a marketing authorization.

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

- **Regarding experimental care:**

- pain when applying the cream to the wound (hyperosmolar activity of the honey cream).
- allergic skin reactions related to the product but also to the dressing

- **Regarding alginate wick dressings:**

- Hyper budding of the wound
- Dressing allergy (inflammatory plaque, allergic reaction)

- **Regarding analgesic treatments:**

- Nausea, vomiting
- Dizziness
- Allergic reactions (generalized skin erythema, angioedema, etc.)

These AEs are listed in the respective SPCs of these medicinal products used within the framework of their MA .

- **Regarding pathology:**

- Bleeding from the wound (chemical cleansing mechanism)
- Occurrence of a local abscess
- The occurrence of a recurrence
- A nauseating chronic suppuration

7.3 Action to be taken by the investigator

7.3.1 Collection of adverse events (EvI), New Facts and Device Defects (DD)

As soon as the consent is signed, the investigator is responsible for collecting all adverse events, new facts and defects in the MD.

It records all serious and non-serious biological and clinical adverse events (EvI), as well as defects in the MD (which could have led to a serious adverse event), which occur between the signing of the consent and the end of the subject's participation included or the end of the EvI collection in the observation book (CRF).

Exceptions to the collection : the following situations will not be collected:

- admission or extension for social or administrative reasons,
- day hospital consultation,
- hospitalization for an act, manifestation or treatment predefined by the protocol,
- hospitalization for medical or surgical treatment scheduled before the research, or in connection with a pre-existing pathology.

7.3.2 Assessment and notification

For each event collected, the investigator rates the severity and intensity (severity) of the event. It also assesses each defect that could have resulted in an EvIG.

The investigator notifies the sponsor without delay and no later than within 3 calendar days from the day on which he becomes aware of any serious adverse event (EvIG) or any defect in the MD which could have led to an EvIG.

The investigator monitors any serious adverse event noted until complete resolution (disappearance of signs and symptoms), or consolidation (return to a state considered medically acceptable), **and communicates to the sponsor any additional information** concerning this event by means of follow-up reports.

Moreover, regardless of the delay in occurrence after the end of the study, any EvIG likely to be due to research must be declared to the sponsor when no cause other than research can reasonably be attributed to it (for example serious effects that may appear at a long distance from the exposure to the drug, such as cancers or congenital anomalies).

7.3.3 Information to send to the sponsor

Each EvIG or new event will be described on the "Initial Declaration of Serious Adverse Event" or "Follow-up Declaration of Serious Adverse Event" form, trying to be as exhaustive as possible.

Defects in medical devices (DD) will be notified via the SIP form ("Situation of Particular Interest").

The investigator must also attach to the EvIG report, whenever possible:

- a copy of the hospitalization or hospitalization extension report,
- a copy of all the results of additional examinations carried out, including the relevant negative results, attaching the normal values of the laboratory,
- any other document that he deems useful and relevant (photos, reports, etc.).

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

In addition to these notifications, the investigator must immediately inform the sponsor of misuse, errors-risk of errors, overdoses, signs of withdrawal and cases of pregnancy of which he is aware, even in the absence of complications and criteria. severity (SIP/pregnancy forms).

7. 3.4 Terms of notification to the sponsor

Any AE that meets the definition of SAE requires the completion of an SAE declaration form whether it is expected or not expected, and regardless of its causal relationship with the treatment(s) of the test or research.

The investigator must check that the information provided on this sheet is precise and clear (do not use abbreviations, etc.).

The SAE must be reported to the sponsor by email to the following address: promotion.urc@chd-vendee.fr

Vigilance analysis is entrusted to the vigilance cell of the Nantes University Hospital - email cell vigilance: recherche-pv@chu-nantes.fr).

Any investigator/vigilance unit correspondence must be copied to the sponsor at the same time.

All other EvIs will be reported on the "adverse event" form in the observation book, specifying the date of occurrence, description, intensity, duration, mode of resolution, etiology, imputability and decisions taken.

Summary table of the notification circuit by type of event:

EVENT TYPE	NOTIFICATION METHODS	PROPONENT NOTICE PERIOD
Non-serious adverse event	In the observation book	As soon as you become aware
Serious adverse event	Initial EvIG/DD declaration form + Follow up if necessary + collection in the observation book	**Without delay to the sponsor, upon becoming aware of it, and no later than within 3 calendar days**
Defect of the DM that could lead to an EvIG	Initial SIP declaration form + Follow up if necessary + collection in the observation book	
New fact	E-mail to sponsor	Notification without delay
Pregnancy	Declaration form Initial pregnancy + Follow up if necessary + collection in the observation book	**Upon confirmation of pregnancy**
Misuse, errors-risk of errors, overdoses, etc.	Initial SIP declaration form + Follow up if necessary + collection in the observation book	As soon as you become aware

7. 4 Role of the sponsor

The sponsor registers:

a) any adverse event defined in the protocol as determining for the evaluation of the results of the clinical investigation.

b) any serious adverse event;

c) any defect in an MD which could have led to a serious adverse event in the absence of appropriate measures or intervention, or if the circumstances had been less favourable;

d) any new element concerning an event referred to in points a) to c).

The sponsor is responsible for the continuous evaluation of the safety of the medical device that is the subject of the research.

The proponent must assess:

- the causal link between the serious adverse event and the medical device and/or research procedures.
- the unexpected nature of the serious adverse effects of the medical device,
- the expected or unexpected/predicted nature of serious adverse reactions. Any serious undesirable effect whose nature, severity, frequency or course does not match the information given in the instruction leaflet or the user guide for the medical device subject to CE marking and the expected or

unexpected character using the reference document (RCP) in force for medicinal products.

- New Facts.

In the event of a different assessment by the sponsor and the investigator, the two opinions are mentioned on the declaration sent to the competent authority if this declaration is necessary.
The assessment of the expected/unexpected/unforeseen nature of a serious adverse effect is carried out by the sponsor and the Nantes University Hospital Vigilance Unit.

Deadlines for declaration by the sponsor to the ANSM :

Type of EvI	**Time limit initial declaration**	**Time limit follow up**
Serious adverse events / defects in the medical device leading to death or a risk of imminent death, injury or serious illness + New fact	WITHOUT DELAY and no later than 2 calendar days	WITHOUT DELAY and no later than 2 calendar days
Other Serious adverse events/ MD defects	WITHOUT DELAY and no later than 7 calendar days	WITHOUT DELAY and no later than 7 calendar days

ANSM reporting procedures : The Cellule Vigilance sends the table by email as presented in the appendix to recommendation MDCG-2020-10/2.

The expected SAEs will be recorded and kept by the sponsor to be the subject of a declaration via the annual safety report.

Transmission of the Annual Safety Report (RAS)

A safety report is produced annually on the anniversary date of the clinical trial authorization (AEC) issued by the competent authority.
The report is produced by the research sponsor in collaboration with the coordinating investigator. A period of 60 days (from the anniversary date of the AEC) is given to the sponsor to send this document to the competent authorities.

8 Statistics:

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

The statistical analyses will be carried out within the clinical research unit of the CHD de Vendée.

The analysis will be performed by the Intent to Treat principle

All the variables will be described globally and by group. The description will include the counts and percentages of the modalities for the qualitative variables and the minimums, maximums, averages, standard deviations and medians for the quantitative variables.

Primary endpoint :
- The time between inclusion of the patient and complete healing of the wound will be compared between the two groups using a Student t-test. Time for Patients who have not healed before the end of the study will be imputed by 180 days (maximum follow-up for a patient).

Secondary criteria:
- The number of dressings used between inclusion and healing will be compared between the 2 groups using a Student t-test.
-The quality of life at healing (or end of follow-up) defined by the VQ-Dermato score will be compared between the 2 groups by a Student t-test.

- The number of days off work will be compared between the 2 groups using a Student t-test.

8.2 Expected number of people to be included in the research, and expected number of people in each research location with its statistical justification.

A preliminary study in our digestive surgery department showed that in patients who had not healed at 45 days, the mean healing time was 75 days with a standard

deviation of 27 days. As this is a sub-population of patients with cavitated wounds, the mean healing time in the “conventional dressing” group is expected to be 95 days.
Assuming that patients treated with honey dressings will heal 20 days faster than patients treated with a conventional dressing, a sample of 84 patients will be needed to show this difference with an alpha risk of 5% and 90% power.
To ensure sufficient power, it is planned to randomize a total of 100 patients.

8.3 Expected level of statistical significance.

The significance threshold was set at 5%.

8.4 Statistical Criteria for Stopping Research.

N / A

8.5 Method for accounting for missing, unused or invalid data.

Each of the missing data as well as the reason for the missing data of the primary endpoint will be reviewed during the data review meeting.
Missing healing time and patients with a recurrence of their pilonidal will be imputed by 180 days.

8.6 Choice of people to include in analyses.

The analysis will be performed by the Intent to Treat principle
A sensitivity analysis on the "Per protocol" population will be carried out and will exclude patients with major deviation from the protocol

8.7 Managing changes to the initial strategy analysis plan.

N/A

9 Right of access to source data and documents.

The medical data of each patient will only be transmitted to the sponsor or any person duly authorized by him, and, if necessary, to the authorized health authorities, under conditions guaranteeing their confidentiality.
The sponsor and the supervisory authorities may request direct access to the medical file for verification of the procedures and/or data of the clinical trial, without breaching confidentiality and within the limits authorized by laws and regulations.

10 Quality control and assurance.

10.1 Test monitoring

Monitoring will be provided by CHD. A Clinical Research Associate (CRA) will visit regularly to carry out quality control of the data. The CRA ensures that the database contains all the information requested and verifies the compliance of the observation book with the protocol and the regulations in force.

The observation notebook for each patient must be in line with the source documents (= patient file). The CRA's access to these documents must be facilitated. The ARC is bound by confidentiality with respect to the information it accesses.

The frequency of visits will depend on the number of patients included, the frequency of inclusions and the difficulties observed during the conduct of the study and will be defined by the study sponsor.

Monitoring visits in the department will be organized after an appointment with the investigator. The CRAs must be able to consult:

- Patient data collection notebooks included,
- Patient medical and nursing records, including patient monitoring records
- The investigator workbook.

Basic monitoring will check at least the following 5 points:

- The presence of signed informed consents,
- Compliance with the inclusion criteria,
- The main judgment criterion,
- Monitoring and reporting of SAEs,
- Reporting of new facts,

The data of all patients will be verified.

10.2 Inspection / Audit

As part of this study, an inspection or audit may take place.

Note: An inspection is an official control carried out by the supervisory authorities in order to assess the admissibility of clinical data, to verify compliance with legislation and the absence of fraud.
Inspectors check documents, logistics, records and any other resources that the authorities consider to be associated with the clinical trial and which may be on

the site of the trial itself, at the sponsor's and/or on the premises of the service provider organization (CRO) or in other establishments deemed relevant.

An audit is a quality control of the trial; it can be conducted by representatives of the sponsor or a company duly mandated by the sponsor.

11 Ethical Considerations

11.1 Written Informed Consent

The investigator undertakes to inform the patient in a clear and fair manner of the protocol and to ask him for informed and written consent (information leaflet and consent form attached).
In the case of a minor patient (14 to 17 years old) the information will also be given to the parents of the minor patient. A specific information letter (adapted to his understanding) will be given to the minor patient accompanied by a consent signed by both parents of the minor patient (unless exceptions authorized by the CPP).

The investigator will give the patient (as well as the parents of the minor patient if applicable) a copy of the information notice and a consent form. The patient can only be included in the study after having read the information notice and after collecting the consent form dated and signed by the patient or the parents of the minor patient.
A minor patient can only be included in the study if:
- the minor patient has been informed and has given his oral consent
- **AND** that both parents have dated and signed the consent collection form intended for the parents of a minor (except exceptions authorized by the CPP).
The investigator must also sign and date the consent form. These documents will be delivered on paper in 2 copies so that the patient and the investigator can each keep a copy. The investigator's original will be filed in the investigator binder.

Derogation from the obligation to obtain the signed consent of both parents requested from the CPP in the following cases:
- if one of the two parents is deceased
- if the child is recognized by only one parent
- if only one parent has been designated as holder of the exercise of parental authority by court decision
- case of separated or divorced parents

In these cases, only the signed consent of the parent accompanying the child and holder of the exercise of parental authority will be collected.

In the case of separated parents, if the second parent (holder of the exercise of parental authority) who has not signed the initial consent wishes to stop the participation of his child in the study, his decision will of course be taken in account.

11.2 Committee for the Protection of Persons

The sponsor undertakes to submit the study project to the prior authorization of a Committee for the Protection of Persons (CPP). The information communicated concerns, on the one hand, the methods and nature of the research and, on the other hand, the guarantees provided for the patients taking part in this trial.

11.3 Protocol Amendments

Requests for substantial modifications will be sent by the sponsor for authorization or information to the ANSM and/or to the committee for the protection of persons concerned in accordance with law 2004-806 of August 9, 2004 and its implementing decrees.

The modified protocol will have to be the subject of a dated updated version.
The patient information and consent forms should be modified if necessary.

11.4 Declaration to competent authorities

This protocol will be the subject of an authorization request from the ANSM.

11.5 Patient anonymity

By signing this protocol, the principal investigator and all of the co-investigators undertake to keep the identities of the patients who participated in the study confidential. The first letter of the surname, the first letter of the first name, and the month and year of birth will be the only information that will appear on the observation book (CRF) and which will make it possible to attach the CRF to the patient a posteriori.
The sponsor is also required to make anonymous all the documents that he may have in his possession (reports of imaging examinations, biology, etc.) which would be attached to the CRF.

A unique number will be assigned to each patient upon inclusion in the study.

11.6 Computerized data

The data collected during the study will be kept in a computer file respecting the law "Informatique et Libertés" of January 6, 1978 amended in 2004 as well as the reference methodology for the processing of personal data operated within the framework of clinical investigations (MR 001).

11.7 File of persons suitable for clinical investigations

N / A

12 Processing of data and storage of documents and data relating to research.

12.1 Data collection

A case report (CRF) will be created per patient. All information required by the protocol must be provided in the CRF. He will take up the different stages of patient care in the protocol. It must include the data necessary to confirm compliance with the protocol, detect major deviations from the protocol and all the data necessary for the analyses.
The anonymity of the subjects will be ensured according to the rules defined by the protocol.
The data will be entered on a secure basis and will only contain the patient's inclusion number as an identity.
Vigilance data will be collected on the EveDrug pharmacovigilance database.

12.2 Data processing

The collection of clinical data will be based on the establishment of a clinical database and the creation of input masks like the observation book in accordance with the protocol and regulations currently in force.
The database structure and entry screens will be approved by the trial sponsor.

12.3 Data Archiving

All study notebooks and documents must be kept in a locked cabinet for 15 years after the end of the study.

This information must be kept by the sponsor and the investigator.

13 Financing and insurance, if these points are not the subject of a separate document (for example, contract or agreement).

In accordance with article L.1121-10 of chapter I of title II of book I of the first part of the CSP, the sponsor assumes compensation for the harmful consequences of the research for the person who takes part in it and that of his beneficiaries, unless it can prove that the damage is not attributable to its fault or that of any party involved, without the fact of a third party or the voluntary withdrawal of the person who had initially agreed to lend themselves being opposed. looking.

The sponsor, CHD Vendée, declares that it has taken out an insurance policy guaranteeing, according to the clauses provided for in the contract and within the limits of the sums fixed, the pecuniary consequences of its civil liability as it results from the application of article L 1121-10 of the Code of la Santé Publique. The subscription of such a policy by the sponsor does not have the effect of depriving it of its rights of recourse against the aforementioned persons in the event of their fault.

14 Publication rules.

A copy of the publication will be given to the CHD of la Rochesur Yon, responsible for the research who will necessarily be quoted. The authors will be the participants in the study, and their order will be established by the coordinating investigator.

The protocol has been declared in the American public database: clinicaltrial.gov.