Clinical Investigation Plan

CP351 – BISIL

Biatain® Silicone 3D fit

A randomised controlled investigation comparing the clinical performance and cost effectiveness of Biatain® Silicone with standard of care dressing including filler in chronic wounds

January 2023 - January 2024

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CHANGE LOG

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1.0	DKKABE	Initial document based on template 9.0
2.0	DKKABE	[redacted]
3.0	DKKABE	[redacted]
4.0	DKKABE	[redacted]

SYNOPSIS OF THE CLINICAL INVESTIGATION

Title and aim
A randomised controlled investigation comparing the clinical performance and cost effectiveness of Biatain® Silicone with standard of care dressing including filler in chronic wounds.

The overall aim of this investigation is to evaluate the clinical performance and cost-effectiveness of Biatain® Silicone compared to standard of care (SoC) defined as Mepilex® Border and AQUACEL® EXTRA™ Hydrofiber® Dressing in the treatment of chronic wounds with wound depth down to 20 mm.

Investigational test product and comparator
The investigational test product is Biatain® Silicone. Biatain® Silicone is intended to be used for moist wound healing and exudate management.

The comparator products are Mepilex® Border and AQUACEL® EXTRA™ Hydrofiber® Dressing.

Intended use and purpose
All products, investigational test products as well as comparator products, are CE-marked and will be used within the intended purpose, indications and user population.

Objectives
The primary objective is to demonstrate that the clinical performance of Biatain® Silicone is comparable to standard of care (Mepilex® Border and AQUACEL® EXTRA™ Hydrofiber® Dressing).

The secondary objective is to evaluate the cost-effectiveness of Biatain® Silicone compared with standard of care (Mepilex® Border and AQUACEL® EXTRA™ Hydrofiber® Dressing).

Design of the investigation
The clinical investigation is a two-arms, open-labelled, stratified, randomized, controlled, multicentre investigation.

The cohort will in total consist of 100 subjects with chronic wounds with wound depth down to 20 mm. The subjects will be included and randomised to one of two groups receiving either Biatain® Silicone or Mepilex® Border and AQUACEL® EXTRA™ Hydrofiber® Dressing at >12 sites across the UK.

The subjects will have a weekly visit during a four-week investigation period where the wound will be assessed, and the investigational test product or comparator products will be applied. The study visits will be overseen by the Principal Investigator (PI), or delegate.

[redacted]

Expected duration of the clinical investigation:
The investigation is expected to be conducted from January 2023 through January 2024

Each subject will undergo screening and baseline visits, which can be performed the same day, followed by a 4-week investigational test period.

Endpoints and assessments	
Primary endpoints	• Percentage wound area reduction during the investigational test period of four weeks
Secondary endpoints	• Total treatment costs during the investigational test period based on the number of dressings used during the investigation and the unit price of the products
Exploratory Endpoints	• Percentage wound depth reduction during the investigational test period • Wound bed, wound edge and peri wound skin condition based on visual assessment by PI, or delegate during the investigational test period, based on an adapted version of the Coloplast Wound Assessment Form • Conformability of the dressing based on PI, or delegate´s evaluation according to a 5-point Liker scale • Responder defined as a subject reaching ≥ 30% wound area reduction within the 4-week investigational test period (Yes/No) • Wound healed during the investigational test period (Yes/No) • Quality of Life evaluated by EQ-5D-5L: o The index score based on the value set published for UK o VAS score on overall health
Assessments:	<u>Safety:</u> • Adverse events • Device deficiencies [redacted]

Population and subjects

The clinical investigation will be conducted in a total of 100 eligible subjects with venous leg ulcers (VLUs) or diabetic foot ulcers (DFUs) with wound depth down to 20 mm.

Inclusion criteria and exclusion criteria:

To be included in the investigation, the subjects must comply with the criteria presented below.

Inclusion criteria	Exclusion criteria
1. Has given written consent to participate by signing the Informed Consent Signature Form	1. Wound is infected. For DFUs, has infection severity mild-severe according to the IWGDF/IDSA guideline (Appendix 5). For VLUs, has 2 or more clinical signs of infection as defined in protocol, based on clinical judgement by investigator/tissue viability nurse (Appendix 6)
2. Is at least 18 years of age and has full legal capacity	2. Wounds is with exposed tendons, is with bones or has fistulas
3. Has a venous leg ulcer (VLU) (C6 of the CEAP classification(1)) or a diabetic foot ulcer (DFU) with a duration longer than 8 weeks but no longer than 24 months (Appendix 4)	3. Wound is with cavity, or is undermined or tunnelling
4. Has a wound with depth[1] down to 20 mm	4. Subject is receiving chemotherapy
5. Has a maximum wound depth[1] relative to wound diameter[2] with specifications presented in table 1	5. Subject has ankle-brachial pressure index (ABPI) below 0.8 (measured at a frequency according to local standards)
6. Has a wound with exudate levels requiring a filler and a standard secondary dressing	6. Wound is larger than 10 x10 cm
7. Has acceptance of compression therapy in case of a VLU or off-loading in case of a DFU, according to local standards	7. Currently enrolled in another wound care device investigation unless co-enrolment has been agreed with the sponsor
8. For subjects with diabetes, has HbA1c ≤ 10% or ≤ 86 mmol/mol, measured within the last 3 months prior to inclusion	

[1] *depth at the deepest point in the wound bed*
[2] *diameter measured at the widest point of the wound*

Table 1: Specifications related to Inclusion criteria 5

Wound diameter (cm)	Maximum wound depth (mm)
6.0-10	20
5.5-5.9	11
5.0-5.4	10
4.5-4.9	9
4.0-4.4	8
3.5-3.9	7
3.0-3.4	6
2.5.2.9	5
2.0-2.4	4
1.5-1.9	3
1.0-1.4	2

LIST OF ABBREBIATIONS

ABBREVIATION	WRITTEN OUT	EXPLANATION
ABPI	Ankle-brachial pressure index	Synopsis
ADE	Adverse Device Effect	See section 18.2
AE	Adverse Event	See section 18.1
ASADE	Anticipated Serious Adverse Device Effect	See section 18.4.2
eCOA	Electronic Clinical Outcome Assessment	
CEAP	C: Clinical findings E: Etiological factors A: Anatomical cause P: Pathophysiological cause	CEAP classification of varicose veins severity
CIP	Clinical Investigation Plan	
CRF	Case Report Form (paper or electronic)	Questionnaire to be used for data collection
CM	Clinical Manager	
DQF	Data Query Forms	A DQF is a query specifically used in clinical research. The DQF is the primary data query tool from the sponsor to clarify discrepancies and ask the investigator for clarification. The DQF is part of the data validation process in a clinical investigation.
DD	Device deficiency	
EC	Ethics Committee	
IB	Investigator's Brochure	Compilation of the current clinical and non-clinical information on the investigational medical device(s,) relevant to the clinical investigation.
IFU	Instruction For Use	
ITT	Intention to Treat	
PI	Principal Investigator	Qualified person responsible for conducting the clinical investigation at an investigation site. If the clinical investigation is conducted by a team of individuals at an investigation site, the PI is the responsible leader of the team. Whether this is the responsibility of an individual or an institution can depend on national regulations.
PP	Per Protocol	
SADE	Serious Adverse Device Effect	See section 18.4.1
SAE	Serious Adverse Event	See section 18.4
SoC	Standard of Care	Synopsis
USADE	Unanticipated Serious Adverse Device Effect	See section 18.4.3
VLU / VLUs	Venous leg ulcer / Venous leg ulcers	Synopsis
DFU / DFUs	Diabetic foot ulcer / Diabetic foot ulcers	Synopsis

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1. List of personnel involved in the Investigation

1.1. Sponsor representatives

CLINICAL MANAGER	PRINCIPAL BIOSTATISTICIAN
[redacted]	[redacted]
SR CLINICAL STRATEGY PROJECT MANAGER	**PRINCIPAL DATA MANAGEMENT SPECIALIST**
[redacted]	[redacted]
SENIOR DIRECTOR, CLINICAL STRATEGIES	**HEAD OF CLINICAL TRIAL MANAGEMENT**
[redacted]	[redacted]
MEDICAL SPECIALIST	**CLINICAL MONITOR**
[redacted]	[redacted]

In case of emergency, please contact Clinical Manager, [redacted] from the sponsor representatives list above

1.2. Chief Principal Investigator

CHIEF PRINCIPAL INVESTIGATOR
David Voegeli, Ph.d., BSc, RN. Professor of Nursing, School of Health & Care Professions, Room 30, Alwyn Hall West, Faculty of Health & Wellbeing, University of Winchester. Tel: +44 (0)1962 827548 Email: David.Voegeli@winchester.ac.uk

2. Rational/justification for conducting the clinical investigation

Best practice wound care should focus on providing an optimal healing environment. Managing the space between the wound bed and the dressing is a critical part of an optimal healing environment to avoid pooling of exudate from the wound bed, to decrease the risk of infection and development of biofilm in the wound and to promote a moist wound healing environment (2).

The ideal wound dressing should therefore manage the gap by conforming to the wound bed and absorbing and retaining wound exudate to help prevent wound complications (3),(4).

Alginates and hydrofibers are highly absorbent advanced wound dressings made to manage moderate to large amounts of exudate. They form a gel when in contact with the wound and thus conforms well to the wound bed. Alginates and hydrofibers are primary dressings and always require a secondary dressing to keep them in place.

Biatain® Silicone is a soft and comfortable polyurethane foam dressing with a silicone adhesive and a conforming 3DFit Technology® that conforms to the wound bed and reduces exudate pooling (5). The foam dressing has a semi-permeable, bacteria- and waterproof top film and a lock-away layer. It is indicated for a wide range of exuding chronic and acute wounds.

Upon exudate absorption, Biatain® Silicone is designed to expand and conform to the wound bed avoiding the gap/dead space between the wound bed and dressing where otherwise exudate can pool. Due to this feature, Biatain® Silicone may perform to the same degree as primary dressing such as an alginate or a hydrofiber in combination with a secondary dressing and thereby lower treatment cost as only one wound care product would be required (Biatain® Silicone) instead of two (alginate/hydrofiber and a secondary dressing).

This investigation aims to assess the clinical performance and cost-effectiveness of Biatain® Silicone compared to current standard of care (filler, that functions as a primary dressing to manage exudate and the gap/space between the wound bed and the dressing, covered by a secondary dressing on top) defined in this study as Mepilex® Border and AQUACEL® Extra Hydrofiber Dressing, in the treatment of chronic wounds - venous leg ulcers and diabetic foot ulcers with wound depth down to 20 mm.

3. Objectives of the clinical investigation

3.1. Primary objective

The **primary objective** is to demonstrate that the clinical performance of Biatain® Silicone is comparable to standard of care (Mepilex® Border and AQUACEL® Extra Hydrofiber Dressing)

3.2. Secondary objective

The **secondary objective** is to evaluate the cost-effectiveness of Biatain® Silicone compared with standard of care (Mepilex® Border and AQUACEL® Extra Hydrofiber Dressing).

4. Investigational test product and comparators

The investigational test product and the comparator products will be used according to intended use and indications during the investigation.

4.1. Description of investigational test product

The Biatain® Silicone dressing was fist CE-marked in 2013 and consists of a sterile foam dressing with soft adhesion. The product is indicated for a wide range of low - to highly exuding wounds*. This includes acute wounds such as donor sites, post-operative wounds, and traumatic wounds; and chronic wounds such as leg ulcers, pressure ulcers and non-infected diabetic foot ulcers.

The product has classification as Sterile class IIb.

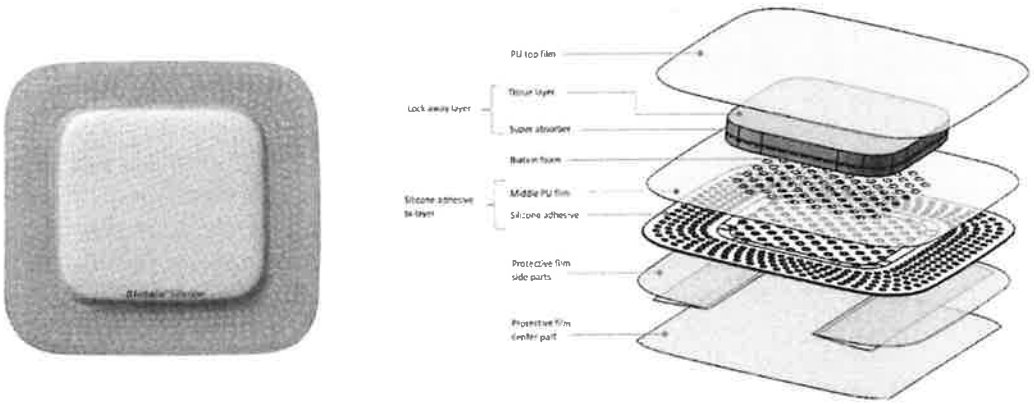

Figure 1: Investigational test product, Biatain® Silicone

Biatain® Silicone is available in different sizes and shapes, as referred to in section 4.3.
The essential components of Biatain® Silicone are demonstrated in Figure 1.

Biatain® Silicone consist of five layers:

- Polyurethan (PU) top film, a 25 µm semi-permeable barrier of PU that is printed with dots
- Tissue layer, a tissue layer of cellulose fibers
- Super absorber layer, a cellulose fiber matrix with super absorbing particles
- Biatain foam, a PU foam with a thickness of 1.7 mm
- Silicone adhesive layer, composed of a middle PU film with a silicone adhesive gel

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* Exuding wounds can be categorized into low, moderate, and high exuding wounds and are defined as follows:
Low exuding: Requires dressing changes less frequently than every 2nd day during use of a conventional dressing (e.g., gauze) or every 3rd day during use of a modern absorbent dressing (e.g., foam, hydrocolloid). Moderate exuding: Requires dressing changes every 2nd day or more frequent during use of a conventional dressing or every 3rd day or more frequent during use of a modern absorbent dressing. High exuding: Requires daily or more frequent dressing changes during use of a conventional dressing or every 2nd day or more frequent during use of a modern absorbent dressing.

Besides the five layers, the silicone adhesive is protected by protective films (release liners), which are to be removed prior to application.

4.2. Manufacturing

Coloplast A/S, Holtedam 1-3, 3050 Humlebæk, Denmark, is the manufacturer of the CE marked investigational test product Biatain® Silicone.

4.3. Identification and traceability of the investigational test product

The investigational test product will be identified as Biatain® Silicone and will in this investigation be available in 5 different sizes:

- 7.5 cm x 7.5 cm
- 10 cm x 10 cm
- 12.5 cm x 12.5 cm
- 15 cm x 15 cm
- Heel 18 cm x 18 cm

The investigational test products and comparator products are labelled as per regulations and include "Exclusively for Clinical Investigational Use" on the label. The devices are also identified with investigation number, product name/code, and item/lot number and accounted for through a master sponsor accountability log.

Upon Ethics Committee approval, investigational test products and comparator products will be shipped to the local Principal Investigator (PI), or delegate. Additionally, all investigational test products and comparator product will be accounted for and documented on a site accountability log. The receipt and disposition of all investigational test products and comparator products will be verified though monitoring. All unused products will be returned to Coloplast at the conclusion of the investigation.

4.4. Intended use of the investigational test product

Biatain® Silicone is intended to be used for moist wound healing and exudate management.

Intended mode of action:

The primary intended mode of action of Biatain® Silicone is to create and maintain a moist wound healing environment and manage wound exudate.

The secondary intended mode of action is the silicone adhesive layer of Biatain® Silicone which is designed to adhere to the skin in a secure, skin-friendly manner and provide an atraumatic removal of the dressing. See instruction for use (IFU) in Appendix 1.

4.5. Intended population for the investigational test product

Biatain® Silicone is indicated for a wide range of low- to highly exuding wounds. This includes acute wounds such as donor sites, post-operative wounds, and traumatic wounds; and chronic wounds such as leg ulcers, pressure ulcers and non-infected diabetic foot ulcers.

4.6. Handling of the investigational test product

The handling of Biatain® Silicone is described in detail in the IFU, which is included in the box containing the device. Storage conditions are also stated in the IFU.

All Principal Investigators, and delegates will receive training by sponsor and/or PI in handling and correct use of the investigational test products.

For further details regarding Biatain® Silicone, please refer to the IFU in Appendix 1.

4.7. Total number of test products intended for the clinical investigation

The subjects will be included for 4 weeks of investigation. On average, it is expected that subjects will require 1-3 dressing changes/week. Therefore, each subject is expected to use a maximum of 12 products during their participation.

4.8. Description of the comparator products

Mepilex® Border is a CE-marked soft silicone full-adhesive wound care dressing intended for moist wound healing (Figure 2). The dressing is produced and marketed by Mölnlycke Health Care. Mepilex® Border is a five-layer bordered foam dressing, indicated for the management of a wide range of exudating wounds, such as leg and foot ulcers, pressure ulcers, surgical and traumatic wounds. See IFU in Appendix 2.

Mepilex® Border will be available in the following sizes in this investigation:

- 7 cm x 7.5 cm
- 10 cm x 10.5 cm
- 15 cm x 17.5 cm
- Heel 22 cm x 23 cm

Figure 2: Investigational comparator product, Mepilex® Border

AQUACEL® EXTRA™ Hydrofiber® Dressing is a CE-marked sterile, white, fibrous dressing derived from 100% sodium carboxymethylcellulose. It is a versatile, primary dressing indicated for use on moderately and highly exuding chronic and acute wounds. The dressing is produced and marketed by ConvaTec. The indication for using AQUACEL® EXTRA™ Hydrofiber® Dressing is for the management of leg ulcers, pressure ulcers, diabetic ulcers, surgical wounds, traumatic wounds and for exudate absorption. Please refer to the IFU in Appendix 3.

AQUACEL® EXTRA™ Hydrofiber® Dressing will be available in the following sizes in this investigation:

- 5 cm x 5 cm
- 10 cm x 10 cm

Figure 3: Investigational comparator product, AQUACEL® EXTRA™ Hydrofiber® Dressing

The investigational comparator products will be used according to intended use and indications during the investigation.

5. Design of the clinical investigation

5.1. General

The clinical investigation is a two-arms, open-labelled, stratified, randomized, controlled, multicentre investigation comparing the clinical performance of Biatain® Silicone with standard of care in chronic wounds with wound depth down to 20 mm.

In total 100 eligible subjects will be randomised to one of two groups receiving either Biatain® Silicone or Mepilex® Border and AQUACEL® EXTRA™ Hydrofiber® Dressing.

Subjects will be stratified according to one of the two chronic wound types: venous leg ulcers or diabetic foot ulcers to account for differences in healing patterns. The subjects will be enrolled at >12 sites in the UK.

The subjects will have a weekly scheduled visit, V1-V5 (- 2 days) during a four-week investigational test period where the wound will be assessed, and the investigational test product or comparator products will be applied. Furthermore, the subject will respond to a questionnaire and discuss any adverse events. (Figure 4 shows the design of the clinical investigation). If needed, unscheduled visits can be performed between the weekly scheduled visits. The weekly scheduled site visits can be performed at the subject´s home if the site provides this service. Sites conducting visits at patients' homes, should follow the NHS Lone Working Policy and any applicable local Trust procedures. Many wound care patients have reduced mobility and some tissue viability services conduct home visits as part of usual care. Home visits for this study should only be conducted at sites where such visits are part of routine care and usual service.

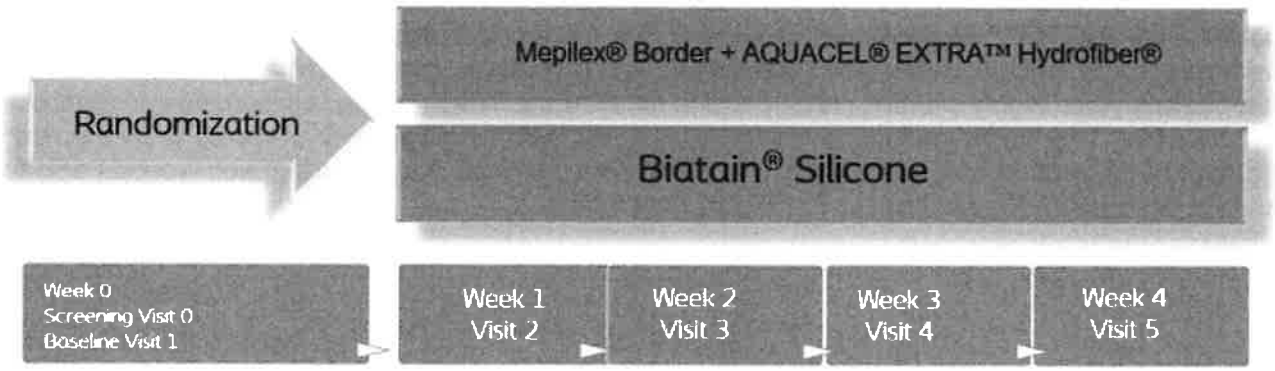


Figure 4: Design of the clinical investigation

Eligible subjects are invited to a Screening Visit (V0). The subjects will be consented prior to any study related procedures. The subjects must be given at least 24 hours to consider their participation, but if the subjects wish to, the Screening visit (V0) and Baseline (V1) visit can be combined and performed on the same day. V0 can be done remotely.

Informed Consent will be signed at the Baseline Visit (V1). After the 4-week investigational test period, a termination visit (V5) will be conducted to complete all 4 test weeks.

Withdrawn subjects must also complete the Termination visit, regardless of the reason for withdrawal. Extra visits for additional wound assessments and dressing changes due to a clinical need will be registered as unscheduled visits. See section 7.2 for clinical investigation related procedures and assessments.

If the wound condition changes during the investigation and requires another treatment, based on a clinical evaluation, the PI or delegate must change the dressing regime and document the alternative treatment or therapy. The subject must continue in the investigation and all procedures must be performed, if possible.

[redacted]

5.2. Primary endpoint

- Percentage wound area reduction during the investigational test period of four weeks

5.3. Secondary endpoints

- Total treatment costs during the investigational test period based on the number of dressings used during the investigation and the unit price of the products

5.4. Exploratory Endpoints

- Percentage wound depth reduction during the investigational test period
- Wound bed, wound edge and peri wound skin condition based on visual assessment by PI, or delegate during the investigational test period, based on an adapted version of the Coloplast Wound Assessment Form
- Conformability of the dressing based on PI, or delegate´s evaluation according to a 5-point Liker scale
- Responder defined as a subject reaching ≥ 30% wound area reduction within the 4-week investigational test period (Yes/No)
- Wound healed during the investigation period (Yes/No)
- Quality of Life evaluated by EQ-5D-5L:
  - The index score based on the value set published for UK
  - VAS score on overall health

Assessments:

Safety:

- Adverse events
- Device deficiencies

[redacted]

5.5. Rationale for selection and measurement of endpoints

The endpoint "Percentage wound area reduction during the investigational test period of four weeks has been selected as the primary endpoint in this investigation. Previous investigations have shown that percentage area reduction is an important indicator for differentiating between healing and non-healing wounds in the first weeks of treatment (6, 7), and for this reason, this has been selected as a primary end point, as an indicator of total wound healing.

To evaluate clinical performance in terms of wound area reduction as an indication of total wound healing, manual wound area measurements with a ruler would be the preferred option, as it is simple and easily available to all practitioners (8),(9). However, there is a risk of overestimating wound area with up to 40%, when using this method (9). For this reason, a planimetric software will be used where the wound is photographed with a ruler or a marker of known dimensions placed at the skin near the wound edge and the image is transferred to a computer and opened in the planimetric software. The ruler or marker is used for calibration of linear dimensions at the image. Once the wound border is manually traced with a computer mouse the area of wound is calculated and displayed.

The picture of the wound will be performed and uploaded by PI or delegated site personnel. The wound dimensions will be manually traced and calculated using a digital photo-planimetry software system.

The secondary endpoint is an objective measurement to evaluate the cost-effectiveness of the investigational product to determine if Biatain® Silicone can replace two dressings (a filler and secondary dressing) as a cost-effective alternative. Cost-effectiveness will be evaluated by the difference in total treatment costs between the two treatments over the period of the study, based on the number of products used during the investigational period and the unit price of the dressing at the time of investigation.

The exploratory endpoints are objective parameters related to the clinical performance to support the primary endpoint, as well as subjective parameters related to subject self-assessment of their quality of life, which is an important patient health outcome measure.

Adverse events and device deficiencies will be collected to ensure safety of the intervention.

5.6. Demography and potential compromising factors

The following baseline data will be collected and reported at the Baseline Visit (V1) by the Principal Investigator or delegate:

- Age (years) at time of inclusion
- Height (cm)
- Weight (kg)
- Gender (male/female)
- Smoking (yes/no)
- Alcohol (units per week)
- Comorbidities affecting wound healing (diabetes, venous insufficiency, peripheral arterial disease, cardiopulmonary conditions, immune deficiencies, dementia or other as assessed relevant by investigator)
- Concomitant medication
- Wound type (VLU or DFU)
- Duration of wound (date of onset)
- Wound dressing at time of inclusion
- Wound size (measured by photo uploaded in a digital photo-planimetry software system)

- Wound depth (mm)

To ensure optimal conditions for wound healing for VLUs, compression therapy must be performed, according to standard of care, such as compression therapy-bandage, compression sock, or other.
To ensure optimal conditions for wound healing for DFUs, off-loading must be performed according to standard of care based on subject need (wound location), preference and resources available. Methods of off-loading must be documented. Common methods to off-load the foot include bed rest, wheelchair, crutch-assisted gait, total contact casts, felted foam, half shoes, therapeutic shoes, and removable cast walkers.
Subjects who may require another dressing than the investigational test product(s) (e.g., an antimicrobial dressing superabsorbent dressing or other) will be followed during the four weeks follow-period. If other relevant wound care products are required to be used in addition to the test products, as part of standard of care (e.g., barrier cream), this must be recorded.

5.7. Equipment

The wound area is measured by an electronic Clinical Outcome Assessment (eCOA) solution delivered by Medidata Solutions Inc. that enables the PI or delegate to take a photo of the wound at every scheduled site visit. The photos are uploaded, stored, and analysed within an Imaging system delivered by Medidata Solution Inc. (Please refer to section 11 Data Management).

5.8. Randomization Procedure

All included subjects that meet the inclusion and exclusion criteria will be randomized to one of two treatment groups. Randomization will be centralized using Medidata RAVE and stratified based on wound type (VLU or DFU).

5.9. Blinding

No blinding will be used in this investigation, as it is not possible to blind the products due to visible differences. The trial statistician will be blinded until database lock to ensure decisions related to data before database lock do not affect the final results.

5.10. Total expected duration of the clinical investigation

The dates below are approximate, and no subjects will be enrolled before all required approvals have been obtained. If changes are required, applicable EC and regulatory authorities will be notified. The end of the investigation is defined as the date of the last visit of the last subject.

First subject enrolled: January 2023

Last subject enrolled: January 2024

Last subject completed: February 2024

Final Report: August 2024

6. Clinical Investigation population

According to the sample size calculation (see section 10.2), 80 subjects are required to complete the study. Assuming a drop-out rate of 20%, the required total number of subjects to be enrolled shall be 100. The subjects will be enrolled at >12 sites.

6.1. Eligibility criteria

To be included in the investigation, the subjects must comply with the selection criteria described below.

6.1.1. Inclusion criteria

Table 2: Inclusion criteria

Inclusion criteria	Justification
1. Has given written consent to participate by signing the Informed Consent Signature Form	To meet Helsinki declaration
2. Is at least 18 years of age and has full legal capacity	To meet Helsinki declaration
3. Has a venous leg ulcer (VLU) (C6 of the CEAP classification(1)) or a non-infected diabetic foot ulcer (DFU) with a duration longer than 8 weeks but no longer than 24 months (Appendix 4)	VLUs and DFUs are some of the most prevalent chronic wounds., they are both categorized as hard to heal ulcers and are most likely to require filler and secondary dressing due to exudate levels and dimensions of the wounds. To ensure reasonable recruitment time, both wound types will therefore be included in the study, and stratification will be made to ensure equal distribution of both wound types in the two arms
4. Has a wound with depth[1] down to 20 mm	To comply with product specification of Biatain ® Silicone in terms of conformability
5. Has a maximum wound depth[1] relative to wound diameter[2] with specifications presented in table 1	To quantify conformability, it is essential to ensure that the dressing can conform relative to the width of the wound, which means how the foam increases in height (the swelling rise), when exposed to wound fluids, relative to the diameter of the wound. In Coloplast, the definition of a wound bed conforming dressing is defined as a dressing that conforms to an Alpha (α) value of 0.2, which is also the lower specification limit for Biatain® Silicone (18).However, swelling rise has demonstrated to reach maximum of ~ 2 cm in tests with fence sizes (simulated wound diameter) ≥ 6 cm (19). Thus, wound-α is therefore not relevant for these wounds in this study due to inclusion criteria #4.
6. Has a wound with exudate levels requiring a filler and a standard secondary dressing	To include wounds that would normally require the comparator dressing regime and ensure that the treatment is aligned with the indications of the dressings

7. Has acceptance of compression therapy in case of a VLU or off-loading in case of a DFU, according to local standards	To ensure optimal conditions for wound healing, compression therapy must be performed for VLUs, according to standard of care. For DFUs, off-loading must be performed according to standard of care based on subject need (wound location), preference and resources available
8. For subjects with diabetes, has HbA1c ≤ 10% or ≤ 86 mmol/mol, measured within the last 3 months prior to inclusion	To mitigate the risk of reduced healing due to poorly managed diabetes

[1] *depth at the deepest point in the wound bed*
[2] *diameter measured at the widest point of the wound*

Table 1: Specifications related to Inclusion criteria 5

Wound diameter (cm)	Maximum wound depth (mm)
6.0-10	20
5.5-5.9	11
5.0-5.4	10
4.5-4.9	9
4.0-4.4	8
3.5-3.9	7
3.0-3.4	6
2.5.2.9	5
2.0-2.4	4
1.5-1.9	3
1.0-1.4	2

6.1.2. Exclusion criteria

Table 3: Exclusion criteria

Exclusion criteria	Justification
1. Wound is infected. For DFUs, has infection severity mild-severe according to the IWGDF/IDSA guideline (Appendix 5). For VLUs, has 2 or more clinical signs of infection as defined in protocol, based on clinical judgement by investigator/tissue viability nurse (Appendix 6)	Anti-microbial dressings are usually used for infected wounds in this study setting, according to recommendation. For identification of infection in DFUs, the validated IWGDF/IDSA system will be used. No similar validated scoring system currently exist for VLUs. For this reason, clinical signs are used as an indicator of infection according to clinical practice; The presence of 2 or more clinical signs of infection, will exclude subjects with VLUs from participating in the study.
2. Wounds is with exposed tendons, is with bones or has fistulas	Complicated wounds which may require different treatments and have different healing patterns
3. Wound is with cavity, or is undermined or tunnelling	Due to potential depth of wounds
4. Subject is receiving chemotherapy	The skin undergoes major changes because of radio- and/or chemotherapy, and therefore it can be more fragile during wound management.
5. Subject has ankle-brachial pressure index (ABPI) below 0.8 (measured at a frequency according to local standards)	Compression therapy is contraindicated in subjects with low ABPI
6. Wound is larger than 10 x10 cm	Larger wounds are likely to have a higher %-area reduction which may cause bias in the overall sample size.
7. Currently enrolled in another wound care device investigation unless co-enrolment has been agreed with the sponsor	To avoid bias

6.2. Recruitment and enrolment

The recruitment of potential subjects will commence only once authorisation has been received from the respective Ethics Committee. Recruitment will occur through competitive enrollment in UK. The recruitment period from first subject enrolled to last subject enrolled will be approximately 12 months.

Recruitment will be via admitted patients in recruiting sites with hospitals, outpatient clinics, community collaborations, subject screening visits or subject records kept at the participating sites and advertisement in paper form and/or digital platforms.

6.2.1. Screening of potential subjects

If a subject is potentially eligible and interested in participating, written information about the investigation (Patient Information Sheet) will be provided to the subject to ensure they are given the opportunity to understand what the investigation is about. Subjects will have time to ask the PI, or delegate, any questions they may have. The subject information provides information to subjects about how to contact the local Principal Investigator or a representative thereof if they wish to learn more about the investigation.

For subjects with more than one eligible wound, only a single wound can be included in the investigation.

If a potentially eligible subject is interested in participating in the investigation a screening visit will be arranged. When arranging the visit, the subject must receive the Patient Information Sheet and given adequate time to review it. The subject will receive both written and verbal information about the possibility of bringing a companion to the visit and to any possible subsequent visits.

The subject has the right to wait before deciding to participate. If/when the subject decides to participate, he/she will be asked to sign the Informed Consent Form If a subject so desires, and it is certain that it is understood what the investigation entails, and the Informed Consent Form has been signed, the subject is considered enrolled/included in the investigation.

The clinical monitor will have close contact with each site during the recruitment period. The PI, or delegate, at each site will notify the clinical monitor when a subject is enrolled and all future planned visits.

Sites will recruit subjects with both VLU's and DFU's. The subject will be stratified according to wound type. It is not required to have an equal number of subjects with VLU's and DFU's. When the Coloplast Clinical Manager becomes aware that 100 subjects have been included and randomised, the recruitment will stop. If, at this time, there are subjects who have been informed of the investigation and are reflecting on participation, they will be given the opportunity to be included within the first 24 hours hereafter.

6.3. Subject withdrawal criteria

A subject can withdraw from the investigation at any time for whatever reason without any consequences for their future treatment outside the clinical investigation. The Investigator may withdraw a subject from the investigation at any time if they judge it to be in the subject's interest.

The investigator must withdraw a subject from the investigation due to:

- Major noncompliance with the Clinical Investigation Plan (CIP) impacting the scientific integrity of the investigation.
- If subject's safety and wellbeing is compromised by further participation.
- Subjects lost to follow-up. At least three documented attempts of contact (phone and/or written) will be made to verify subjects lost to follow-up.

6.4. Point of enrolment

A subject is considered enrolled/included in the investigation when written informed consent is obtained.

6.5. Screening Failures and randomisation failures

Subjects that have signed the informed consent form but fail to comply with inclusion or exclusion criteria are considered screening failures.

A subject can be randomized by mistake e.g., if the investigator realizes that the subject is not eligible after the subject has been randomised. If the subject has not started study treatment and has no data registered on endpoints the subject can be replaced by a new subject if the new subject can complete the investigation within timelines (before last subject last visit and within visit windows).

If a subject is randomized to one product but by mistake gets the opposite product it will be regarded as a randomization failure. As this is an exploratory investigation the statistical analyses will in that case be based on the actual product and not the randomized product.

6.6. Subject Identification and Confidentiality

Subjects will be identified in the electronic CRF (eCRF) and any other document transmitted to the sponsor by the principal investigator or clinical site staff, by a unique identification number (subject number).

Data entered into the eCRF are confidential and will only be available to the sponsor (including sponsor delegates), members of data management teams, the statistician and if requested to regulatory authorities.

The Principal Investigator at each clinical investigational site will maintain, as part of the investigator site file, a list identifying all subjects entered in the clinical investigation (Subject Identification Code and Enrolment List). This list is confidential to all others than the Principal Investigator, or designee at the site.

7. Procedures

7.1. Clinical investigation-related procedures

Before initiation of the clinical investigation, Coloplast must be provided with a signed and dated curriculum vitae from the Principal Investigator and delegated personnel from each participating site (curriculum vitae not more than two years old) to verify qualifications. Coloplast will ensure that the Principal Investigator and delegated site personnel are trained in the investigational procedures, completion of the eCRFs, procedure for reporting a device deficiency, an adverse event or serious adverse event and who to contact in case of emergency related to the investigational products.

See section 7.3: Schedule of Assessments for an overview of the clinical investigation-related procedures during the investigation.

7.2. Clinical investigation related procedures and assessments

Screening Visit (V0), week 0:

- Introduction to the investigation and review of Patient Information Sheet/Informed Consent Form
- Distribution of Patient Information Sheet/Informed Consent Form
- Review of Inclusion- and exclusion criteria
- Scheduling Baseline Visit (V1) within 3 days unless performed the same day as Screening Visit (V0)

Baseline Visit (V1), week 0:

- Introduction to the investigation reviewed and confirmed
- Checking and verification of Inclusion- and exclusion criteria
- Signing of Informed Consent Form
- Enrolment in the investigation and allocation of subject number
- Collect Baseline information:
    - Age (years) at time of enrolment
    - Height (cm)
    - Weight (kg)
    - Gender (male/female)
    - Smoking (yes/no)
    - Alcohol (units/week)
    - Comorbidities affecting wound healing (diabetes, venous insufficiency, peripheral arterial disease, cardiopulmonary conditions, immune deficiencies, dementia or other as deemed relevant by investigator)
    - Wound type; venous leg ulcer or diabetic foot ulcer
    - Duration of wound (date of onset)
    - Wound treatment at time of inclusion
    - Wound size (measured by photo uploaded to a digital photo-planimetry software system)
    - Wound depth (mm)
    - For Venous Leg Ulcers: compression therapy –bandage, compression sock, other (yes/no)
    - For Diabetic Foot Ulcers: offloading (bed rest, wheelchair, crutch-assisted gait, total contact casts, felted foam, half shoes, therapeutic shoes, removable cast walkers, other).
    - Record concomitant medication.

- Cleansing of wound according to standard of care
- Debridement (yes/no)
- Photo of wound and upload to a digital photo-planimetry software system
- Wound assessment based on the Coloplast Wound Assessment Form (Appendix 7)
- Rave Randomization
- Dressing application according to randomization and record of dressing size used
- Additional relevant wound care products (e.g., barrier cream)
- Quality of Life assessment (Appendix 8)
- Instruction to the subject (including sheet for dressing changes between scheduled visits)
- Review potential AE/ADE/SAE/SADE/device deficiencies/Protocol Deviations
- Scheduling Visit 2 in Week 1, 7 days (-2 days) after Visit 1
- Complete eCRF
- Perform device accountability

[redacted]

Site visit (V2), Week 1:

- Number of dressing changes since last scheduled visit and device accountability
- Cleansing of wound according to standard of care
- Debridement (yes/no)
- Photo of wound and upload to a digital photo-planimetry software system
- For patients treated with Biatain® Silicone: photo of the dressing next to the wound bed must also be taken to assess conformability with wound bed and uploaded to a digital photo-planimetry software system
- Wound depth (mm)
- Wound assessment based on the Coloplast Wound Assessment Form (Appendix 7)
- Status of wound
- Wound healed (yes/no) if yes, the following assessments do not require completion: cleansing of wound, debridement, wound depth, wound assessment based on the Coloplast Wound Assessment Form, dressing application according to randomization, additional relevant wound care products and changes in wound dressing
- Dressing application according to randomization and recording of dressing size
- Additional relevant wound care products (e.g., barrier cream)
- Record any changes in wound dressing and specify reason and product(s)
- Record any changes in concomitant medication
- Review potential AE/ADE/SAE/SADE/device deficiencies/Protocol Deviations
- Scheduling next Study visit in the following week.
- Visit 3 must be 14 days after Visit 1 (-2 days)
- Complete eCRF

Site visit (V3), Week 2:

- Number of dressing changes since last scheduled visit and device accountability
- Cleansing of wound according to standard of care
- Debridement (yes/no)
- Conformability assessment on a 5-point Liker scale
- Photo of wound and upload in a digital photo-planimetry software system
- For patients treated with Biatain® Silicone: photo of the dressing next to the wound bed must also be taken to assess conformability with wound bed and uploaded to a digital photo-planimetry software system
- Wound depth (mm)
- Wound assessment based on the Coloplast Wound Assessment Form (Appendix 7)
- Status of wound
- Wound healed (yes/no) if yes, the following assessments do not require completion: cleansing of wound, debridement, wound depth, wound assessment based on the Coloplast Wound Assessment Form, dressing application according to randomization, additional relevant wound care products and changes in wound dressing
- Dressing application according to randomization and recording of dressing size
- Additional relevant wound care products (e.g., barrier cream)

- Record any changes in wound dressing and specify reason and product(s)
- Record any changes in concomitant medication
- Review potential AE/ADE/SAE/SADE/device deficiencies/Protocol Deviations
- Scheduling next Study visit in the following week.
- Visit 4 must be 21 days after Visit 1 (-2 days)
- Complete eCRF

[redacted]

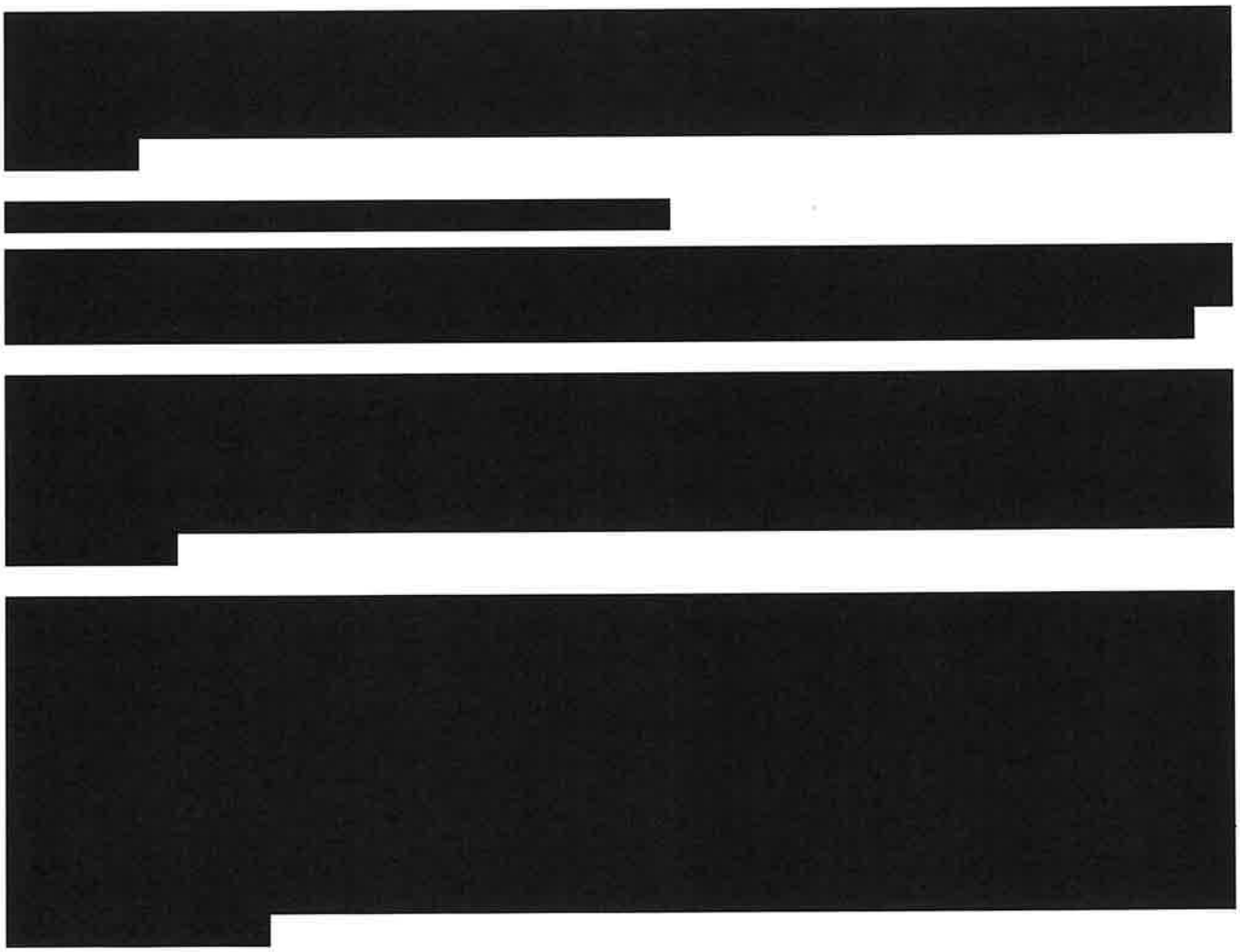
Site visit (V4), Week 3:

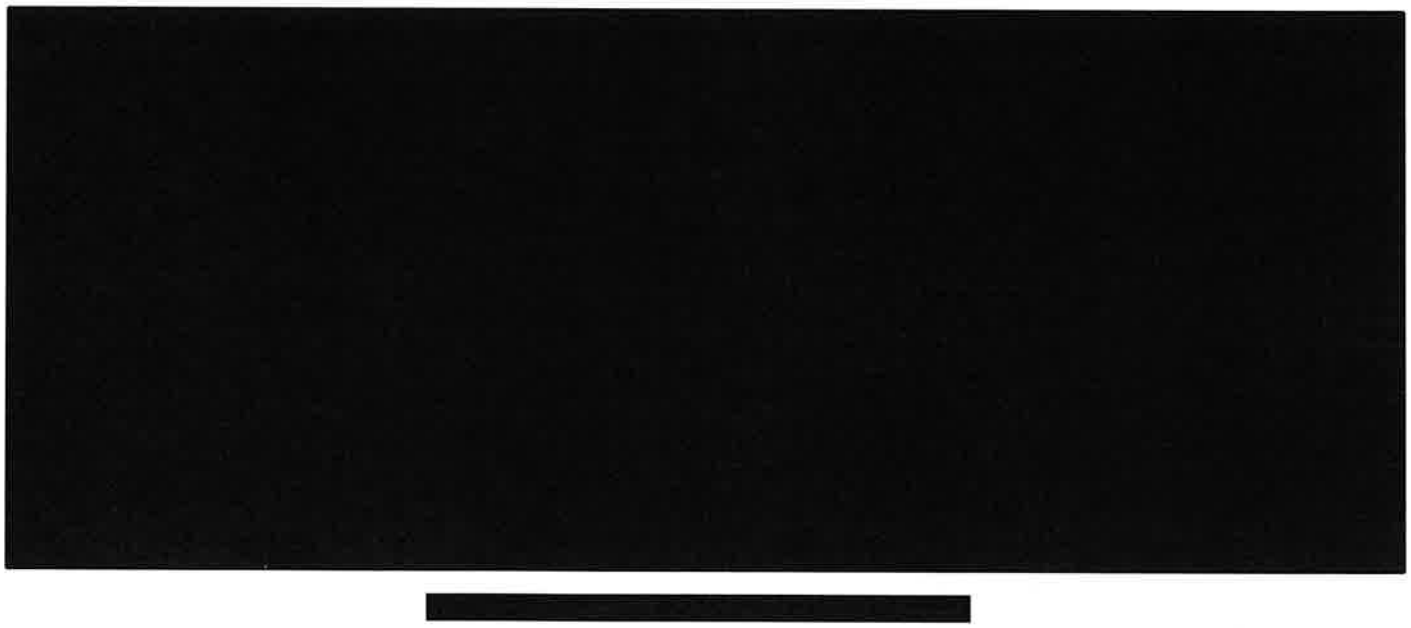
- Number of dressing changes since last scheduled visit and device accountability
- Cleansing of wound according to standard of care
- Debridement (yes/no)
- Photo of wound and upload to a digital photo-planimetry software system
- For patients treated with Biatain® Silicone: photo of the dressing next to the wound bed must also be taken to assess conformability with wound bed and uploaded to a digital photo-planimetry software system
- Wound depth (mm)
- Wound assessment based on the Coloplast Wound Assessment Form (Appendix 7)
- Status of wound
- Wound healed (yes/no) if yes, the following assessments do not require completion: cleansing of wound, debridement, wound depth, wound assessment based on the Coloplast Wound Assessment Form, dressing application according to randomization, additional relevant wound care products and changes in wound dressing
- Dressing application according to randomization and recording of dressing size
- Additional relevant wound care products (e.g., barrier cream)
- Record any changes in wound dressing and specify reason and product(s)
- Record any changes in concomitant medication
- Review potential AE/ADE/SAE/SADE/device deficiencies/Protocol Deviations
- Scheduling next Study visit in the following week.
- Visit 5 must be 28 days after Visit 1 (- 2 days)
- Complete eCRF

Termination Visit (V5), Week 4:

- Number of dressing changes since last scheduled visit and device accountability
- Cleansing of wound according to standard of care
- Debridement (yes/no)
- Conformability assessment on a 5-point Liker scale
- Photo of wound and upload to a digital photo-planimetry software system
- For patients treated with Biatain® Silicone: photo of the dressing next to the wound bed must also be taken to assess conformability with wound bed and uploaded to a digital photo-planimetry software system

- Wound depth (mm)
- Wound assessment based on the Coloplast Wound Assessment Form (Appendix 7)
- Status of wound
- Wound healed (yes/no) if yes, the following assessments do not require completion: Cleansing of wound, debridement, wound depth, wound assessment based on the Coloplast Wound Assessment Form, dressing application according to randomization, additional relevant wound care products and changes in wound dressing
- Additional relevant wound care products (e.g., barrier cream)
- Record any changes in wound dressing and specify reason and product(s)
- Record any changes in concomitant medication
- Review potential AE/ADE/SAE/SADE/device deficiencies/Protocol Deviations
- Quality of Life assessment (Appendix 8)
- Handover to routine care
- Complete eCRF





7.2.2. Dressing changes between site visits

If the wound requires frequent dressing changes (more than once scheduled visit per week), unscheduled visits at the site can be scheduled for dressing changes.

The dressing change can also take place at the subjects home by the subject or by a homecare nurse. The subject will be provided with the additional study products to which he/she is allocated at each visit to use at home in case of additional dressing changes in between visits. An information sheet for the homecare nurse will be distributed to the subjects to be shared with the homecare nurse, providing information about the study and the study treatment to ensure that the protocol is followed between scheduled visits.

In the event of a completed dressing change between the weekly scheduled visits, it must be documented at the next scheduled weekly visit in the eCRF to capture the total number of dressings since last scheduled visit. The subject will be instructed to complete a sheet for dressing changes between the scheduled weekly site visits capturing the dressing change and date of the event.

No clinical investigation-related wound assessments are conducted during the unscheduled visits and/or dressing changes at the subjects home. Cleansing of wound must be done according to standard of care and debridement, if needed. The dressing applications between weekly scheduled visits must be according to randomization.

The total number of dressings, the sizes of the dressings used and frequency of dressing changes per subject is part of the cost-effectiveness analysis.

7.3. Schedule of clinical related procedures and assessments

Table 4: Chart showing the connection between visits and assessments.

	PER-FORMED BY	SCREEN-ING VISIT	BASELINE VISIT	VISIT 2	VISIT 3	VISIT 4	TERMI-NATION VISIT	UNS VISIT
VISIT	-	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	
WEEK	-	**WEEK 0**	**WEEK 0**	**WEEK 1**	**WEEK 2**	**WEEK 3**	**WEEK 4**	
VISIT WINDOW	-	-	**0-3 days after V0**	**-2 days 7 DAYS**	**-2 days 14 DAYS**	**-2 days 21 DAYS**	**-2 days 28 DAYS**	
GENERAL								
Introduction to the investigation and review of Patient Information Sheet/Informed Consent Form	Investigator or delegate	X	X					
Check and verification of in- and exclusion criteria	Investigator or delegate		X					
Review of in- and exclusion criteria		X						
Informed Consent Signed	Investigator and Subject		X					
Enrollment in the investigation allocation of subject number	Investigator or delegate		X					
Randomization	Investigator or delegate		X					
Collect Baseline information	Investigator or delegate		X					
Record concomitant medication	Investigator or delegate		X					
Review of AE/ADE/SAE/SADE/device deficiencies/Protocol Deviations	Investigator or delegate		X	X	X	X	X	X
QUESTIONNAIRES AND ASSESSMENTS								
Number of dressing changes since last visit	Investigator or delegate			X	X	X	X	
Cleansing of wound according to standard of care	Investigator or delegate		X	X	X	X	X	X
Debridement yes/no	Investigator or delegate		X	X	X	X	X	

	PER-FORMED BY	SCREEN-ING VISIT	BASELINE VISIT	VISIT 2	VISIT 3	VISIT 4	TERMI-NATION VISIT	UNS VISIT
Photo of wound and upload to a digital photo-planimetry software system	Investigator or delegate		X	X	X	X	X	
Wound assessment based on the Coloplast Wound Assessment Form	Investigator or delegate		X	X	X	X	X	
Wound depth (mm)	Investigator or delegate		X	X	X	X	X	
Status of wound	Investigator or delegate			X	X	X	X	
For patients treated with Biatain® Silicone: photo of the dressing next to the wound bed must also be conducted to assess conformability with wound bed and upload to a digital photo-planimetry software system	Investigator or delegate			X	X	X	X	
Wound healed (yes/no) if yes, the following assessments do not require completion: Cleansing of wound, debridement, wound depth, wound assessment based on the Coloplast Wound Assessment Form, dressing application according to randomization, additional relevant wound care products and changes in wound dressing	Investigator or delegate			X	X	X	X	X
Conformability assessment	Investigator or delegate				X		X	
Quality of Life *assessment*	Subject		X				X	
Dressing application according to randomization	Investigator or delegate		X	X	X	X		X
Additional relevant wound care products (e.g., barrier cream)	Investigator or delegate		X	X	X	X	X	
Record any changes in wound dressing and specify reason and product(s)	Investigator or delegate			X	X	X	X	X
Record any changes in concomitant medication				X	X	X	X	X

	PER-FORMED BY	SCREEN-ING VISIT	BASELINE VISIT	VISIT 2	VISIT 3	VISIT 4	TERMI-NATION VISIT	UNS VISIT
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	
Instruction to the subject (including sheet for dressing changes between scheduled visits)	Investigator or delegate		X					
Complete eCRF	Investigator or delegate		X	X	X	X	X	X
Handover to routine care	Investigator or delegate						X	
Perform device accountability	Investigator or delegate		X	X	X	X	X	
Schedule Baseline Visit 1	Investigator or delegate	X						
Schedule Visit 2	Investigator or delegate		X					
Schedule Visit 3	Investigator or delegate			X				
Schedule Visit 4	Investigator or delegate				X			
Schedule Termination Visit V5	Investigator or delegate					X		

7.4. Case Report Forms

All assessments, questionnaires, and observations throughout the investigation for each subject must be carefully recorded in an electronic CRF (eCRF). Details about data capture can be found in section 11 (Data Management).

eCRFs will be completed by the Principal Investigator or delegate, who have signed the Site Personnel Signature and Delegation List and Clinical Investigation Training Log. The delegated site personnel will be required to complete e-learning prior to system access. After completed training delegated personnel will receive credentials.

It is the responsibility of the investigator to ensure that all data, all measurements, and observations are entered promptly and correctly and preferably immediately after the subject has been at site or after a phone call. In case this is not possible the data should be entered no later than 7 days after the visit / procedure.

7.5. Concomitant treatment

Concomitant treatment is any medication or medical product which is taken or used during the investigation period.

If other relevant wound care products are required to be used in addition to the study products, as part of standard of care (e.g., barrier cream), this must be documented as well.

Subjects who may require another dressing than the investigational test product(s) (e.g., an antimicrobial dressing superabsorbent dressing or other) will be followed during the four-week investigation period and included in the ITT (intention to treat) analysis but excluded from the PP (per protocol) analysis. The subjects will follow the study procedures except for conformability assessment if possible.

7.6. Supplementary materials and equipment

The Sponsor will provide the Principal Investigators with supplementary materials for the investigation such as computers with access to eCRF if needed and phones with the Medidata eCOA solution installed to obtain photos.

[redacted]

8. Risk – benefit analysis and ethical considerations

8.1. Risk-benefit analysis of the investigational test product

The investigational test products are already CE-marked and will be used according to the IFU.

8.2. Risk-benefit for subjects participating in the clinical investigation

The investigation is conducted in accordance with current law and applicable standards, see section 15. Statement of Compliance. The rights, safety and well-being of human subjects shall prevail over the interest of science of society.

Risks in this investigation are considered equal to the use of other wound care products on the market. Risks associated with the use of wound care products are skin irritation/inflammation, maceration, pain, hyper granulation, and blistering. Section 18 Adverse Events and Adverse Device Effects describe the risks in detail.

There is no known interaction between the use of the investigational test product and the medication that subjects can take. except for what is stated in the exclusion criteria. Disadvantages of testing (trial engagement) may be time spent on visits and responding to questions during visits.

The participating subjects will contribute with important information on the use of wound care products and the socio-economic benefits. Possible benefits for the subjects may be wound healing with fewer products.

8.3. Risk Analysis for the conduct of the clinical investigation

A risk assessment of the clinical investigation will be conducted initially prior to the first subject enrolment and will be periodically re-assessed based on any new risks identified through the process. This assessment will be completed throughout the duration of the investigation, as defined by the study team. A risk-based monitoring strategy may be implemented including on-site remote, and central monitoring. Details of the strategy are defined in the monitoring plan in Section 9.

8.4. Delegation of responsibility

Before initiation of the clinical investigation, sponsor must be provided with key personnel signed and dated curriculum vitae (not more than 2 years old) to verify their qualifications. Key site personnel are those, who treat or evaluate subject data in the clinical investigation. Also, the sponsor will ensure that all site personnel are trained in the investigation procedures, how to complete the eCRFs, procedure for reporting an adverse event or serious adverse event (how, when, to whom), and who to contact in case of emergency related to the investigational device.

9. Monitoring Plan

The sponsor is responsible for ensuring appropriate monitoring of the clinical investigation activities as described below. This study specific monitoring plan includes details regarding the monitoring strategy (i.e., onsite, remote, and centralized).

The clinical monitor will be the primary contact for the PI and delegates.

Monitoring activities are mandatory as per good clinical practice. However, the extend and depth of these activities depend on the criticality of the clinical investigation, speed of enrolment, the experience of the clinical investigation personnel in carrying out clinical investigations and specific study designs.

For the purpose of this clinical investigation the below described monitoring procedures have been selected.

The data collected throughout the investigation and the conduct of the investigation, will be monitored per the monitoring plan to ensure, and verify, that the rights and well-being of the subjects are protected, that the reported data are accurate, complete, and verifiable from source documents, and that the conduct of the investigation complies with the approved CIP, subsequent amendment(s), ISO14155 and the applicable regulatory requirement(s).

The monitoring process is described below.

The monitoring in this investigation will be conducted periodically at all sites by the clinical monitor.

The investigator must be available for and agree to cooperate with Coloplast clinical monitor during their visits and ensure that they have direct access to all documents that they require, including direct access to the subject's files.

The investigation will be subject to internal audits if relevant. All monitoring visits and possible audits will be followed by internal reports and corrective actions, if needed.

Follow-up letters will be forwarded to sites after all visits and any findings should be addressed by the investigator or delegate.

To ensure proper conduct of the investigation, the following visits on site will be performed before/ during the investigation:

- Site selection visit
- Site initiation visit
- Periodic monitoring visits
- Close out visits

9.1. Site selection visit

Depending on the prospective clinical investigation sites experience with the specific investigational device, an on-site qualification or site selection visit shall be performed during which the feasibility of the clinical investigation requirements will be discussed and common agreement between sponsor and Principal Investigator shall be reached. This visit may also be replaced by one or more phone calls or conducted remotely, using Microsoft Teams.

9.2. Initiation visit

All clinical investigation sites will complete an initiation visit during which full training on all aspects of the clinical investigation will be provided. The initiation visit will be held as close to the study start as possible.

Before initiation of the clinical investigation, sponsor must be provided with key personnel signed and dated curriculum vitae and documentation of current ISO14155 training (within the last two years) to verify their qualifications.

initiation visit will include training in handling of the investigational products. This visit can also be conducted on-site or remotely if the site is restricting visitors due to the Covid-19 pandemic or other unforeseeable circumstances which may prohibit site visits.

9.3. Monitoring visits

The sponsor shall determine the extent and nature of monitoring appropriate for the clinical investigation based on the risk assessment. The sponsor shall ensure, through oversight of the clinical investigation and timely adverse event reporting, that unanticipated adverse device effects are identified and investigated rapidly so that, where necessary, additional risk control measures can be implemented.

The clinical monitor is to ensure adherence to the clinical investigation plan, the safety of the subjects, accurate data recording on the eCRFs and to monitor recruitment rates and adherence to follow-up schedules. During the clinical investigation, monitors shall check that appropriate written informed consents have been obtained. The Principal Investigator shall permit and assist the monitor to carry out verification of completed eCRFs against data in the source documents.

The principal investigator can delegate tasks to his/her collaborators, however the roles and responsibilities as the time period of involvement for each clinical site personnel must be documented on the Site Personnel signature and Delegation list as well as training received before getting involved with the clinical investigation must be documented in the Clinical Investigation Training Log.

The clinical monitor shall inform the sponsor about any problems relating to facilities, technical equipment or medical staff at the clinical investigation site. The clinical monitor shall also be responsible for notifying such deficiencies in writing to the principal investigator and convene with the clinical investigation site personnel appropriate and timely corrective actions.

The sponsor, or delegate, will provide clinical monitoring, including review of eCRF with verification to the source documentation, as defined in the monitoring plan.

Before doing any review of subject data, the monitor must review the signed Informed Consent Forms and only monitor data from subjects with a correct signature on these forms. The clinical monitor shall also be responsible for notifying such deficiencies in writing to the investigator and convene with the clinical investigation site personnel appropriate and timely corrective actions.

The first monitoring visit at the site should be conducted as soon as reasonably possible after the first subject(s) has(have) completed the first visit of the investigation. This is to minimise systematic errors done by site and to clarify potential questions before proceeding with enrolment of more subjects.

Additional monitoring will be conducted in accordance with the recruitment rate or if there is a need for more frequent visits upon request from site, clinical monitor, or clinical manager.

The Investigation Site File shall be monitored for 100% completion per the Investigation File Requirement Checklist. Monitoring activities will be documented in a site visit report. A follow up summary describing the observations, including documentation of any deviations and actions required

shall be provided as soon as reasonably possible to the Principal Investigator and/or delegate after the conducted monitoring visit.

All data collected can be directly entered in the eCRF. The monitor will by edit checks ensure that all fields are completed in the eCRF. Monitor will ensure by closely monitoring, that all queries are resolved in a timely manner.

The clinical monitor will have close contact with the sites during the recruitment period to ensure that any concerns, problems, or recruitment challenges are solved with the site in a timely manner.

Only the Principal Investigator, delegated site personnel, the clinical monitor and the sponsor representatives will have access to all the eCRF records.

9.4. Source data verification

Source data is all information in original records, certified copies of original records of clinical findings, observations, or other activities in the clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. This includes source data initially recorded in an electronic format. A source document is a document in which data collected for a clinical investigation is first recorded.

All documents and data related to the clinical investigation handled by site personnel, shall be produced, and maintained in a way that assures reliability, integrity, control, and traceability, and shall be appropriately stored to provide a complete history.

The Principal Investigator shall ensure the accuracy, attribution, completeness, legibility, and timelines of the data reported to the sponsor in the eCRFs and in all required reports. All printed copies of electronic source documents shall be certified, as indicated by a dated signature by the investigational site personnel at the time the document is printed. Special requirements should be applied to the capture, review, and retention of electronic source data, to ensure reliability, quality, integrity, and traceability.

The data reported in the eCRF shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The eCRF can serve as the source document and this must be documented on the Source Data Specification Form. The Source Data Specification Form must be completed at the initiation visit detailing the location of the source data for each data point agreed upon by the Principal Investigator.

Data points for data verification:

- Informed Consent Form
- In- / Exclusion criteria
- AE/ADE/SAE/SADE/DD
- Other

Written informed consent, in- and exclusion criteria and all AE´s, ADE´s, SAE´s, SADE´s and DD occurring in the investigation will be 100% verified for timely completion for all subjects enrolled in the investigation.

9.5. Remote monitoring

Remote or centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., data management personnel, statisticians, or clinical monitors) at a location other than the site(s) at which the clinical investigations is being conducted. Remote monitoring processes can provide many of the capabilities of on-site monitoring as well as additional capabilities.

In addition to onsite monitoring visits, remote monitoring of the data entered in the eCRF system could be used to achieve the following:

- Conduct activities such as: standard checks of range, consistency, and completeness of data and checks for unusual distribution of data, such as to little variance.
- Special attention will be given in case of frequent data anomalies or errors, protocol deviations/violations or excessive dropouts.
- Augment on-site monitoring by performing monitoring activities that can only be accomplished using centralized processes.
- Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indictive of systemic and/or significant errors in data collection and reporting at the site.
- Verify source data remotely, provided that both source data and eCRF´s can be assessed remotely.
- Conduct aggregate statistical analyses of the study data for plausibility and completeness.
- Conduct analyses of site characteristics, performance metrics (e.g., high screen failure rates, high frequency of eligibility violations, and delays in reporting data), and clinical data to identify early on corrective actions needed for characteristics correlated with poor performance or noncompliance.

10. Statistical considerations

10.1. Statistical design, method, and analytical procedures

The primary objective will be evaluated by analyzing the primary endpoint whereas the analyses of the exploratory endpoints will be used to further evaluate and explore the primary objective. The secondary objective will be evaluated by analyzing the secondary endpoint.

All baseline measurements, endpoints and assessments will be summarized by descriptive statistics and/or listed. Descriptive statistics for continuous variables are presented with N, Mean, SD (standard deviation), Median, Min and Max, where N denotes the number of subjects contributing with non-missing data. For discrete variables, descriptive statistics are presented with N and percentage, where percentage is based on the total number of subjects/observations with non-missing data.

As it is an exploratory study no adjustment for multiple testing will be applied.

All statistical analysis will be performed with SAS (version 9.4/Enterprise Guide version 7.1)

Definition of analysis populations:

The Intention to Treat (ITT), Safety and Per Protocol (PP) populations will be defined at a formal data review meeting before data base lock. As a minimum, the data manager, the clinical manager, the scientific manager, and the statistician will be involved in the classification of subjects according to the below described criteria.

The ITT population (full analysis set) will be constituted by all randomized subjects with valid informed consent who have been exposed to at least one product.

The PP population will constitute a subset of ITT subjects who:

- fulfill the inclusion/exclusion criteria

- have not used other dressings than the investigational test product(s) during the study period
- Have not had a wound infection during the study period
- have not shifted therapy during the study period

Any exclusion of subjects from the ITT/PP populations must be documented.

Invalid individual datapoints may be omitted from the analysis even though the corresponding subject is part of the ITT/PP populations. Any exclusion of data points will be documented

The Safety Population will constitute by subjects who have given informed consent.

All statistical analysis will be based upon the ITT and PP populations, whereas adverse events and device deficiencies will be assessed based on the Safety population.

Considering the data obtained, it may be considered to make additional explorative analysis, based on a subset of ITT/PP populations.

Analysis of the primary endpoint:

The percent wound area reduction (WAR) will be analyzed by an analysis of variance with treatment and wound type (VLU and DFU) as fixed effects and wound area at baseline as covariate.

The mean WAR for each treatment group will be estimated together with the 95% confidence interval. Further, the difference in mean including a 95% confidence interval between the 2 treatments will be estimated.

Analysis of the secondary endpoint:

The secondary endpoint, total cost, will be calculated as the number of products used during the investigational period multiplied by the unit price of the product. Unit price will be extracted from Drug Tarif on the date of Last Patient Out.

This secondary endpoint will be analyzed by comparing the mean cost in the two groups assuming the cost data to be normally distributed. It will be tested on a 2-sided 5% test level if the difference in mean between the two treatments is zero. Further, the mean cost for each treatment will be estimated together with a 95% confidence interval.

Analysis of exploratory endpoints:

Percentage wound depth reduction will be analyzed by the same model as described for the primary endpoint but with wound depth at baseline as covariate.

Similarly, the two endpoints related to EQ-5D-5L (the index score and the VAS score) will be analyzed by an analysis of variance with treatment as a fixed effect and the baseline measure as covariate.

The two endpoints; responder defined as a subject reaching ≥ 30% wound area reduction within the 4-week investigation period (Yes/No) and wound healed during the investigation period (Yes/No) will be analyzed by a logistic regression model with treatment and wound type (VLU or DFU) as fixed effects and wound area at baseline as covariate.

Analysis of safety endpoints:

Adverse events will be listed and summarized, if relevant. Device deficiencies and concomitant medication will be listed.

10.2. Sample size

The primary endpoint is the percent WAR from baseline to week 4. The sample size calculation assumes that the standard deviation of WAR in each group will be similar to what was estimated in the Biatain-Ag meta-analysis, namely SD=43%(13).

A sample size of 40 completing subjects in each arm will result in a study that is powered by 80% to get a width of a 95% confidence interval for the difference in mean WAR between the two treatments of less than +/-21%. This is based on an analysis of assumed normally distributed data.

Further, the width of the 95% confidence interval for the estimated mean WAR in each treatment group will with high probability (power of 89%) be less than +/- 15%.

The expected width of the confidence intervals based on a total of 80 subjects is deemed adequate to be able to compare the performance of the 2 treatments.

To account for lost to follow-up/dropout rate of 20%, 100 subjects are required for this study.

10.3. Level of significance and power

A two-sided significance level of 5% will be applied. For information regarding the power see section 10.2.

10.4. Pass/fail criteria

The purpose of this investigation is fulfilled if the performance of the products in the two arms is comparable in terms of wound area, while the mean total cost for Biatain® Silicone is significantly lower than for Standard of Care.

10.5. Statistical reason for termination of investigation

There will be no interim analysis and therefore no reason to terminate the investigation based on statistical considerations.

10.6. Deviations from statistical design, method, or analytical procedures

Any deviations from the statistical plan will be documented in the clinical investigation report.

11. Data management

11.1. Data collection and data management

Data management and the final statistical analyses of all measurements described in this protocol are carried out by the Medical Affairs, Coloplast A/S.

Data will be collected through an electronic data capturing (EDC) system on electronic Case Report Forms (eCRF), a secure, internet-based case report form.

The data management system used in this investigation is Rave delivered by Medidata Solutions Inc. The system is designed to be compliant with the FDA requirements of 21 CFR part 11. It is a validated data management system allowing only qualified and trained personnel to enter the system. The system has full audit trail and electronic signature. The system has restricted role-based access control.

Rave EDC, current version 2022.1.1 will be used to collect all study data.

The applications Medidata eCOA and Rave Imaging will be used to collect and measure photos of the wounds. This App is used during the investigation at every site visit where the investigator or

delegated will take a photo of the wound. A trained person will afterwards be drawing the circumference of the wounds and Rave Imaging will calculate the area of the wound. If needed, the investigator will receive an iPhone with the Medidata eCOA solution installed.

The Quality-of-Life questionnaires will be handed out to the subjects and completed on paper.

This system will be used to record all subject information collected in the investigation. for secure data tracking and centralised data monitoring ("remote monitoring") done by monitors, as defined in the monitoring plan.

The principal investigator or designee must be trained in the system prior to getting access. The training is web-based and must be completed before access to the investigation is granted. Only the principal investigator, or delegate, will be authorised to enter data in the eCRF. The sponsor will be responsible for the study specific training the investigator, or designee, in completion of the eCRF.

Principal Investigator, or designee, at the clinical site will perform primary data collection directly into the eCRF or drawn from source-document (medical records) reviews. The eCRF will be completed on a continuous basis starting from the point of enrolling the subject to final follow up.

The eCRF will be completed by the investigator, or delegate, who have signed the Site Personnel Signature and Delegation List and Clinical Investigation Training Log. It will be the responsibility of the investigator to ensure that all measurements and observations are correctly noted in the eCRF.

Adverse events should be registered following the timelines described in the Adverse Event section.

When subject and investigator are required to complete different sections in the CRF, it will be specified which sections the subject will fill in and which sections the investigator will fill in. Please see the flow chart in section 7.3 for details.

In the unforeseen situation, where site cannot establish connection to the EDC system a paper CRF (pCRF) has been printed and supplied by sponsor.

The investigator will keep a separate list of the subjects' ID numbers, names and addresses in a locked room/cabinet. Only data referred to in this clinical investigation plan will be recorded in the CRFs.

11.2. Database Management, Queries and Quality Control

The monitor, using his/her personal login information shall verify all critical data points against the source documents and issue electronic queries for the authorised clinical site personnel to respond, as defined in the monitoring plan.

The Principal Investigator, using his/her personal login information shall sign each eCRF.

Electronic edit checks are described in the Data Validation Plan and will be set up to ensure data quality. A critical quality control will be performed by the sponsor's data management team and queries issued where needed.

At the end of the study a formal data review meeting will be performed before the database will be locked.

The Data Management Procedures are further described in the Data Management SOPs

11.3. Data retention

The Investigator file must be archived for a minimum period of 10 years after the final clinical investigation report has been signed.

12. Amendments to the Clinical Investigation Plan

No changes in the clinical investigation procedures shall be implemented without mutual agreement between the principal investigator and the sponsor. The agreement of the changes must be documented by signing the corresponding clinical investigation plan amendments and registered in the Change Log.

All significant changes require notification to the EC. Substantial changes may require approval from the EC prior to implementation. (Example of significant change: Changes of inclusion criteria, end points or assessment methods)

13. Deviations from the Clinical Investigation Plan

Deviations to the Clinical Investigation Plan occurs when the activities during the clinical investigation do not comply with the EC approved investigation plan.

Minor deviations are defined as those that do not increase risk, decrease benefit, or do not have a significant effect on the subject's rights, safety, or welfare; and/or on the integrity of the data. If a deviation increases risk or decreases benefit and/or has a significant effect on the subject's rights, safety, or welfare and/or has a significant effect on the integrity of the data it is defined as a major deviation and the Investigator must inform the monitor immediately, and the monitor will report and inform the Clinical Manager or designee immediately.

The investigator is not allowed to deviate from the Clinical Investigation Plan unless, under emergency circumstances or to protect the rights, safety, and welfare of the subject(s).

For the purposes of this investigation, any variance from the protocol is considered a deviation and is to be reported.

The site will complete a deviation eCRF form for all data-related deviations and all deviations that are not related to the data (for example, an untrained nurse performing study procedures) are reported by the monitor in the Site Report – Periodic Monitoring and actions are addressed to the Investigator for completion.

If any deviations to the investigation plan are detected during the monitoring visit, the Monitor shall ensure the site reports all deviations in the eCRF or on the Deviation log in the Investigator File. Additionally, the monitor must report any deviation noted during the visit in the Periodic Monitoring Report.

Monitor will align with data management in each investigation, how data management will be informed about all deviations.

The following information about the deviation will be collected:

- Site ID, Subject ID
- Deviation Date and Investigation Visit
- Date deviation was discovered
- Clear and concise description of the event
- Does the deviation affect the safety of the subject?

- Corrective action taken, including the date of the corrective action. Please note corrective action can be site was re-educated on a procedure. Ensure the corrective action is documented.

14. Device Accountability

All access to the investigational devices, including comparators, used in the clinical investigation is controlled by storage procedures and device accountability logs as described below. The investigational devices must only be used in this clinical investigation and only according to the CIP.

Sponsor keeps a device accountability log that states the physical location of all investigational devices from shipment of investigations devices to the investigational sites until return or disposal.

The PI, or delegate, keeps records documenting the receipt, use and return and disposal of the investigational devices, which includes:

- Name of the product received
- Date of receipt.
- Identification of each investigational device (batch no./lot no)
- The expiry dates.
- Number of products received
- Number of products distributed to subjects
- The date(s) of use.
- Subject identification.
- The date on which the investigational device was returned/explanted from the subject.
- The date of return unused, expired or malfunctioning investigational products was returned to Sponsor, if applicable

15. Statement of compliance

The clinical investigation is conducted in accordance with:

- Ethical principles that have their origin in the Declaration of Helsinki, 1964, Last amended at the 59th WMA General Assembly, Brazil, October 2013.
- MDD 93/42/EEC as amended by Directive 2007/47/EC (commonly known as the Medical Device Directive).
- MDR (EU) 2017/745
- ISO 14155:2020 "Clinical Investigation of medical devices for human subjects – Good clinical practices".
- The EU General Data Protection Regulation (2016/679)
- Any applicable regional or national regulations will be specified in the country specific CIP.

15.1. Ethics committee and regulatory authorities

The CIP and/or other relevant documents are submitted to the appropriate EC(s). This clinical investigation will not begin until the required approval from the EC has been obtained. Any amendment to the protocol will be submitted to the same EC(s). Sponsor will notify the relevant EC(s) concerned of the end of the clinical investigation.

15.2. Data protection

As part of the investigation Coloplast A/S, Holtedam 1, 3050 Humlebæk, Denmark ("Coloplast") will collect and process the personal information the subject provides for the investigation ("subject personal data"). This includes identification and contact information (which may be anonymised depending on the nature of the investigation) as well as information about product usage experience and your health. Coloplast will comply with the EU General Data Protection Regulation (GDPR) and the Danish act on data protection ("databeskyttelsesloven"), including in connection with transfer of data to third countries, cf. chapter V of GDPR, Coloplast will only process the subjects' personal data:

1. To conduct the investigation and carry out related research based on subject consent (primary use), cf. articles 6(1)(a) and 9(2)(a) of GDPR,
2. To comply with applicable legal obligations to e.g., ensure reliability and safety, cf. article 6(1)(c) in conjunction with article 9(1)(i) of GDPR, and
3. If separate consent is given for secondary use of subject personal data, cf. articles 6(1)(a) and 9(2)(a) of GDPR – carry out research outside the clinical protocol to improve Coloplast's products and services, and for use in education.

Part of Coloplast's processing is carried out on third-party platforms (clinical trial databases) and certain third parties are assisting Coloplast in the processing (e.g., the investigator). Such cases will imply a transfer of your personal data to the third parties, but solely for the specified purposes and with the third parties acting on instruction from Coloplast. Data may be collected and processed across the Coloplast network, which may entail processing of personal data outside the European Economic Area. In such cases, an adequate level of protection will be ensured by the third parties being subject to the standard contractual clauses on data protection adopted by the EU or to an EU-approved certification mechanism on data protection. For further information about this please the subject can always consult Coloplast's data protection officer (details below).

Subject personal data will be kept as long as required under applicable laws and regulations. The EU Medical Device Regulation obligates Coloplast to keep the data for a period of at least ten years after the investigation is completed, or, in the event that the device is subsequently placed on the market, at least ten years after the last device has been placed on the market.

If the subject has questions or queries regarding Coloplast's handling of personal information, the subject can always contact Coloplast's Data Protection Officer at dataprotectionoffice@coloplast.com. Complaints related to Coloplast's handling of subject personal information may similarly be sent to the Data Protection Officer, and the subject is also entitled to file a complaint with the relevant supervisory authority, which in the case of Denmark is the Danish Data Protection Agency (www.datatilsynet.dk).

The subject can write to privacyrequests@coloplast.com at any time to request:

- Access to personal data
- Correction of errors in personal data or to erase personal data
- Limit what can be done with personal data
- To receive personal data in machine-readable format (data portability).
- Withdrawal of consents the subject has given Coloplast to process personal data

15.3. Indemnity

All subjects are fully covered by Coloplast A/S insurance throughout the investigation.

Insurance has been signed with:

XL Insurance Company SE
Kungsgatan 5, 2nd floor
SE-111 36 Stockholm
Phone +46 8 440 89 80

15.4. Financial conditions

Coloplast A/S will compensate the investigator involved in the clinical investigation for his/her time and resources spent on the investigation.

The expenses include the salary to the Principal Investigator and study nurses, the cost of test products, shipments, transportation, and vouchers. All financial agreements with the investigation sites involved in the clinical investigation will be specified in the Sponsor Investigator contracts.

16. Informed consent process

Written informed consent must be obtained from all subjects participating in the investigation after thorough written and verbal information. The information is given by the Principal Investigator or his/her representative in a non-technical language. Each subject will be fully informed about the aim of the investigation, procedures, potential risks, or inconveniences and/or expected benefits, all anticipated adverse device effects and ensure ample time before deciding on participation. The subjects will be informed that their participation is voluntary and that they may leave the investigation at any time, without this having any influence on their further treatment.

The informed consent signature form includes personally dated signatures of the subject and the PI, or his/her representative. A copy will be provided to the subject.

If relevant new information is to be given during the investigation, sponsor will inform the investigators, and the new information is given to the subjects by the investigator. If new information becomes available that can significantly affect a subject's future health and medical care that information will be provided to the subject in written form. The Clinical Manager is responsible for writing the information and providing the approved Patient Information Sheet and the Consent Form to investigators that will further provide it to the subjects. If applicable, all affected subjects shall be asked to confirm their continuing informed consent in writing.

17. Subject compensation

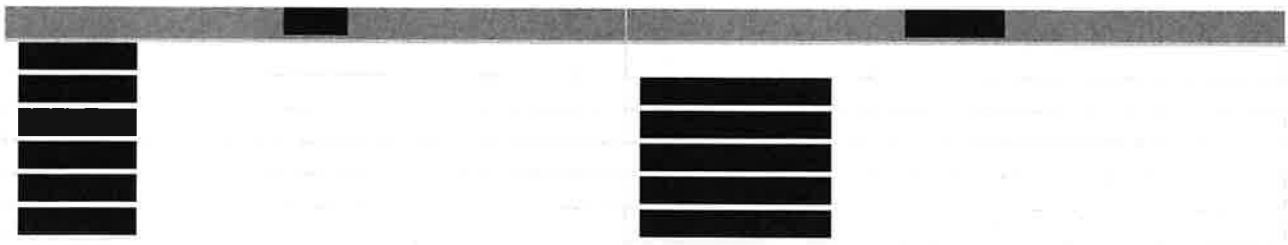
17.1. Compensation in case of injury

Product liability and No-Fault Clinical Investigation Insurance covering the duration of the clinical investigation is in place, to enable compensation in the event of an injury to a participating subject.

17.2. Compensation for participating in the clinical investigation

Subjects are compensated for any transportation costs.

Reimbursement of transportation expenses are not taxable per local legislation. Transport expenses will be paid in appropriate portions that justify the administration throughout the investigation period.



18. Adverse events, adverse device effects and device deficiencies

18.1. Adverse events

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, whether related to the investigational medical device(s) or the comparator(s), or the procedures involved. The adverse event shall be marked with the intensity mild, moderate, or severe. This could include events such as headache or dizziness.

18.2. Adverse device effect

An adverse event, which is related to the use of the investigational medical product, is an adverse device effect, and should be marked as related or possibly related with causal relationship on the adverse event form.

The definition of an adverse device effect includes any event resulting from insufficiencies or inadequacies in the instruction for use, or any malfunction of the medical device, as well as any event resulting from use error or from intentional misuse of the device.

Table 5 lists anticipated adverse device effects that may occur, based on the IFU and their likely incidence rates based on adverse events reported in clinical studies (17).

Table 5: Anticipated adverse device effects and their likely incidence rates

ANTICIPATED ADE	INCIDENCE RATE
Skin irritation/inflammation/itching	0.13 %
Maceration	0.09 %
Pain	0.09 %
Hyper granulation	0 %
Blistering	0 %
Allergic skin reaction	0.09 %

Temporary skin irritation upon removal of the dressing is not considered an adverse device effect, however an abnormal development in intensity or duration should be considered as such.

18.3. Device deficiency

A device deficiency is the inadequacy of the investigational medical device or comparator with respect to its identity, quality, durability, reliability, usability, safety, or performance. This includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

18.4. Serious adverse events (SAE)

A serious adverse event is an adverse event that:

- Led to death,

- Led to a serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
  1) a life-threatening illness or injury, or
  2) a permanent impairment of a body structure or a body function including chronic diseases, or
  3) in-patient 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.
- Led to foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.

This includes device deficiencies that might have led to a serious adverse event if:

1) Suitable action had not been taken, or
2) Intervention had not been made, or
3) Circumstances had been less fortunate.

These are handled under the serious adverse event reporting.

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.

18.4.1. Serious adverse device effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

18.4.2. Anticipated serious adverse device effect (ASADE)

Anticipated serious adverse device effect is any effect that by its nature, incidence, severity, or outcome has been previously identified in the risk analysis report.

18.4.3. Unanticipated serious adverse device effect (USADE)

An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

Reporting in the eCRF of any ADE, SADE and/or DD of the investigational test product Biatain® Silicone will be reported by the Clinical Manager to Vigilance.

18.5. Medical care of subjects

Principal investigator shall ensure that adequate medical care is provided to a subject experiencing an adverse event during and after participation in the clinical investigation. All serious adverse events will be followed until a resolution is addressed.

The current status of all ongoing adverse events is documented during site close-out.

Principal Investigator or delegate shall provide the subject with the necessary instructions on proper use, handling, storage and return of the test products, when it is used or operated by the subject.

18.6. Reporting and timelines

All adverse events and device deficiencies will be reported in the eCRF. If, for some reason, the system is off-line, investigators (or designee) are required to report the event to:

clinical-studies@coloplast.com

18.7. Investigator's reporting responsibilities

PI at each site must assess all (S)AE`s that occur at his/her site.

- All serious adverse events and serious adverse device effects must be reported to sponsor within 24 hours of the site becoming aware of the event.
- A device deficiency that could have led to a serious adverse event but did not because suitable action was taken, intervention had been made or because of fortunate circumstances should be reported to sponsor within 24 hours of the site becoming aware of the event.
- New findings and/or updates in relation to already reported serious events should also be reported to sponsor within 24 hours of the site becoming aware of the event.
- Device deficiencies and all adverse device effects related to CE marked Coloplast investigational product and/or comparator must be reported to sponsor within 24 hours of becoming aware of the event.

When reporting the SAE, the relationship to the test material shall be described whether the event is considered:

- **Not related**, the event has no temporal relationship with the use of the test material or the
- procedures.
- **Unlikely related,** the relationship with the use of the test material seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible related,** the relationship with the use of the test material is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
- **Probably related,** the relationship with the use of the test material seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
- **Definitely related/Causal relationship,** the event has a temporal relationship with the test material use/application or procedures.

The investigator will assess intensity for each AE and SAE reported during the investigation and assign it to one of the following categories:

- **Mild,** the intensity of the event is mild with no further action or intervention
- **Moderate,** the intensity of the event will lead to an action or intervention to solve the event
- **Severe,** the intensity of the event will lead to follow up on the action or intervention, as the effect of the action or intervention may not decrease the symptoms.

All above events must be reported by use of the relevant adverse event/serious adverse event/device deficiency form.

Please report to:

Coloplast A/S
Holtedam 1-3
3050 Humlebæk, Denmark

18.8. Sponsors reporting responsibilities

It is the responsibility of sponsor to ensure that the following are reported to national regulatory authorities and EC, as applicable, immediately, but no later than 7 calendar days following the date of awareness by sponsor.

- All serious adverse events.
- All serious device effects.
- All device deficiencies that could have led to serious adverse events but did not because suitable action was taken; intervention had been made or because of fortunate circumstances.
- New findings and/or updates in relation to already reported events.

If the serious adverse event results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other subjects, users or other persons or a new finding to such a serious adverse event, sponsor must immediately but no later than 2 calendar days after awareness by sponsor report the event to national regulatory authorities and ethics committees, as applicable.

It is the responsibility of sponsor to inform all investigators in writing within 10 working days if device deficiencies, adverse events, adverse device effects, near-incidents, serious adverse events, serious adverse device effects or unanticipated serious adverse device effects lead to corrective actions (*e.g.*, change of IFU).

19. Suspension or premature termination of the clinical investigation

Sponsor may suspend or prematurely terminate an investigation site or the entire clinical investigation for documented significant reasons.

If a suspicion of an unacceptable risk to subjects develops during the clinical investigation, sponsor will suspend the investigation while the risk is assessed. Sponsor will terminate the investigation if an unacceptable risk is confirmed. Sponsor will ensure that the premature termination will be justified in writing and will promptly inform the regulatory authorities and relevant EC(s). If monitoring or auditing of the clinical investigation identifies serious or repeated deviations at one of the participating investigation sites, sponsor will suspend or terminate the particular investigational site. The sponsor or investigator will inform the regulatory authority as appropriate and notify the EC about the termination of the site.

If suspension or termination of the clinical investigation occurs, the investigator will promptly inform the enrolled subjects. Sponsor will provide resources to fulfil the obligations from the CIP for follow-up of the subjects as necessary.

20. Clinical investigation report

At completion of the investigation sponsor is responsible for writing the clinical investigation report. The report is retained on file. The report contains a critical evaluation of all data, which have been collected during the investigation. The report describes the methodology and design and a data analysis, including statistical preparation and conclusion.

Sponsor and coordinating investigator must sign the final version of the clinical investigation report or an affidavit, indicating their agreement with the contents. If no coordinating investigator is appointed, then the signatures of the principal investigator(s) should be obtained.

The clinical investigation report must be submitted to EC and regulatory authorities.

21. Publication policy

Coloplast, sponsor, is referring to the internal document 'Clinical Publication Policy' that will be available for internal and external persons involved in the publication process.

The investigation will be registered in a publicly accessible database before recruitment of the first subject. The results of the investigation, positive as well as inconclusive and negative will be published in the same publicly accessible database. The subjects' identity will remain confidential. Publication of results in the database will be conducted per the law of personal data protection and will be initiated as soon as scientifically acceptable, however, within one year after the last subject has completed the investigation. Data from the investigation is considered confidential until it is published per the conditions of this Clinical Investigation Plan and the 'Clinical Publication Policy'. Sponsor may publish anonymous single subject case stories (or public, if the subject consents) at any time during and after the investigation. The identification of the participant must not be possible. Sponsor reserves the right to use the data (published and unpublished) for reimbursement or regulatory purposes.

The results of the investigation, positive as well as negative, may be communicated by abstracts, posters, or oral presentations provided that opportunity is given for sponsor to discuss the contents and any conclusions drawn, before the abstract, paper, or visual presentations are finalised. In all cases the subject's identity will remain confidential.

Sponsor will undertake to comment on the draft documents within 30 working days of receipt, but the final decision on the contents and format of the publication from the conclusions drawn, will remain with the authors.

No preliminary results will be published.

Data from the investigation is considered confidential until it is published according to the conditions of this CIP. Sponsor may publish single subject case stories at any time during and after the investigation.

Sponsor reserves the right to use the data (published and unpublished) for reimbursement or regulatory purposes.

22. Suspension/termination of the clinical investigation

Sponsor will withdraw from sponsorship of the clinical investigation if

- Major non-adherence to the clinical investigation plan is occurring
- It is anticipated that the subject recruitment will not be adequate to meet the investigation objectives at least 75% of the subjects should be entered within the recruitment time

In case sponsor withdraws, sponsorship for the subjects already recruited into the clinical investigation will continue.

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Appendix 1: IFU Biatain® Silicone

Biatain® Silicone Coloplast

en Silicone foam dressing

CE 2460 Coloplast A/S Holtedam 1 3050 Humlebæk Denmark

Instructions for use
Please read the following instructions carefully.

Intended purpose
The product is intended for moist wound healing and exudate management.

The product is intended to be used by health care professionals and patients under the supervision of health care professionals.

Indications
Biatain Silicone
- is indicated for a wide range of low - to high exuding wounds. This includes acute wounds such as donor sites, post operative wounds and traumatic wounds; and chronic wounds such as leg ulcers, pressure ulcers and non-infected diabetic foot ulcers.
- may be used to prevent post-operative blistering.

Warnings
Do not re-use the single use product as cross contamination may occur, potentially leading to infection.

Reprocessing, washing, disinfection and/or resterilisation may compromise product characteristics, causing additional risk of physical harm or infection to the user.

Cautions
A health care professional should frequently inspect and manage infected wounds, diabetic wounds and wounds which are solely or partially caused by arterial insufficiency, in accordance with local guidelines.

Do not use the product with oxidising solutions e.g. hypochlorite and hydrogen peroxide solutions, as this may cause product degeneration which may lead to deterioration of the wound. Ensure that any other evaporating solution is completely dried off before applying the product.

Do not cut the foam part of the product as this may lead to wound deterioration due to product residues left in the wound.

Do not use if package is damaged, as sterility of the product may have been compromised, potentially leading to infection.

Keep away from sunlight as it may impact product performance which may lead to maceration.

The product is not made with natural rubber latex, however rare contamination with trace amounts of natural rubber latex during manufacturing or packaging may occur, potentially leading to allergic reactions in patients with known or suspected allergies to natural rubber latex.

Possible side-effects related to the use of wound dressings may include: skin irritation/inflammation, allergic skin reaction, maceration, pain, hyper granulation, and blistering.

Information
The product is a sterile, single use polyurethane foam dressing with a silicone adhesive.

Biatain Silicone
- may be left in place for up to 7 days depending on the amount of exudate, dressing conditions and type of wound
- may be left in place during shower
- may be used together with Purilon Gel for autolytic debridement of necrotic tissue
- may be used on patients who are in treatment for a local or systemic infection at the discretion of a health care professional
- is suitable for use in combination with compression therapy

The product consists of:
- a vapour permeable top film which is bacteria- and waterproof
- a lock away layer
- an absorbent polyurethane foam
- a perforated silicone adhesive
- turquoise protective films

If you experience a suspected allergic reaction or any other side effects, please contact your health care professional.

Sterilised using ethylene oxide (EO).

Coloplast accepts no liability for any injury or loss that may arise if this product is used in a manner contrary to Coloplast's current recommendations.

Special storage conditions
Keep away from sunlight.

How to use

Preparation
Cleanse the wound and periwound skin in accordance with local guidelines, e.g. lukewarm water or physiological saline solution.

Gently dry the periwound skin.

If any film, cream, ointment or similar product is used, allow the periwound skin to dry before applying the product.

Application
Select a product where the foam overlaps the wound edge by approximately 1-2 centimetres.

Open the pouch and pick up the product from the packaging.

Use the protective films to avoid touching the adhesive side and to ensure aseptic application.

Remove the center protective film.

Apply the adhesive side towards the wound.

Remove the remaining protective films, one at a time.

Gently run your fingers around the edge of the product to ensure an even and smooth fit to the skin.

Removal
The product should be changed when clinically indicated, when visible signs of exudate approach the edge of the foam or after 7 days.

Loosen the adhesive border before gently lifting the product away from the wound and removing the product. If the product is difficult to remove, it should be moistened with water or physiological saline solution until it removes easily.

Disposal
The product is intended for single use only and should be disposed of in accordance with local guidelines, e.g. with normal household waste.

Do not flush the product down the toilet.

Reporting of incidents
If, during the use of this device or as a result of its use, a serious incident has occurred, please report it to the manufacturer and to your national authority.

Explanation of symbols

MD	Medical device
CE 2460	Indicates that the product is in compliance with European legislation for medical devices
REF	Catalogue number
	Use-by date (YYYY-MM-DD)
LOT	Batch code
	Date of manufacture (YYYY-MM-DD)
	Manufacturer
	Consult instructions for use
	Do not re-use
STERILE EO	Sterilised using ethylene oxide
	Single sterile barrier system
	Not made with natural rubber latex
	Do not use if package is damaged and consult instructions for use
UDI	Indicates a carrier that contains Unique Device Identifier information
GTIN	Global Trade Item Number
	Keep away from sunlight
	Recyclable packaging
	Absorption capability

Appendix 2: Instruction for Use Mepilex® Border

(14)

Mepilex® Border EM

Self-adherent soft silicone foam dressing

en

Product description

Mepilex Border EM is a self-adherent, absorbent dressing that maintains a moist wound environment. The waterproof outer layer protects the wound from dirt and bacteria. The dressing has a Safetac® wound contact layer that is a unique adhesive technology. It minimises pain to patients and trauma to wound and skin at dressing removal.

Mepilex Border EM consists of:

- a wound contact layer consisting of soft silicone adhesive (Safetac) and a film carrier
- a flexible absorbent pad in two layers: a foam and a non-woven spreading layer
- an outer film which is breathable but waterproof, providing a barrier to external contaminants

Dressing material content:
Silicone, polyurethane, polyacrylate, viscose, polyester and polyolefin.

Indications for use

Mepilex Border EM is designed for the management of a wide range of non/low exuding wounds, such as leg and foot ulcers, pressure ulcers, surgical wounds and traumatic wounds e.g. abrasions, blisters and skin tears.
Mepilex Border EM can also be used as protection of compromised and/or fragile skin.

Precautions

- Do not use on patient with known hypersensitivity to the dressing or its ingoing materials.
- Do not use together with oxidising agents such as hypochlorite solutions or hydrogen peroxide.
- If you see signs of clinical infection e.g. fever or the wound or surrounding skin becoming red, warm or swollen, consult a health care professional for appropriate treatment.
- Do not reuse. If reused performance of the product may deteriorate, cross contamination may occur.
- Sterile. Do not use if sterile barrier is damaged or opened prior to use. Do not re-sterilise.

en

Instructions for use

Mepilex Border EM may be used by lay persons under supervision of health care professionals.

1. Cleanse the wound according to clinical practice. Dry the surrounding skin thoroughly.
2. Select an appropriate dressing size/shape. The wound pad should cover the dry surrounding skin by at least 1-2cm.
3. Remove the first release film and apply the adherent side to the wound.
4. Remove the remaining release film(s) and smooth down the border on the skin. Do not stretch the dressing.

The dressing change interval may be several days. Change the dressing before it is fully saturated, at signs of leakage, or as indicated by clinical practice. Mepilex Border EM can be used under compression bandaging, and in combination with gels.

Special storage conditions and handling conditions

Mepilex Border EM should be stored in dry conditions.
The foam may change colour to more yellow when exposed to light, air and/or heat. This has no influence on product properties.
Disposal should be handled according to local environmental procedures.

Other information

If any serious incident has occurred in relation to the use of Mepilex Border EM, it should be reported to Mölnlycke Health Care.

Appendix 3: Instruction for Use - AQUACEL® Extra™ Hydrofiber® Dressing

CE 0086

AQUACEL™ EXTRA™

Hydrofiber™ Dressing with Strengthening Fibre / Hydrofiber™ Verband mit Verstärkenden Fasern / Medicazione in Hydrofiber™ con Fibra Rinforzante / Pansement Hydrofiber™ avec Renfort Fibre / Apósito de Hydrofiber™ con fibra reforzante / Penso Hydrofiber™ com Fibra de Reforço / Hydrofiber™ Verband met Versterkende Vezels / Hydrofiber™ Förband med Förstärkande fibrer / Kuituvahvistettu Hydrofiber™-haavasidos / Hydrofiber™ Bandage med forstærkende fibre / Hydrofiber™ Bandasje med Forsterkende Fibrer / Επίθεσμος Hydrofiber™ με ενισχυτικές ίνες / ضمادة Hydrofiber™ مع تسريح مقوى

INSTRUCTIONS FOR USE / GEBRAUCHSANLEITUNG / ISTRUZIONI PER L'USO / CONSEILS D'UTILISATION / INSTRUCCIONES DE USO / INSTRUÇÕES DE USO / GEBRUIKSINSTRUCTIES / BRUKSANVISNING / KÄYTTÖOHJEET / BRUGSANVISNING / BRUKSANVISNING / ΟΔΗΓΙΕΣ ΧΡΗΣΗΣ / تعليمات الاستعمال

ConvaTec

ENGLISH

PRODUCT DESCRIPTION
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.

INDICATIONS
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).
- exudate 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 of 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 bandaging 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

DIRECTIONS FOR USE
1. Exuding Wounds (Excluding Partial Thickness Burns)
- Before applying the dressing, cleanse the wound area with an appropriate wound cleanser.
- AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre should overlap 1cm onto the skin surrounding the wound.
- Apply the dressing to the wound and cover with a moisture retentive dressing (e.g., DuoDERM™ Extra Thin or Versiva® XC), or other appropriate secondary dressing. See relevant individual package inserts for complete instructions for use.
- All wounds should be inspected frequently. Remove the AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre when clinically indicated (i.e., leakage, excessive bleeding, or suspicion of infection).
- AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre can be left in place for up to 7 days, where clinically indicated, (except in burns and donor sites where it can be left in place for up to 14 days).

2. Dry Wounds
In addition to the directions for use set forth above:
- Place the AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre on the wound and wet with sterile water or saline over the wound area only.
- Cover the dressing with a moisture retentive dressing such as DuoDERM™ Extra Thin to avoid drying out of the dressing and subsequent dressing adherence to the wound.

3. Partial thickness burns
- Before applying the dressing, cleanse the wound area with an appropriate wound cleanser.
- The AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre should overlap at least 5cm onto the skin surrounding the burn or other adjacent AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre, as the dressing will shrink as it absorbs the exudate.
- The AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre should be covered with a sterile loosely woven gauze pad and appropriately secured. In the immediate post burn period (up to 4 days) large volumes of wound exudate may require that the saturated dressing be removed and replaced with new AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre.
- Remove the cover periodically and inspect the AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre while it remains in place on the burn.
- In this indication adherence to the wound bed of the AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre is a desired characteristic. Non adherence of areas of the dressing may indicate deepening of the wound or infection. Areas of the dressing may be cut away to facilitate assessment. The exposed areas should then be treated appropriately.
- As the burn wound re-epithelialises, the AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre will detach or be easily removed.
- For partial thickness burns and donor sites, AQUACEL EXTRA Hydrofiber Dressing with Strengthening Fibre may be left in place for up to 14 days or until clinically indicated.
- If the burn is infected frequent inspection of the wound may be necessary.

Discard any unused portion of the dressing.

Store in cool dry place. (10°C - 25°C/50°F – 77°F).

If further information or guidance is needed, please contact ConvaTec Professional Services

DEUTSCH

PRODUKTBESCHREIBUNG:
Der AQUACEL™ EXTRA™ Hydrofiber™ Verband mit Verstärkungsfasern ist eine weiche, sterile, nicht gewebte Wundauflage aus Natriumcarboxymethylzellulose und chemisch veränderten Cellulosefasern zur Verstärkung. Dieser stark absorbierende Verband nimmt Wundexsudat auf und bildet ein weiches Gel. Durch das Gel wird die Wunde feucht gehalten und ein optimales Wundheilungsmilieu geschaffen. AQUACEL unterstützt den Heilungsprozeß und erleichtert den Abtransport von abgestorbenem Gewebe aus der Wunde (autolytisches Debridement) ohne Beschädigung des neugebildeten Gewebes.

INDIKATIONEN:
Unter Aufsicht von medizinischem Fachpersonal kann der AQUACEL EXTRA Hydrofiber Verband mit Verstärkenden Fasern eingesetzt werden zur Behandlung von:
- Beingeschwüren, Druckgeschwüren (Grad II-IV) und

Appendix 4: CEAP Classification

(1)

C class	Description
C_0	No visible or palpable signs of venous disease
C_1	Telangiectasias or reticular veins
C_2	Varicose veins
C_{2r}	Recurrent varicose veins
C_3	Edema
C_4	Changes in skin and subcutaneous tissue secondary to CVD
C_{4a}	Pigmentation or eczema
C_{4b}	Lipodermatosclerosis or atrophie blanche
C_{4c}	Corona phlebectatica
C_5	Healed
C_6	Active venous ulcer
C_{6r}	Recurrent active venous ulcer

CVD, Chronic venous disease.
Each clinical class subcharacterized by a subscript indicating the presence (symptomatic, *s*) or absence (asymptomatic, *a*) of symptoms attributable to venous disease

Appendix 5: IWGDF/IDCA Guideline

(15, 16)

Clinical manifestations	Infection severity	PEDIS grade
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
Presence of ≥2 manifestations of inflammation (purulence, or erythema, tenderness, warmth, or induration), but any cellulitis/erythema extends ≤2cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild	2
Infection (as above) in a patient who is systemically well and metabolically stable but which has ≥1 of the following characteristics: cellulitis extending >2cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint or bone	Moderate	3
Infection in a patient with systemic toxicity or metabolic instability (e.g. fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)	Severe	4

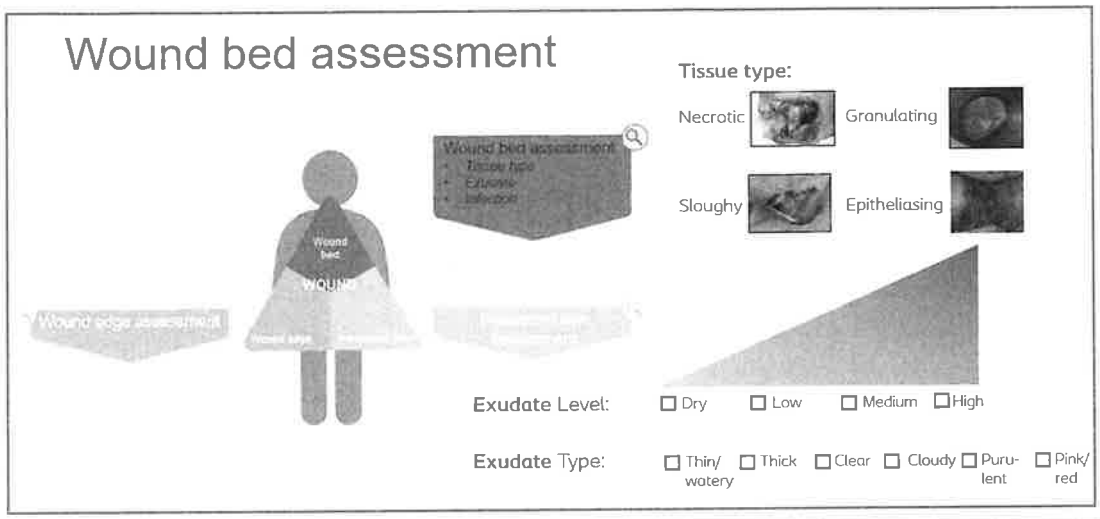
Appendix 6: Venous Leg Ulcers – signs of infection

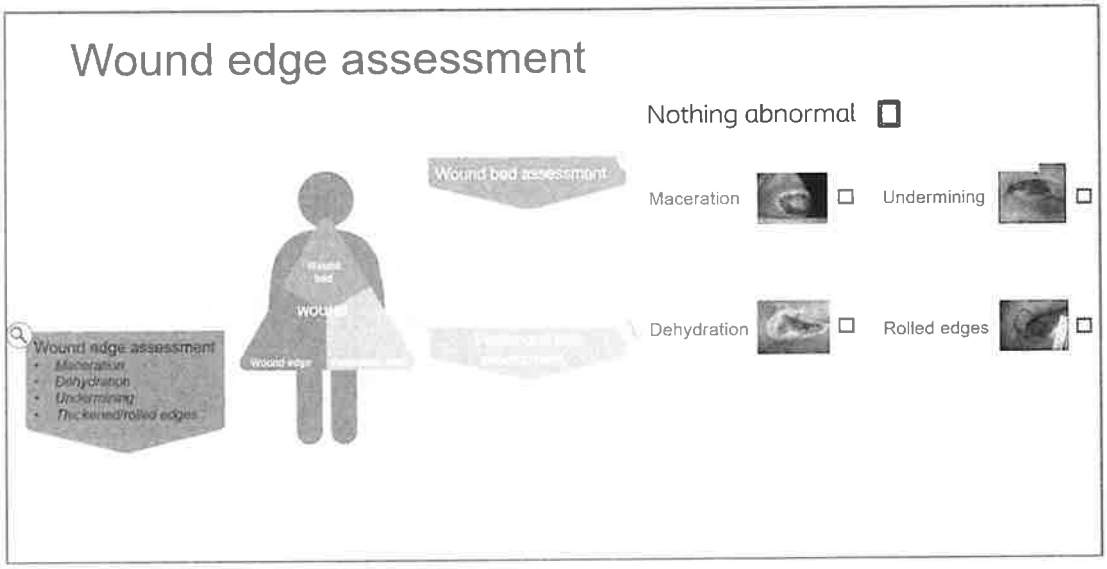
(15)

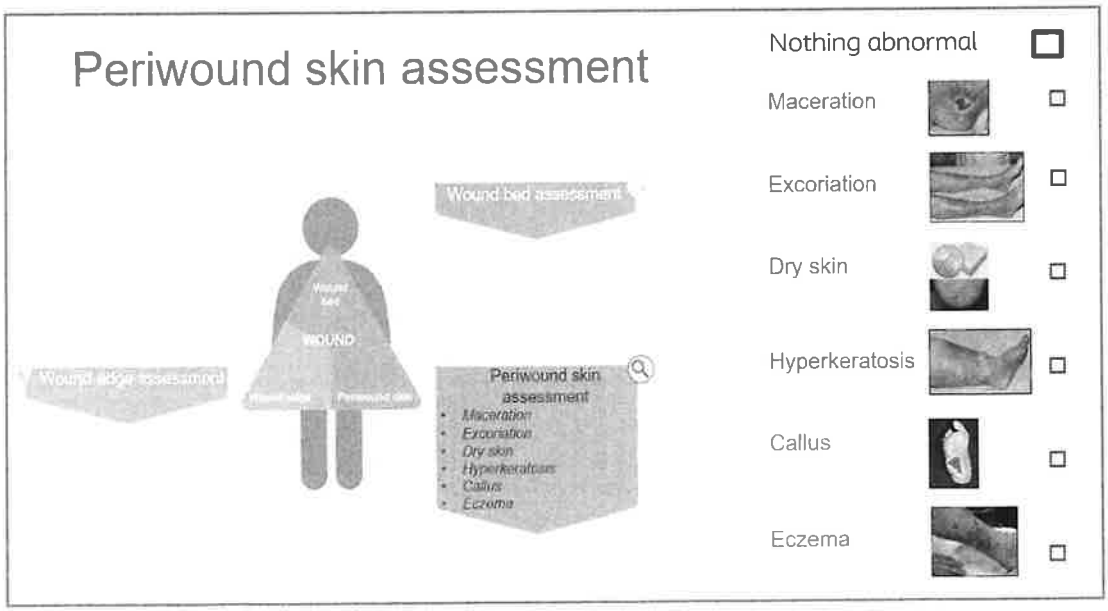
2 or more of the following criteria:

Signs of infection	Yes	No
New pain, increasing pain, or altered pain in the ulcer area;		
Malodor		
Increase in ulcer area		
Wound breakdown		
Delayed or non-healing		
Erythema		
Increase in local temperature		

Appendix 7: Coloplast Wound assessment Form







Appendix 8: Quality of Life (EQ-5D-5L)

Health Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- ☐ 1 I have no problems in walking about
- ☐ 2 I have slight problems in walking about
- ☐ 3 I have moderate problems in walking about
- ☐ 4 I have severe problems in walking about
- ☐ 5 I am unable to walk about

SELF-CARE

- ☐ 1 I have no problems washing or dressing myself
- ☐ 2 I have slight problems washing or dressing myself
- ☐ 3 I have moderate problems washing or dressing myself
- ☐ 4 I have severe problems washing or dressing myself
- ☐ 5 I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- ☐ 1 I have no problems doing my usual activities
- ☐ 2 I have slight problems doing my usual activities
- ☐ 3 I have moderate problems doing my usual activities
- ☐ 4 I have severe problems doing my usual activities
- ☐ 5 I am unable to do my usual activities

PAIN / DISCOMFORT

- ☐ 1 I have no pain or discomfort
- ☐ 2 I have slight pain or discomfort
- ☐ 3 I have moderate pain or discomfort
- ☐ 4 I have severe pain or discomfort
- ☐ 5 I have extreme pain or discomfort

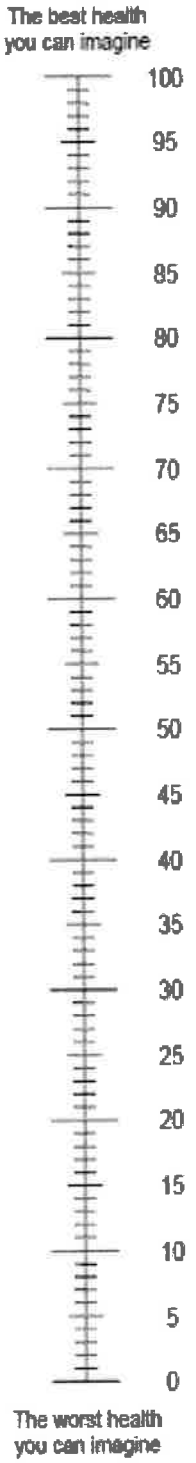
ANXIETY / DEPRESSION

- ☐ 1 I am not anxious or depressed
- ☐ 2 I am slightly anxious or depressed
- ☐ 3 I am moderately anxious or depressed
- ☐ 4 I am severely anxious or depressed
- ☐ 5 I am extremely anxious or depressed

Health Questionnaire (EQ-5D-5L)

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**
- Now, please write the number you marked on the scale in the below.

YOUR HEALTH TODAY = ☐



Appendix 9: Endpoints and assessments

	Endpoints and assessments	Assessed by	V1 (Baseline)	V2	V3	V4	V5 (Termination)
Primary endpoint	Percentage wound area reduction during the investigational test period of four weeks	**Investigator/ delegate**		X	X	X	X
Secondary endpoint	Total treatment costs during the investigational test period based on the number of dressing used during the investigation and the unit price of the products	**Investigator/ delegate**	X	X	X	X	X
Exploratory endpoints	Percentage wound depth reduction during the investigational test period	**Investigator/ delegate**	X	X	X	X	X
	Wound bed, wound edge and peri wound skin condition based on visual assessment based on the Coloplast Wound Assessment Form	**Investigator/ delegate**	X	X	X	X	X
	Conformability of the dressing based on PI or delegates evaluation according to a 5-point Liker scale	**Investigator/ delegate**			X		X
	Responder defined as a subject reaching ≥ 30% wound area reduction within the 4-week investigational test period (yes/no)	**Data Management**					X
	Wound healed during the investigation period (yes/no)	**Investigator/ delegate**		X	X	X	X
	Quality of Life evaluated by EQ-5D-5L	**Subject**	X				X
Safety Assessments	Averse events Device Deficiencies	**Investigator/ delegate**	X	X	X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]