Floor of Investigation
Clinic

Study randomized, checked For there assessment from the performance And from the safety Of a device doctor to basic Of acid hyaluronic linear In the treatment from the wounds. WOUND-H study

Date and version : 26 June 2023, version 2.
Typology of the study : Interventional, randomized, checked, monocentric.
Responsible scientific : Dr. Marco Daniel
P romotor : Nova Argentia srl
Typology Study : Profit
Costs : Not And expected any compensation For The experimenters And no cost additional to load of the NHS.
Responsible of the monitoring of the data : Doctor Brunella Orru
Centers participants : Home From Treatment Rehabilitation Villa Sofia, Acireale (Ct)

Summary

1 Generality

1.1 Identification of the sponsor

Nova Argentia srl- Street Carlo Brings 49 – 20064 – Gorgonzola (Me) | PI 02387941202 | REA: no 1737348

1.2 Information on experimenters

Experimenter principal: Dr. Marco Daniele, Manager Doctor, Home From Treatment Rehabilitation VillaSofia, Acireale (Ct). Contacts of emergency: +39 095 763 1997

1.3 Method Of financing of the investigation clinic

The study is financed by the sponsor. A contract/agreement will be stipulated between the sponsor and the experimental site where compensation and responsibilities are established. A draft of this convention was submitted to approval of the competent Ethics Committee.

1.4 Device Doctor

Nova.Emostop Re-epithelizing [Acid hyaluronic linear 0.2%]

The device Yes presents in formulation gel to basic Of acid hyaluronic linear. Yes deals with Of a device medical based substances, non-sterile. The formulation does not contain substances of animal origin, substances deriving from human blood or tissues, CRM substances or substances with pharmacological action ancillary. This medical device falls into class IIb, based on the classification criteria expressed in the EU Regulation on medical devices 2017/745, Annex VIII, paragraph 5.4, rule 4 That defines "Everyone the devices Not invasive in contact with there skin or there mucosa injured they fall… in the class IIb if they are intended to be used primarily for skin wounds that have vulnerated The dermis or there mucosa And That can heal Alone second intention,".

Intended use : The medical device promotes the healing of wounds thanks to its action Hyaluronic acid moisturizer. Hyaluronic acid deposited on the wound surface forms a film moisturizing That protects The tissue give it agents external And maintains The correct degree Of hydration promoting there healing from the wound.

Directions : treatment Of injuries acute superficial, burns superficial And small wounds.

Traceability: there traceability of the device And guaranteed from the a number identifier of the lot Ofproduction.

Materials That they enter in contact with The body human: Everyone the materials That make up The devicethey have a long history Of usage within clinical e a proven one profile of safety.
They are:
High molecular weight sodium hyaluronate (2500-3500
Kd)D-Panthenol
Triethanolamine
(TEA)Carbomer 940
Symdiol 68T

Medical or surgical procedures related to the use of the device and experience necessary for its use usage
The device must be applied to the wound which must then be covered with an appropriate bandage. Considered there simplicity from the procedure Of application That Not differs from numerous others devices having the same indications, the device can be applied by healthcare personnel (doctors or nurses) without there need Of a specific training.

2 Introduction And rational:

Wound healing is a complex and dynamic process, which is still far from being completely understood. Wounds can be classified based on different characteristics such as trigger factor, exposure to the external environment, the depth of the wound, the period of time recovery, the potential risk of infections [1] . Two main processes are involved in healing of wounds: regeneration and repair. Regeneration involves the activation of stem cells in able to reconstitute the integrity of the tissue which will be indistinguishable from the tissue before the injury. To the Conversely, repair involves the formation of fibrotic scar tissue in which the architecture and the functionality of the original tissue are partially lost. Wound healing can be classified into three different categories: by primary, secondary or tertiary intention. The healing of wound For intention primary happens when there is a minimal loss Of tissue, to example suture from the wounded or taped. This wound will heal with a thin, clean scar, low inflammation, edema and ache. Wound healing by secondary intention occurs when part of the tissue is lost And there is a defect Very more great. In This case, The process restorative And Very more complicated That involves a greater inflammation, edema And ache prolonged For a time more long respect at the

wound healing with primary intention. Wound healing by tertiary intention yes verify when a process For intention secondary he comes intentionally interrupted And there wound will be closed mechanically, for example After That Yes And format the fabric of granulation.
Many strategies And products I am States proposed to the end Of improve there healing from the wounds, reduce Thepain and morbidity for patients such as wound dressings, growth factors, substitutes forskin, there dressing of the collagen, insulin topical, the antioxidant, there room hyperbaric, etc. [1] The acid hyaluronic (HAS) And state discovery In the 1934 from Meyer And Palmer In the vitreous bovine eye. AND aglycosaminoglycan present in nature That, in virtue from the her viscosity, elasticity And other propertyrheological, acts as lubricant eye And as fluid lubricant And shock-absorbing injoints. He comes product come on fibroblasts inside of from the membrane mobile phone And Therefore released inspace extracellular. Inside of from the skin, carries out a role important in hydration of the spaceextracellular; constitutes a matrix For hold up the normal functions from the cells; has Also functionsIn the filling of the space, in the lubrication, in the healing from the wounds, in the modulation from thecells inflammatory And in scavenging of the radicals free [2,3] . There concentration Of HAS in the epidermisAnd Of 15 µg/g And In the dermis And Of 740 µg/g; there mass molecular Of HAS in the skin And Of 1 kDa. IT HAS nativeAnd a chain polysaccharide linear similar to the HA In the dermis. AND a gel viscoelastic translucent That canbe obtained in highly purified form from rooster combs or through bacterial fermentation.Not has specificity Of species And The risk Of a reaction Of hypersensitivity And Like this Bass That Not Andnecessary The test cutaneous. There her mass molecular varies Between 0.1 And 2.5 kDa. A gram Of HAS canbind until to 6 litres Of waterfall. That is it means That greater And there percentage Of HAS in a product, greaterwill be there her capacity Of hold back the water. Thank you to the his remarkable potential biomedical And Of regenerationof the fabrics, It has And widely employee In the treatment from the wounds under different formulations asgauze, creams And gel [4] , showing results clinical significance [5–11] .

3 Risks And benefits clinicians of the device

AND was prepared a careful one procedure Of check of the risks connected with use of the device. The level Of Everything is fine risk And state valued in basic at the her severity and at the chance That it Yes check.The level of risk of all risks residues And acceptable result.
The clinical benefits of the device are supported by substantial supporting scientific literature the use of hyaluronic acid-based devices to improve wound regeneration. For an analysis more detailed from the literature relevant see there Investigator Brochures.

4 Goals:

The primary objective of the study is to evaluate the safety and performance of a medical device Of Class IIB to basic Of acid hyaluronic linear used In the treatment from the wounds post-surgery. The outcomes of the study are the improvement of wound healing assessed through the Clinical Healing

score (score from 0 to 5), That includes there assessment Of: redness, edema,

suppuration, healthy granulation tissue and signs of re-epithelization; the percentage of patients with wounds completely healed at day 30 post-treatment; the pain perceived by the patient when changing from the dressing; there frequency of events adverse.

Team Of operators involved in study

The team Of operators involved in study And Like this composed:
Scientific director and coordinator of the study: Dr. Marco Daniele
Members effective of the team: Dr. Salvo Balm
All members of the team are surgeons specializing in Physiatry belonging to the Operating Unit Simple Rehabilitation Nursing Home Villa Sofia. The CVs of the team members are available in attached hereto clinical protocol.

5 Drawing Of the Study

This is an interventional, single-center study. The aim of the study is to evaluate the safety and performance of a class IIB medical device based on linear hyaluronic acid in treatment from the wounds surgical.

Patients who have undergone surgery for knee prosthesis implantation will be chosen hip and recruited based on the selection criteria described below. Patients will be randomized into two groups in which the control group will receive the normal standard therapies for the treatment of wound (typically cleaning and disinfection only) while the treated group will receive two applications daily use of the medical device. The following visits are scheduled for patients: screening (visit 0) to collect the patient's demographic and clinical data, compliance with the inclusion/exclusion criteria; Baseline (visit 1) evaluation of the wound through the Clinical Healing score and start of treatment; follow up 1 (visit 2 – 7 days of treatment) clinical evaluation of the wound, Clinical Healing score, pain assessment upon dressing change; follow up 2 (visit 3 – de-suturing of the wound (18-20 days Of treatment) assessment clinic, Clinical Healing scores, assessment ache to the exchange dressing; follow up 3 (visit 4 – 30 days of treatment) clinical evaluation, Clinical Healing scores, assessment ache to the exchange dressing, determination healing wound (self completely cured or not). A photographic documentation of the wound during the healing process will come collected at visits 1, 2, 3 and 4. For safety assessment all adverse events and events adverse serious they will come sign in And evaluated in relation to those to report from the literature scientific Fordevices similar doctors.

Scheme of the Clinical Healing Score [12]

Healing score	Wound characteristics
5 – excellent	All wound area is pink; no bleeding on palpation; no granulation tissue; no connective tissue at incision margin.
4 – very good	Less than one quarter of wound area is red, no bleeding on palpation, no granulation tissue; no connective tissue at incision margin.
3 – good	Less than half of the wound area is red; no bleeding on palpation; no granulation tissue; no connective tissue at incision margin.
2 – poor	More than half of the wound area is red; bleeding on palpation; granulation tissue evident; incision margin not epithelialised.
1 – very poor	Two or more of the following features: More than half of the wound area is red; bleeding on palpation; granulation tissue evident; no epithelium at incision margin; infection present with suppuration.

5.1 Scheme of the protocol clinical

Visit 0 Screening: collection information clinics on the patient, inclusion
Visit 1 Baselines: assessment clinic, Clinical Healing scores, photography from the wound, start Treatment.
Visit 2 Follow up 1 (7 days Of treatment): assessment clinic, Clinical Healing scores, assessmentache to the dressing change, assessment reactions adverse, photography from the wound.
Visit 3 Follow up 2 (at the desaturation): assessment clinic, Clinical Healing scores, assessment acheto the dressing change, assessment reactions adverse, photography from the wound.
Visit 4 (30 days Of treatment): assessment clinic, Clinical Healing scores, assessment ache to the exchange dressing, determination healing wound, photography from the wound And collection events adverse.

5.2 Population in study

The study concerns the population of adult patients who have undergone surgery knee, at the hip or to the femur And That present wounds surgical from deal with. The study it will come conducted in a hospital setting at the Simple Operational Unit of Orthopedic Rehabilitation - of the Casa di Villa Sofia rehabilitation care. The enrollment procedure involves screening of patients who are present the UOS Of Rehabilitation orthopaedic Of Villa Sofia with wounds post-surgical And The following enlistment Of those patients respondents to the criteria of the study. Not And expected inclusion Of subjects fragile in study. The patient can retreat give it study in any moment declaring it to the Responsible of the study, in such case he comes asked to the patient Of make the themselves procedures expected for visit 4. The patient is excluded from the study if: 1- deviations from the protocol are detected;2- events arise serious adverse events That prejudice the continuation of study.

5.3 Criteria Of selection of the patients:

- Patients adults with wounds postsurgical.
- Subjects in degree Of respect the procedures of the protocol;
- Signature of the Consent informed

5.4 Criteria Of exclusion:

- pregnancy or feeding time;
- procedures contraceptives inadequate in women fertile;
- treatment concomitant chronic with antiseptics locals, use Of drugs anti-inflammatories (steroids AndNot steroids), analgesics, antineoplastics or immunosuppressants
- use Not therapeutic Of substances psychoactive, abuse Of drugs and/or alcohol
- immunodeficiencies (included infection from HIV)
- Patients oncology;
- allergies Note, hypersensitivity or intolerance to a any from the substances administered in This study
- any condition medical or Not medical That can reduce significantly there possibility Ofobtain reliable data e reach the objectives of study
- Participation to Education clinicians with devices or drugs in the 3 months precedents at the visit Of screening.

5.5 Intervention

THE patients included in study they will be randomized through blocks Of randomization (1:1) generated by a computer and assigned to one of the two treatment groups. Patients assigned to the group of control will receive the treatment required by normal clinical practice, i.e. cleaning and disinfection of the wound the uninjected socket acts as a control; patients assigned to the treatment group they will receive, beyond at the cleaning And disinfection, two applications daily of the device doctor object of study. The medical device is released in the form of a pre-filled 30 g tube. in tube of aluminium with label descriptive of the product. A example Of packaging and labelling And available in Annex I. The Follow-up period lasts 30 days from the end of treatment, this corresponds to an overall duration (from recruitment to the end of the study) of approximately 40 days For Everything is fine patient.

5.6 Endpoints:

Performance

The endpoint primaries Of This study I am:

1. The improvement In the Clinical Healing score at the visit 3 (desaturation 18-20 days After Thetreatment)
2. There reduction from the dimension from the wound at the visit 4 (30 days Of treatment) measuredthrough the morphometric analysis of wound.

The endpoints secondary I am:

1. improvement In the Clinical Healing score at the visit 2 And at the visit 4.
2. There percentage Of patients with wound completely healed at the visit 4.
3. The ache perceived from the patient to the exchange from the dressing at visits 2, 3 And 4 (stairs NRS).

Safety

To evaluate the safety of the devices, all adverse reactions will be collected and recorded (if present). The rate of adverse reactions and the occurrence of adverse reactions not described in literature will be submitted to assessment descriptive.

5.7 Strategies For there reduction of the bias

To the end Of reduce the possible bias in the assessment from the healing from the wound from part of the experimentedori he comes introduced a further analyses For to determine The degree Of healing from the wound: morphometric analysis of the wound. A digital photograph of the lesion will be taken at each visit for a total Of 4 Images (baseline, visit 1-3). The photos they will be taken following the recommendations of the Work Of Checked et to the. “Lieutenant top tips: wound photo documentation” [13] For obtain Images standardized. The analysis morphometric from the wound consists in the assessment from the healing from the wound through there measurement from the wound performed with a software specific. Such measurement it is objective and not subject to the experimenter's interpretation. The size of the lesion will vary calculated at baseline and visits 1-3, healing will be expressed as a percentage of baseline.

6 Collection Data

6.1 Consent informed

After have received the instructions complete concerning there nature, The meaning, the impact And the risks Of this clinical investigation, the patient must give written consent to participate in the study. During education patients must be informed that they can withdraw their consent, without provide reasons, at any time without their further medical care being affected in any way. In addition to the comprehensive instructions given to patients by the investigator, patients receive Also a form information written For The patient in a language understandable, That explains there nature And the scope of the study And The his progress. THE patients they must accept there possibility That the data concerning at the study are transmitted to the competent authorities. Patients must be informed in detail of the They obligations in relation to insurance For Not to compromise there coverage insurance

6.2 Information clinics

The clinical/medical history of the patients will be obtained at the screening visit (Visit 0) with particulars Attention to as follows:

- Acquisition of information clinics on state general of the patient included pathologies previousor current, including The conditions Of interest, habits regard to smoking.
- Pharmacotherapy, use chronic Of any drug (prescribed And to the bench, included The supplementsfood);
- History Of allergies or reactions idiosyncratic to the drugs;

6.3 Examination Physicist

A complete physical examination will be conducted at visit 1 and will include measurements of height, weight. The weight will be measured on a standard calibrated scale. Subjects must be dressed in indoor clothing light without shoes. Weight will be documented in kilograms to the nearest tenth of a kilogram. For the measurements of the height, the subjects they must to be measure yourself without shoes. The height will be documented to the tenth Of centimeter more Neighbor. The exam physicist will be executed from a doctor authorized. Full details of the physical examination will be recorded in the source documents at the implementing siteof the study.

6.4 Registration of the data

The use of black ink is required for completed subject questionnaires. If they are necessary changes, subjects need to be asked to make changes by drawing a line on the unwanted response, and then recording the desired response. Once a subject returns the questionnaire, it will not be allowed any edit.

6.5 Collection And storage of the questionnaires

Upon completion of the questionnaires, the investigator will retrieve the questionnaires and check that the section of the header (Number object, Date Of visit, etc.) is was completed. The experimenter (or designated qualified member of their staff) will use the questionnaires completed by the individual to insert the data sign in in the section appropriate eCFR. There version original of the questionnaires filled out will remain with the documents originals of the subject. A survey compiled Not needs to to be returned to thesubject when they will be returned to the documents originals.

7 Management of the data

The information on subjects of the study they will be maintained confidential And managed in basic at laws in force and regulations. The data collection system for this study uses security features built-in for all data to be transmitted in both directions, preventing non-access authorized at information on participants. Access to the system will be checked from a sequence Of codes Of identification And password assigned to users, returns available Alone to the personal authorized who have completed the necessary training. Before starting the study, and at each meeting, the staff will review the protocol and CRFs. During the study, you will need to periodically check the completeness from the folders clinics of the patients, the accuracy registrations to the CRF, membership to the protocol to Good Clinical Practice and the advancement of patient enrollment. The experimenter must maintain original documents for each patient in the study including hospital medical records containing demographic and medical data, laboratory data, electrocardiograms and the results of any other test or assessment. All information recorded on CRFs must be traceable to original documents in the patient file. Staff must also keep the consent form informed signed in original (a copy signed he comes released to the patient)

8 Risks For the patients

Not I am States identified details risks tied to the treatment topical with acid hyaluronic linear in wounds post-surgical.

9 Management of the events adverse

9.1 Events adverse

The events adverse due to use Of acid hyaluronic In the treatment from the wounds I am generally traceable to phenomena Of intolerance to the product And solvable in few days without treatment. Everyone The events adverse insurgents during The treatment, right away After The treatment And In the period Of follow up will be recorded in the "Adverse Event Form" (Annex I of the CRF). Adverse events will come classified by severity, relationship with the device being studied, intended or not, need Of treatment.

9.2 Definition Of event adverse (AE) and effect adverse of the device (HADES)

A AE / HADES And any change adverse respect at the condition basal of the subject, it's worth it to to say any unfavorable and unintended sign including an abnormal laboratory result, symptom or illness That And considered clinically relevant For The doctor That Yes verify In the course from the testing, regardless of whether it is considered device-related or not doctor.
The AE /HADES include:
• Exacerbation Of a illness pre-existing.
• Increase from the frequency or of intensity Of a illness episodic pre-existing or Of a condition medical.
• Illness or condition medical detected or diagnosed After The treatment with The device doctor,Also self could be to be was present Before of the beginning of the investigation clinic.
• Illness persistent continues or symptoms present to the basal That they get worse After the beginning of the investigationclinic.
• Lack Of effectiveness In the treatment acute Of a illness dangerous For there life.
• Events considered give it experimenter as related to procedures of the investigation clinic.
• Abnormal assessments, such as ECG and physical examination findings, should be reported as events adverse / HADES self they represent a result clinically significant That Not era present to the basal or worsened over the course of the investigation clinic.
• The anomalies of the test Of laboratory they must to be reported as AE/ADE self they represent a find clinically significant, symptomatic or less, That Not era present to the basal or got worse In the course

of the investigation clinic has carried to the interruption or at the Suspension of the treatment with The devicedoctor.

The AE/ADE Not include:
• The interventions planned or The occur Of endpoint specified In the CIP Not I am considered AE/ADE,self not otherwise defined.
• Medical or surgical procedure, for example surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the storytelling SAE/SADE.
• Illness pre-existing or condition medical That Not it gets worse.
• Situations in which Not Yes And verified a change adverse, to example hospitalizations For surgery aestheticselective or for reasons social and / you hate convenience.
• Improper use of medical devices or concomitant medications without signs or symptoms. However, the use improper needs to to be mentioned In the register Of inventory of the devices doctors/card Of treatment.

Events adverse serious (SAE)/Effects adverse serious of the devices (SADE)

A event adverse serious (SAE)/effect adverse serious of the device (SADE) And defined as anyAE/ADE That satisfy at least one of the following criteria:
• bring to death,
• brings to a serious deterioration from the Health of the subject That
1) has caused a illness or a wound dangerous For there life,
2) has behaved a compromise permanent Of a structure corporeal or Of a function bodily,
3) has behaved The recovery hospital or The extension of the recovery in course,
4) has behaved a intervention doctor or surgical For to prevent a compromise permanentfrom the structure corporeal you hate a function corporeal.
• leads suffering fetal, death fetal or anomaly congenital or defect congenital.
• And a event doctor important That could be Not provoke immediately there death, to be dangerous For there life or request The recovery in hospital, but can to be considered as SAE / SADE when, based on appropriate medical judgment, it may compromise the subject and may require a intervention doctor or surgical For to prevent one of the outcomes listed in definitions Of which above.
• show the onset Of a cancer malignant.

The danger Of life Yes reports to a event in which The subject era to risk Of death to the moment of the event.Not Yes reports to a event That hypothetically it would have could to cause there death self is state more serious

All adverse events that occurred during treatment, immediately after treatment and in the follow-up period up will be recorded in the “Adverse Event Form” (Annex I of the CRF). Adverse events will come classified by severity, relationship with the device being studied, intended or not, need Of treatment.

9.3 Hospitalization – Extension of the recovery existing

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room.
A overnight stay additional defines a extension of the recovery existing.
How much follows Not And considered a SAE/SADE And needs to to be reported Alone as AE/ADE:
• Treatment in case Of emergency or For a event That Not satisfies there definition Of severity Of whichabove And does not entail hospital admission.

THE following reasons For the hospitalizations Not I am considered events adverse And Therefore Not SAE:
• Hospitalizations For surgery aesthetics elective, reasons social and/or Of convenience.
• Monitoring standard Of a illness pre-existing or condition medical That Not And worsened, to example, hospitalization For angiography coronary in a subject with angina pectoris stable.
• Treatment elective Of a illness pre-existing or condition medical That Not And worsened, to example, hospitalization For chemotherapy For cancer, replacement elective of the hip For arthritis.

9.4 SAE/SADE relative at procedures mandatory of the study

Such SAE/SADE are defined as SAE/SADE that appear to have a reasonable possibility of relation causal (valid to to say, a relation Not can to be excluded) with the procedures mandatory of the study (excluded there administration Of devices doctors) as the interruption of the previous treatment of the subject or the complication of a mandatory invasive procedure (for example, blood sampling, cardiac catheterization) or car accident on the way to the hospital for a visit Of study, etc.

9.5 Pregnancy

Any pregnancy that occurs during study participation must be reported to the sponsor/principal investigator. To ensure the safety of the subject, every pregnancy must be reported immediately at the sponsor /experimenter principal. A pregnancy needs to to be followed to determine the outcome (including premature termination) and the status of the mother and baby. The complications from the pregnancy And the interruptions elective For reasons doctors they must to be reported as AE / ADE or SAE. Spontaneous abortions they must be reported as SAE.
Any SAE That Yes check in Association with a pregnancy, scope to your attention of the experimenter after the subject has completed the study and considered by the experimenter as possibly related to the product in study, needs to to be promptly reported at the sponsor/ experimenter principal.

9.6 Severity of the events adverse/effects adverse of the device

The severity of AEs/ADEs is classified on a three-point scale: mild, moderate, severe and reported on a specific section of the CRF.
If the severity of an AE/ADE worsens during administration of a medical device, only the worst intensity must be reported on the AE page. If the AE decreases in intensity, it is not necessary no change in severity.

Mild
The event can to be obvious to the subject; Not influence the activity daily; the AE/ADE Yes solvesspontaneously or can request a therapeutic intervention minimum;

Moderate
The event can put to unease The subject; the progress from the activity daily can to beinfluenced; can be necessary a intervention; the AE/ADE does not produce sequelae.

Serious
The event can cause considerable discomfort; usually interferes with daily activities; the subject you may not be able to continue studying; AE/ADE produces sequelae, which require a intervention prolonged therapeutic.

A AE/ADE light, moderate or serious can or Not can to be serious. These terms I am used For to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction). However, a serious event may have relatively minor medical significance (such as a severe headache) or otherwise And necessarily serious. To example, there nausea That tough different hours can to be classified as serious, but it may not be clinically important. Fever of 39°C which is not considered serious can become serious if it prolongs hospital discharge by one day. The clinical importance rather than there severity it works from guide to define obligations regulatory Of report.

9.7 Relation with The device doctor

For all, the investigator will evaluate the causal relationship between the medical device and the AE/ADE using there her experience clinic And The his judgment second The following algorithm That Better Yes suitableat circumstances of the EA / ADE:

Not related
• Can follow or less a sequence storm reasonable from the administration of the product in study
• AND biologically Not plausible And Not follows a model Of answer known to the device doctor (self Themodel Of answer And previously known)
• Can to be explained give her characteristics Note of the state clinical of the subject or from other mode Oftherapy administered to the subject.

Possibly related
• Continued a reasonable sequence storm from the administration of the device doctor.
• Can follow a model Of answer known to the device doctor (self The model Of answer And previously known).
• Could be Not to be reasonable Not to be reasonably explained give her characteristics Note of the state clinical of the subject or from other mode Of therapy administered to the subject, self applicable.

Surely related
• Continued a reasonable sequence storm from the administration of the device doctor.
• Continued a model Of answer known to the device doctor (self The model Of answer And known inprecedence).
• Not And present no one else cause reasonable.

9.8 Procedures Of report

A section special And dedicated to AE/ADE In the CRF. They have to Therefore to be inserted the following data:
• Type of AE/ADE
• Start (date And Now)
• end (date And Now)
• Severity (mild, moderate, serious)
• Serious (no Yes)
• Unexpected (no / Yes)
• Outcome (Resolved, in course, in course – improved, in course – worsening)
• Relationship with the medical device (unrelated, possibly related, definitely related) The events adverse related to the device they must to be documented In the CRF in compliance with the criteria above mentioned e reported to the Sponsor.

9.9 Procedures Of report For SAE/SADE

In case Of event adverse serious (serious adverse event), the experimenter needs to use all the measures support for the best treatment of the patient. A written report must also be prepared And mass immediately to disposition of the sponsor. They should to be available at least the followingdetails:
• Initials And code of the patient
• Patient: date Of birth, sex, origin ethics
• The device doctor used
• The event adverse valued as serious
• Brief description of the event And of the outcome

• Self related or Not related to the device

There relation written And split in two set off:
• Relationship initial: in shape on that is That And happened (AE / HADES valued as serious), self exists arelation with the medical device ... And Which action And was set.
• Follow-up Report: in shape on the outcome

The Sponsor is responsible for the classification of adverse events and the ongoing evaluation of the safety of the investigation clinic And needs to:
• to review there assessment of the experimenters Of everyone The events adverse And to determine And to document For recorded their severity and relationship with the investigation device; in case of disagreement between the sponsor and the experimenter principal
• to examine all the shortcomings of the devices And to determine And to document For signed up self they would have could bring to a serious effect adverse of the device; in case Of disagreement Between the sponsor And the experimenterprincipal
• report or guarantee there report, to the THERE IS And to the AR (Ministry from the Health) Of everyone The events adverseserious.

10 Withdraw of the patients give it study

10.1 Criteria For The withdraw of the subjects give it study

THE subjects can to interrupt prematurely the investigation clinic in any moment. The interruption premature study is to be understood when the subject has not been subjected to evaluation safety it's at all the clinical evaluations during the investigation clinic.

THE subjects they must to be retreat in following circumstances:
• on own request
• self the investigator believes That Not would be In the improve interest of the subject to continue
• self The subject viola the conditions established In the module Of consent / form information or ignore theinstructions receipts.
• self arise events adverse serious such from to compromise there assessment clinic.

In everyone the cases, The reason For which the subjects they come retreat needs to to be registered in detail in the CRF And in the subject's medical records. If the clinical investigation is terminated prematurely, all of the material of the investigation clinic (CRF complete, partially completed And empty) will be preserved.

10.2 Follow up of the patients retreat from the investigation clinic

In case Of break premature After The treatment with The device doctor, the investigations expected For there assessment from the safety they will be performed 7 days After the interruption. THE subjects they will be informed that participation in these investigations is voluntary. Furthermore, they can ask that from the moment of withdraw no more data is recorded.

10.3 Politics Of replacement of the subjects retreat

THE subjects That Yes they withdraw give it study Before from the execution from the procedure surgical or immediately after, i.e. before visit 2 (7 days after treatment) they may be replaced by new subjects who meet the inclusion/exclusion criteria. Those who withdraw give it study after visit 2 will be included in the analysis.

10.4 Conclusion anticipated of the investigation clinic

The sponsor has The right Of close this investigation clinic in any moment. The THERE IS And The AI they mustto be informed.
The investigation clinic can to be interrupted prematurely in the following cases:
• Self Yes verify events adverse/events adverse of the device Like this serious That The relationship risk-benefitNot And acceptable
• Self The number Of dropouts And Like this high That Not There Yes can realistically wait a correctcompletion of the investigation clinic.

If the sponsor or investigator decides to terminate the clinical investigation before it is completed, yes will inform each other in writing indicating the reasons for the early termination. In finishing the study, the sponsor and the investigator will ensure that adequate consideration is given to the protection of the subject's interests. The sponsor will inform the Competent Authorities and the CE. There documentation will be archived in Clinical Trial Masters File in Investigators Files.

11 Monitoring plan

The Monitor will contact and visit the investigator regularly and will be authorized, upon request, to have access to all source documents needed to verify entries in CRFs and other documents relating to the CIP, provided that the confidentiality of patient data is maintained in accordance with the local regulations. It will be the Monitor's responsibility to inspect the CRFs at regular intervals during the study, to verify adherence to the CIP and the completeness, consistency and accuracy of the data entered on of them. Monitoring standards require full verification of the presence of consent informed, adhesion to the criteria Of inclusion/exclusion, there documentation from the SAE/SADE And there

registration of the main efficacy, safety and tolerability endpoints. To be compliant with ISO 14155 standard requires at least 3 monitoring visits. A study start visit, a visit routine and a final visit after the last patient has finished the study. For the present study 8 monitoring visits are planned: an initial visit (centre opening), 6 routine visits and one final visit. Routine visits will be conducted once a month. 100% of the source data will be monitored by the monitor (which means 100% of Source Data Verification). Monitoring will come conducted according to SOPs and will provide an ISO 14155 compliant monitoring report afterwards each visit for the sponsor and investigator. Depending on the quality of the data, they may be necessary more visits Of monitoring a discretion of the sponsor.

12 Changes of the floor Of investigation clinic

The proposed changes to the clinical investigation plan be submitted to the Competent Authority (CA) and to Ethics Committee (EC) of reference. Substantial changes can only be implemented after Obtained the approval of AC/CE. The changes intended to eliminate an apparent immediate danger for subjects can be implemented before receiving AC/EC approval. However, in this case, approval must be obtained as soon as possible after implementation. It is forbidden to apply exceptions to this clinical investigation plan without prior authorization from the AC/EC. The deviations from the clinical investigation plan occurring for any reason must be reported immediately to the Responsible Scientific who will be able to to determine self to exclude The patient from the study.

13 Responsibility relative to the device

The device will be sent to the Villa Sofia Rehabilitation Care Home Pharmacy which will take care of check the good state of conservation of the device and store it in the conditions indicated by manufacturer. THE devices they will come delivered to the Responsible Scientific or his delegate That will provide to store them in the conditions indicated by the manufacturer. The Scientific Manager is responsible for storage and maintenance of devices. Access to the devices is permitted only to members of the team Of research And The withdraw Of Everything is fine device needs to to be annotated on the Device Log File reporting The first name of the member of the team, there date And The lot. THE devices expired or unused they will come retreat give it Sponsors.

14 Calculation from the dimension sample collection

The sample size was calculated based on estimates of possible improvement in the Clinical Healing score at the desaturation (18-20 days) respect at the baseline using the information obtained from the literature [5,6,8,10,11,14] . Sample size estimates were calculate in terms Of a variable Of answer continues hypothesizing a distribution Not normal, The change of the Clinical Healing score at the desaturation with a effect size (dz) Of 0.5 And considering 80% power. With these assumptions, the minimum required sample size is 53 subjects per treatment group. Therefore, considering a dropout rate of 5%, it is necessary the recruitment of 112 subjects.

15 Analyses statistics

the primary endpoint is the improvement in the Clinical Healing score at visit 3 compared to baseline (visit 1). Assuming that the average change in Clinical Healing score for each treatment is Like this represented: Prog = result of the Clinical Healing score at the visit 2; BAS = result of the Clinical Healing score at baseline, the null hypothesis is represented by Prog = BAS and the alternative one by Prog ≠ BAS. Statistical tests (Mann-Whitney test) will be conducted at a significance level of 0.05 per show improvement in Clinical Healing score at visit 3. Secondary endpoints will be analyzed as follows: Clinical Healing score at visits 2 and 4 - Mann-Whitney tests conducted at significance level equal to 0.05; The pain perceived by the patient when changing the dressing visits 2, 3 and 4 - Mann-Whitney tests conducted at the significance level of 0.05; The percentage of patients with a completely healed wound at visit 4 - two proportion z tests conducted at the level of significance even to 0.05.

16 Timings

The study involves the recruitment of 112 patients, it is estimated that this number of patients will be recruited a time of approximately 8 months. Considering that the time required to complete the follow-up for each patient is 30 days the overall duration of the study is estimated from the first date visit of the first patient will be Of 10 months. There relation the final will be provided After 3 months from the conclusionof the study.

17 Publication of the results

Within one year of the end of the trial the results will be published by the sponsor in agreement with The investigators second the mode established in the convention Between the sponsor And The center experimental. The study data will be published in a scientific journal appropriate to the type of study And introduce yourself to congresses scientific. THE data of the investigation clinic they will be deposited at a bank data accessible to the public (e.g. clinicaltrial.gov). There confidentiality of the data of the participants will be Alwaysguaranteed.

18 Ethics And requirements legal

The investigator will present this CIP and any related documents provided to the subject (such as information used For obtain The consent informed) to a Committee Ethical to to the Authority Qualified. Approval from the committee and the AC must be obtained before commencing the investigation clinic And needs to to be documented.

18.1 Declaration Of Helsinki

The investigator will ensure that this study is conducted in full compliance with the principles of "Declaration Of Helsinki" (as modified at the 56a Assembly General of the AMM, Tokyo, Japan, 2008).

18.2 Good practice clinic (EN ISO 14155)

ISO 14155 addresses good clinical practice for design, conduct, recording and reporting of clinical investigations performed in human subjects to evaluate safety and performance medical devices to ends regulatory .

Specific the requirements general understood to:
• to protect the rights, there safety And The well being of the subjects humans,
• guarantee there management scientific of the investigation clinic And there credibility of the results of the investigation,
• assist sponsors, monitors, investigators, ethics committees, regulators and other bodiesinvolved in the assessment from the compliance of the devices doctors.

The experimenter principal of the investigation clinic guarantees That you participate Alone personal adequately format. All the investigations clinics they must follow the standard EN ISO 14155.
Therefore, this study follows the EN ISO guidelines incorporated into the Italian device law doctors.

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