CLINICAL INVESTIGATION PLAN (CIP)

INVESTIGATIONAL DEVICE:

MEPILEX® BORDER FLEX

INVESTIGATION TITLE:

A PROSPECTIVE, RANDOMIZED, CONTROLLED, STUDY USING CROSS-OVER DESIGN TO EVALUATE AND COMPARE 3 MULTI-LAYERED FOAM DRESSINGS FOR THE MANAGEMENT OF CHRONIC WOUNDS

CO-ORDINATING INVESTIGATOR:
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PROTOCOL SYNOPSIS

PROTOCOL TITLE:

A PROSPECTIVE, RANDOMIZED, CONTROLLED STUDY USING CROSS-OVER DESIGN TO EVALUATE AND COMPARE 3 MULTI-LAYERED FOAM DRESSINGS FOR THE MANAGEMENT OF CHRONIC WOUNDS

Clinical Study Site:

Multiple Sites

Investigational Device (test dressings):

Mepilex® Border Flex, Mölnlycke Health Care; Optifoam Gentle EX Wound Dressing, Medline Industries Inc.; Allevyn Life Wound Dressing, Smith and Nephew Inc.

Study Objectives

Primary Objective

To demonstrate superiority in efficacy of Mepilex® Border Flex versus Optifoam Gentle EX and Allevyn Life in the management of venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs) in an outpatient setting, as determined by dressing durability (i.e. wear time).

Secondary Objectives

- To compare clinical wound characteristics during wound management with each of the test dressings (in combination with standard care), including the rate of wound healing, peri-wound skin condition, and local pain levels.
- To evaluate the safety of the three test dressings in terms of occurrence of device related adverse events (AEs).
- To study subject-centric outcomes associated with each of the test dressings.

Health Economics Objective

- To retrospectively compare the cost-effectiveness of the three wound dressings.

Primary Endpoint:

Wound dressing durability, as defined as the interval of time to dressing strike-through and need for dressing change (dressing wear time [days]).

Secondary Endpoints:

- Clinical wound characteristics: wound healing status, condition of surrounding skin, signs of infection, and local pain levels.

- The number of device related (AEs) associated with each of the test dressings.

- Subject-centric outcomes between three treatment groups.

Health Economics Endpoint

To retrospectively compare resource-use as related to:

- Quantity of dressing changes per week (stratified by wound type)

- Time required per dressing change (in minutes)
  a. Start time: Initiation of old dressing removal
  b. End time: New dressing is securely in place

- Staff cost associated with dressing change
  a. Identification of those involved with dressing change (e.g., MD, Nurse, Assistant, etc.)
  b. Average hourly rate for those individuals directly involved with dressing change (this can be market data if individuals do not want to provide actual salary information)

- Material Cost
  a. Quantity of each product (dressing) used per week
  b. Size of dressings used
  c. Cost of each dressing used per week
  d. Other material cost used in dressing change
     i. Identification of products used per week
     ii. Quantity of each product used per week
     iii. Cost of each product used per week

Additional Safety Measures

- The incidence of AEs and serious adverse events (SAEs)associated with each of the test dressings.

Study Design

Prospective, randomized, controlled clinical trial (RCT) using a cross-over (repeated measures) design to evaluate safety and efficacy. The study will be conducted at multiple sites in an outpatient setting.

Each subject will be randomly assigned to one of four treatment groups. The treatments and treatment schedule are detailed in the table below:

	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4
Week 1	Tr. B	Tr. A	Tr. C	Tr. A
Week 2	Tr. B	Tr. A	Tr. C	Tr. A
Week 3	Tr. A	Tr. B	Tr. A	Tr. C
Week 4	Tr. A	Tr. B	Tr. A	Tr. C

*A=Study Product, B=Comparator Product 1, C=Comparator Product 2

Approximately 40 subjects will be enrolled to have 32 subjects for the evaluation. There will be two subject groups: those with VLU and those with DFU. Approximately 50% of the subjects will be in the VLU group and 50% of the subjects in the DFU group. Treatment sequence will be randomized so that a fair distribution is achieved. The total duration of the study will be approximately 4 weeks or 28 ± 2 days.

Visit Schedule

Potential study subjects will be screened for eligibility. Inclusion and exclusion criteria, vital signs, medical record reviews, subject demographics and informed consent will be performed and obtained at the Screening Visit (Day 0). If the patient meets the eligibility criteria, he or she will be enrolled and randomized into one of four treatment groups. The test wound dressing will be applied on the screening day (Day-0) and evaluations will take place twice weekly throughout the 4-week Treatment Period. The dressing will only be changed at Day 7 of each treatment week (e.g. Visit Days 7, 14, 21 and 28) or as needed at the discretion of the study doctor or investigator. There will be a total of 8 visits to the Vascular and Wound Care Center during the Treatment Period. During those visits, evaluations will be performed to assess the condition of the wound dressing, the wound, wound pain and patient comfort.

All study evaluations will be performed by a study doctor or nurse during the follow-up visit at the Vascular and Wound Care Center.

All subjects in the VLU group will receive the same compression therapy and all subjects in the DFU group will receive the same off-loading footwear throughout the entire study period.

Study Methods

- Wound dressings will be evaluated twice weekly by the study doctor or study nurse. All other evaluations will be performed once weekly before dressing change.
- There may be an initial debridement (at the investigator's discretion prior to enrollment).
- Additional debridement is not allowed.
- Wound dressing wear time and durability will be determined by study doctors' judgement and by photography.
- Exudate absorption and exudate dispersion will be determined clinically and by photodigital planimetry.
- Wound surface area will be measured serially using photo-digital planimetric software.
- Wound and surrounding skin characteristics will be evaluated by the study doctor at dressing change.
- Dressing comfort and subject-centric outcomes will be captured at the end of weeks 2 and 4.
- SF12 will be captured at the on Day 0 Screening & Baseline Visit and bi-weekly thereafter. Please see Appendix E for sampling of questions.
- Local wound pain will be evaluated using the Baker-Wong (Faces) Scale before and after each dressing change.

Inclusion Criteria

1. Male and female subjects 18-85 years of age with leg and foot ulcers (i.e. VLU, DFU).
2. Subject's Ankle-Brachial Index (ABI) by Doppler is ≥ 0.7.
3. The subject has adequate circulation to the foot to allow for healing. This must be demonstrated by methods described in Section 4.3.3
4. Signed informed consent.
5. Subject and/or caregiver must be willing and able to tolerate multi-layered compression bandages when applicable and offloading footwear.
6. Study subject must be available and able to visit the clinic twice weekly for the full 4-week period.

Exclusion Criteria

1. Pressure injury (as defined by the National Pressure Ulcer Advisory Panel [NPUAP]) in any anatomical location

2. Presence of local wound infection as determined by study doctor based on clinical signs and symptoms
3. Subject's ABI is <0.7 or has any evidence of peripheral arterial disease (PAD).
4. Subject diagnosed with malignancy other than cutaneous basal cell carcinoma.
5. Subject has received growth factor therapy (e.g. autologous platelet-rich plasma gel, becaplermin, bilayered cell therapy, dermal substitute, extracellular matrix) within 2 weeks of screening date.
6. Pregnancy or lactation at time of study participation.
7. Subject is currently receiving or has received radiation or chemotherapy within 3 months of randomization.
8. Subject is currently enrolled or participated in another investigational device, drug or biological trial within 30 days of baseline of this study.
9. Present history of alcohol or drug abuse.
10. Known allergy/hypersensitivity to any of the components of the dressing.
11. Subject not suitable for the investigation according to the investigator's judgment.

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LIST OF APPENDICES

LIST OF ABBREVIATIONS

ADE	**Adverse Device Effect**
AE	**Adverse Event**
CA	**Competent Authority**
CIP	**Clinical Investigation Plan**
CRF	**Case Report Form**
CTA	**Clinical Trial Agreement**
DD	**Device Deficiency**
DFU	**Diabetic Foot Ulcer**
EC	**Ethics Committee**
eCRF	**Electronic Case Report Form**
FAS	**Full Analysis Set**
ICF	**Informed Consent Form**
IRB	**Institutional Review Board**
NPUAP	**National Pressure Ulcer Advisory Panel**
PAD	**Peripheral Arterial Disease**
PCG	**Pharma Consulting Group**
PP	**Per Protocol**
SAE	**Serious Adverse Event**
SADE	**Serious Adverse Device Effect**
SD	**Standard Deviation**
UADE	**Unanticipated Adverse Device Effect**

VLU	**Venous Leg Ulcer**

1. INTRODUCTION

The impact of living with a wound is multifactorial and chronic wounds are associated with a range of morbidities; these wounds and their associated complications can have a significant effect upon a patient's quality of life (QoL) (1, 2). Ineffective wound assessment and management can exacerbate this negative impact upon the patient (3). Wound management strategies should be optimized not only to effectively manage the wound, but also to avoid further wound complications. Frequently reported patient issues associated with chronic wounds include discomfort, pain, malodor, leakage and restriction to daily activities (2).

Whilst dressings are an essential part of wound management, dressing-associated complications can hinder wound healing progression and cause unnecessary distress to the patient. Potential disturbances to the wound can occur as a result of suboptimal dressing choice. There are many potential ways in which a wound dressing, in close contact with the wound bed and surrounding skin, can damage or disturb the wound. These include: sub-optimal moisture balance, adherence, mechanical stress, presence of foreign bodies, sub-optimal temperature, chemical imbalance, and chemical stress (4). Of particular focus in the literature in recent years is the trauma and pain that wound dressing may cause, with the repeated application and removal of dressings that adhere to the wound bed causing trauma and epidermal stripping (5). Frequent application and removal of wound dressings can cause damage to the fragile wound or surrounding skin; this can cause considerable suffering for the patient (4). Ultimately, this trauma to the wound can lead to an increase in wound size, exacerbated pain and delay healing (5).

Pain is an important issue for clinicians to consider when managing chronic wounds. Wound pain can occur from many sources, with wound management procedures (including dressing changes) contributing to this pain (5). When compared to dressings with traditional adhesives, the use of wound dressings incorporating soft silicone can minimize traumatic injuries to the wound/peri-wound skin, as well as minimizing dressing-associated pain (6-8). Research has demonstrated the potential of these atraumatic wound dressings in overcoming these issues.

Whilst optimal dressing choice is important in achieving good healing progression, it is also important to minimize the frequency of dressing changes to enable healing to occur undisturbed (9). Frequent removal and reapplication of wound dressings may delay wound healing through mechanical disturbance to the healing process, temperature loss at the wound site (affecting the cellular healing process) and potential increase in the ingress of harmful bacteria to the wound site (9). Wound healing may be further hindered as a result of psychological stress and pain during dressing changes (9).

A dressing's ability to absorb and retain wound exudate is a key influential factor in terms of dressing wear time (9). Whilst exudate production is a part of the normal wound healing trajectory and an essential component to healing, when excessive exudate is not managed effectively it can have a negative impact on the patient (3). Wound exudate is associated with

several complications. These include: leakage, maceration, pain and discomfort, malodor, and psychological and psychosocial implications, all of which can impede patient QoL (3, 10-13). Chronic wounds may produce high levels of exudate as a result of a prolonged inflammatory response. Both diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) are often associated with high levels of wound exudate (14-16).

In terms of exudate management, the ideal wound dressing has several key functions: to optimally handle fluid (absorption and retention of exudate and its components, even under pressure); to reduce the risk of leakage; to reduce the spread of exudate onto the peri-wound area (thus reducing the risk of maceration); and to act as a bacterial barrier. The dressing should also ensure conformability, provide patient comfort, be easy to use, provide optimal dressing change frequency, minimize wound disturbance, and should be cost-effective (14). Previous research has demonstrated the ability of a layered foam dressing with siliconized adhesive to effectively manage wound exudate in exuding wounds, whilst maintaining a moist wound healing environment (6, 8, 17, 18). The adhesion of the dressing to the wound or surrounding skin is a further contributory factor that affects dressing wear time. The ability of the dressing to conform to body contours helps to ensure dressing adhesion (9).

Extended dressing wear may add value not only to the patient, but also to the health care provider. Frequent dressing changes are a huge cost driver and can impact greatly on resources (9). Minimizing the number of dressing changes (depending on the condition of the wound), may help to minimize unnecessary disturbance to the wound, minimize pain and stress for the patient, limit exposure of the wound to contamination and help to limit wound care costs (associated with nursing time, materials, pain medication, and medication for dressing-related trauma).

The aim of this clinical investigation is to evaluate and compare three different foam dressings in the local management of chronic wounds (i.e. VLUs and DFUs) in an outpatient setting. Mepilex® Border Flex will be evaluated versus Optifoam (Medline) and Allevyn Life (Smith&Nephew) within three focus areas; efficacy and safety of the dressings, subject-centric outcomes and health economic evaluation.

2. OBJECTIVES

Primary Objective

To demonstrate superiority in efficacy of Mepilex® Border Flex versus Optifoam Gentle EX and Allevyn Life in the management of venous leg ulcers (VLUs) and diabetic foot ulcers (DFUs) in an outpatient setting, as determined by dressing durability (i.e. wear time).

Secondary Objectives

- To compare clinical wound characteristics during wound management with each of the test dressings (in combination with standard care), including the rate of wound healing, peri-wound skin condition, and local pain levels.

- To evaluate the safety of the three test dressings in terms of occurrence of device related adverse events (AEs).
- To study patient-centric outcomes associated with each of the test dressings.

Health Economics Objective

- To retrospectively compare the cost-effectiveness of the three wound dressings.

Primary Endpoint:

Wound dressing durability, as defined as the interval of time to dressing strikethrough and need for dressing change (dressing wear time [days]).

Secondary Endpoints:

- Clinical wound characteristics: wound healing status, condition of surrounding skin, signs of infection, and local pain levels.
- Number of device related (AEs) associated with each of the test dressings.
- Patient-centric outcomes between three treatment groups.

Additional Safety Measures

- The incidence of AEs and SAEs associated with each of the test dressings.

Health Economics Endpoint

To retrospectively compare resource-use as related to:

- Quantity of dressing changes per week (stratified by wound type)
- Time required per dressing change (in minutes)
  a. Start time: Initiation of old dressing removal
  b. End time: New dressing is securely in place
- Staff cost associated with dressing change
  a. Identification of those involved with dressing change (e.g., MD, Nurse, Assistant, etc.)
  b. Average hourly rate for those individuals directly involved with dressing change (This can be market data if individuals do not want to provide actual salary information)
- Material Cost
  a. Quantity of each product (dressing) used per week
  b. Size of dressings used
  c. Cost of each dressing used per week

d. Other material cost used in dressing change
   i. Identification of products used per week
   ii. Quantity of each product used per week
   iii. Cost of each product used per week

3. CLINICAL INVESTIGATOR(S) AND INVESTIGATION ADMINISTRATIVE STRUCTURE

3.1 Staff at Investigation site

Investigators

Oscar M. Alvarez, PhD (Coordinating Principal Investigator – Study wide)

Mark S. Granick, MD (Principal Investigator)
Oscar M. Alvarez, PhD (Co-Investigator, Medical Officer)
Sonia Mvuemba, DPM (Sub-Investigator)
Evelyn Obando, BSN, WOCN Study Nurse

Site 02 – TBD
Site 03 – TBD

3.2 Mölnlycke Investigation Personnel

David Pham, Clinical Project Manager, Mölnlycke Health Care

3.3 Other Participants

Supplier of the eCRF system
Pharma Consulting Group
Kungsängsvägen 19, 1tr
753 23 Uppsala, Sweden

Supplier of SF12 Questionnaire Database
Optum
1301 Atwood Ave, Suite 311N
Johnston, RI 02919

Statistician
Statistiska Konsultgruppen
Nils-Gunnar Pehrsson
CEO / Senior Biostatiscian
Thorild Wulffsgatan 1

413 19 Gothenburg
Sweden

4. INVESTIGATION PLAN AND PROCEDURES

4.1 Overall Design and Flow Chart

Study Design

Prospective, randomized, controlled clinical trial (RCT) using a 2x2 cross-over (repeated measures) design to evaluate safety and efficacy. The study will be conducted in an outpatient setting of an academic clinical center.

Each subject will be randomly assigned to one of four treatment groups. The treatments and treatment schedule are detailed in the table below:

Table 1. Treatment Groups

	Treatment Group 1	Treatment Group 2	Treatment Group 3	Treatment Group 4
Week 1	Tr. B	Tr. A	Tr. C	Tr. A
Week 2	Tr. B	Tr. A	Tr. C	Tr. A
Week 3	Tr. A	Tr. B	Tr. A	Tr. C
Week 4	Tr. A	Tr. B	Tr. A	Tr. C

*A=Study Product, B=Comparator Product 1, C=Comparator Product 2

Approximately 40 subjects will be enrolled to have 32 subjects for the evaluation. Approximately 50% of the subjects will be in the VLU group and 50% of the subjects in the DFU group. Treatment sequence will be randomized so that a fair distribution is achieved. The total duration of the study will be approximately 4 weeks or 28 ± 2 days.

Visit Schedule

Potential study subjects will be screened for eligibility. Inclusion and exclusion criteria, vital signs, medical record reviews, subject demographics and informed consent will be performed and obtained at the Screening Visit (Day 0). If the patient meets the study eligibility criteria, he or she will be asked to sign consent. Study subjects will be randomized into one of four treatment groups. The test wound dressing will be applied at screening (Day-0) and evaluations will take place twice weekly throughout the Treatment Period. The scheduled dressing change will be on Day 7 of each treatment week (e.g. Visit Days 7, 14, 21 and 28), unless a dressing change is necessary because of strikethrough loss of adherence or discomfort. There will be a total of 8 visits to the Wound Care Center during the Treatment Period. During those visits, evaluations will be performed to assess the condition of the wound dressing, the wound, wound pain and patient comfort.

All study evaluations will be performed by a study doctor or nurse during the follow-up visit at the Wound Care Center.

All subjects in the VLU group will receive the same compression therapy and all subjects in the DFU group will receive the same off-loading footwear throughout the entire study period.

Study Methods

- Wound dressings will be evaluated twice weekly by the study doctor or study nurse. All other evaluations will be performed once weekly before dressing change.
- There may be an initial debridement (at the investigator's discretion prior to enrollment).
- Additional debridement is not allowed.
- Wound dressing wear time and durability will be determined by study doctors' judgement and by photography.
- Exudate absorption and exudate dispersion will be determined clinically and by photodigital planimetry.
- Wound surface area will be measured serially using photo-digital planimetric software.
- Wound and surrounding skin characteristics will be evaluated by the study doctor at dressing change.
- Dressing comfort and subject-centric outcomes will be captured at the end of weeks 2 and 4.
- SF12 will be captured at the initial visit and then bi-weekly
- Local wound pain will be evaluated using the Baker-Wong (Faces) Scale before and after each dressing change.

4.2 Procedures and Assessments

4.2.1 Schedule of Assessment

Table 2. Schedule of Assessment

Assessments	Screening & Baseline Visit (Day 0)		Treatment Phase							
			Week 1 Day 3 (-1/+2)	Week 1 Day 7 (-1/+2)	Week 2 Day 10 (-1/+2)	Week 2 Day 14 (-1/+2)	Week 3 Day 17 (-1/+2)	Week 3 Day 21 (-1/+2)	Week 4 Day 24 (-1/+2)	Week 4 Day 28 (-1/+2)
Inclusion/ Exclusion Criteria	√									
Informed Consent	√									
Subject ID	√									
Subject Randomization	√									
Subject Demography	√									
Medical/ Surgical History	√									
Vascular Studies ABI, Duplex, PVR, Toe Pressures	√									
Wound Assessment	√			√		√		√		√
Performance of the Dressing			√	√	√	√	√	√	√	√
Dressing Application	√			√		√		√		
Application of Compression Bandages or Off-Loading Footwear	√		√	√	√	√	√	√	√	√
Dressing Removal				√		√		√		√
Dressing change (if needed)$_2$			√	√	√	√	√	√	√	√
Concomitant medication	√		√	√	√	√	√	√	√	√
Pain Assessment	√			√		√		√		√
Photo of the wound	√		√$_5$	√	√$_5$	√	√$_5$	√	√$_5$	√
Photo of dressing *in situ*	√		√$_4$	√$_4$	√$_4$	√$_4$	√$_4$	√$_4$	√$_4$	√$_4$
Photo of dressing	√		√$_5$	√	√$_5$	√	√$_5$	√	√$_5$	√
Subject-Centric Outcomes						√				√

Health related quality of life SF12	√					√				√
Reason for Termination			√6	√6	√6	√6	√6	√6	√6	√6
AE/ADE/SAE/SADE /DD	√		√	√	√	√	√	√	√	√

1 make sure subject is still eligible
2 dressing change to be performed if there is strikethrough of exudate, i.e. loss of edge seal or adherence, leakage, dislodgement, etc.
3 after dressing is applied
4 after outer dressing/compression is removed and before investigational dressing is removed (i.e. 2 photos where applicable)
5 if dressing is changed only
6 if subject is terminated for reasons other than study completion

In case of an unscheduled study visit, safety parameters will be assessed as well as parameters related to the wound status and dressing change.

4.3 Study subject selection

4.3.1 Inclusion Criteria

1. Male and female subjects 18-85 years of age with leg and foot ulcers (i.e. VLU, DFU).
2. Subject's Ankle-Brachial Index (ABI) by Doppler is ≥ 0.7.
3. The subject has adequate circulation to the foot to allow for healing. This must be demonstrated by methods described in Section 4.3.3
4. Signed informed consent.
5. Subject and/or caregiver must be willing and able to tolerate multi-layered compression bandages when applicable and offloading footwear.
6. Study subject must be available and able to visit the clinic weekly for the full 4-week period.

4.3.2 Exclusion Criteria

1. Pressure ulcers should not be included. Pressure injury as defined by the National Pressure Ulcer Advisory Panel (NPUAP).
2. Presence of local wound infection as determined by study doctor based on clinical signs and symptoms
3. Subject's ABI <0.7 or has any evidence of peripheral arterial disease (PAD).
4. Subject diagnosed with malignancy other than cutaneous basal cell carcinoma.

5. Subject has received growth factor therapy (e.g. autologous platelet-rich plasma gel, becaplermin, bilayered cell therapy, dermal substitute, extracellular matrix e.g. amnion, amniotic tissue) within 2 weeks of screening date.

6. Pregnancy or lactation at time of study participation.

7. Subject is currently receiving or has received radiation or chemotherapy within 3 months of randomization.

8. Subject is currently enrolled or participated in another investigational device, drug or biological trial within 30 days of baseline of this study.

9. Present history of alcohol or drug abuse.

10. Known allergy/hypersensitivity to any of the components of the dressing.

11. Subject not suitable for the investigation according to the investigator's judgment.

4.3.3 Evaluations

1. Vascular testing (ABI or PVR or other non-invasive vascular examination) by one of the following methods:
   - The subject has a palpable pulse on the study foot (either dorsalis pedis or posterior tibial artery) and has clinical signs of adequate circulation in the foot (e.g., toes are warm and pink).
   - If there are either no palpable pulses or clinical signs of adequate circulation are lacking, the Principal Investigator must perform an additional assessment to assure that there is adequate circulation to the leg and foot: Transcutaneous oxygen tension (TcPo2), photoplethysmography (PPG), Toe-Arm Index, Doppler wave form, Cardiosynchronous Limb Compression (CSC), Pulse Volume Recording (PVR) or exercise Ankle-Brachial Index (ABI). Determination of adequate circulation must be according to generally accepted criteria for the particular test employed. The additional assessments must be documented in the subject's source document and Case Report Form.
2. Abbreviated physical exam, medical/surgical history, demographic information, concomitant medications and history of non-healing, weight for Body Mass Index (BMI)
3. High resolution ultrasonography (Duplex) to confirm CVI diagnosis and rule out DVT
4. Pre-debridement photos, wound measurements including surface area
5. Informed Consent Process, Inclusion/Exclusion Criteria

4.3.4 Withdrawal of Subjects from Treatment or Assessment

A subject may be discontinued from the study at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Screen failure
- Subject withdrawal of consent
- Subject is not compliant with study procedures
- AE that in the opinion of the Investigator would be in the best interest of the subject to discontinue study participation
- Protocol violation requiring discontinuation
- Lost to follow-up
- Sponsor request for early termination of study
- Subject death

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the Investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents and the Case Report Form (CRF).

If a subject is withdrawn from treatment due to an AE, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

The Investigator must make every effort to contact subjects who are lost to follow-up. Three (3) attempted telephone contacts should be documented by key research personnel in order to consider the participant lost to follow-up. Furthermore, a certified letter will be mailed to the participant's address. If the participant does not respond, the certified letter receipt should be filed in the individual's research record with a copy of the letter sent. Attempts to contact such subjects must be documented in the patients' records (e.g., times and dates of attempted telephone contact, receipt for sending a registered letter, etc.).

Handling of Participant Withdrawals or Termination

Although subjects may withdraw from the study at any time and for any reason, (or may be withdrawn at the Investigator's discretion), subject withdrawal should be avoided as much as reasonably possible. In any case, appropriate follow-up for endpoints should be continued. The reason for study discontinuation will be recorded on the subject's source document and CRF.

Subjects who prematurely discontinue are not to be replaced. For subjects considered lost to follow-up, the CRF must be completed up to the last visit performed.

Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigator, the Sponsor and the Institutional Review Board (IRB), as appropriate. If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor and/or the IRB.

4.4 Investigational Device

4.4.1 Summary description of the Investigational Device and Comparators

For full package inserts of all study dressings see Appendix B

Investigational Device

Study dressing 1 (T1)
Bordered, five-layer, flexible foam dressing with soft silicone adhesive technology
(Mepilex® Border Flex, Mölnlycke Health Care)

Study dressing 2 (T2)
Hydropolymer, adhesive foam island dressing
(Optifoam Gentle EX, Medline Industries)

Study dressing 3 (T3)
Multi-layered, hydrocellular foam dressing with silicone adhesive
(Allevyn Life, Smith and Nephew, Inc.)

4.4.2 Labelling

All devices under investigation in this study have a market authorization in US. They will be supplied with their standard product labelling, and no study-specific labelling will be applied.

4.4.3 Accountability

Full device accountability will be performed on all the Investigational Devices: Mepilex® Border Flex, Allevyn Life and Optifoam. Mepilex® Border Flex will be provided to the investigation site by Mölnlycke Health Care free of charge. Allevyn Life and Optifoam dressings will be shipped

directly to site via an independent distributor and the costs of these dressing will be reimbursed to the site by Mölnlycke Health Care.

4.4.4 Storage conditions

All study dressings should be stored in dry conditions, below 35°C, and be protected from direct sunlight. All study dressings will be stored in a locked and secured space with restricted access. The study dressings will be kept separately from normal hospital inventory.

4.4.5 Returns and Destruction

According to instructions specified in the Clinical Trial Agreement with the hospital.

4.4.6 Method of Assigning Subjects to Device Groups

Each subject will be randomized to one of four treatment groups as follows: 1) Mepilex® Border Flex, Allevyn Life cross-over group; 2) Allevyn Life, Mepilex® Border Flex crossover group; 3) Mepilex® Border Flex, Optifoam cross-over group and; 4) Optifoam, Mepilex® crossover group. A computer-generated randomization schedule will be provided by Pharma Consulting Group (PCG).

4.4.7 Sizes to be used of Investigational Devices

Test dressing pad size should be >60% of the surface area of the wound. The following dressing sizes will be used:

Sizes for VLU
Mepilex® Border Flex: 10x10cm (6.5x6.5cm pad) and 15x15cm (11x11cm pad)
Optifoam Gentle EX: 10.2x10.2cm (6.3x6.3cm pad) and 15.2x15.2cm (11.4x11.4cm pad)
Allevyn Life: 10.3x10.3cm (5.1x5.1cm pad) and 15x15cm (10.2x10.2cm pad)

Sizes for DFU
Mepilex® Border Flex: 15x15cm (11x11cm pad)
Optifoam Gentle EX: 15.2x15.2cm (11.4x11.4cm pad)
Allevyn Life: 15x15cm (10.2x10.2cm pad)

4.5 Concomitant Treatments

Standard Static Compression Therapy:

All subjects with VLU will have their affected leg treated with one of two static compression bandage systems:

1. Modified Unna's Boot (Unna's paste bandage plus cohesive bandage)
2. 4-Layer Compression Bandage System

The Compression bandages are removed and reapplied at each dressing evaluation/change.

Off-Loading Footwear:

All subjects with DFU will have their affected foot treated with the following off-loading footwear:

1. OPTIMA® Diabetic boot with the appropriate insole kit based on subject weight and wound size and make the boot non-removable by using the locking system.

Any additional post-operative medication which is considered necessary for the subject's safety and well-being is permitted, However, topical medication applied to the wound is not allowed. All concomitant medication and relevant treatment must be recorded in the appropriate section of the (CRF).

4.6 Efficacy and Safety

4.6.1 Subject Baseline Characteristics

Date of birth	DD/MMM/YYYY
Gender	Male/Female/other
Vital signs	Height (cm/ft and in) Weight (kg/pounds) BMI (kg/m^2)
Relevant current medical history Relevant such as diabetes, arterial disease lower leg, anemia, cardio-vascular disease, thrombosis, that may affect the evaluation of dressings performance	Medical condition Date of initial diagnosis/procedure Past/current Ongoing medication
Relevant surgical history Relevant such as varicose vein, amputation defined as surgery that may affect the evaluation of dressings performance.	Surgical procedure Date of surgical procedure Ongoing medication
Type of wound	Venous leg ulcer Diabetic foot ulcer
Wound location	VLU Right lower leg Left lower leg Medial/Lateral Below Malleolus Above Malleolus DFU Right foot Left foot Plantar surface (Y/N) Toe (specify) Forefoot

	Midfoot Heel Other (specify)
Wound history	Responded to previous treatment (Y/N) Debridement procedure (type and instrument) Number of wounds Duration of target wound <1week ≥1 week to <6 weeks ≥6 weeks to <12 months ≥12 months
Wound status	Type of Wound Drainage (Serous, Sanguineous, Serosanguinous, Purulent) Exudate amount (None, Scant/minimal, Moderate, Heavy) Wound size (from pictzar)
Previous dressing	Number of days Brand name of dressing Reason for dressing change Compression type Duration of compression Off-loading
Condition of surrounding skin and wound bed	**Condition of surrounding skin (Healthy/not healthy)** Inflammatory signs (Y/N) Skin irritation at dressing site (Y/N) Allergic rash/eczema (Y/N) Blistering (Y/N) Skin maceration (None, Slight, Moderate, Severe)
Dressing application	Dressing size Type of compression Off-loading (Y/N) (if yes, specify)
Photo of the wound	Y/N
Photo of the dressing *in situ* after first initial application	Y/N

4.6.2 Efficacy Measurements and Variables

Primary Endpoint	**Outcome variable**
The Mepilex® Border Flex versus Optifoam and Allevyn Life dressings.	Interval of time (measured in days) to strikethrough, i.e. loss of edge seal/adherence, leaks, dislodgement.
Secondary Endpoints	**Outcome variable**
Dressing evaluation	Unchanged - Dressing looks the same as when put on the wound. Partly Saturated - Dressing is <50% saturated with exudate but remains intact. Mostly Saturated – Dressing is >50% saturated with exudates Strike-through – Dressing is completely saturated and exudates have leaked outside the bandage.
Clinical wound characteristics during wound management with each of the test dressings (in combination with standard care).	**Wound status** Type of Wound Drainage (Serous, Sanguineous, Serosanguinous, Purulent) Exudate amount (None, Scant/minimal, Moderate, Heavy) Exudate Absorption (Very Poor/Poor/Good/Very Good/NA) Exudate Dispersion 1. wound exudate dispersed 1-25% of pad 2. wound exudate dispersed 26-50% of pad 3. wound exudate dispersed 51-75% of pad 4. wound exudate dispersed 76-100% 5. Is wound dressing completely saturated **with no strike through**

	6. Is wound dressing completely saturated **with strike through** Wound granulation None Trace islands of granulation tissue, less than 25% 25% - 49% Wound base is covered with granulation tissue 50% - 74% Wound base is covered with granulation tissue 75% - 99% Wound base is covered with granulation tissue 100% - Wound base completely filled with granulation tissue (%, captured via photodigital planimetry and visual judgement by research doctor/nurse) Non-viable tissue (eschar, fibrin slough, both) None Less than 25% 25% - 49% 50% - 74% 75% - 100% (captured via photodigital planimetry and visual judgement by research doctor/nurse as above) Wound size (captured via photodigital planimetry) Rate of wound healing (%, captured via photodigital planimetry) **Condition of surrounding skin (Healthy/not healthy)** Signs of inflammation (erythema, edema, induration) (Y/N) Signs of skin irritation at dressing site (Y/N) Skin rash/skin erosion, eczema (Y/N) Stasis dermatitis (Y/N)

	Vesicular erosion (blistering) (Y/N) Skin maceration (None, Slight, Moderate, Severe) **Clinical signs/symptoms of acute infection** Increased pain and tenderness (Y/N) Increased warmth (Y/N) Sudden increase in ulcer size (Y/N) Is there localized Erythema (Y/N) Foul smelling exudates (Y/N) Does the wound bleed easily (Y/N) **Wound odor (before and after cleansing)** (None, Minimal, barely noticeable, Moderate, noticeable but not offensive, Moderate, offensive, Putrid)
Safety Evaluation	Number of device related safety events associated with each of the wound dressings (ADEs/SADEs/DDs)
Patient-centric outcomes.	***Patient Reported outcomes*** **Pain** Local wound and skin pain before dressing removal (Baker-Wong) Pain at removal (Baker-Wong) Pre-procedural or intra-procedural pain medication administration at the time of dressing removal (Concomitant Medical) Local wound and skin pain immediately after dressing removal (Baker-Wong)

	12-item Short Form Survey (SF12) **Comfort and conformability** Comfort during wear of the dressing (Very Poor/Poor/Good/Very Good/NA) Overall impression of the dressing (Very Poor/Poor/Good/Very Good/NA) Bulkiness of the dressing (Very Poor/Poor/Good/Very Good/NA) Friction of the dressing (Very Poor/Poor/Good/Very Good/NA) Appearance of dressing is discreet (Very Poor/Poor/Good/Very Good/NA) The stay-on-ability of the dressing (Very Poor/Poor/Good/Very Good/NA) Dressing stick to “hairy” skin (Very Poor/Poor/Good/Very Good/NA) Showerablility of the dressing (Very Poor/Poor/Good/Very Good/NA) ***Investigator Reported outcomes*** Ease of handling (Very Poor/Poor/Good/Very Good/NA) Ability to maintain its integrity (Very Poor/Poor/Good/Very Good/NA) Ease of application (Very Poor/Poor/Good/Very Good/NA) Ability to be repositioned (Very Poor/Poor/Good/Very Good/NA) Conformability (Very Poor/Poor/Good/Very Good/NA) Ability to stay in place (Very Poor/Poor/Good/Very Good/NA)

	Ease of removal (Very Poor/Poor/Good/Very Good/NA) Does the dressing cause skin stripping (Y/N) Presence of material remnant (None, Some) Is dressing adherent to the wound bed? (No/Yes, mild adhesion without bleeding/Yes, severe adhesion with bleeding) Wound re-injury or trauma to skin upon removal (Y/N) Exudate absorption even under compression (Y/N) Trauma to wound edges (Y/N)
Additional Endpoint	**Outcome variable**
Safety Evaluation	Number of safety events, not device related, associated with each of the wound dressings (AEs/SAEs)
Health Economics Endpoint	**Outcome variable**
To retrospectively compare cost effectiveness parameters of each of the study dressings	**Health Economics** To retrospectively compare resource-use as related to: • Quantity of dressing changes per week (stratified by wound type) • Time required per dressing change (in minutes) a. Start time: Initiation of old dressing removal b. End time: New dressing is securely in place • Staff cost associated with dressing change a. Identification of those involved with dressing change (e.g., MD, Nurse, Assistant, etc.) b. Average hourly rate for those individuals directly involved with dressing change (This can be market data if individuals do not want to provide actual salary information) • Material Cost

	a. Quantity of each product (dressing) used per week b. Size of dressings used c. Cost of each dressing used per week d. Other material cost used in dressing change i. Identification of products used per week ii. Quantity of each product used per week iii. Cost of each product used per week • Additional medication or management to address pain or injury during dressing removal

4.6.3 Safety Measurements and Variables

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

Signs of local infection will be judged by the investigator:

- Pain and/or trauma since last dressing change
- Foul odor
- High levels of exudates

4.6.4 Anticipated ADEs

The conclusion of the Product Risk Management Record (PD-518122 rev 05) and the Clinical Evaluation Report (PD-511948 rev 3) of Mepilex® Border® is: Mepilex® Border has substantial support for both performance and safety given the substantial amount of clinical investigations performed on the device, together with the low risk and long term performance and safety of the device. Before reaching the above conclusion, the identified risks of the investigational device were mitigated to an acceptable level in the risks analysis process (following ISO 14971, Application of Risk Management to Medical Devices).

The following events have been identified as anticipated effects in the Clinical Evaluation Report based on the Product Risk Management Record:

- Pain at dressing removal
- Trauma to the wound bed or surrounding skin
- Skin stripping/irritation

- Skin irritation or local allergic reactions
- Maceration
- Infection

All identified risks have been assessed. It is concluded that all applicable risk mitigation actions have been performed and verified to be effective. No unacceptable risks remain. Thus, the benefit of using the products outweighs the remaining risks.

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

Concomitant treatments that are known to potentially affect the performance of the investigational device must be registered in the eCRF.

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

4.7 Data Quality Assurance

4.7.1 Monitoring, Audits and Inspections

During the investigation, the monitor will have regular contacts with the investigation site. These contacts will include visits to confirm that the facilities remain adequate to specified standards and that the investigation site team is carrying out the procedure stated in the Clinical Investigation Plan and supports the investigator. All data must be accurately recorded in the CRF. Source data verification (a comparison of data in the CRF with the subject's hospital/practice and other records at the investigation site) with direct access to records will also be performed.

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

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

4.7.2 Training of Staff

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

4.7.3 Data Management

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

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

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

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

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

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

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

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

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

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

4.8 Statistical Methods and Determination of Sample Size

4.8.1 Statistical Evaluation

Two cross-over studies AB/BA will be performed. In the first one Mepilex® Border Flex will be compared with Optifoam and in the second one Mepilex® Border Flex will be compared with Allevyn Life. Exactly the same statistical methods will be used in both these cross-over studies. In this statistical section Optifoam and Allevyn Life will be substituted with active control.

Primary efficacy variable, days to strikethrough, and probably all of the other efficacy variables are non-normal distributed. Therefore, non-parametric tests are used.

it is likely the status of the wounds will be better in the second period of the cross-over. This implies that the statistical analysis must adjust for period effect in the AB/BA crossover study. For primary efficacy variable days to strikethrough, all other continuous outcome variables, all ordered categorical variables and all dichotomous variables the adjustment for period effect will be performed in the following way:

For all subjects the difference in the efficacy variable between Period 2 and Period 1 in the cross-over will be calculated.

These differences will then be compared between subjects started with Mepilex® Border Flex in Period 1 and subjects started with active control in Period 1 with an optimal two-sided two-sample test. For continuous variables the differences will be analyzed with Fisher's non-parametric permutation tests between the two groups and for ordered categorical variables and dichotomous variables the differences, number and percentages improved, not changed and worsened, will be analyzed with Mantel-Haenszel Exact Chi-square test.

The main statistical analysis will be performed on the full analysis set (ITT). Complementary statistical analysis will be performed on the Per Protocol (PP) set.

The Full Analysis Set will include all subjects with at least one measurement of follow up. The Per Protocol population will include all subjects that fulfil all inclusion/exclusion criteria and that are not described as protocol violators. They should have been followed for the 2x2 weeks treatment period. Subjects identified as protocol violators will be documented and agreed between Mölnlycke Health Care and the Principal Investigator before declaration of clean-file, please see Section 4.7**.**

The Safety population include all subjects that have at least one application of the Mepilex® Border dressing or at least one of the other study dressings.

The distribution of continuous variables and change in continuous variables will be given as mean, standard deviation, median, minimum and maximum and the distribution of categorical and dichotomous variables will be given as numbers and percentages.

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

A baseline table will be given for all included subjects with the distribution of demographics and baseline variables.

4.8.2 Primary Efficacy Analysis

Primary efficacy analysis comparison of days to strikethrough between Mepilex® Border Flex and active control will be performed on the full analysis set (FAS) in the following way.

For subjects randomized to Mepilex® Border Flex in the first period the difference in days to strikethrough between period 2 (active control) and period 1 (Mepilex® Border Flex) will be compared to subjects randomized to active control in the first period regarding the differences in days to strikethrough between period 2 (Mepilex® Border Flex) and period 1 (active control) with two-sided Fisher's non-parametric permutation tests at significance level 0.05. Period adjusted mean differences in days to strikethrough between Mepilex® Border Flex and active control will be given with 95% confidence interval based on Fisher's non-parametric permutation tests.

In both cross-over studies, Mepilex® Border Flex compared to Optifoam study and Mepilex® Border Flex compared to Allevyn Life, the same above analysis will be the primary analyses. Since there are two separated studies no multiplicity adjustment will be performed.

4.8.3 Determination of Sample Size

The expected mean differences in days to strikethrough between the differences Period 1-Period 2 between the two groups Mepilex® Border Flex and active control will be two times the difference in the effect Mepilex® Border Flex minus active control.

We estimate (assume) the SD for the difference in time to strikethrough between Period 2 and Period 1 to be 0.65 days both in the group started with Mepilex® Border Flex and in the group started with active control.

In order to find a difference in one half day between days to strikethrough between Mepilex® Border Flex and active control with a power of 80% a total of 16 evaluable subjects is needed.

This implies that in the first cross-over study 16 subjects will be randomized to the sequence Mepilex® Border Flex in the first period and Optifoam in the second period and to the sequence Optifoam in the first period and Mepilex® Border Flex in the second period in proportions 1:1.

In the second cross-over study 16 subjects will be randomized to the sequence Mepilex® Border Flex in the first period and Allevyn Life in the second period and to the sequence Allevyn Life in the first period and Mepilex® Border Flex in the second period in proportions 1:1. Both

the randomizations above will be stratified by diagnosis Venous Leg Ulcer / Diabetic Foot Ulcer.

A total of 32 subjects will be included in the two cross-over studies.

4.9 Changes to the Clinical Investigation Plan

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

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

Mölnlycke Health Care will distribute Clinical Investigation Plan amendments to the Principal Investigator who is responsible for the distribution of these documents to the EC/IRB and staff concerned at his/her site. The distribution of these documents to the CA will be handled according to local practice.

5. STATEMENTS OF COMPLIANCE

5.1 Ethics

5.1.1 Ethics review

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

5.1.2 Ethical Conduct of the Investigation

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

5.1.3 Patient Information and Consent Form

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

specifically for the investigation. The original must be filed by the Principal Investigator. A copy of the Patient Information including the signed Consent Form should be given to the subject.

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

5.2 Regulatory and standards

5.2.1 Regulatory review

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

5.2.2 Standards and other

The most recent version of ISO 14155 is followed in addition to national regulations. 21 CFR 50 Protection of Human Subjects, 21 CFR 56 Institutional Review Boards and 21 CFR 54 Financial Disclosure. The abbreviated requirements as described in 21 CFR 812.2(b).

5.2.3 Subject Data Protection

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

5.3 SUBJECT PROTECTION PROCEDURES

5.3.1 Procedures in Case of Medical Emergency

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

5.3.2 Insurance

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

6. INVESTIGATION TIMETABLE AND TERMINATION

Investigation start: November 2018

Inclusion completed: May 2019

Last subject out: June 2019

The investigation could be prematurely discontinued if the dropout rate is higher than 15% and/or the investigation site is unable to fulfill the inclusion period according to the Clinical Trial Agreement.

7. LITERATURE REVIEW AND REFERENCES

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

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4. Rippon M, Davies P, White R. Taking the trauma out of wound care: the importance of undisturbed healing. Journal of Wound Care. 2012;21(8):359-68.
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6. Van De Looverbosch D, Andersson A, Husmark A, Körner V. An open randomized explorative study comparing Mepilex® Border with Tielle in patients with pressure ulcers according to stage II, EPUAP guidelines. Clinical Investigation Report (MPXB201), Mölnlycke Health Care. 2001.
7. White R. A multinational survey of the assessment of pain when removing dressings. Wounds UK. 2008;4:14-22.

8. Woo K, Bergström C. An Open Randomised Cross-over Investigation Assessing Perceived Pain at Dressing Change Comparing A Soft Silicone Dressing, Mepilex® Border, with a Adhesive hydrocellular polyurethane dressing, Allevyn® Adhesive in Patients with chronic ulcer. Clinical Investigation Report (MXB408, Part A, Mölnlycke Health Care). 2007.
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14. Chadwick P, McCardle J. Exudate management using a gelling fibre dressing. The Diabetic Foot Journal. 2015;18(1):43-8.
15. González de la Torre H, Quintana-Lorenzo M, Perdomo-Pérez E, Verdú J. Correlation between health-related quality of life and venous leg ulcer's severity and characteristics: a cross-sectional study. International Wound Journal. 2016.
16. Jones J, Robinson J, Barr W, Carlisle C. Impact of exudate and odour from chronic venous leg ulceration. Nursing Standard. 2008;22(45):53-61.
17. Pukki T, Tikkanen M, Halonen S. Assessing Mepilex® (registered trademark) border in post-operative wound care. Wounds UK. 2010;6:30-40.
18. Woo K, Thorell J. An open, randomised, cross-over investigation assessing perceived pain at dressing change comparing a soft silicone dressing, Mepilex® Border, with an adhesive hydrocellular polyurethane dressing, Allevyn, in patients with chronic ulcers Clinical Investigation Report (MXB408, Part B), Mölnlycke Health Care. 2008.
19. Registry study Bordered foam products (including Mepilex® Border). PowerPoint presentation GVW [unpublished data]. 2016.

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

Definitions:

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

Note: Device Deficiencies include malfunctions, use errors, and inadequate labelling.

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

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

Note:

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

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

Note:

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

Serious Adverse Event (SAE)
Adverse Event that:

a) led to death,

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

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) inpatient hospitalization or prolonged hospitalization or,

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

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

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

Serious Adverse Device Effect (SADE)

ADE that has resulted in any of the consequences characteristic of a SAE.

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

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

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

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

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

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

PROCEDURES FOR DD REPORTING

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

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

Procedures for ADE reporting

All ADE shall be reported by the investigator to Mölnlycke Health Care as soon as possible without unjustified delay. When a ADE has been entered into the eCRF by the investigator /authorized site staff, the eCRF system will automatically generate a report to: Clinical_Investigations_Event_Reporting@molnlycke.com

This includes also ADEs occurring in the comparator arm.

Causality Assessment

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