Title: CIP with integrated central Amendments 1 and 2 ExufiberAg+01

Investigation Code	**ExufiberAg+01**	**Final Version**	**Approval date 2017-05-10**
		Amendment 1	**Approval date 2017-05-26**
		Amendment 2	**Approval date 2018-08-07**
		Amendment 3	**Approval date 2018-08-21**
		Amendment 4	**Approval date 2019-02-19**

CLINICAL INVESTIGATION PLAN (CIP)

INVESTIGATIONAL DEVICE:

Exufiber Ag+

INVESTIGATION TITLE:

A clinical investigation to study the effect of Exufiber Ag+ and other gelling fibre dressings on wound exudate and bioburden in medium to high exuding w

CO-ORDINATING INVESTIGATOR:
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Title: CIP with integrated central Amendments 1 and 2 ExufiberAg+01

Investigation Code	**ExufiberAg+01**	**Final Version**	**Approval date**	**2017-05-10**
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		Amendment 4	**Approval date**	**2019-02-19**

CLINICAL INVESTIGATION PLAN (CIP) SYNOPSIS

INVESTIGATION TITLE:

A clinical investigation to study the effect of Exufiber Ag+ and other gelling fibre dressings on wound exudate and bioburden in medium to high exuding wound.

Objectives

This investigation is undertaken to investigate the impact of Exufiber Ag+ and other gelling fibre dressings on handling exudate, changes in aerobic counts and microbial diversity of bioburden by collecting tissue and associated microbial virulence factors in the wound exudate by collecting wound exudate, in medium to high exuding wound.

Primary objective

- To evaluate reduction in exudate from baseline to last visit*.

Secondary objective

- To evaluate changes in bioburden from baseline to visit 3.
- To evaluate the status of the wound and peri-wound skin from baseline to last visit*
- To evaluate the handling and technical performance of the dressing from baseline to last visit*
- To evaluate comfort, conformability and acceptability of the dressing from visit 3 to last visit*
- To evaluate safety from baseline to last visit*

*Last visit = Visit 5. Last visit occur earlier if the wound is dry or healed.

** Distribution of patients included in the bioburden analysis can be found under 4.5.4

For details please see section 4.5.2.

Overall Design

This is a non-randomised, prospective, multi-center, clinical investigation on medium to high exuding wound that will be conducted on approximately 105 subjects in US.

An eligible subject is defined as a subject that fulfils all the inclusion and none of the exclusion criteria. Both inpatients and outpatients/subjects will be eligible.

The target subjects are male or female, 18 years or older who have a medium to high exuding wound. The objectives are to investigate the impact of Exufiber Ag+ and other gelling fibre dressings on handling wound exudate, bioburden and possible associated molecular biomarkers.

Each subject will be evaluated during 5 visits, with a total treatment period of 4 weeks (28 days (± 2 days)) or earlier if the wound is dry (see Table 1) or healed.

Only one target wound per patient (indication specified in Appendix D, Instruction for use) will be included in this investigation.

Dressing changes will be done every 7 days or earlier if needed according to instruction for use (see Appendix D) and the sites local routines. Dressing changes will be recorded in the "Dressing Log". Dressing changes between the scheduled visits will be recorded on the " Dressing Log" at the next scheduled visit.

The subject will be assigned either to Exufiber®Ag+, Exufiber® or Aquacel™Ag Extra™ (For details see Figure 1).

Study Period

Estimated date of first subject enrolled Q2 2017

Estimated date of last subject completed Q3 2019

Estimated date of end of clinical investigation (database lock) Q3 2019

Inclusion Criteria

1. Subjects or subject's legal authorized representative (LAR) able to read and sign the Patient Information and Consent Form
2. Both gender ≥18 years old
3. From Medium (defined as Wet specified in section 4.5.6) to High exuding (defined as Leaking specified in section 4.5.6) wound

Exclusion Criteria

1. Known allergy/hypersensitivity to any of the treatment dressings
2. Pregnant/lactating females
3. Subjects with a target wound that is ≤ 1 cm^2
4. Subjects with a target wound that is a full thickness burn
5. Subjects with known immunodeficiency
6. Subject taking systemic antibiotics for wound infection
7. Subject were the target wound is located on an infected limb interfered by minimal blood flow (in the opinion of the investigator).
8. Subject with a target wound with unexplored enteric fistula
9. Subjects who, in the opinion of the investigator, will have problems following the protocol
10. Subjects needing treatment with oxidizing agents such as hypochlorite solutions or hydrogen peroxide

11. Previously enrolled in the present investigation
12. Inclusion in other ongoing investigations at present that would preclude the subject from participating in this investigation as judged by the investigator
13. Involvement in the planning and conduct of the clinical investigation (applies to all Mölnlycke staff, investigational site staff and third party vendor)

Schedule of Assessment

Week number	Visit 1 (Baseline)	Visit 1b **Only applicable for site no 01** (4 days from baseline)	Visit 2 (7 days from baseline)	Visit 3 (14 days from baseline)	Visit 4 (21 days from baseline)	Visit 5 (28 days from baseline)
Visit window	NA	± 1 days	± 2 days	± 2 days	± 2 days	± 2 days
Informed consent	√					
Inclusion and exclusion criteria	√					
Subject demographics	√					
Vital Signs	√					
Type, location and duration of the wound	√					
Relevant Medical History [a]	√					
Relevant surgical history [b]	√					
Current wound treatment [c]	√					
Compression (if applicable)	√	√	√	√	√	√
Evaluation of the exudate [d]	√	√	√	√	√	√
Wound size measurement [h]	√	√	√	√	√	√
Status of the wound and peri-wound evaluated by the study personnel	√	√	√	√	√	√

Week number	Visit 1 (Baseline)	Visit 1b **Only applicable for site no 01** (4 days from baseline)	Visit 2 (7 days from baseline)	Visit 3 (14 days from baseline)	Visit 4 (21 days from baseline)	Visit 5 (28 days from baseline)
Handling and technical performance of the dressing.	√		√	√	√	√
Signs of clinical infection	√	√	√	√	√	√
Photo [e]	√	√	√	√	√	√
Tissue sampling [f] **Only applicable for site no 01**	√	√	√	√		
Wound exudate sampling [f] **Only applicable for site no 01**	√	√	√	√		
Subject evaluation			√	√	√	√
Dressing application (First Visit)	√					
Dressing change		√ [i]	√	√	√	
Dressing removal (Final Visit)						√
Relevant concomitant medication	√	√	√	√	√	√
AE/ADE/SAE/SADE/DD	√	√	√	√	√	√

a) Relevant medical history specified in section 4.5.1.
b) Relevant surgical history specified in section 4.5.1.
c) Current wound treatment (name of the primary dressing and frequency of dressing changes/per week).
d) Changes in exudate defined in details 4.5.6.
e) PHOTOGRAPHS: Please see Appendix E for a detailed instruction of when photos should be taken. Please include measuring scale (ruler) with date, subject number and visit number and please respect the confidentiality of the subject by not including any personal numbers or identifying characteristic.

f) TISSUE and EXUDATE SAMPLING: Please see Appendix F for detail instruction how to collect tissue and exudate. **Only applicable for site no 01 for subjects recruited before September 2018.**
g) Relevant concomitant medication specified in section 4.4.
h) Wound size measurement before and after debridement (if applicable).
i) Dressing change only applicable for site no 01 (included into the tissue and exudate sampling part in the clinical investigation).

Investigational Devices

Exufiber Ag+

Exufiber Ag+ wound dressing is a sterile, soft and nonwoven pad. Exufiber Ag+ consists of highly absorbent and gel forming polyvinyl alcohol (PVA) nonwoven fibres. The nonwoven pad is coated with silver sulphate on both sides. The silver is released within the dressing in contact with fluid, and acts as a preservative in the dressing to inhibit or reduce microbial growth in the dressing. The investigational device fall under FDA-premarket notification K160379. The dressing is sterilized in EtO (ethylene oxide).
For this clinical investigation, Exufiber Ag+ will be available in the following sizes:

Dressing sizes		Total silver content
cm	Inches	mg
5 x 5	2x2	5
15 x15	6x6	45

Manufacture registered trademark of Mölnlycke Health Care AB.

Exufiber

Exufiber is a sterile nonwoven dressing made from highly absorbent and gel forming polyvinyl alcohol fibres. Exufiber is available as pad. Exufiber wound dressing absorbs and retains wound exudate. It is transformed into a soft gel that facilitates moist wound healing and ease of removal during dressing change. The investigational device is exempt and fall under FDA regulation number 878.4018. The dressing is sterilized in EtO
For this clinical investigation, Exufiber will be available in the following sizes:

Dressing sizes	
cm	Inches
5 x 5	2x2
15 x15	6x6

Manufacture registered trademark of Mölnlycke Health Care AB.

AquacelAg Extra

Dressing with Silver and Strengthening Fibre is a one piece wound dressing comprised of two layers of soft, sterile non-woven material. The non-woven pads are comprised of Hydrofiber dressing and ionic silver stitch-bonded together with regenerated cellulose fibres and designed to provide additional absorbency and tensile strength properties. The investigational device fall under FDA-premarket notification K121275.

Dressing sizes	Total silver content

cm	Inches	Mg
5 x 5	2x2	4.5
15 x15	6x6	40.5

Manufacture registered trademark of ConvaTec Inc.

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Appendix D Instructions for Use

Appendix E Photograph Manual

Appendix F Tissue and Exudate Sampling

LIST OF ABBREVIATIONS

ADE Adverse Device Effect

AE Adverse Event

CA Competent Authority

CFU Colony Forming Units

eCRF Electronic Case Report Form

DD Device Deficiency

EC Ethics Committee

GCP Good Clinical Practice

IRB Institutional Review Board

PCR Polymerase Chain Reaction

SAE Serious Adverse Event

SADE Serious Adverse Device Effect

1. INTRODUCTION

Non-healing wounds are a significant problem for health-care systems worldwide. The presence of microorganisms in the wound, referred to as bioburden, negatively interferes with the healing process[1].

Assessing the bioburden in slow healing wounds relies on the assessment of clinical signs of infection, which in many cases is a very blunt tool to predict the wound bioburden in patients[2]. While many dressings are designed or marketed to address the bioburden in wounds and suggest the reduction of bioburden, very few methods are available to monitor this performance of a wound dressing in patients.

While biopsies, the golden standard, provide an accurate picture of CFU counts even in the deeper layer of skin tissue, they are invasive and offer only a small window into the total surface area of wounds. Some other methods commonly used, such as swabbing provide a snapshot of the bioburden over the whole surface area of the wound but fail to provide an accurate measurement of the total bioburden deeper in the tissue.

Some attempts have been made to identify chemical biomarkers to assess the bioburden status of the wound in an attempt to make the link between healing and non-healing wounds[3].

To correlate molecular biomarkers with overall reduction of the bioburden in the wound is difficult due to the time dependent appearance of biomarkers as well as their selectivity for certain strains. 16S DNA sequencing provides as fast and detailed assessment of the wound microbiota and the relative amount of the various present species[4]. Viability PCR or Pre-rRNA analysis (MVT) allow a dead or alive distinction[9].

Culture testing is not as sensitive as molecular testing, so culturing often fails to detect bacteria, even bacteria that are present in a high relative abundance. Bacteria that are present in high relative abundance are likely of high clinical relevance, including the bacteria that are not detected by culture. It also allows an absolute quantification of the CFU count of the test sample[5].

Wound exudate samples can be used to identify molecular biomarkers such as enzymes, cytokines and metabolites. The significance of the appearance and relative fold change of such biomarkers in combination with the change of bioburden of the wound is investigated and could provide crucial information to predict bioburden in wounds.

Wounds that produce an excessive amount of exudate is in an, inflammatory state. By reducing exudate the conditions for bacterial growth become less optimal. Gelling fibre dressings are developed to absorb and retain large amount of exudate to support an optimal wound healing process. Gelling fibre dressings with additional silver ions have *in vitro* models shown to decrease the number of microorganisms.

Delayed healing often defined as clinical signs of infection (exudate, pain, discoloration, odour)[6]. Infected wounds are likely to be more painful and associated with high exudate levels which can increase the number of dressing changes required. The negative effect on excess exudate on wound healing can result in delayed healing, maceration of peri-wound skin and embarrassing

leakage for the patient. It is important that modern wound dressing can maintain moisture balance by absorbing excess exudate and preventing the wound drying out, in addition to being able to afford bacterial barrier properties in the wound are risk of infection, when required[7]. Majority of the silver dressing studies have included endpoints related to healing, however more appropriate endpoints for silver dressing may related to measure microbial burden or assessment of clinic indicators of infection[8].

The current golden standard of antimicrobial gelling fibre dressings is today Aquacel Ag and its further developed range of products such as Aquacel Ag Extra and Aquacel Ag+ Extra (not on the US only EU market). A new antimicrobial gelling fibre dressing (Exufiber Ag+) has been developed and is 510(k) cleared for sales in the United States.

Exufiber Ag+ has been shown to have a higher retention capacity than Aquacel Ag Extra. The non-silver version (Exufiber) has been on the market for a couple of years and both clinical investigations and customer feedback have confirmed the dressings high performance in exudate management. Two *in vivo* studies on pigs where the antimicrobial properties of Exufiber Ag+ were compared to both Exufiber and Aquacel Ag+ Extra have been performed. The results from these studies showed that Exufiber Ag+ was the most efficient treatment at reducing bioburden measured as established biofilms of MRSA and *Pseudomonas aeruginosa*[10],**Error! Reference source not found.**.

Our study purpose is to investigate the impact of Exufiber Ag+ and other gelling fibre dressing on handling wound exudate, bioburden and possible associated molecular biomarkers. The study is expected to provide a lot of important knowledge by combining advanced microbial detection techniques with dressing performance and clinical outcomes.

2. OBJECTIVES

This investigation is undertaken to investigate the impact of Exufiber Ag+ and other gelling fibre dressings on handling exudate, changes in aerobic counts and microbial diversity of bioburden by collecting tissue and associated microbial virulence factors in the wound exudate by collecting wound exudate, in medium to high exuding wound.

Primary objective

- To evaluate reduction in exudate from baseline to last visit*.

Secondary objective

- To evaluate changes in bioburden from baseline to visit 3.
- To evaluate the status of the wound and peri-wound skin from baseline to last visit*
- To evaluate the handling and technical performance of the dressing from baseline to last visit*

- To evaluate comfort, conformability and acceptability of the dressing from visit 3 to last visit*
- To evaluate safety from baseline to last visit*

*Last visit = Visit 5. Last visit occur earlier if the wound is dry or healed.

** Distribution of patients included in the bioburden analysis can be found under 4.5.4

For details please see section 4.5.2.

3. CLINICAL INVESTIGATOR(S) AND INVESTIGATION ADMINISTRATIVE STRUCTURE

3.1 Staff at Investigation site(s)

Name and addresses of principal investigators are listed in Appendix A

3.2 Mölnlycke Investigation Personnel

Role in the investigation	Name	Contact information
Clinical Study Manager Author of the CIP	Tina Kjellén	Mölnlycke Health Care AB Byfogdegatan 1 SE-415 05 Göteborg, SWEDEN Phone: +46 31 722 30 00 E-mail: tina.kjellen@molnlycke.com
Clinical Study Manager Responsible for the clinical investigation	Channing Wood	Molnlycke Health Care US, LLC 5550 Peachtree Parkway Suite 500 Norcross, GA 30092 USA Phone: +1 4703750186 E-mail: channing.wood@molnlycke.com
Clinical Research Administrator	Annika Rydström	Mölnlycke Health Care AB Byfogdegatan 1 SE-415 05 Göteborg, SWEDEN Phone: +46 31 722 3000 E-mail: annika.rydstrom@molnlycke.com
Clinical Data Manager	Ann-Sofie Svensson	Mölnlycke Health Care AB Byfogdegatan 1 SE-415 05 Göteborg, SWEDEN Phone: +46 31 722 30 00 ann-sofie.svensson@molnlycke.com
Global Clinical Research Director	Markus Wittebo	Mölnlycke Health Care AB Byfogdegatan 1 SE-415 05 Göteborg, SWEDEN Phone: +46 31 722 3000 E-mail: markus.wittebo@molnlycke.com

3.3 Other Participants

Role in the investigation	Contact information
Supplier of the electronic data capture (EDC) system	Pharma Consulting Group AB Kungsängsvägen 19 SE-753 23 Uppsala Sweden Phone: +46 18 430 3100

Biostatistician	Statistiska Konsultgruppen Nils-Gunnar Pehrsson Stigbergsliden 5 SE-414 63 Göteborg
CRO	Peachtree BioResearch Solutions, Inc. 4985 Lower Roswell Rd., Bldg. 100 Marietta, GA 30068

4. INVESTIGATION PLAN AND PROCEDURES

4.1 Overall Design and Flow Chart

This non-randomised, prospective, multi-center, clinical investigation on medium to high exuding wound, will be conducted at up to 15 sites on approximately 105 subjects in US.

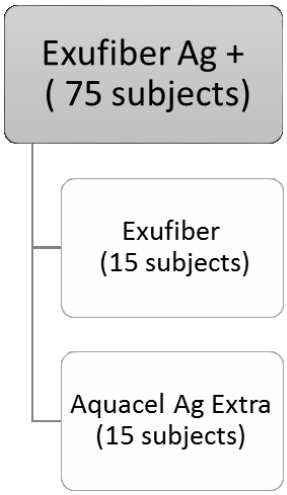
An eligible subject is defined as a subject that fulfils all the inclusion and none of the exclusion criteria. Both inpatient and outpatient/subjects will be eligible. The target subject are male or female, 18 year or older who have a medium to high exuding wound. The objectives are to investigate the impact of Exufiber Ag+ and other gelling fibre dressing on handling wound exudate, bioburden and possible associated molecular biomarkers

Each subject will be evaluated during 5 visits, with a total treatment period of 4 weeks (28 days (± 2 days)) or earlier if the wound is dry (see Table 1) or healed.

Only one target wound per patient (indication specified in Appendix D, Instruction for use) will be included in this investigation.
The subject will be assigned either to Exufiber Ag+, Exufiber or Aquacel Ag Extra according to Figure 1 Dressing distribution flow chart.
Dressing change will be done every 7 days or earlier if needed according to instruction for use (see Appendix D) and the sites local routines. Dressing changes will be recorded in the “Dressing Log”. Dressing changes between the scheduled visits will be recorded in the “ Dressing Log” at the next scheduled visit.

Secondary dressing will be chosen according to local routine.

Figure 1 Dressing distribution flow chart


Exufiber Ag +
(75 subjects)
Exufiber
(15 subjects)
Aquacel Ag Extra
(15 subjects)

4.2 Procedures and Assessments

4.2.1 Schedule of Assessment

Week number	Visit 1 (Baseline)	Visit 1b **Only applicable for site no 01** (4 days from baseline)	Visit 2 (7 days from baseline)	Visit 3 (14 days from baseline)	Visit 4 (21 days from baseline)	Visit 5 (28 days from baseline)
Visit window	NA	± 1 days	± 2 days	± 2 days	± 2 days	± 2 days
Informed consent	√					
Inclusion and exclusion criteria	√					
Subject demographics	√					
Vital Signs	√					
Type, location and duration of the wound	√					
Relevant Medical History [a]	√					
Relevant surgical history [b]	√					
Current wound treatment [c]	√					
Compression (if applicable)	√	√	√	√	√	√
Evaluation of the exudate [d]	√	√	√	√	√	√
Wound size measurement [h]	√	√	√	√	√	√
Status of the wound and peri-wound evaluated	√	√	√	√	√	√

Week number	Visit 1 (Baseline)	Visit 1b **Only applicable for site no 01** (4 days from baseline)	Visit 2 (7 days from baseline)	Visit 3 (14 days from baseline)	Visit 4 (21 days from baseline)	Visit 5 (28 days from baseline)
by the study personnel						
Handling and technical performance of the dressing.	√		√	√	√	√
Signs of clinical infection	√	√	√	√	√	√
Photo [e]	√	√	√	√	√	√
Tissue sampling [f] **Only applicable for site no 01**	√	√	√	√		
Wound exudate sampling [f] **Only applicable for site no 01**	√	√	√	√		
Subject evaluation			√	√	√	√
Dressing application (First Visit)	√					
Dressing change		√ [i]	√	√	√	
Dressing removal (Final Visit)						√
Relevant concomitant medication	√	√	√	√	√	√
AE/ADE/SAE/SADE/DD	√	√	√	√	√	√

a) Relevant medical history specified in section 4.5.1.
b) Relevant surgical history specified in section 4.5.1.
c) Current wound treatment (name of the primary dressing and frequency of dressing changes/per week).
d) Changes in exudate defined in details 4.5.6.

e) PHOTOGRAPHS: Please see Appendix E for a detailed instruction of when photos should be taken. Please include measuring scale (ruler) with date, subject number and visit number and please respect the confidentiality of the subject by not including any personal numbers or identifying characteristic.

f) TISSUE and EXUDATE SAMPLING: Please see Appendix F for detail instruction how to collect tissue and exudate. **Only applicable for site no 01 for subjects recruited before September 2018.**

g) Relevant concomitant medication specified in section 4.4.

h) Wound size measurement before and after debridement (if applicable).

i) Dressing change only applicable for site no 01 (included into the tissue and exudate sampling part in the clinical investigation).

4.2.2 Inclusion Criteria

For inclusion in the investigation, the subjects must fulfil all of the below criteria prior to enrolment:

1. Signed Informed Consent Form
2. Both gender ≥18 years old
3. From Medium (defined as Wet specified in section 4.5.6) to High exuding (defined as Leaking specified in section 4.5.6) wound

4.2.3 Exclusion Criteria

Subjects who meet any of the below criteria will be excluded from the investigation

1. Known allergy/hypersensitivity to any of the treatment dressings
2. Pregnant/lactating females
3. Subjects with a target wound that is ≤ 1 cm^2
4. Subjects with a target wound that is a full thickness burn
5. Subjects with known immunodeficiency
6. Subject taking systemic antibiotics for wound infection
7. Subject were the target wound is located on an infected limb interfered by minimal blood flow (in the opinion of the investigator).
8. Subject with a target wound with unexplored enteric fistula
9. Subjects who, in the opinion of the investigator, will have problems following the protocol
10. Subjects needing treatment with oxidizing agents such as hypochlorite solutions or hydrogen peroxide
11. Previously enrolled in the present investigation
12. Inclusion in other ongoing investigations at present that would preclude the subject from participating in this investigation as judged by the investigator
13. Involvement in the planning and conduct of the clinical investigation (applies to all Mölnlycke staff, investigational site staff and third party vendor)

4.2.4 Withdrawal of Subjects from Treatment or Assessment

Subjects are free to discontinue participation in the investigation at any time, and without prejudice to further treatment. Subjects who discontinue the investigation should always be asked about the reason(s) for their discontinuation and about the presence of any Adverse Event/Adverse Device Effect or Device Deficiency and, if possible, be assessed by an investigator. Adverse Event/Adverse Device Effect should be followed up.
Subjects may be withdrawn from investigation treatment and assessments at any time, at the discretion of the investigator.
Incorrectly enrolled subjects will be withdrawn from further investigation treatment and assessments. A subject may, however, continue the investigation under special circumstances (i.e. if continuation of investigation treatment or follow-up actions are necessary for the subject's safety and well-being, or if only a follow-up period remains, and the continuation of the investigation is not expected to be associated with any risk or discomfort for the subject).

Title: CIP with integrated central Amendments 1 and 2 ExufiberAg+01

Investigation Code	**ExufiberAg+01**	**Final Version**	**Approval date** **2017-05-10**
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		Amendment 3	**Approval date** **2018-08-21**
		Amendment 4	**Approval date** **2019-02-19**

4.3 Investigational Device

4.3.1 Summary description of the Investigational Device(s)

Exufiber Ag+

Exufiber Ag+ wound dressing is a sterile, soft and nonwoven pad. Exufiber Ag+ consists of highly absorbent and gel forming polyvinyl alcohol (PVA) nonwoven fibres. The nonwoven pad is coated with silver sulphate on both sides. The silver is released within the dressing in contact with fluid, and acts as a preservative in the dressing to inhibit or reduce microbial growth in the dressing. The investigational device fall under FDA-premarket notification K160379. The dressing is sterilized in EtO (ethylene oxide).
For this clinical investigation, Exufiber Ag+ will be available in the following size:

Dressing sizes		Total silver content
cm	Inches	mg
5x5	2x2	5
15x15	6x6	45

Manufacture registered trademark of Mölnlycke Health Care AB.

Exufiber

Exufiber is a sterile nonwoven dressing made from highly absorbent and gel forming polyvinyl alcohol fibres. Exufiber is available as pad. Exufiber wound dressing absorbs and retains wound exudate. It is transformed into a soft gel that facilitates moist wound healing and ease of removal during dressing change. The investigational device is exempt and fall under FDA regulation number 878.4018 The dressing is sterilized in EtO.
For this clinical investigation, Exufiber will be available in the following size:

Dressing sizes	
cm	Inches
5x5	2x2
15x15	6x6

Manufacture registered trademark of Mölnlycke Health Care AB.

Aquacel Ag Extra

Dressing with Silver and Strengthening Fibre is a one piece wound dressing comprised of two layers of soft, sterile non-woven material. The non-woven pads are comprised of Hydrofiber dressing and ionic silver stitch bonded together with regenerated cellulose fibres and designed to provide additional absorbency and tensile strength properties. The investigational device fall

under FDA-premarket notification K121275. The dressing is sterilized by radiation.
For this clinical investigation, Aquacel Ag Extra will be available in the following size:

Dressing sizes		Total silver content
cm	Inches	mg
5x5	2x2	4.5
15x15	4x4	40.5

Manufacture registered trademark of ConvaTec Inc.

For more information regarding the dressings, instructions for use and precautions see Appendix D, Instruction for use.

4.3.2 Additional products

All additional products must be record in the “Dressing Log”. The secondary dressing will be chosen according to local routine.

4.3.3 Labelling

Mölnlycke will provide the investigational devices to the investigation site for free, the study dressings should only be used within the clinical investigation.

The Exufiber Ag+ is a 510(k) cleared device the additional labels are just there to assist the study site in identifying investigational device.

Exufiber and Aquacel Ag Extra will not be labelled with an extra label. Labelling of the investigational medical device will be performed in accordance with Good Manufacturing Practice (GMP). The labels will be produced in the local language and in accordance with local regulations for the US.

The Exufiber Ag+ will be labelled with the following text:
Exufiber Ag+
Study code: Exufiber Ag+ 01
Investigational device – Not for Resale

4.3.4 Accountability

The investigational device dressings will not be distributed to the investigation site until all agreements between the investigator and Mölnlycke are finalized and IRB approval has been obtained. All investigational device dressings must be kept in a secure place under appropriate storage conditions.

Use of Exufiber Ag +, Exufiber, Aquacel Ag Extra and the secondary dressing will be recorded in the “Dressing Log” and will be reviewed at each monitoring visit. The investigational device may only be used in this clinical investigation and according to the CIP.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices.
Unused products are accounted for and returned to Mölnlycke for destruction, or destroyed locally upon agreement with and approval from Mölnlycke.

Applicable documents are the “Certificate of Delivery of Investigational Device/Material” and the “Certificate of Return and Destruction of Investigation Product”.

4.3.5 Storage conditions

Investigational device dressings are to be handled and stored safely (locked place), properly and in agreement with the given storage instructions.

A description of the appropriate storage and shipment conditions are specified on the investigational device label and in the instructions for use documentation (IFU), Appendix D.

4.3.6 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned according to section 4.1. The first eligible 50 subjects will be assigned by the investigator to Exufiber Ag+, Subjects 51 to 65 will be assigned to Exufiber, Subjects 66 to 85 will be assigned to Aquacel Ag Extra and recorded in the eCRF. Subjects 86 to 105 will be assigned to Exufiber Ag+ on eligible pressure ulcer subjects. Mölnlycke or delegate will notify the study investigator when each treatment group has been fully enrolled. Each treatment group may be adjusted due to enrolment by approximately 20%.

The secondary dressing will be chosen according to local routine.

If a subject discontinues from the investigation, the Subject ID will not be reused and the subject will not be allowed to re-enter the investigation.

4.4 Concomitant Treatments

Medication, which is considered necessary for the subject’s safety and well-being, may be given at the discretion of the investigator. Except the study dressings, usage of other antimicrobial dressings or antimicrobial topical agents on the target wound during the study is not allowed.

All relevant concomitant medication that may have an impact of the wound condition, safety for the subject or may affect the evaluation of dressings performance as justified by the investigator should be recorded in the appropriate section of the electronic Case Report Form (eCRF).

4.5 Performance and Safety

4.5.1 Subject Characteristics

Date of birth	DD/MMM/YYYY
Gender	Male/Female

Vital signs	Height (cm/feet and inches) Weight (kg/pounds) BMI
Relevant 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 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 Past/current Ongoing medication
Type of wound and location of the wound	Venous leg ulcer Arterial leg ulcer Mixed ethology Pressure ulcers (partial) Diabetic foot ulcer Traumatic wounds Partial thickness burns (second degree) Donor site Malignant wounds
Duration of wound	< 1week ≥ 1 week to <6 weeks ≥ 6 weeks to <12 month ≥12 month

Current wound treatment	Primary dressing (Y/N) Name of the current primary dressing Frequency of dressing change/per week Secondary dressing (Y/N) Name of the current secondary dressing

4.5.2 Performance Measurements and Variables

Primary objective	**Primary outcome variable**
To evaluate changes in exudate status (see Table 1) from baseline to last visit. *Dry and healed wounds counts as successful wound*	Dry Moist Wet Saturated Leaking

Secondary objective	**Secondary outcome variable**
To evaluate the status of the wound and peri-wound skin from baseline to last visit (by visit)	**Status of the wound and peri-wound skin evaluated by study personnel** Exudate nature (Serous/Serosanguinous/Sanguinous/Purulent/NA) Malodour (None, Slight, Moderate, Strong) Redness/Irritation under the Primary dressing (Y/N) Redness/irritation outside the Primary dressing (Y/N) Maceration under the Primary dressing (Y/N) Maceration outside the Primary dressing (Y/N) Wound size (as described in section 4.5.5) Tissue type of the wound bed: Necrotic%, Sloughy%, Granulation% Epithelization%, Other if applicable in % Wound status (Stagnated, Aggravated, Same as baseline, Improved, Healed)

Secondary objective	Secondary outcome variable
To evaluate the handling and technical performance of the dressing from baseline to last visit (by visit)	**Investigator and Nurse Evaluation** Primary dressing, ease of application (Very Poor/Poor/Good/Very Good/NA) Primary dressing, ease of removal without moistening the dressing (Very Poor/Poor/Good/Very Good/NA) Primary dressing, can be removed in one piece (Very Poor/ Poor/ Good/ Very Good/ NA) Primary dressing, adherent to the wound bed (Y/N). If Yes, specify: Primary dressing, ability to rehydrate (Very Poor/ Poor/ Good/Very Good/NA) Primary dressing, ease of removal after moistening the dressing (Very Poor/ Poor/ Good/Very Good/NA) Primary dressing, residuals of the dressing material in the wound or surrounding skin (Very Poor/Poor/ Good/ Very Good/NA) Primary dressing, ability to absorb exudate (Very Poor/Poor/Good/Very Good/NA) Primary dressing, ability to absorb blood (Very Poor/Poor/Good/Very Good/NA) Primary dressing, ability to retain exudate (Very Poor/Poor/Good/Very Good/NA) Primary dressing, ability to retain slough (Very Poor/Poor/Good/Very Good/NA) Primary dressing, ability to clean the wound bed (remove blood, pus, slough etc.) (Very Poor/Poor/Good/Very Good/NA) Primary dressing, ability to retain the soft and gelling properties (Very Poor/Poor/Good/Very Good/NA) Primary dressing, ability to retain a balanced moist environment in the wound (Very Poor/Poor/Good/Very Good/NA)

Secondary objective	Secondary outcome variable
	Primary dressing conforms to the wound contours (Very Poor/Poor/Good/Very Good/NA) Primary dressing, overall experience (Very Poor/ Poor/ Good/Very Good/NA)
To evaluate the dressing stay on ability and preparation of the skin from baseline to last visit (by visit)	Compression therapy (Y/N/NA) Cleansing (Y/N/NA) Debridement (Y/N/NA) Frequency of dressing change? If Primary dressing is change due to leaking Y/N if yes, please specify - Dressing, is full - Dressing shrinks and doesn't fill up the wound - Other
To evaluate comfort, conformability and acceptability of the dressing from visit 3 to last visit (by visit) from a subject view	**Subject Evaluation** Comfort when wearing the primary dressing (Very Poor/Poor/Good/Very Good/NA) Ease of mobility while wearing the primary dressing (Very Poor/Poor/Good/Very Good/NA) Primary dressing remained in place (Very Poor/Poor/Good/Very Good/NA) Stinging or burning while wearing the primary dressing (Y/N/NA) Primary dressing, overall experience (Very Poor/Poor/Good/Very Good/NA)

Secondary objective	Secondary outcome variable
To evaluate the bioburden from baseline to visit 3	**Microbial detection** Change in the aerobic counts (Log CFU/cm^2) and microbial diversity from baseline to visit 1b (4 days after baseline) Change in the aerobic counts (Log CFU/cm^2) and microbial diversity from baseline to visit 2 (7 days after baseline) Change in the aerobic counts (Log CFU/cm^2) and microbial diversity from baseline to visit 3 (14 days after baseline)

4.5.3 Safety Measurements and Variables

To evaluate safety from baseline to last visit	**Signs of clinical infection (**Figure 3**)** **Acute wounds** Classical signs (new and increasing pain, erythema, local warmth, swelling, purulent discharge) (Y/N) Pyrexia (Y/N) Delayed or stalled healing (Y/N) Abscess (Y/N) Malodour (Y/N) **Chronic wounds** New, increased or altered pain (Y/N) Delayed (or stalled) healing (Y/N) Periwound oedema (Y/N) Bleeding or friable (easily damaged) granulation tissue (Y/N) Distinctive malodour or change in odour (Y/N) Wound bed discolouration (Y/N) Increased, altered or purulent exudate (Y/N) Induration (hardening of a tissue, particularly the skin, caused by inflammation) (Y/N)

	Pocketing-granulation tissue does not grow in a uniform manner across the entire wound, pockets can harbour bacteria (Y/N) Bridging-presence of strands of tissue across the wound bed (Y/N)
	Adverse Event (AE)/Adverse Device Effect (ADE), Serious Adverse Event (SAE)/Serious Adverse Device Effect (SADE), Device deficiency (DD)

4.5.4 Identification and quantification of microorganisms presents in the wound

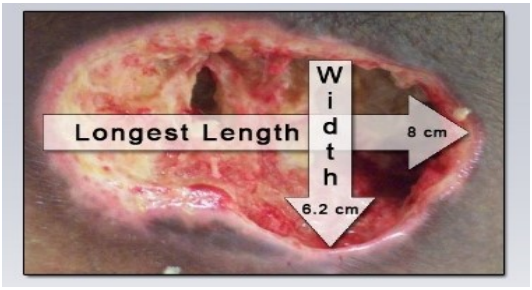
This section is only applicable for site no 01 (only subjects enrolled before September 2018) since they are the only site collecting tissue and exudate.

Evaluation of antimicrobial activity of Exufiber Ag+ and Exufiber on wound bioburden by collection of tissue and exudate (specified in Appendix F). Following analysis will be performed on approximately 30 subjects, equally distributed between Exufiber Ag+ and Exufiber.

- ✓ overall quantification of microbial counts by traditional culturing under aerobic conditions
- ✓ identification of bacteria/fungi by Next Generation Sequencing (16S rRNA for bacteria, ITS1 or ITS2 for fungi)
- ✓ evaluate inflammatory biomarkers and virulence factors via collecting wound exudate

4.5.5 Wound size measurement

Figure 2 Measure wound size



Wound size will be measured according to schedule of assessment (4.2.1), if debridement, wound size will be measured before and after debridement, record in inches/mm.

4.5.6 Exudate Management

Table 1 Evaluate changes in exudate status. [12]

	Indicators		
Status	**Wound bed**	**Dressing**	**Surrounding skin**
Dry	Wound bed is dry; there is no visible moisture	Primary dressing is unmarked; dressing may be adherent to wound	Skin may be scaly, atrophic, hyperkeratotic
Moist	Small amounts of fluid are visible when dressing is removed; wound bed may appear glossy	Primary dressing may be lightly marked; dressing change frequency is appropriate	Skin is likely to be intact, hydrated, no lesions
Wet	Small amounts of fluid are visible when the dressing is removed	Primary dressing is extensively marked, but strikethrough does not	Initial fragmented areas of maceration may be apparent

		occur; appropriate dressing change frequency	
Saturated	Free fluid is visible when the dressing is removed	Primary dressing is wet and strikethrough occurs; dressing change is required more frequently than usual	Peri-wound skin is likely to be macerated or denuded with extensive involvement
Leaking	Free fluid is visible when the dressing is removed	Dressings are saturated and exudate is escaping from primary and secondary dressings onto clothes or beyond; dressing change is required much more frequently than usual	Peri wound skin is likely to be macerated or denuded with extensive involvement

4.5.7 Signs of local infection split between acute and chronic wound

Figure 3 Local infection, definition for acute and chronic wounds [8]

Signs and symptoms of localised infection in wounds.
ACUTE WOUNDS e.g. surgical or traumatic wounds, burns
• Classical signs and symptoms: new or increasing pain erythema local warmth swelling purulent discharge • Pyrexia • Delayed or stalled healing • Abscess • Malodour
CHRONIC WOUNDS e.g. diabetic foot ulcers, venous leg ulcers, arterial leg/foot ulcers, pressure ulcers
• New, increased or altered pain • Delayed (or stalled) healing • Periwound oedema • Bleeding or friable (easily damaged) granulation tissue • Distinctive malodour or change in odour • Wound bed discolouration • Increased, altered or purulent exudate

- Induration (hardening of a tissue, particularly the skin, caused by inflammation)
- Pocketing-granulation tissue does not grow in a uniform manner across the entire wound, pockets can harbour bacteria
- Bridging-presence of strands of tissue across the wound bed

4.5.8 Anticipated ADEs

The following possible clinical outcomes have been identified as anticipated adverse device effects in connection to the risks evaluated in the Product Risk Management Record for:

Exufiber Ag+

- Maceration
- Prolonged wound healing
- Leakage leading to cross contamination or infection
- Infection due to contamination
- Bacterial growth/Infection
- Discolouration
- Local allergic reaction
- Sensitisation, cytotox, skin irritation
- Selection for resistant microorganisms
- Anaemia due to potential systemic absorption of silver

Exufiber

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

Aquacel Ag Extra is assumed to have the same identified risk as Exufiber Ag+, since Exufiber Ag + is substantially equivalent with Aquacel Ag Extra.

The investigator should take the above mentioned list of events in consideration when reporting and assessing events in accordance with section 9 of the CIP.

Based on the risk management record it can be concluded, that for Exufiber Ag+, Exufiber and Aquacel Ag Extra, there are no unacceptable risks of harm for the patient, the user nor third part involved in this clinical investigation, if the treatment dressings are used under normal conditions and within its intended use.

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

4.6 Data Quality Assurance

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

A Monitoring Plan will be developed to be followed by the monitor.

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

Authorized representatives of Mölnlycke and/or a Competent Authority (CA) and/or the Institutional

Review Board (IRB) may visit the investigation site to perform audits/inspections, including source data verification.

4.6.2 Training of Staff

The Principal Investigator will ensure that appropriate training relevant to the investigation is given to investigators and investigation site staff as well as community nurses and that new information of relevance to the performance of this investigation is forwarded to the staff involved. The Principal Investigator will also ensure that the involved site staff are experienced in wound care.

Before the first subject is entered into the investigation, Mölnlycke personnel or delegate will conduct a site initiation visit. The purpose of the visit is to provide training to the involved personnel including, but not limited to the following items:

- Clinical investigation plan (CIP) and execution thereof
- Good Clinical Practice (GCP)
- Use of eCRF system (Viedoc)
- Use of investigational devices, and additional dressings used in the investigation. A training record will be provided to all trained staff.
- Tissue and Exudate sampling **(only applicable for site no 01 for subjects recruited before September 2018)**
- Safety Handling
- Maintenance of the Investigator Study File

4.6.3 Data Management

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

- Set-up of eCRF and database
- Specification of on-line checks
- Data entry / Data editing
- Export of data from Viedoc to SAS

- Creation of post-entry checks and listings
- Reconciliation of Serious Adverse Event (SAE), Serious Adverse Device Effect (SADE), Adverse Devise Effect (ADE) and Device Deficiency (DD)
- Clean-file process including execution of post-entry checks and listings
- Post clean-file tasks

Viedoc, a web based eCRF 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 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 and stored in the company database. All data entered in Viedoc will be encrypted. The physical database will be stored in Sweden.

Records will be retained for a minimum of 10 years after end of the clinical investigation or last product is manufactured whichever is more stringent. In addition investigation sites shall keep their records longer if in accordance with local requirements.

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 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.

4.7 Statistical Methods and Determination of Sample Size

4.7.1 Statistical Evaluation

General Methodology

The main focus and analysis will be the analysis of the subjects treated with Exufiber Ag+.

The main analyses will be change in primary and secondary efficacy endpoints from baseline to 4 weeks on the ITT population in this group treated with Exufiber Ag+. If missing values at 4 weeks

last observation carry forward (LOCF) will be applied from 1 week.
A sensitivity analysis will be performed for primary analysis with complete cases.

Complementary analyses will be performed on the PP population and for change from baseline to 3 days, 1 week, 2 weeks and 3 weeks.

Since primary efficacy variable and most of the secondary efficacy variables are ordered categorical or dichotomous variables the Sign test will be used for analysis of change within groups for these types of variables and described with number and percentages of improved, not changed and worsened. For primary efficacy variable and important secondary efficacy variables a complete cross tabulation baseline and 4 weeks will be given.

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

Continuous variables will be described with mean, SD, median, minimum and maximum and categorical variables will be given with number and percentages. All measured variables will be describes by visit.
The statistical analysis of the groups treated with Exufiber or Aquacel Ag Extra will be analysed separately with the same statistical methods as specified above. The database for Exufiber Ag+ will be declare clean and will be analysed before the other two treatment groups are finalised.

Patient Disposition and Data Sets Analysed

The number of subjects included in each of the ITT, PP and safety populations will be summarized. The number and percentage of subjects enrolled and treated will be presented. Subjects who completed the study and subjects who withdrew from study prematurely will also be presented with a breakdown of the reasons for withdrawal for the ITT, PP and safety populations.

Protocol Violations/Deviations

Major protocol deviations are those that are considered to have an effect on the primary analysis. A list of potential major protocol deviations will be generated programmatically from the data captured before the clean file meeting. The listings from the clinical investigation will be reviewed and the finalisation of the major protocol deviations will be done at the clean file meeting.

The number of patients with major protocol deviations will be summarized.

Demographics and Baseline Characteristics

All variables measured at baseline will be summarized for the ITT- and PP population using appropriate summary statistics for the three treatment groups.

Medical and Surgical History

Listings of all medications collected for each subject by the investigator will be produced.

Prior and Concomitant Medications

Listings of all medications collected for each subject by the investigator will be produced.

4.7.2 Performance Analysis

Primary Performance Analyses

The primary performance analysis will be the analysis of change in Exudate level from baseline to 4 weeks in the Exufiber Ag+ treatment group with the two-sided Sign test on the Intent To Treat (ITT)-population at significance level 0.05. If the 4 weeks value is missing last observation carry forward (LOCF) will be allied from 1 week.

A complementary sensitive analysis will be performed with the same analysis on complete cases. (No imputation)

Secondary Efficacy Analyses

All secondary efficacy variables will be analysed within the treatment groups for the ITT- and Per Protocol (PP) population using the statistical methods given in section general methodology. Primary efficacy variable will also be analysed on the PP-population

4.7.3 Determination of Sample Size

In the study PUMA 416, with 100 subjects treated with Mepilex without Ag, the result regarding change in Exudate level from baseline to 4 weeks was 56.5 % improved, 32.9 % unchanged and 10.6 % worsened. Assuming the same proportions in this study 38 subjects are needed to find a significant improvement with the Sign test with 95% power and significance level 0.05. If we expect a dropout rate of around 20% we will include 50 subjects in the Exufiber Ag+ treatment group.

4.8 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.

An amendment to the Investigation Plan may require notification or approval from IRB before implementation. Local requirements must be followed.

Mölnlycke will distribute clinical investigation plan amendments to the Principal Investigator who is responsible for the distribution of these documents to the IRB and staff concerned at his/her site.

5. STATEMENTS OF COMPLIANCE

5.1 IRB

5.1.1 IRB review

The final clinical investigation plan, including the final versions of the Patient Information and Consent Form, must be approved or given a favourable opinion in writing by an IRB before

enrolment of any subject into the investigation. The Principal Investigator is responsible for informing the IRB of any amendment to the 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, ISO 14155:2011 and with applicable regulatory requirements.
Patients, who are close colleagues, associates, or family members of, or in any way dependent on the sponsor or the investigator, will not be included in this investigation.

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 (including photo consent) about the nature, purpose, possible risks and benefits of the investigation.

For subjects unable to consent, permission will be obtained from their legally authorized representative (LAR). In this case, the priority order to obtain authorization will be as follows: spouse, adult child, durable power of attorney for health care, court appointed guardian for healthcare decisions. Assent from patients will not be collected nor documented as subjects unable to consent will be unresponsive and/or unconscious.

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.

The Principal Investigator will also ensure that subjects are informed if any new relevant information becomes available during the investigation.

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

5.2 Regulatory and standards

5.2.1 Regulatory review

Not applicable. The investigational device are 510(k) cleared.

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 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 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 has product liability insurance, which also covers test products.

6. INVESTIGATION TIMETABLE AND TERMINATION

Estimated date of first subject enrolled Q2 2017

Estimated date of last subject completed Q1 2019

Estimated date of end of clinical investigation (database lock) Q1 2019

The investigation could be prematurely discontinued if the investigation site is unable to fulfil the inclusion period according to the Clinical Investigation Agreement.

7. PUBLICATION

7.1 Publication policy

Exufiber Ag+ 01 will be registered in a public database, ClinicalTrails.gov.

8. LITERATURE REVIEW AND REFERENCES

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

1. EWMA document, Antimicrobials and Non-healing wounds, Evidence, controversies and suggestions. Journal of Wound Care, 2013; 22 :1-92

2. Tegel G, Schiffer D, Sigl E, Heinzel A, Guebitz G. Biomakers for infection: enzymes, microbes, and metabolites. Appl Micorbiol Biotechnol, 2015; 99: 4595-4614.

3. Lindley L, Stojadinovic O, Pastar I, Tomic-Canic M. Plast. Biology and Biomarkers for Wound Healing. Reconstr. Surg, 2016; 138: 18S.

4. Hodkinson B, Grice E. Next-Generation Sequencing: A Review of Technologies and Tools for Wound Microbiome Research Advances in Wound Care, 2015; 4: 50-58

5. Rhoads D, Wolcott R, Sun Y, Dowd S. Comparison of Culture and Molecular Identification of Bacteria in Chronic Wounds, Int. J. Mol Sci. 2012; 13: 2535-2550.

6. Leaper D, Münter C, Meaume S, Scalise A, Blanes Mompó N, Petersen Jakobsen B, Gottrup F. The Use of Biatain Ag in Hard-to-Heal Venous Leg Ulcers: Meta-Analysis of Randomised Controlled Trails. Plos One.,2013; 8:1-7.

7. Kotz P, Fisher J, McClunskey P, Hartwell S, Dhrama H. Use of a new silver barrier dressing, Allevyn Ag in exuding chronic wounds. International Wound Journal, 2009; 6:186-194

8. International Consensus, Appropriate use of sliver dressing in wounds. Wounds International, 2012: 1-20

9. Cangelosi G, Meschke J. Dead or Alive: Molecular Assessment of Microbial Viability. Appl. & Enviro. Microbiol., 2014;80: 5884-5891.

10. Gil et al. Gil J, Valdes J, Solis M, Higa A, Parajon F, Li J, and Davis SC. Evaluation of a gelling fibre dressing with silver to eliminate Methicillin Resistant Staphylococcus aureus (MRSA) biofilm infection and enhance the healing in partial thickness porcine wound model. Poster presented at 30th SAWC meeting in San Diego 2017.

11. Valdes et al. Valdes J, Gil J, Higa A, Solis M, Parajon F, Li J and Davis SC . Evaluation of a gelling fibre dressing with silver to eliminate Pseudomonas aeruginosa biofilm infection and enhance the healing in partial thickness porcine wound model. Poster presented at 30th SAWC meeting in San Diego 2017.

12. Romanelli M, Vowden K, Weir D. Exudate Management. Wounds International, 2009; 1-6

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

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

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

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

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

Note:

- This definition includes events related to the treatment dressings.
- This definition includes events related to the procedures involved.
- For users or other persons, this definition is restricted to events related to treatment dressings.

Adverse Device Effect (ADE)
Adverse Event related to the use of the treatment dressings

Note:

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

Serious Adverse Event (SAE)
Adverse Event that:

a) led to death,

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

   1) a life-threatening illness or injury, or

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

3) in-patient hospitalization or prolonged hospitalization or,

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

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

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

Pregnancy is not considered a Serious Adverse Event.

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

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

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

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

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

This includes also ADEs occurring in all treatment groups.

Causality Assessment

The relationship between the use of the investigational devices 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.

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

Report by the investigator to Mölnlycke

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

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

All SAEs/SADEs that occur during the Clinical Investigation and new findings/updates in relation to already reported events must be reported, whether or not they are considered causally related to the investigational device [comparator] or procedure.

Device Deficiencies that might have led to SAE 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 SAE.

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

An assessment including causality to the investigational device or procedure and the seriousness of the ADE will be done by the investigator and Mölnlycke Any event reported by the investigator

as serious but assessed as non-serious by Mölnlycke will be reported to the Competent Authorities as described below for SAE reporting to CA. Both Investigators and Mölnlycke opinion will be communicated.

PROCEDURES FOR DD REPORTING

All DD shall be reported by the investigator to Mölnlycke 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 device was used by a subject or not. Separate forms are used for subject related and non-subject related DDs. When a subject related DD has been entered into the eCRF by the investigator /authorised site staff, the eCRF system will automatically generate a report to: Clinical_Investigations_Event_Reporting@molnlycke.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

An assessment will be done by the investigator and Mölnlycke including a determination if the DD could have led to a SAE if either a) suitable action had not been taken, b) if intervention had not been made, or c) if circumstances had been less fortunate will be done. If the result by the assessment by the investigator or Mölnlycke is that the DD could have led to a SAE it must be reported as described above for SAE reporting to CA. In case of differences in the assessment by the investigator or Mölnlycke both opinions will be communicated.

Procedures for ADE reporting

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

This includes also AEs occurring in the comparator arm if applicable.

An assessment including causality to the investigational devices or procedure and the seriousness of the ADE will be done by the investigator and Mölnlycke.