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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

Study code: CHEXU03

Clinical Investigation Plan
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MÖLNLYCKE
HEALTH CARE

STATISTICAL ANALYSIS PLAN

PRODUCT: **EXUFIBER**

INVESTIGATION CODE: CHEXU03

VERSION/DATE: Final / 2016-06-08

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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1. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADE	Adverse Device Effect
AE	Adverse Event
CIP	Clinical Investigation Plan
DD	Device Deficiency
e-CRF	Electronic Case Report Form
EC	Ethics Committee
GVW	Gesellschaft für Versorgungskonzepte in der Wundbehandlung mbH
ICC	Intra-class Correlation Coefficient
ITT	Intention to Treat
PP	Per Protocol
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
VAS	Visual Analogue Scale

2. STUDY OBJECTIVES

The overall 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 is to evaluate 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;

- 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
- Relative reduction (%) of sloughy tissue
- 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
- 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 from the wound care centers owned by GVW (Gesellschaft für Versorgungskonzepte in der Wundbehandlung mbH) in Germany 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. 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 with at least 70% of the wound bed covered with slough at baseline. 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 (from the wound care centers owned by GVW in Germany) 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 by treatment group 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 electronic Case Report Form (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 (from the wound care centers owned by GVW in Germany) 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 e.g. 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 at 6 or 24 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.

3.1.1 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[b]/debridement)	√	√	√	√
Dressing application[c]	√	√[d]	√	√[d]
Dressing removal[e]		√	√	√
EQ-5D-3L	√	√[f]		√[f]
Photograph[g]	√	√		√
Clinician's evaluation	√	√		
Subject's evaluation		√		
Technical performance		√		

Week number	Week 0 (Baseline)	Week 1,2,3,4 and 6	Unscheduled visits*	Week 8-24**
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 from the wound care centers owned by GVW in Germany, 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 allowed on the wound. Local applications such as pastes and corticosteroids are allowed outside the lesions. 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).

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

4. POPULATIONS OF ANALYSIS SETS

4.1 Intention to treat Population

The Intention to Treat (ITT) population will include all randomised subjects with at least one follow-up measurement. The ITT population will be defined at the clean file meeting.

4.2 Per Protocol Population

The Per Protocol (PP) population will include all subjects in the ITT population with a wound area measurement at baseline and at week 6, or earlier if wound is healed prior to week 6, and without significant protocol violations. Subjects identified as protocol violators will be documented and agreed between Mölnlycke Health Care and statistician at the clean-file meeting.

4.3 Safety population

The population for the assessment of safety will include all randomised subjects with application of the dressing

5. VARIABLES OF ANALYSIS

5.1 Subjects Characteristics

- Age
- 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

5.2 Medical condition and Surgical history

- Ongoing relevant medical conditions
- Relevant surgical history

5.3 Efficacy variables

5.3.1 Primary Efficacy Endpoint

Primary efficacy variable is 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).

A supportive primary efficacy variable will be the relative reduction of wound area (%) from baseline to end of investigation (up to 6 weeks) with measurements from the supportive blind review done by an independent French expert.

5.3.2 Secondary Efficacy Endpoints

- 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 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 VAS 0-100mm)
  - ✓ Any intake/application of analgesics within 3 hours?
  - ✓ Pain before dressing assessment
  - ✓ Pain DURING dressing removal
  - ✓ Pain during debridement
- Wound status
  - Exudate amount and nature
  - Wound bed aspect after debridement/cleansing
    - ✓ % of fibrin 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
- Health related quality of life using EQ-5D-3L at baseline, 4 and 6 weeks
  - ✓ Mobility
  - ✓ Self-care
  - ✓ Usual activities
  - ✓ Pain discomfort
  - ✓ Anxiety/depression
  - ✓ Single Index from the five questions
  - ✓ VAS 0-100 of health status
- 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

Ancillary endpoint to evaluate (extended substudy 24 weeks);

- ✓ Wound area reduction (compared to baseline) of 80% or more
- ✓ Wound closure (100% epithelialization confirmed by photo) rate
- ✓ Health related quality of life using EQ-5D-3L

5.3.3 Safety Measurements and Variables

The safety variables are Adverse Event (AE) / Adverse Device Effect (ADE), Serious Adverse Event (SAE)/Serious / Adverse Device Effect (SADE), and Device Deficiencies (DD). The definitions and procedures for reporting are presented in section 8 of the CIP.

6. STATISTICAL METHODOLOGY AND SAMPLE SIZE DETERMINATION

6.1 General Methodology

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 wound area reduction from

baseline to 6 weeks follow-up. 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 wound area reduction from baseline to 6 weeks follow-up does not overpass zero.

There will also be a second blinded assessment carried out by an independent French expert (not using the PictZar system) that will support the primary efficacy analysis done by PictZar.

For comparison between the two randomized groups regarding baseline variables and secondary efficacy variables Fisher's non-parametric permutation will be used for continuous variables, Mantel-Haenszel chi-square test for ordered categorical variables, Pearson Chi-square test for non-ordered categorical variables and Fishers exact test will be used for dichotomous variables.

For continuous variables 95% confidence intervals based on Fisher's non-parametric permutation tests will be calculated for the mean differences between the two groups. For dichotomous variables 95% confidence intervals for difference in proportion will be calculated.

If significant differences are found in baseline variables between the two treatments, complementary analyses of treatment adjusted for these baseline variables will be performed. These adjustments for baseline variables will be done with multiple logistic regression analyses for dichotomous variables and with covariance analysis for continuous variables.

For the primary efficacy endpoint, and for applicable secondary efficacy endpoints, last observation carried forward will be applied for the last follow-up measurement before 6 weeks and forward to the final 6 week measurement. No other imputation methods will be used.

For the primary efficacy endpoint a sensitivity analysis will be performed using complete case.

Frequency tables (including n, mean, median, standard deviation, minimum and maximum for continuous variables and n, frequency and percentage for categorical values) will be provided for all variables by treatment, as well as for the changes from baseline within each treatment by treatment.

Sub-group analyses by country will be performed.

Exploratory interaction analyses will be performed for primary efficacy variable and selected secondary variables between study groups and selected baseline variables in order to find subgroups were the effect of Exufiber in relation to Aquacel Extra is significantly improved.
All statistical tests will be two-sided and conducted at the 5% significance level.
All analysis will be performed with SAS software version 9.4 or later.

6.2 Demographics and Baseline Characteristics

The variables listed in section 5.1 and 5.2 will be described and analyzed between the two treatment groups according to the general methodology in section 6.1 above. These analyses and tables will be given for both the ITT and PP population.

6.3 Efficacy Analyses

6.3.1 Primary efficacy analysis

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 wound area reduction from baseline to 6 weeks follow-up using PictZar on the PP population. A corresponding complementary two sided 95% confidence interval on the ITT population will also be constructed. If the lower limits of both these confidence intervals are greater than 12% non-inferiority will be established.

For the primary efficacy endpoint last observation carried forward will be applied for the last follow-up measurement before 6 weeks and forward to the final 6 week measurement. Supporting identical analyses will be performed on the primary efficacy variable using the values from a second supportive blind review of the independent French expert.

Also a sensitive analysis using PictZar will be performed using complete cases.

Tables will be given for wound area by visit and analysed between treatments and for wound area reduction (%) from baseline to each visit and analysed between treatments.

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 wound area reduction from baseline to 6 weeks follow-up using PictZar on the ITT population does not overpass zero.

6.3.2 Secondary efficacy analyses

All secondary efficacy variables given in section 5.3.2 above will be analysed between Exufiber® and Aquacel® Extra on both the PP population and the ITT population according to the statistical methods given in section 6.1. The main analyses will be performed at the 6 weeks follow-up and /or change from baseline to 6 weeks follow-up. For applicable secondary efficacy endpoints last observation carried forward will be applied for the last follow-up measurement before 6 weeks and forward to the final 6 weeks measurement.

Where appropriate, the statistical analyses will also be performed at the 4 week follow-up and /or change from baseline to 4 week follow-up.

For continuous variables and dichotomous variables 95% confidence intervals will be calculated for the mean difference between the two study groups.
Tables with descriptive statistics will be given for all secondary efficacy variables by visit, by treatment group and change from baseline to each visit

6.3.3 Subgroups analyses

6.3.3.1 By country

Subgroups analyses will be performed by country for primary efficacy variable and for selected secondary efficacy variables.

6.3.3.2 Interaction analyses

Exploratory interaction analyses will be performed for primary efficacy variable and selected secondary variables between the two randomized groups and selected baseline variables in order to find subgroups were the effect of Exufiber in relation to Aquacel Extra is significantly improved.

6.3.4 Analyses of 50 subjects long-term study (24 weeks)

Analyses of wound area reduction (compared to baseline) of 80% or more at week 24 and Wound closure (100% epithelialization confirmed by photo) rate between the two randomised groups will be performed with Fisher's exact test for these 50 subjects followed to 24 weeks. 95% confidence intervals for the difference in proportions between the two groups will be given.

All measurement week 8 to 24 will be analysed between the two randomised groups in the same way as secondary efficacy variables in section 6.3.2 above.

6.3.5 Analysis of agreement between PictZar judgement and French expert.

If inconsistencies are found in the results from the PictZar judgement and the independent French expert then an analysis of agreement between the PictZar judgements and the independent French expert's judgements will be performed with distribution of the differences between the measurements; Bland-Altman Plots, Limits of Agreement and calculation of Intra-class Correlation Coefficient (ICC). The primary efficacy analysis will be done using the PictZar judgments.

6.4 Safety

All safety variables will be summarized and analysed descriptively by treatment group on the safety population.

The number of subjects reporting one or more AE/ADE/SAE/SADE/DD will be summarised by treatment group using frequency counts. If very few AE/ADE/SAE/SADE/DD these will only be listed.

The incidence (%) of AE/ADE/SAE/SADE/DD reported during the investigation will be summarised in an overview table and by treatment group.

6.5 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 previously been conducted on Exufiber®, one on diabetic foot ulcer and one on 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.

6.6 Listings of Tables, Figures and Listings

6.6.1 Listing of Tables

Will be defined before clean file meeting.

6.6.2 Listing of Figures

Will be defined before clean file meeting

6.6.3 Listings of Listings

Will be defined before clean file meeting

7. SIGNED AGREEMENT TO THE STATISTICAL ANALYSIS PLAN

7.1 Signatures of Mölnlycke and Statistician

I agree to the terms of this statistical analysis plan

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