NCT02921750 Clinical investigation plan

Title
A randomised multi-centre non-inferiority investigation to evaluate the efficacy and safety of Exufiber versus Aquacel Extra in moderately or strongly exuding venous and mixed ulcers of predominantly venous origin

Study code
CHEXU03

CLINICAL INVESTIGATION PLAN (CIP)

INVESTIGATIONAL DEVICE:

Exufiber

INVESTIGATION TITLE:

A randomised multi-centre non-inferiority investigation to evaluate the efficacy and safety of Exufiber versus Aquacel Extra in moderately or strongly exuding venous and mixed ulcers of predominantly venous origin

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CLINICAL INVESTIGATION PLAN (CIP) SYNOPSIS

INVESTIGATION TITLE:

A randomised multi-centre non-inferiority investigation to evaluate the efficacy and safety of Exufiber versus Aquacel Extra in moderately or strongly exuding venous and mixed ulcers of predominantly venous origin

Objectives

The primary objective of this non-inferiority investigation is to compare Exufiber® versus Aquacel® Extra™ in terms of efficacy and safety, measured in moderately or strongly exuding venous and mixed ulcers of predominantly venous origin during a period of 6 weeks investigation period.

The primary endpoint will be;

Wound area reduction (%) from baseline until end of investigation (up to 6 weeks). Wound area reduction will be centrally measured by one blinded independent review using the validated system PictZar®. A second supportive blind review will be done by an independent French expert

Secondary endpoints are to evaluate;

- Relative reduction (%) of fibrin/sloughy tissue
- Wound area reduction (absolute change in cm^2) from baseline until end of investigation (up to 6 weeks)
- Linear advance of the wound margin according to Gilman's formula (Cardinal et al, 2008) based on the digital photos and calculated by PictZar
- Percentage of patients with a debrided wound at end of investigation (at least 70% of the wound surface area covered with granulation tissue (confirmed using PictZar). Number of additional debridements used during the investigation. Pain during the debridement and ease of debridement
- Changes from baseline in the condition of the peri-wound skin measured by the following variables; maceration, redness/irritation, blistering, skin stripping, trauma to wound edges
- The level of pain in connection to removal of dressing
- Changes in wound status including exudates management
- Clinician's and subject's opinion related to the dressing (subject to fill in the

questionnaire him/herself in applicable local language)

- Cost effectiveness and health economics will be measured using EQ-5D-3L and wound management related material use
- Tolerance such as adverse events and adverse device effects including those reported to be serious

Ancillary objective

- In order to support that wound area reduction at week 6 is a clinically relevant parameter to predict long-term favorable wound healing, a sub-group of at least 50 subjects will be assessed at 24 weeks post-inclusion. Favorable trajectory will be defined by an area regression, compared to baseline, of 80% or more at week 24. Additionally, wound closure (100% re-epithelialization confirmed by photo) rate will also be evaluated. All these parameters will be centrally measured on photos according to previously described procedure.

Overall Design

The investigation is designed as an open, randomized, non-inferiority, multi-centre investigation. 212 subjects will be randomised (subjects lost to follow-up will be replaced). Subjects to be included will suffer from an exuding venous or mixed ulcer of predominantly venous origin. Both in and out-subjects will be eligible. Each subject will be treated according to the local clinical routine and evaluated during a total treatment period of maximum 6 weeks or until the wound is healed. At least 50 subjects out of the total 212 subjects will be followed for maximum 24 weeks to investigate wound closure. Subjects will either be randomized to Exufiber® or Aquacel® Extra using centralized randomization. The secondary dressing will be according to the normal praxis at each clinic and preferably **one** secondary dressing should be chosen by investigational site to be used for all subjects at the same site although no active dressings such as anti-microbial dressings are allowed. Simple gauzes or polyurethane films are recommended (see schedule of assessment for details). Patients should be treated with a recognized efficient compression system (e.g. multicomponents such as 2-, 3- or 4-LB (two-, three- or four-layer bandage) or SSB (short stretch bandage)). The nature of applied bandages will be captured in the eCRF.

Visits are planned for baseline followed by 1, 2, 3, 4 and 6 weeks post treatment. The sub-group of at least 50 subjects will also be followed at week 8, 12, 16, 20, and 24 post treatment or until wound is healed if earlier. Dressing changes in-between visits are allowed and should be carried out according to normal praxis/intended use eg when the dressing is saturated. These can be performed at the subject's home according to normal routine. At each dressing change, the wound is to be inspected and cleaned exclusively with normal saline or warm water (or Actimaris Rinsing Solution). When the wound is dry, Exufiber® is no longer applicable. The treatment should then continue with the secondary dressing or other suitable dressing according to local guidelines and compression followed until end of investigation (6 weeks or earlier if the wound heals). Aquacel® Extra is also intended for dry wounds but should be used in the same way as Exufiber® for consistency.

A record (dressing log) for Exufiber® or Aquacel® Extra will be filled in to capture all dressing changes at the scheduled visits including secondary dressing and compression applied. The number of dressing changes in-between scheduled visits will be asked for at

each visit as well as number of dispensed and returned dressings. A nurse book can be used to collect the data related to the dressing change (number of dressings, reason for dressing change) between scheduled visits.

Subjects will be screened on a daily basis and if they seem evaluable they will be given a patient information.

At the baseline visit the following will be registered for all enrolled subjects;

- Subjects characteristics including vital signs, informed and photograph consent, medical and surgical history, ulcer duration, size, location and ABPI (ankle brachial pressure index using hospital routine and most recent value obtained), current dressing and compression type and duration (if applicable)
- Cleansing/debridement according to details in schedule of assessment 4.2.1
- Level of pain before dressing assessment measured by validated Visual Analogue Scale (VAS) 0-100mm
- Wound status using colorimetric scale = Percentage of fibrin/sloughy tissue, granulation tissue, epithelialization etc. Total should be 100%. Evaluated before and after cleansing/debridement.
- Photos will be taken according to guidelines in Appendix D and details in Appendix C. Photos from before and after debridement will be analysed using PictZar by a blinded reviewer
- Signs of local infection such as pain between dressing changes, perilesional skin erythema, oedema, foul odour and high levels of exudates
- Dressing application including secondary dressing and compression according to details in schedule of assessment and in Appendix C
- Clinician's evaluation according to details in Appendix C

At each follow-up visit until week 6 the following should be registered;

- Cleansing/debridement according to details in schedule of assessment 4.2.1
- Wound status using colorimetric scale = Percentage of fibrin/sloughy tissue, granulation tissue, epithelialization etc. Total should be 100%. Evaluated before and after cleansing/debridement.
- Dressing application including secondary dressing and compression according to details in schedule of assessment and in appendix C
- Photos will be taken according to guidelines in Appendix D and details in Appendix C. At week 4 and 6 or final visit the photos before and after debridement will be analysed using PictZar by a blinded reviewer. Other photos taken after debridement can be analysed using PictZar if deemed necessary for primary endpoint
- Level of pain during dressing removal measured by validated Visual Analogue Scale (VAS) 0-100mm and analgetics used within 3 hours

- Signs of local infection such as pain between dressing changes, perilesional skin erythema, oedema, foul odour and high levels of exudates
- Technical performance according to details in Appendix C
- Subject evaluation according to details in Appendix C
- Clinician's evaluation according to details in Appendix C
- All relevant concomitant medications during the investigation period will also be collected including antibiotics and analgesics. Adverse events will be collected according to details in section 8.
- Debridement is allowed during the treatment period but should be specified as well as ease of debridement and pain during the debridement (VAS).

Variables to be collected at week 8-24 for the sub-group of at least 50 subjects are specified in schedule of assessment 4.2.1 and in appendix C.

Health related quality of life (HRQoL);

Patient reported HRQoL will be measured by using the standardized generic EQ-5D-3L instrument (EuroQol, 1990).

The EQ-5D-3L consists of two parts: a descriptive system and a visual analogue scale (VAS). The descriptive system records HRQoL in five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which dimensions has three levels of possible responses indicating (1) no problems, (2) some problems or (3) extreme problems. The responses of the patient results in a 5-digit code (e.g. 21223) defining his/her health state. These health states can be converted to a single index value representing how a particular health state is valued by the general population.

Using the second part of the instrument, the VAS, patients rate their health state on a 0-100 vertical scale.

Subjects will be provided with the paper version of the EQ-5D-3L three times during the investigation: (1) at baseline (2) at four weeks and (3) at six weeks (final visit).
Subjects followed for up to 24 weeks will however be provided with the EQ-5D-3L a fourth time i.e. at week 24 (final visit).

All outputs of the EQ-5D-3L instrument, the descriptive health states, the single index value and the VAS scores will be analysed.

Inclusion Criteria

1. Provision of informed consent i.e. subject must be able to understand and sign the Patient Information and Consent Form
2. Both gender ≥18 years old
3. Ulcer moderately or strongly exudative justifying the use of an absorbent dressing
6. 0.7 ≤ ABPI < 1.3

7. Ulcer duration 6 weeks to 60 months
8. Ulcer size 3 cm^2 -100 cm^2
9. Target ulcer at least 3 cm away from any other lesion

The subject can have multiple wounds but only the largest eligible wound per subject is to be included in the investigation. The remaining ulcers should be treated according to normal praxis.

Exclusion Criteria

1. Known allergy/hypersensitivity to the dressings
2. Pregnant or breastfeeding
3. Circumferential wounds (the entire wound should be able to be captured on a single image/photo)
4. Subjects who will have problems following the protocol
5. Subjects included in other ongoing clinical investigation evaluating wound dressings at present or during the past 30 days
6. Patient with a systemic infection not controlled by suitable antibiotic treatment
7. Clinically infected wound according to the judgement of the investigator (heat, pain, swelling, redness or purulent secretion)
8. Wound covered with black necrosis
9. Dry wounds
10. Malignant wound degeneration
11. Current treatment with radiotherapy, chemotherapy, immunosuppressant drugs or high doses of oral corticosteroids if any
12. Subject with deep vein thrombosis within 3 months prior to inclusion

Investigational Device - Exufiber®

Gelling Fibre Dressing

Product Description

Exufiber® is a sterile nonwoven dressing made from highly absorbent polyvinyl alcohol fibres. In contact with wound exudate, Exufiber® transforms into a gel that facilitates moist wound healing and ease of removal during dressing change. Exufiber® absorbs and retains wound exudate. Exufiber® is available both as sheet and ribbon dressings.

Intended use

Exufiber® wound dressing is intended to be used on a wide range of exuding wounds:

- Leg and foot ulcers
- Pressure ulcers
- Partial thickness burns
- Surgical wounds
- Donor sites

- Malignant wounds

Precautions

- All wounds should be inspected frequently. In case of signs of clinical infection, consult a health care professional for adequate infection treatment.
- Exufiber® is not intended for dry wounds, full thickness burns.
- If the dressing dries out and is difficult to remove, it should be moistened according to local policies (e.g. with sterile saline or sterile water) and allowed to soak until it lifts easily. It may take several minutes for Exufiber® to transform into a gel. Remove the dressing by gently cleansing/flushing.

Other Information

- Exufiber® is for single-use only and should not be re-used. Re-use may lead to product deterioration or cross contamination may occur.
- Sterility is guaranteed unless pouch is opened or damaged prior to use. Do not re-sterilise.
- Exufiber® can be left in place for up to 7 days depending on wound condition or as indicated by clinical practice.

See also Appendix E, Instructions For Use.

Comparator - Aquacel® Extra™

Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre is a soft, sterile, non- woven pad dressing composed of sodium carboxymethylcellulose and regenerated cellulose fibre for strengthening. This conformable and highly absorbent dressing absorbs wound fluid and transforms into a soft gel, which maintains a moist environment to support the body's healing process and aid in the removal of nonviable tissue from the wound (autolytic debridement), without damaging newly formed tissue.

Intended use

Under medical supervision Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre may be used for the management of:

- leg ulcers, pressure ulcers (Stage II-IV) and diabetic ulcers.
- surgical wounds (e.g., post-operative, wounds left to heal by secondary intent and donor sites).
- partial thickness burns
- traumatic wounds (e.g. abrasions and lacerations).
- exudates absorption in oncology wounds (eg., fungating cutaneous tumours, cutaneous metastases and Kaposi's sarcomas).

Contraindications

Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre should not be used on individuals who are sensitive to or who have had an allergic reaction to the dressing or its components.

Precautions and observations

- Caution: Sterility is guaranteed unless pouch is damaged or opened prior to use.
- This device is for single-use only and should not be re-used. Re-use may lead to increased risk for infection or cross contamination. Physical properties of the device may no longer be optimal for intended use.
- Appropriate supportive measures should be taken where indicated (e.g. use of graduated compression in the management of venous leg ulcers or pressure relief measures in the management of pressure ulcers/sores).
- The control of blood glucose, as well as appropriate supportive measures, should be provided with diabetic foot ulcers.
- Infection is not a contraindication to the use of Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre. Should infection develop during the use of the dressing antibiotic therapy should be initiated, as clinically indicated, by a health care professional.
- Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre can facilitate the control of minor bleeding.
- If removing the dressing is difficult, the dressing should be fully saturated with sterile saline or water and removed slowly.
- Because Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre provides a moist environment that supports the growth of new blood vessels, occasionally the delicate newly formed blood vessels may produce a blood stained wound fluid.
- Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre is not intended for use as a surgical sponge.
- Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre is not intended for use within internal body cavities or within closed wounds.

Other Information

- Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre can be left in place for up to 7 days, where clinically indicated.
- Discard any unused portion of the dressing.
- If the immediate product packaging is damaged, do not use.

See also Appendix F, Instructions For Use.

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Appendix D *Guide for Digital Photography*

Appendix E *Instructions For Use, Exufiber®*

Appendix F *Instructions For Use, Aquacel® Extra™*

LIST OF ABBREVIATIONS

ADE	**Adverse Device Effect**
AE	**Adverse Event**
CA	**Competent Authority**
CRF	**Case Report Form**
DD	**Device Deficiency**
EC	**Ethics Committee**
HAS	**French Health Authority**
IRB	**Institutional Review Board**
MHC	**Mölnlycke Health Care**
SAE	**Serious Adverse Event**
SADE	**Serious Adverse Device Effect**
VAS	**Visual Analogue Scale**

1. INTRODUCTION

It is often misunderstood that wound exudate is 'bad' (WUWHS, 2007). In fact, wound exudate has a number of beneficial properties for the healing wound. These include the maintenance of a moist wound bed, preventing the wound from drying out, aiding the migration of skin cells, providing essential nutrients to the wound for cell metabolism, as well as encouraging autolysis (WUWHS, 2007). However, when the volume of exudate becomes excessive and when the composition of the exudate changes (e.g. when the exudate becomes thick), steps must be taken to manage the exudate to prevent wound deterioration, peri-wound skin damage and wound infection. Poor management of exudate in chronic wounds can lead to a number of problems, including wound and peri-wound breakdown of maceration due to leakage and a delay in healing. Excess levels of exudate within the wound bed can also lead to elevated proteolytic activity due to an imbalance in the levels of certain matrix metalloproteinases, resulting in tissue destruction and a delay in healing (WUWHS, 2007; EWMA, 2004; Romanelli, Vowden & Weir, 2010).

Changes in the type and volume of exudate can be indicators of a number of underlying factors, such as infection, and should alert the clinician that the wound is not following the normal phases of healing. Wounds which produce this type of exudate or slough not only impact on the clinical outcome of the wound (i.e. prevention or delay in wound healing) and health care resources, but can also have a huge impact on physical and psychosocial morbidity and patient quality of life (WUWHS; 2007). Other patient-related problems concerning the management of wound exudate include leakage and malodour (Vowden, Bond & Stryja, 2015). Production of high levels of thick exudate in venous leg ulcer patients may indicate inflammation and infection, longer periods spent with the legs in a dependent position reduced compliance to compression therapy or the development or deterioration of congestive cardiac failure and peripheral oedema (WUWHS, 2007). *Robson* et al (2006) presented evidence to verify wound management guidelines, including the selection of dressings that will manage wound exudate and protect the peri-wound skin around venous leg ulcers. This is based on the principle that peri-wound maceration and continuous contact with wound exudate can enlarge the wound and impede healing (ROBSON et al, 2006). Whilst the primary dressing is not usually considered the most important factor in the healing of leg ulcers, it does have a significant bearing on the cost of wound management, particularly in those ulcers which are heavily exuding (Harding, Price, Robinson et al, 2001). Problems associated with poor exudate management in patients with venous leg ulcers can result in a multitude of physical, psychological and psychosocial issues (Maddox, 2012).

Whilst the initial cost of the dressing is one consideration in terms of the impact on health care costs, it is certainly not the only factor. It is difficult to evaluate the true costs of wound management since the process involves more than just material costs. They so-called 'hidden costs' of wound care must be appreciated (Vowden, Bond & Stryja, 2015; Tickle, 2012). These include increased demands on the clinicians' time and resources as a result of poor management (Tickle, 2012; Department of Health, 2009). This is a particular concern when treating wounds with high levels of thick or sloughy exudate which, if not managed effectively, can result in iatrogenic complications including peri-wound skin maceration and pain during the process of dressing changes.

Dressing selection is a fundamental aspect of effective wound management, particularly in those wounds with high levels of viscous exudate or slough. A dressing that is able to adapt to a changing wound environment is important, particularly in chronic wounds which do not follow the usual steps of healing. The chosen dressing, therefore, needs to not only generate and maintain an optimal wound environment conducive to healing but also to respond and adapt to the changing demands of the wound (Walker & Parson, 2010). Matching the characteristics of the dressing to the exudate profile of the wound is important in the maintenance of a moist wound environment (Bishop et al, 2003). The absorption capacity, ability to retain exudate, loss of fluid by evaporation and how the dressing can modify the rate of exudate production are important considerations when choosing the optimal dressing. Again, it is about creating an optimal moisture balance (EWMA, 2004; Romanelli, Vowden & Weir, 2010; Wounds UK Best Practice Statement, 2013). Insufficient absorption will result in leakage and maceration (thus requiring more frequent dressing changes), whilst excessive absorption will effect patient comfort and will dry the wound out (Walker & Parsons, 2010).

Debridement is a vital stage of the healing process and can be defined as the removal of all material that forms a barrier to wound healing, including necrotic and devitalised tissue, slough or any other type of bioburden from a wound (Meaume et al, 2014). Autolytic debridement is one type of non-surgical debridement that allows the removal of unwanted slough from the wound via the release of the body's endogenous proteolytic enzymes (Meaume et al, 2014). This method is often chosen as a first line treatment, providing a moist environment whilst sparing healthy tissue (Meaume et al, 2014). Hydrofiber dressings have been shown to aid this type of debridement (Meaume et al, 2014).

Hydrofiber wound dressings are recommended for their ability to maintain a moist wound healing environment by absorbing wound fluid to form a cohesive gel. The gelling action of this type of dressing also helps to debride the wound of sloughy tissue by autolysis (Tickle, 2012; Barnea *et al*, 2004, Kogan *et al*, 2004) which, if unmanaged, can delay the healing process. Hydrofibers also act by protecting the delicate peri-wound skin from maceration and pain associated with dressing changes (Tickle, 2012). These dressings are recognized for their ability to manage exudate throughout the healing process, adapting to the changing environment of the wound. Hydrofibre dressing is a sterile dressing nonwovens carboxymethylcellulose fiber with a high absorbency. In the French list of products and benefits, the support is provided for managing exuding wounds associated with a secondary dressing to keep the wound moist. The recommandations from the consensus conference "Prévention et traitement des escarres de l'adulte et du sujet âgé" organised by French Health Authority (HAS) suggest a dressing type depending on the condition of the wound. So, for exuding wound, they recommend to use hydrofibre dressing, alginate or hydrocellular dressing.

A wealth of evidence is available to support the use of Aquacel® in wounds with elevated levels of exudate in terms of aiding wound progression towards healing (Brunner & Euberlein, 2000; Barnea et al, 2004; Ravenscroft, 2006). Tickle *et al* (2012), demonstrated the clinical effectiveness of Aquacel® Extra (a hydrofiber dressing designed to provide additional properties relating to extra dressing strength and absorbency) in the management of wet, sloughy wounds. This case study series concluded that Aquacel® Extra can effectively manage moderate to high levels of exudate, resulting in reduced dressing changes and reduced nursing time/resources, a reduction in cost and improved patient comfort and a reduction in patient distress. Therefore, this dressing was chosen as a comparative dressing in the present non-inferiority study, given that it is one of the most frequently used dressings for wet or sloughy chronic wounds. It is well

documented that venous leg ulcers (VLUs) are difficult to manage, not least due to patient intolerance of certain therapies due to associated pain (Reyzelman & Vartivarian, 2015). VLUs are often associated with pain and increased exudate production, which can lead to a reduction in patient quality of life (Do, Edwards & Finlayson, 2015). As such, VLUs were chosen as a model wound type for the present study.

Exufiber® is a highly absorbent primary dressing indicated for the management of moderately-to-highly exuding wounds. The dressing absorbs and retains wound exudate, blood and bacteria by forming a gel. In a recent publication by Chadwick and McArdle (2015), the effectiveness of Exufiber® was demonstrated in diabetic foot ulcers. Ease of use, patient satisfaction and exudate management were all rated highly. The potential of Exufiber® to provide an effective alternative dressing in the management of exuding wounds will be investigated throughout the entire healing process as well as its ability to adapt to a changing wound environment.

The primary objective of the current non-inferiority investigation is to compare Exufiber® versus Aquacel Extra in terms of efficacy, measured in exuding venous and mixed ulcers of predominantly venous origin during a period of 6 weeks. The primary endpoint will be wound area reduction (%) from baseline until the end of investigation (up to 6 weeks). Secondary endpoints will relate to reduction of sloughy tissue, autolytic debridement capability, pain at debridement and during dressing removal, condition of the peri-wound skin, dressing tolerance, health status, cost-effectiveness and wound closure from baseline up to maximum 24 weeks for a sub-group of at least 50 subjects. The assumptions of the sample size calculation have been based on previous pilot investigations on Exufiber® and especially the EARTH investigation (Meaume el al 2014).

This investigation supports the renewal application reimbursement of Exufiber®, to the French Health Authority, on the list of products and benefits mentioned in the article L165-1 of the National Health Service Code.

2. OBJECTIVES

The primary objective of this non-inferiority investigation is to compare Exufiber® versus Aquacel Extra in terms of efficacy and safety, measured in moderately or strongly exuding venous and mixed ulcers of predominantly venous origin during a period of 6 weeks investigation period.

The primary endpoint will be;

Wound area reduction (%) from baseline until end of investigation (up to 6 weeks). Wound area reduction will be centrally measured by one blinded independent review using the validated system PictZar®. A second supportive blind review will be done by an independent French expert

Secondary endpoints are to evaluate;

- Relative reduction (%) of fibrin/sloughy tissue
- Wound area reduction (absolute change in cm^2) from baseline until end of investigation (up to 6 weeks)
- Linear advance of the wound margin according to Gilman's formula (Cardinal et al, 2008) based on the digital photos and calculated by PictZar
- Percentage of patients with a debrided wound at end of investigation (at least 70% of the wound surface area covered with granulation tissue (confirmed using PictZar). Number of additional debridements used during the investigation. Pain during the debridement and ease of debridement
- Changes from baseline in the condition of the peri-wound skin measured by the following variables; maceration, redness/irritation, blistering, skin stripping, trauma to wound edges
- The level of pain in connection to removal of dressing
- Changes in wound status including exudates management
- Clinician's and subject's opinion related to the dressing (subject to fill in the questionnaire him/herself in applicable local language)
- Cost effectiveness and health economics will be measured using EQ-5D-3L and wound management related material use
- Tolerance such as adverse events and adverse device effects including those reported to be serious

Ancillary objective

- In order to support that wound area reduction at week 6 is a clinically relevant parameter to predict long-term favorable wound healing, a sub-group of at least 50 subjects will be assessed at 24 weeks post-inclusion. Favorable trajectory will be defined by an area regression, compared to baseline, of 80% or more at week 24. Additionally, wound closure (100% re-epithelialization confirmed by

photo) rate will also be evaluated. All these parameters will be centrally measured on photos according to previously described procedure.

3. CLINICAL INVESTIGATOR(S) AND INVESTIGATION ADMINISTRATIVE STRUCTURE

3.1 PI at Investigation site(s)

Name and addresses of principal investigator(s) are listed in Appendix A.

3.2 Mölnlycke Investigation Personnel

Viktoria Ahlenius Körner, Senior Clinical Research Manager, Author of the CIP

Caroline Gröndahl, Clinical Research Manager, Author of the CIP

Wassila Drareni, Project Leader Clinical Research, France

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Roland Sobenius, Regulatory Affairs Manager

Annika Rydström, Clinical Research Administrator

Markus Wittebo, Director of Clinical Research

Ann-Sofie Svensson, Clinical Project Manager/Clinical Data Manager

3.3 Other Participants

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4. INVESTIGATION PLAN AND PROCEDURES

4.1 Overall Design and Flow Chart

Overall Design

The investigation is designed as an open, randomized, non-inferiority, multi-centre investigation. A total of 212 subjects will be randomised. Subjects to be included will suffer from a moderately or strongly exuding venous or mixed ulcer of predominantly venous origin. Both in and out-subjects will be eligible. Each subject will be treated according to the local clinical routine and evaluated during a total treatment period of maximum 6 weeks or until the wound is healed. At least 50 subjects out of the total 212 subjects will be followed for maximum 24 weeks to investigate wound closure. Subjects will either be randomized to Exufiber® or Aquacel Extra using a centralized randomization. The secondary dressing will be according to the normal praxis at each clinic and preferably **one** secondary dressing should be chosen to be used for all subjects although no active dressings such as anti-microbial dressings are allowed. Simple gauzes or polyurethane (PU) films are recommended (see schedule of assessment for details). Patients should be treated with a recognized efficient compression system (e.g. multicomponents such as 2-, 3- or 4-LB (two-, three- or four-layer bandage) or SSB (short stretch bandage)). The nature of applied bandages will be captured in the eCRF.

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- Subjects characteristics including vital signs, informed and photograph consent, medical and surgical history, ulcer duration, size, location and ABPI (ankle brachial pressure index using hospital routine and most recent value obtained),

current dressing and compression type and duration (if applicable)

- Cleansing/debridement according to details in schedule of assessment 4.2.1
- Level of pain before dressing assessment, measured by validated visual analogue scale (VAS) 0-100mm
- Wound status using colorimetric scale; Percentage of fibrin/sloughy tissue, granulation tissue, epithelialization etc. Total should be 100%. Evaluated before and after cleansing/debridement.
- Photos will be taken according to guidelines in Appendix D and details in appendix C. Photos from before and after debridement will be analyzed using PictZar and by a blinded reviewer
- Signs of local infection such as pain between dressing changes, perilesional skin erythema, oedema, foul odour and high levels of exudates
- Dressing application including secondary dressing and compression according to details in schedule of assessment and in appendix C
- Clinician's evaluation according to details in appendix C

<u>At each follow-up visit until week 6 the following should be registered;</u>

- Cleansing/debridement according to details in schedule of assessment 4.2.1
- Wound status using colorimetric scale = Percentage of fibrin/sloughy tissue, granulation tissue, epithelialization etc. Total should be 100%. Evaluated before and after cleansing/debridement.
- Dressing application including secondary dressing and compression according to details in schedule of assessment and in appendix C
- Photos will be taken according to guidelines in Appendix D and details in appendix C. At week 4 and 6 or final visit, the photos before and after debridement will be analyzed using PictZar by a blinded reviewer. Other photos taken after debridement can be analysed using Pictar if deemed necessary for primary endpoint
- Level of pain during dressing removal measured by validated Visual Analogue Scale (VAS) 0-100mm and analgetics used within 3 hours
- Signs of local infection such as pain between dressing changes, perilesional skin erythema, oedema, foul odour and high levels of exudates
- Technical performance according to details in appendix C
- Subject evaluation according to details in appendix C
- Clinician's evaluation according to details in appendix C
- All relevant concomitant medications during the investigation period will also be collected including antibiotics and analgesics. Adverse events will be collected

according to details in section 8.

- Debridement is allowed during the treatment period but should be specified as well as ease of debridement and pain during the debridement (VAS).

Variables to be collected at week 8-24 for the sub-group of at least 50 subjects are specified in schedule of assessment 4.2.1 and in appendix C.

Health related quality of life (HRQoL);

Patient reported HRQoL will be measured by using the standardized generic EQ-5D-3L instrument (EuroQol, 1990).

The EQ-5D-3L consists of two parts: a descriptive system and a visual analogue scale (VAS). The descriptive system records HRQoL in five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), each of which dimensions has three levels of possible responses indicating (1) no problems, (2) some problems or (3) extreme problems. The responses of the patient results in a 5-digit code (e.g. 21223) defining his/her health state. These health states can be converted to a single index value representing how a particular health state is valued by the general population.

Using the second part of the instrument, the VAS, patients rate their health state on a 0-100 vertical scale.

Subjects will be provided with the paper version of the EQ-5D-3L three times during the investigation: (1) at baseline, (2) at four weeks and (3) at six weeks (or final visit). Subjects followed for up to 24 weeks will however be provided with the EQ-5D-3L a fourth time i.e. at week 24 (or final visit).

All outputs of the EQ-5D-3L instrument, the descriptive health states, the single index value and the VAS scores will be analyzed.

4.2 Procedures and Assessments

4.2.1 Schedule of Assessment

Week number	Week 0 (Baseline)	Week 1,2,3,4 and 6	Unscheduled visits*	Week 8-24**
Visit window	NA	± 2 days	NA	± 3 days
Informed Consent	√			
Inclusion and Exclusion Criteria	√			
Subject Demographics including vital signs	√			
Relevant medical condition and surgical procedure	√			
Current treatment	√			
History of Leg ulcer	√			
Wound status (colorimetric scale)	√	√		√
Condition of peri-wound skin	√	√		√
Signs and symptoms of local infection	√	√		
Pain assessment (VAS)[a]	√	√		
Wound preparation (cleansing/debridement) [b]	√	√	√	√
Dressing application[c]	√	√[d]	√	√[d]
Dressing removal[e]		√	√	√
EQ-5D-3L	√	√[f]		√[f]
Photograph[g]	√	√		√
Clinician's evaluation	√	√		
Subject's evaluation		√		

Week number	Week 0 (Baseline)	Week 1,2,3,4 and 6	Unscheduled visits*	Week 8-24**
Technical performance		√		
Medicine log	√	√	√	√
Adverse Events	√	√	√	√

***: Unscheduled visits can be performed at the clinic if/when deemed necessary for dressing changes. Cleansing should be performed according to intended use. Only saline and warm water or Actimaris Rinsing Solution are allowed on the wound. Debridement is not allowed at unscheduled visits. The dressing log should only be filled in at scheduled visits.**

****: At least 50 subjects out of the total 212 subjects, will be followed for 24 weeks or until wound is healed if earlier. Visits will be performed once a month e.g. at week 8, 12, 16, 20 and 24.**

a: Document any analgesics used under Medicine Log.

b: Only saline and warm water or Actimaris Rinsing Solution is allowed on the wound. Local applications such as pastes and corticosteroids are allowed outside the lesions. Any type of mechanical debridement is allowed in the investigation and it will be up each site to decide what mechanical debridement includes. Surgical debridement is not allowed. Debridement is not allowed at unscheduled visits.

c: Exufiber® or Aquacel Extra should be applied after cleaning/debridement and according to the randomisation schedule. Secondary dressing should be applied according to hospital praxis, simple gauzes of PU films are preferred and active dressings such as anti-microbial dressings are not allowed. Details to be recorded in the eCRF. The ulcer should be treated with a recognized efficient compression system (e.g. multicomponents such as 2-,3- or 4-LB or SSB). Record the nature of applied bandages in the eCRF.

d: Not at week 6/24 (i.e. final visit).

e: The number of dressing changes in-between visits should be captured at each scheduled visit, only changes in the dressing routine will be captured at each scheduled visit.

f: Only at week 4, 6 and 24.

g: Please see Appendix C for a detailed instruction of when photos should be taken.

Please include measuring scale (ruler) with date, subject number and visit number and please respect the confidentiality of the subject by not including any personal numbers or identifying characteristics. A digital camera will be distributed by Mölnlycke Health Care at or before the initiation. The ruler is used for calibration of the photograph for objective measurements in the PictZar program. The PictZar analysis including wound size measurement will be performed on the photos taken after debridement at week 0, 4 and 6 or the final visit if sooner. For subjects that are followed up to 24 weeks, an additional PictZar analysis including wound size measurement will be performed on photos taken at week 24 (or last visit). The PictZar analysis including tissue type measurement will be performed on the photos taken before debridement at week 0, 4 and 6 or the final visit if sooner.

Please refer to Appendix D for a complete digital photography guideline.

4.3 Selection of Population for Investigation

4.3.1 Inclusion Criteria

1. Provision of informed consent i.e. subject must be able to understand and sign the

Patient Information and Consent Form
2. Both gender ≥18 years old
3. Ulcer moderately or strongly exudative justifying the use of an absorbent dressing
6. 0.7 ≤ ABPI < 1.3
7. Ulcer duration 6 weeks to 60 months
8. Ulcer size 3 cm^2 -100 cm^2
9. Target ulcer at least 3 cm away from any other lesion

The subject can have multiple wounds but only the largest eligible wound per subject is to be included in the investigation. The remaining ulcers should be treated according to normal praxis.

4.3.2 Exclusion Criteria

1. Known allergy/hypersensitivity to the dressings
2. Pregnant or breastfeeding
3. Circumferential wounds (the entire wound should be able to be captured on a single image/photo)
4. Subjects who will have problems following the protocol
5. Subjects included in other ongoing clinical investigation evaluating wound dressings at present or during the past 30 days
6. Patient with a systemic infection not controlled by suitable antibiotic treatment
7. Clinically infected wound according to the judgement of the investigator (heat, pain, swelling, redness or purulent secretion)
8. Wound covered with black necrosis
9. Dry wounds
10. Malignant wound degeneration
11. Current treatment with radiotherapy, chemotherapy, immunosuppressant drugs or high doses of oral corticosteroids if any
12. Subject with deep vein thrombosis within 3 months prior to inclusion

4.3.3 Withdrawal of Subjects from Treatment or Assessment

Subjects are free to discontinue participation in the investigation at any time, and without prejudice to further treatment. Subjects who discontinue the investigation should always be asked about the reason(s) for their discontinuation and about the presence of any Adverse Event/Adverse Device Effect or Device Deficiency and, if possible, be assessed by an investigator. It is however up to the subject to provide a reason or not. Adverse Event/Adverse Device Effect should be followed up.

Subjects may be withdrawn from investigation treatment and assessments at any time, at the discretion of the investigator.

Incorrectly enrolled or randomised subjects will be withdrawn from further investigation treatment and assessments. A subject may, however, continue the investigation under special circumstances (i.e. if continuation of investigation treatment or follow-up actions are necessary for the subject's safety and well-being, or if only a follow-up period remains, and the

continuation of the investigation is not expected to be associated with any risk or discomfort for the subject).

4.4 Investigational Device

4.4.1 Summary description of the Investigational Device(s) and Comparator(s)

Investigational Device - Exufiber®

Gelling Fibre Dressing

Product Description

Exufiber® is a sterile nonwoven dressing made from highly absorbent polyvinyl alcohol fibres. In contact with wound exudate, Exufiber® transforms into a gel that facilitates moist wound healing and ease of removal during dressing change. Exufiber® absorbs and retains wound exudate. Exufiber® is available both as sheet and ribbon dressings.

Intended use

Exufiber® wound dressing is intended to be used on a wide range of exuding wounds:

- Leg and foot ulcers
- Pressure ulcers
- Partial thickness burns
- Surgical wounds
- Donor sites
- Malignant wounds

Precautions

- All wounds should be inspected frequently. In case of signs of clinical infection, consult a health care professional for adequate infection treatment.
- Exufiber® is not intended for dry wounds, full thickness burns.
- If the dressing dries out and is difficult to remove, it should be moistened according to local policies (e.g. with sterile saline or sterile water) and allowed to soak until it lifts easily. It may take several minutes for Exufiber® to transform into a gel. Remove the dressing by gently cleansing/flushing.

Other Information

- Exufiber® is for single-use only and should not be re-used. Re-use may lead to product deterioration or cross contamination may occur.
- Sterility is guaranteed unless pouch is opened or damaged prior to use. Do not re-sterilise.

- Exufiber® can be left in place for up to 7 days depending on wound condition or as indicated by clinical practice.

See also Appendix E, Instructions For Use.

Comparator - Aquacel® Extra™

Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre is a soft, sterile, non- woven pad dressing composed of sodium carboxymethylcellulose and regenerated cellulose fibre for strengthening. This conformable and highly absorbent dressing absorbs wound fluid and transforms into a soft gel, which maintains a moist environment to support the body's healing process and aid in the removal of nonviable tissue from the wound (autolytic debridement), without damaging newly formed tissue.

Intended use

Under medical supervision Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre may be used for the management of:

- leg ulcers, pressure ulcers (Stage II-IV) and diabetic ulcers.
- surgical wounds (e.g., post-operative, wounds left to heal by secondary intent and donor sites).
- partial thickness burns
- traumatic wounds (e.g. abrasions and lacerations).
- exudates absorption in oncology wounds (eg., fungating cutaneous tumours, cutaneous metastases and Kaposi's sarcomas).

Contraindications

Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre should not be used on individuals who are sensitive to or who have had an allergic reaction to the dressing or its components.

Precautions and observations

- Caution: Sterility is guaranteed unless pouch is damaged or opened prior to use.
- This device is for single-use only and should not be re-used. Re-use may lead to increased risk for infection or cross contamination. Physical properties of the device may no longer be optimal for intended use.
- Appropriate supportive measures should be taken where indicated (e.g. use of graduated compression in the management of venous leg ulcers or pressure relief measures in the management of pressure ulcers/sores).
- The control of blood glucose, as well as appropriate supportive measures, should be provided with diabetic foot ulcers.
- Infection is not a contraindication to the use of Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre. Should infection develop during the use of the dressing antibiotic therapy should be initiated, as clinically indicated, by a health care professional.
- Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre can facilitate the control of minor bleeding.

- If removing the dressing is difficult, the dressing should be fully saturated with sterile saline or water and removed slowly.
- Because Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre provides a moist environment that supports the growth of new blood vessels, occasionally the delicate newly formed blood vessels may produce a blood stained wound fluid.
- Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre is not intended for use as a surgical sponge.
- Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre is not intended for use within internal body cavities or within closed wounds.

Other Information

- Aquacel® Extra™ Hydrofiber® Dressing with Strengthening Fibre can be left in place for up to 7 days, where clinically indicated.
- Discard any unused portion of the dressing.
- If the immediate product packaging is damaged, do not use.

See also Appendix F, Instructions For Use.

4.4.2 Labelling

Labeling of the Investigational Devices will be in accordance with ISO 14155, the Medical Devices Directive (MDD) and Mölnlycke Health Care's Quality Management System.

The labels will be produced in accordance with local regulations for each participating country.

4.4.3 Accountability

Accountability will be performed on the Investigational Device (Exufiber®) and the comparator (Aquacel® Extra) provided to the investigation site by Mölnlycke Health Care free of charge.

The sites will be provided with the size 10x10 cm free of charge for both Exufiber® and Aquacel® Extra. More than one dressing can be used on a wound when deemed necessary.

The Principal Investigator is responsible for establishing routines for correct handling of the Investigational Devices to ensure that:

- Deliveries of products from Mölnlycke Health Care are correctly received
- Accurate records are maintained, accounting for the receipt of the investigational device (a delivery note will be provided with the shipments) and for the return or destruction of the products.
- Investigational Devices are handled and stored safely, properly and in agreement with the provided storage conditions.
- The Investigational Devices are prescribed only by the Principal Investigator or by a person authorized to do so by the Principal Investigator.

- The Principal Investigator will under no circumstances allow the Investigational Devices to be used for other purposes than directed by this Clinical Investigation Plan.
- Use of Investigational Devices must be documented on a subject specific level in the eCRF. Information to be documented includes identification of the subject using the device, identification and quantity of the medical device dispensed, date of dispensing and documentation of returned devices (if any) from the subject

Returned and unused products are accounted for and returned to Mölnlycke Health Care for destruction. All returned or destroyed products should be documented on a specific form provided by Mölnlycke Health Care.

4.4.4 Storage conditions

Exufiber® should be stored below 25°C (77°F) in dry conditions and protected from direct sunlight.

Aquacel® Extra should be stored in a cool dry place. (10°C - 25°C/50°F - 77°F).

4.4.5 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized to either Exufiber® (6w) or to Aquacel® Extra (6w). At least 50 out of the total 212 subjects will be randomized to Exufiber® (24w) or to Aquacel® Extra (24w). The randomization will be centralized performed after cleansing/debridement using an electronic system using the minimization technique and with the following strata; Wound duration (6w-12m,>12m), wound area (<10cm^2,≥10cm^2), ABPI (0.7-0.9,>0.9), Compression at inclusion (No, Yes) (Margolis, 2004 (2)).

4.5 Concomitant Treatments

Medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator. All concomitant relevant medication and treatment must be recorded in the appropriate section of the Case Report Form (CRF).

4.6 Efficacy and Safety

4.6.1 Subject Characteristics

See appendix C for details.

- Date of birth
- Gender
- Race (where applicable)
- Mobility

- Height, weight and BMI (calculated)
- Duration of leg ulcer and wound location
- Latest ABPI value
- Recurrent ulcer
- Current dressing and current compression type and duration (if applicable)

4.6.2 Medical condition

All ongoing **relevant** medical conditions must be recorded in the appropriate section of the eCRF.

Relevant medical condition is defined as an existing condition that may potentially affect the performance of the primary dressing according to the best judgement of the investigator.

4.6.3 Surgical history

All **relevant** surgical history must be recorded in the appropriate section of the eCRF.

Relevant surgical history is defined as previous surgery that may potentially affect the performance of the primary dressing according to the best judgement of the investigator.

4.6.4 Efficacy Measurements and Variables

See appendix C for details.

The primary endpoint will be

- Relative reduction of wound area (%) from baseline to end of investigation (up to 6 weeks) measured by the validated system PictZar on the photos taken after debridement at week 0, week 4 and week 6 (or final visit).

Secondary endpoints are to evaluate;

- Wound area reduction (absolute change in cm^2) from baseline to end of investigation (up to 6 weeks). Also measured by PictZar.
- Linear advance of the wound margin according to Gilman's formula (Cardinal et al, 2008) based on the digital photos and calculated by PictZar
- Relative reduction of fibrin/sloughy tissue after the 6-week treatment period or when the wound is dry/healed. (Measured with PictZar and according to the judgment of the clinician)
- Debrided wound at end of investigation

- ✓ at least 70% of the wound surface area covered with granulation tissue confirmed using PictZar

- Changes from baseline in the condition of the peri-wound skin measured by the following variables; maceration, redness/irritation, blistering, skin stripping, trauma to wound edges
- The level of pain in connection to dressing changes and during debridement (measured by visual analog scale 0-100mm)
  - ✓ Any intake/application of analgesics within 3 hours?
  - ✓ Pain before dressing assessment
  - ✓ Pain DURING dressing removal
  - ✓ Pain during debridement
- Cost effectiveness and health economics will be measured using EQ-5D-3L and dressing material used
- No of dressing changes per week and during the total treatment period
- Wound status
  - Exudate amount and nature
  - Wound bed aspect before and after debridement/cleansing
    - ✓ % of fibrin/sloughy tissue
    - ✓ % of granulation tissue
    - ✓ % of epithelialization
    - ✓ % other
- Clinician's opinion in relation to the dressing
  - ✓ Ease of application of the dressing
  - ✓ Ease of removal of the dressing
  - ✓ Non-adherence to wound bed at removal of primary dressing
  - ✓ Non-adherence to peri-wound skin at removal of primary dressing
  - ✓ Flexibility of dressing
  - ✓ Overall experience of the dressing
  - ✓ Conformability to the wound
- Subject's opinion in relation to the dressing
  - ✓ Experience anxiety during study product change

- ✓ Ease of movement while wearing study product
- ✓ Study product remained in place while wearing it
- ✓ Sting or burning while wearing study product
- ✓ Comfortable to wear
- ✓ Would you use this product again (only at last visit)

- Technical performance in relation to the dressing
  - ✓ Presence of residual in the wound after dressing removal
  - ✓ Ability to absorb exudate
  - ✓ Ability to retain exudate within the study product
  - ✓ Ability to absorb blood
  - ✓ Ability to keep slough and blood within study product

Ancillary endpoint is to evaluate;

- ✓ Wound area reduction (compared to baseline) of 80% or more at week 24
- ✓ Wound closure (100% epithelialization confirmed by photo) rate

4.6.5 Safety Measurements and Variables

Adverse Event (AE)/Adverse Device Effect (ADE), Serious Adverse Event (SAE)/Serious Adverse Device Effect (SADE), and Device Deficiencies (DD). The definition of AE, ADE, SAE, SADE and DD and procedures for reporting**,** SAE and SADE and DD that could have led to a SADE are presented in section 8 of this CIP. All AE, ADE, SAE, SADE and DD must also be recorded in the appropriate section of the CRF. It is of utmost importance that all staff involved in the investigation is familiar with the content of section 8. It is the responsibility of the Principal Investigator to ensure this.

Signs of local infection will be judged by the investigator;

- ✓ Pain since last dressing change
- ✓ Perilesional skin erythema
- ✓ Oedema
- ✓ Foul odour
- ✓ High levels of exudates

4.6.6 Anticipated ADEs

The conclusion of the Product Risk Management Record (PD-411100) and the Clinical Evaluation Report (PD- 474698) of Exufiber® is that the benefits of using the investigational device outweigh the residual risks and that there are no unacceptable risks of harm for the patient, the user nor third part involved in this device when used under normal conditions and within its intended use.

Before reaching the above conclusion, the identified risks of the investigational device, which had been ranked for severity, occurrence and detectability according to Mölnlycke Health Care risk management process, were mitigated as far as possible in the risk management process (following ISO 14971, Application of Risk Management to Medical Devices).

The following possible clinical outcomes are connected to the risks evaluated in the Product Risk Management Record:

- Maceration
- Prolonged wound healing
- Dressing related pain and/or trauma to the wound bed and edges
- Infection

The Principal Investigator or designee is responsible for judging whether the appearance of any of the above mentioned events are considered to be adverse events or adverse device effects. If this is the case, the event must be reported in the applicable section of the eCRF according to the timelines and definitions mentioned in section 8. Furthermore, worsening of an existing medical history during the intervention group may also be relevant to report as an adverse event or adverse device effect and the Principal Investigator or designee is responsible for making this judgment.

Concomitant treatments that are known to potentially affect the performance of the investigational device are mentioned in section 4.5 and any such medication must be registered in the eCRF.

There are no additional risks to the subjects by participating in this clinical investigation than there would be if the subject was treated with the investigational device (or standard care) under non-investigational settings. An additional benefit of participation may be more frequent and/or thorough wound assessments as part of this Clinical Investigation Plan.

4.7 Data Quality Assurance

4.7.1 Monitoring, Audits and Inspections

During the investigation, the monitor will have regular contacts with the investigation site. These contacts will include visits to confirm that the facilities remain adequate to specified standards and that the investigation site team is carrying out the procedure stated in the clinical investigation plan and supports the investigator. All data must be accurately recorded in the

CRF. Source data verification (a comparison of data in the CRF with the subject's hospital/practice and other records at the investigation site) with direct access to records will also be performed according to the monitoring plan.

The monitor or other Mölnlycke Health Care (MHC) personnel will be available between visits if the investigator or other staff at the site needs information and/or advice.

Authorised representatives of MHC and/or a Competent Authority (CA) and/or the Ethics Committee (EC)/Institutional Review Board (IRB) may visit the investigation site to perform audits/inspections, including source data verification.

4.7.2 Training of Staff

The Principal Investigator will ensure that appropriate training relevant to the investigation is given to the medical, nursing and other staff at the site involved and that new information of relevance to the performance of this investigation is forwarded to the staff involved.

4.7.3 Data Management

The Data Management process includes all activities related to data handling regarding:

- Randomisation
- Set-up of eCRF and database
- Specification of on-line checks
- Data entry / Data editing
- Export of data from Viedoc to SAS
- Creation of post-entry checks and listings
- Reconciliation of Serious Adverse Event (SAE), Serious Adverse Device Effect (SADE), Adverse Devise Effect (ADE) and Device Deficiency (DD)
- Clean-file process including execution of post-entry checks and listings
- Post clean-file tasks

Viedoc, a web based electronic CRF system, will be used to capture data in this investigation. The eCRF system complies with FDA Title 21 CFR part 11 (ER/ES) requirement.

eCRF training will be given to appropriate personnel before/at initiation of the investigation site(s).

Data entry will be done by investigators and other authorized personnel at the site(s). When entering data on-line checks are incorporated in Viedoc for consistency and validation. Pharma Consulting Group will support with a helpdesk function taking care of system user questions regarding Viedoc.

When data has been entered authorized personnel at MHC can immediately view the data, send queries if necessary and lock eCRF pages when they have been validated.

Photos will be uploaded in Viedoc and are marked with the subject code. Uploaded photos shall not contain any information that can reveal the identity of the subject. All uploaded photos will be reviewed by personnel at MHC and stored in the company database. All data entered in Viedoc will be encrypted. The physical database will be stored in Sweden.

Programs for post-entry checks and data listings will be created and executed for validation of data.

Completeness will be checked by authorized personnel at MHC so that there are no unexplainable empty fields in Viedoc. This is done in order to prevent that data have been overlooked by personnel entering the data.

A clean-file meeting will be held prior to database lock. All decisions on the evaluability of the data from each individual subject for the statistical analysis and final definition of ITT, PP and safety populations must be made and documented before locking the database.

A blinded observer will do the measurements (from the validated tool PictZar which complies with FDA cleared under CFR part 11 (ER/ES) requirement) of the primary endpoint based on digital photos uploaded in the electronic CRF. The blinded observer will not know the treatment that each subject received.

4.8 Statistical Methods and Determination of Sample Size

4.8.1 Statistical Evaluation

The intent-to-treat (ITT) population is defined as all randomised patients with at least one follow up planimetry value (from the validated tool PictZar) and the per-protocol (PP) population as all patients with a wound area measurement till the fourth week of follow-up, at least. Subjects with significant protocol deviations will be excluded from the PP population.

PictZar has received 510k notification and is compliant with CFR Part 11.

In this non-inferiority study the primary efficacy analysis will be constructing a two sided 95% confidence interval, using Fisher's non-parametric permutation test, for between-treatment differences (Exufiber® - Aquacel® Extra) in the mean percentage area change from baseline to 6 weeks. This means that if the lower limit of this confidence interval is greater than 12% non-inferiority will be established.

All the main efficacy analyses will be performed on the PP population. Complementary efficacy analyses will be performed on the ITT-population for further confirmation. The ITT and PP analyses will have to provide the same results to establish the non-inferiority. All safety analysis will be performed on the safety population.

Superiority can be concluded if the lower bound of a two sided 95% confidence interval for between-treatment differences (Exufiber® - Aquacel® Extra) in the mean percentage area change from baseline to 6 weeks does not overpass zero.

There will also be a second blinded assessment carried out (not using the PictZar system) that will support the main analysis done by PictZar.

For secondary variables Fishers exact test for dichotomous variables, Mantel-Haenszel chi-square test for ordered categorical variables and Pearson Chi-square test for non-ordered categorical variables and Fisher's non-parametric permutation will be used for continuous variables.

If necessary adjustment for baseline variables will be done with multiple logistic regression for dichotomous variables and with covariance analysis for continuous variables.

All statistical tests will be two-sided and conducted at the 5% significance level.

A sub-group analysis by country will be performed.

For the primary endpoint last observation carried forward will be applied for the final measurement. No other imputation methods will be used.

For all secondary endpoints differences between Exufiber® and Aquacel® Extra will be analyzed with the statistical methods given above and 95% confidence interval for the differences between the two groups will be given when appropriate.

The distribution of continuous variables as for changes in continuous variables will be given as mean, SD, median, minimum and maximum and as number and percentages for categorical variables.

Other endpoints will be summarized using descriptive statistics only.

A complete statistical analysis plan (SAP) with the details for all analyses for the whole study will be finalized before first patient in.

A blinded observer will do the measurements of the primary endpoint based on digital photos uploaded in the electronic CRF. The blinded observer will not know the treatment that each subject received.

4.8.2 Determination of Sample Size

This investigation was designed to document the non-inferiority of the test dressing, Exufiber®, compared with the control dressing, Aquacel® Extra, on the relative reduction/change in wound size from baseline to end of investigation (6w). Applying a non-inferiority margin of 12% (same as EARTH investigation, Meaume el al 2014) and a standard deviation of 35%, 106 subjects were necessary in each group (i.e. 212 subjects in total) with a power level at 80%. Two investigations have been conducted on Exufiber®, one on DFU (diabetic foot ulcer) and one on PU (pressure ulcer). The SD are a little higher than 35% but since those investigations were quite small (21 subjects) it is reasonable to expect a smaller SD which justifies the calculation above.

4.9 Changes to the Clinical Investigation Plan

No change in the investigation procedure will be effected without the mutual agreement of the Principal Investigator and MHC.

An amendment to the Investigation Plan may require notification or approval from EC/IRB and, in many countries, also the CA before implementation. Local requirements must be followed.

MHC will distribute clinical investigation plan amendments to the Principal Investigator who is responsible for the distribution of these documents to the EC/IRB and staff concerned at his/her site. In France it is the sponsor who is responsible for this distribution. The distribution of these documents to the CA will be handled according to local practice.

5. STATEMENTS OF COMPLIANCE

5.1 Ethics

5.1.1 Ethics review

The final clinical investigation plan, including the final version of the Patient Information and Consent Form, must be approved or given a favorable opinion in writing by an EC/IRB before enrolment of any subject into the investigation. The Principal Investigator (in France the Sponsor) is responsible for informing the EC of any amendment to the investigation plan as per local requirements.

5.1.2 Ethical Conduct of the Investigation

The investigation will be performed in accordance with the ethical principles that have their origin in the most recent version of the Declaration of Helsinki, and with applicable regulatory requirements.

5.1.3 Patient Information and Consent Form

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the investigation. Subjects must also be notified that they are free to discontinue participation in the investigation at any time. The subject should be given the opportunity to ask questions and time for consideration. The subject's signed informed consent has to be obtained before conducting any procedure specifically for the investigation. The original must be filed by the Principal Investigator. A copy of the Patient Information including the signed Consent Form should be given to the subject.

A sample of the Patient Information and Consent Form is enclosed (Appendix B). If modifications are made according to local requirements, the new version must be approved by MHC.

5.2 Regulatory and standards

5.2.1 Regulatory review

If applicable, the final clinical investigation plan, including the final version of the Patient Information and Consent Form, must be approved or given a favorable opinion in writing by a CA before enrolment of any subject into the investigation. MHC is responsible for informing the CA of any amendment to the investigation plan as per local requirements.

5.2.2 Standards and other

The most recent version of ISO 14155 is followed in addition to national regulations.

5.2.3 Subject Data Protection

The written Patient Information explains that the data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation and that authorised representatives of MHC and/or a CA and/or EC/IRB, require direct access to those parts of the hospital/practice records relevant to the investigation, including medical history, for verification of data. All data computerized by MHC will be identified by subject number only.

5.3 SUBJECT PROTECTION PROCEDURES

5.3.1 Procedures in Case of Medical Emergency

The Principal Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the investigation.

5.3.2 Insurance

Mölnlycke Health Care AB has product liability insurance, which also covers test products.

5.4 Publication of results

The results from this investigation are intended to be published.

The investigation will be registered on a web site for free access (ClinicalTrials.gov) before the inclusion of the first subject.

6. INVESTIGATION TIMETABLE AND TERMINATION

Investigation start: Q2/Q3 2016

Inclusion completed: Estimated Q1/Q2 2019

Last subject out: Estimated Q3 2019

The investigation could be prematurely discontinued if the dropout rate is higher than 20% and/or the investigation site is unable to fulfill the inclusion period according to the Clinical Investigation Agreement.

7. LITERATURE REVIEW AND REFERENCES

In order to determine the scientific background for this clinical investigation as well as to assess risks/benefits of the device, a literature review was conducted. The literature listed below was critically evaluated before serving as background information.

1. Barnea, Y. Amir, A., Lesham, D *et al*. Clinical comparative study of Aquacel and paraffin gauze dressings for Split-skin donor site treatment. Ann Plast Surg. 2004 Aug; 53(2):132-136.

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3. Brunner, U., Eberlein, T. Experiences with hydrofibres in the moist treatment of chronic wounds, in particular of diabetic foot. Vasa 2000; 29(4):253-257.

4. Chadwick, P., McCardle, J. Exudate management using a gelling fibre dressing. The Diabetic Foot J 2015; 18(1):43-48.

5. Department of Health (2009) NHS 2010–2015 from Good to Great: Preventative, People-centred, Productive. http://tinyurl.com/9lnwdmh (accessed 24 August 2012).

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7. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health policy. 1990;16(3):199-208. PubMed ID: 10109801.

8. Harding, KG., Price, P., Robinson, S et al. Cost and dressing evaluation of hydrofiber and alginate dressings in the management of community-based patients with chronic leg ulceration. Wounds 2001; 13(6):229-236.

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10. Margolis, D. et al. The accuracy of venous leg ulcer prognostic models in a wound care system, Wound Repair Regen 2004; 12(2): 163-168.

11. Meaume, S. Evaluation of two fibrous wound dressings for the management of leg ulcers: Results of a European randomized controlled trial, J Wound Care 2014; 23(3).

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15. Tickle, J. Effective management of exudate with Aquacel Extra. Br J Community Nurs. 2012 (Supplement); S38:S40-S46.

16. Walker, M., Parsons, D. Hydrofiber® technology: its role in exudate management. Wounds UK 2010; 6(2):31-38.

17. World Union of Wound Healing Societies (WUWHS). Principles of best practice: Wound exudate and the role of dressings. A consensus document. London: MEP Ltd, 2007.

18. Wounds UK Best Practice Statement. Effective exudate management. London: Wounds UK, 2013.

19. Vowden, P., Bond, E., Stryja, J. Meeting report: Changing the way we look at viscous exudate. Wounds International 2015; 6(3):35-41.

20. Cardinal M, Eisenbud DE, Phillips T, Harding K. Early healing rates and wound area measurements are reliable predictors of later complete wound closure. Wound Repair Regen. 2008;16(1):19–22.

8. DEFINITIONS AND PROCEDURES FOR REPORTING OF ADVERSE EVENT, ADVERSE DEVICE EFFECT, SERIOUS ADVERSE EVENT, SERIOUS ADVERSE DEVICE EFFECT AND DEVICE DEFICIENCY

Definitions:

Device Deficiency (DD)
Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note:

- Device Deficiencies include malfunctions, use errors, and inadequate labelling.

All Device Deficiencies that might have led to a Serious Adverse Device Effect shall be reported in accordance with Serious Adverse Event reporting procedures, as specified below.

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

Note:

- This definition includes events related to the investigational medical device or the comparator.
- This definition includes events related to the procedures involved.
- For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE)
Adverse Event related to the use of an investigational medical device

Note:

- This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, or operation, or any malfunction of the investigational medical device.
- This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Event (SAE)
Adverse Event that:

a) led to death,

b) led to a serious deterioration in the health of the subject, that either resulted in

1) a life-threatening illness or injury, or
2) a permanent impairment of a body structure or a body function, or
3) in-patient hospitalization or prolonged hospitalization or,
4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

Note:
Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE)

Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

PROCEDURES FOR SAE AND/OR SADE REPORTING OR REPORTING OF DD THAT COULD HAVE LED TO A SADE

The investigator must inform Mölnlycke Health Care (MHC), within 1 calender day of awareness of the event. When a SAE/SADE has been entered into the eCRF by the investigator /authorised site staff, the eCRF system will automatically generate a report to: Clinical_Investigations_Event_Reporting@molnlycke.com.

In case of problem with the eCRF, a paper based version of the SAE/SADE report form (available in the Investigator Site File) shall be used and sent by email to: Clinical_Investigations_Event_Reporting@molnlycke.com.

All SAEs/SADEs that occurs during the Clinical Investigation shall be reported, whether or not they are considered causally related to the investigational device.

Device Deficiencies that might have led to SADE if either a) suitable action had not been taken, b) if intervention had not been made, or c) if circumstances had been less fortunate must be reported as a SADE.

The investigator is responsible for informing the EC/IRB and/or the Competent Authority of the SAE/SADE as per local requirements.

PROCEDURES FOR DD REPORTING

All DD shall be reported to MHC as soon as possible, without unjustified delay . If the DD might have led to a SADE the reporting requirements for SADE described above must be followed. DDs can be either subject related or non-subject related depending on if the investigational device was used by a subject or not. Separate forms are used for subject related and non-subject related DDs. When a subject related DD has been entered into the eCRF by the investigator /authorised site staff, the eCRF system will automatically generate a report to: Clinical_Investigations_Event_Reporting@molnlycke.

Non-subject related DDs are reported using the paper based report form located in the Investigator Site File. The completed form shall be sent by email to Clinical_Investigations_Event_Reporting@molnlycke.com

Causality Assessment

The relationship between the use of the investigational device and the occurrence of each AE/SAE shall be assessed by the investigator and the sponsor and classified as investigational device related or not related to investigational device.