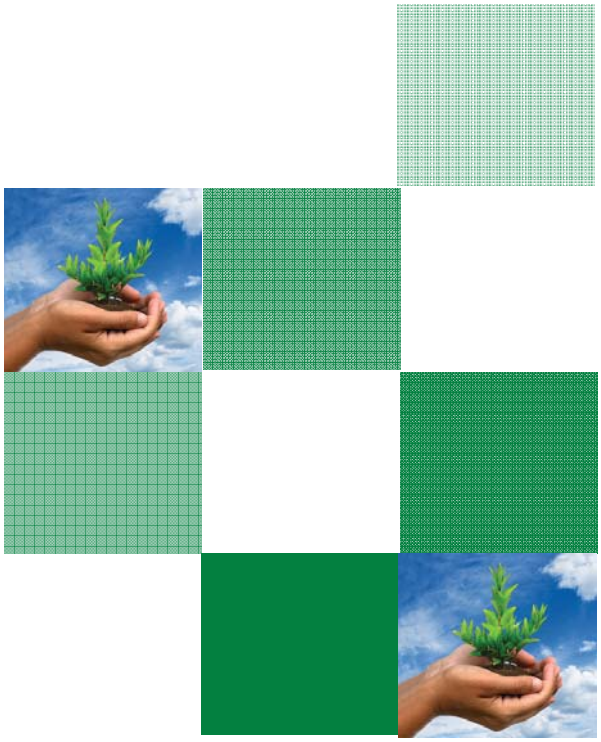
CLINICAL INVESTIGATION PLAN (CIP)

INVESTIGATIONAL DEVICE:

Avance® Negative Pressure Wound Therapy System

INVESTIGATION TITLE:

A RANDOMIZED, INTRA-PATIENT, OPEN, CONTROLLED PILOT INVESTIGATION COMPARING TRAUMA TO THE PERI-WOUND SKIN AFTER TREATMENT WITH AVANCE NPWT SYSTEM WHEN USING TWO DIFFERENT FIXATIONS



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CLINICAL INVESTIGATION PLAN (CIP) SYNOPSIS

INVESTIGATION TITLE:

A RANDOMIZED, INTRA-PATIENT, OPEN, CONTROLLED PILOT INVESTIGATION COMPARING TRAUMA TO THE PERI-WOUND SKIN AFTER TREATMENT WITH AVANCE NPWT SYSTEM WHEN USING TWO DIFFERENT FIXATIONS

Objectives

Primary objective
The primary objective of this investigation is to compare trauma and/or other changes to the peri-wound skin during treatment with Avance® Negative Pressure Wound Therapy System when using two different fixation films. The primary objective will be measured as:

- Changes from baseline in condition of the peri-wound skin defined as skin under the dressing, excluding the area were the films are overlapping

Secondary objectives
Secondary objectives are to evaluate:

- the ease of use for the subject and care giver when using the NPWT system
- the comfort, conformability and the acceptability of the dressings
- pain before, during and after dressing and foam removal
- SADE, ADE and, DD, i.e. safety data related to the device

Overall Design

This investigation is designed as a randomized, intra-patient, controlled open clinical investigation . The outcome will be used to guide us to the design and implementation of a larger scale randomized study. This pilot study will include 23-30 subjects across 1sites in Sweden to yield a total of 7-23 evaluable subjects, all subjects who has not previously been treated with NPWT and fulfill all inclusion and none of the exclusion criteria and have signed signed a written inform consent will be enrolled.

This investigation is comparing trauma and/or other changes to the peri-wound skin during treatment with Avance NPWT system when using two different fixation films, Avance film with Safetac® Technology and KCI acrylic film (V.A.C.® Drape). Since the investigation is comparing films with clear visual differences, it is not possible to blind neither the investigator nor the patients.

Dressing change
Dressing change will be performed at the investigation site and the frequency of dressing change will be depending on the condition of the wound and the peri-wound skin. Recommended dressing change frequency according to Avance system is every 48-72 hours.

A record (dressing log) specifying the type of film and other relevant treatment information will be completed for every dressing change

Investigation Visit frequency and subject participation
Eligible subjects will be enrolled at the baseline visit (Visit 1), where the first dressing applications take place. From Visit 2 and onwards, one dressing application is considered as

one study visit, e.g. the study visits are flexible and depending on the dressing changing frequency of the individual subject. The total treatment time for a subject may vary, depending on the wound type and condition. Each subject will be followed in the investigation for a maximum of five (5) dressing changes or until treatment with NPWT is no longer indicated (withdrawal criterion) . After termination from the investigation, subjects will, if necessary, be treated according to standard clinical practice at the investigation site. No additional data (except for follow up information on ongoing safety events) will be collected after termination. Subjects will be recruited at the investigation site, which have experience in managing the investigation population with NPWT and have access to a suitable number of subjects (based on historic data).

Following variables should be considered (Appendix C):

At visit 1

- Informed consent
- Subject demographic details
- Inclusion and exclusion criteria
- Vital signs
- Care
- Medical and surgical history
- Wound history
- Skin assessment
- Medication
- Cleansing
- Debridement
- Wound status after cleansing and/or debridement
- Clinical signs of local infection
- Photo
- Pain (VAS)
- Adverse Event (AE)/ Adverse Device Effect (ADE)/ Serious Adverse Event (SAE) /Serious Adverse Device Effect (SADE)/Device Deficiency (DD)
- Apply the Investigational Device (ID) and measuring (proximal cm, distal cm, sinister cm and dexter cm) the length between the wound edges and film edges according to the Figure 1
- Investigator and nurse evaluation
- Apply the IP
- Randomization

At visit 2-5

- Skin assessment
- Medication
- Cleansing
- Debridement
- Wound status after cleansing and/or debridement
- Clinical signs of local infection
- Apply the IP and measuring (proximal cm, distal cm, sinister cm and dexter cm) the length between the wound edges and film edges according to the Figure 2
- Photo
- Pain (VAS)
- Change and removal of IP
- Investigator/Nurse and subject evaluation
- AE/ ADE/ SAE/SADE/DD

Only one target wound per patient will be included in this investigation.

* Evaluation of the skin se Appendix E

Schedule of Assessment

Day	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	**Termination End of treatment**
Visit (number)	1	2	3	4	5	Termination
Subject demography	✓					
Inclusion and Exclusion Criteria	✓					
Inform Consent	✓					
Vital Signs	✓				✓	✓
Medical and surgical history	✓					
Skin assessment	✓	✓	✓	✓	✓	✓
Wound History	✓					
Randomization	✓					
Cleansing and/or Debridment	✓	✓	✓	✓	✓	
Signs of symptoms of infection	✓	✓	✓	✓	✓	✓
Pain (VAS)	✓	✓	✓	✓	✓	✓
Wound status after (cleansing, debridement)	✓	✓	✓	✓	✓	
Dressing application	✓	✓	✓	✓		
Dressing removal		✓	✓	✓	✓	✓
Photo	✓	✓	✓	✓	✓	✓
Investigator/nurse evaluation	✓	✓	✓	✓	✓	✓
Subject evaluation		✓	✓	✓	✓	✓
Medication log	✓	✓	✓	✓	✓	
AE/ADE/DD	✓	✓	✓	✓	✓	✓
SAE/SADE	✓	✓	✓	✓	✓	✓
Dressing Log	✓	✓	✓	✓	✓	✓

Inclusion/Exclusion Criteria

Inclusion Criteria

1. Exuding wound indicated for treatment with NPWT therapy
2. In case of multiple wounds, target wound must be ≥ 10 cm distant from other wounds. Selection of target wound is according to the investigator's preference
3. Peri-wound skin assessable and 5 cm of peri-wound skin present around the wound
4. Male or female, 18 years of age and above
5. Signed Informed Consent

Exclusion Criteria

1. Dressing sizes does not fit the target wound
2. Unexplored blind tunnels or non-enteric fistula
3. Untreated osteomyelitis
4. Malignant wounds
5. Wounds with necrotic tissue or eschar (if not adequately debrided)
6. Bleeding wounds
7. Subject not suitable for the investigation according to the investigator's judgment
8. Subject included in other ongoing clinical investigation which could interfere with this investigation, as judged by the investigator
9. Known allergy/hypersensitivity to any of the components included into the investigation.

Investigational Device

Treatment

System

All subjects will receive treatment with the Avance® Negative Pressure Wound Therapy System consisting of:

- Avance® Pump
- Avance® View Pad
- Avance® Foam
- Film sealant (either the **Investigational device,** Avance Film® with Safetac®Technology or the **Comparator,** V.A.C. Drape,)

Pump settings (pressure and mode intermittent or constant pressure) will be registered in the relevant section of the CRF.

Other materials

Actual use of supporting and/or protecting materials must be registered in the relevant section in the CRF.

- *Skin fixatives*
  Mepiseal® will be available for use in combination with the Avance film with Safetac, according to investigators preference.
  Mepiseal is a flexible sealant intended to use on the surrounding skin of wounds or stomas that are difficult to dress due to uneven skin surfaces, location or mobility.

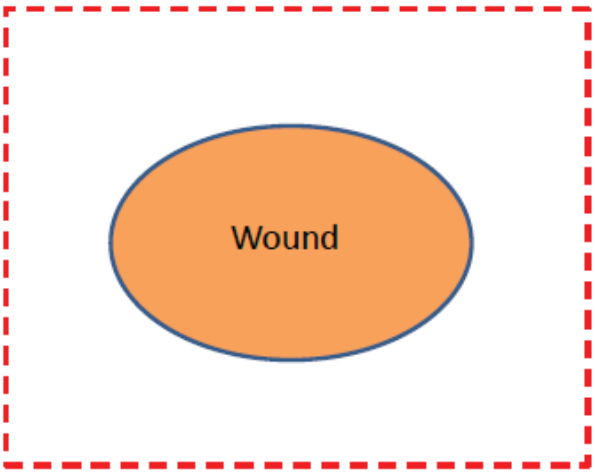
Mepiseal helps prevent leakage and premature loosening of the wound dressing, NPWT or ostomy systems. Mepiseal can also be used as a filler uneven surrounding skin.

- *Wound contact layers*
- Non-adherent dressing materials Mepitel can be used to protect fragile tissue such as bones, tendons and nerves. It can also be used to cover sharp edged or bones to prevent puncture of blood vessels or organs.
- *Skin protection*
  In this investigation, use of additional film (other transparent film), Cavilon or hydrocolloids is **not allowed** to be used as protection of the peri-wound skin as this could potentially interfere with the measurement of the primary objective.

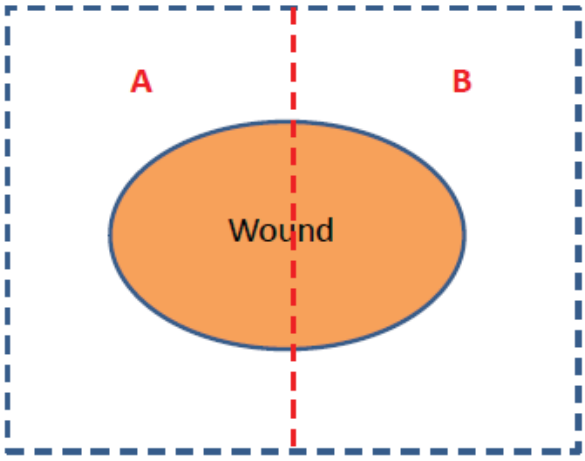
All medical devices are CE marked and used according to intended use, with the exception of the overlapping Avance Film® with Safetac with V.A.C. Drape and V.A.C. Drape together with Avance System and Avance Foam, which is used outside intended use. Based on product risk management for the investigational device, it can be concluded that there are no unacceptable risks of harm for subject, the user nor third party involved.
The investigational device meets all relevant essential requirements except for those being investigated in the clinical investigation, as declared separately.

Randomization
Eligible subjects will have the investigated wound randomly divided into two halves. One half of the wound will be dressed with Avance Film with Safetac while the other half on top of the Avance Film with Safetac will be dressed with V.A.C. Drape.

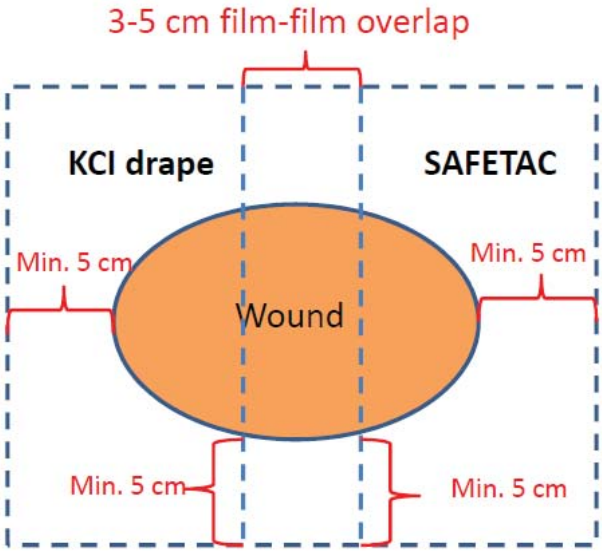
1. The area which is intended to be covered with film will be drawn on the subject's skin with a semi-permanent marker pen:



2. This skin area will be divided into two approximately equal halves and A or B will be written on each half (to allow for correct positioning of new films in connection with dressing changes). The intended direction of film application will be according to the location of the wound, anatomy of the relevant body part and the investigators best judgment for how the best seal can be obtained.



3. Instruction about the film-film overlap and the overlap from wound edge on dry peri-wound skin to ensure an optimal vacuum is described in the application step-by-step guide.



Assignment to treatment group for a given subject will be randomly provided by the electronic eCRF system (Viedoc) in as indicated below:

Treatment group 1:
Film A (subject right side) = Avance Film with Safetac
Film B (subject left side) = V.A.C. Drape

Treatment group 2:
Film A (subject right side) = V.A.C. Drape
Film B (subject left side) = Avance Film with Safetac

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ADE	Adverse Device Effect
CA	Competent Authorities
CDM	Clinical Data Manager
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRA	Clinical Research Associate
CRF	Case Report Form
CRM	Clinical Research Manager
DCF	Data Clarification Forms
DD	Device Deficiency
FSI	First subject in
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
ID	Investigational Device
ITT	Intention to Treat
LSO	Last subject out
MHC	Mölnlycke Health Care AB
PI	Principal Investigator, a person responsible for the conduct of the clinical investigation at the investigational investigation site. Every investigational investigation site has a principal investigator.
PIC	Patient Information and Consent Form
RA	Regulatory Authority
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SDV	Source Data Verification

INTRODUCTION

Negative pressure wound therapy (NPWT), also referred to as topical negative pressure (TNP), negative pressure therapy (NPT), sub-atmospheric pressure wound therapy, and sealed surface wound suction, is a modality that has found significant use in complex acute surgical, delayed healing surgical and hard to heal chronic wounds, including those with elevated bacterial contamination. Negative pressure wound therapy manages exudate, combats peri-wound oedema, increases blood flow to the wound, maintains optimal moist wound conditions and encourages the formation of wound bed granulation tissue. A meta-analysis reported a significant reduction in time to healing for wounds treated with NPWT when compared to those treated with standard care (1). The Avance NPWT System comprises a range of CE marked products which are used collectively as a NPWT system. The Avance NPWT System has been marketed by Mölnlycke Health Care AB since May 2010.

Despite the research support for its effectiveness in wound healing, fewer studies have considered the impact of NPWT on the patient in terms of the pain that can be experienced. Wound care and dressing changes can be very painful for patients, and this pain can also cause patients to feel stressed or anxious, thus impacting negatively on both their physical and psychological well-being. Such factors need to be considered in any evaluation of NPWT or other treatment (2).

Trauma and pain caused by the removal and reapplication of the NPWT dressings and/or removal of the foam has been identified as a major contributor to wound pain (2). Film-based dressings with adhesive skin contact layers are used to keep NPWT system in place and skin stripping may occur because the film can adhere to aggressively to the peri-wound skin, resulting in trauma and pain (2). Trauma may also occur when tissue grows into the foam on the dressing and this tissue becomes torn during dressing change (3). Damage to the wound and surrounding skin can involve bleeding, blisters, skin stripping and other skin damage, leading to a higher frequency of dressing changes, a greater level of pain and a longer time taken for the wound to heal (3). Despite the importance of minimizing trauma during NPWT and other wound care, few researchers have focused on this area (3)

Although not focusing on NPWT specifically, a study by Upton and Solowiej also demonstrated how dressing type can affect the level of pain experienced during dressing change. In 49 patients with chronic wounds, the authors explored differences in pain and stress levels between those who received conventional dressings ($n = 39$) and those who were given atraumatic dressings with Safetac technology. Physiological and psychological measures of pain and stress were taken. It was found that self-reported pain and stress were significantly lower in those who were given atraumatic dressings as part of their care routine (2).

In the literature there are numerous supporting articles reporting effectiveness of NPWT treatment. However, information regarding choice of dressing materials are lacking. Should for example the adhesive material of the dressing have a protecting effect on the surrounding skin around the NPWT treated wound?

What is known from other studies in other stages of the wound healing is that skin trauma such as bleeding, redness, irritation, skin stripping and blisters might occur when a film dressing is removed. Such trauma can lead to delayed healing and prolonged treatment of the patient.

In a study made by Upton in 2013, half of the participating patients reported skin trauma or irritation.

The purpose of this study is to compare with two different types of film dressings one with silicon adhesive (Avance Film with Safetac) and one with acrylic adhesive(V.A.C drape) to see if there is a difference in skin damage.

1. OBJECTIVES

Primary objective
The primary objective of this investigation is to compare trauma and/or other changes to the peri-wound skin during treatment with Avance® Negative Pressure Wound Therapy System when using two different fixation films. The primary objective will be measured as:

- Changes from baseline in condition of the peri-wound skin defined as skin under the dressing, excluding the area were the films are overlapping

Secondary objectives
Secondary objectives are to evaluate:

- the ease of use for the subject and care giver when using the NPWT system
- the comfort, conformability and the acceptability of the dressings
- pain before, during and after dressing and foam removal

2. CLINICAL INVESTIGATOR(S) AND INVESTIGATION ADMINISTRATIVE STRUCTURE

2.1 Staff at Investigation site(s)

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

2.2 Mölnlycke Investigation Personnel

Tina Kjellén, Clinical Study Manager

Roland Frösing, Medical Doctor

Lennart Wäne, Clinical Data Manager

2.3 Other Participants

Pharma Consulting Group
Kungsängsvägen 19, 1 tr
753 23 Uppsala, Sweden

Statistiska Konsultgruppen
Nils-Gunnar Pehrsson, Biostatistician
Stigbergsliden 5
SE-414 63 Göteborg

3. INVESTIGATION PLAN AND PROCEDURES

3.1 Overall Design and Flow Chart

This investigation is designed as a randomized, intra-patient controlled open clinical investigation comparing trauma and/or other changes to the peri-wound skin during treatment with Avance NPWT system when two different fixation films are used. Avance film with Safetac Technology and V.A.C. Drape (KCI Film). Since the investigation is comparing films with clear visual differences, it is not practically possible to blind neither the investigator nor the patients.

The outcome will guide in to the design of a larger scale randomized study. This pilot study will include 23-30 subjects across 1 sites in Sweden to yield a total of 7-23 evaluable subjects, all subjects who fulfill all inclusion and none of the exclusion criteria and have by them signed a written inform consent will be enrolled. An evaluable subject is defined as a subject that is enrolled and has data for at least one visit after baseline visit

The target populations are male or female, 18 years and above, which have exuding wounds indicated for treatment with NPWT therapy. The subject should not previously been treated with NPWT, previous treatment, may have an bias on the skin evaluation.
The study visits are flexible and depending on the dressing changing frequency of the individual subject. The total treatment time for each subject may vary depending on the wound type and condition of the wound. Each subject will be followed for a maximum of five (5) dressing changes or until treatment with NPWT is no longer indicated (withdrawal criterion). After termination from the investigation, subjects will, if necessary, be treated according to standard clinical practice at the investigation site. No additional data (except for follow up information on ongoing safety events) will be collected after termination.

3.2 Procedures and Assessments

<u>Following variables should be considered (Appendix C):</u>
At visit 1

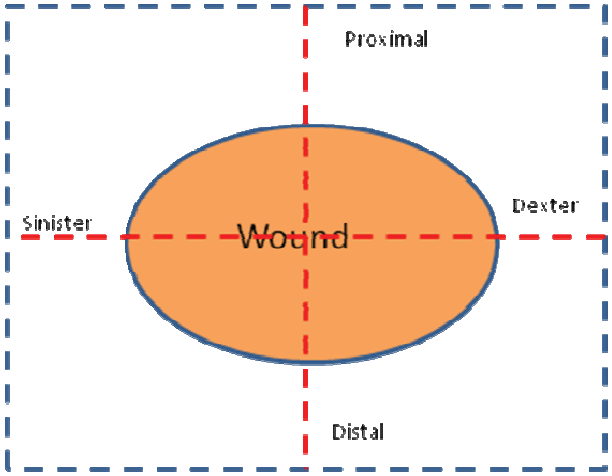
- Informed consent
- Subject demographic details
- Inclusion and exclusion criteria
- Vital signs
- Care
- Medical and surgical history
- Wound history
- Skin assessment
- Medication
- Cleansing
- Debridement
- Wound status after cleansing and/or debridement
- Clinical signs of local infection
- Photo
- Pain (VAS)
- Adverse Event (AE)/ Adverse Device Effect (ADE)/ Serious Adverse Event (SAE) /Serious Adverse Device Effect (SADE)/Device Deficiency (DD)

- Apply the Investigational Device (ID) and measuring (proximal cm, distal cm, sinister cm and dexter cm) the length between the wound edges and film edges according to the Figure 1
- Investigator and nurse evaluation
- Apply the IP
- Randomization

At visit 2-5
- Skin assessment
- Medication
- Cleansing
- Debridement
- Wound status after cleansing and/or debridement
- Clinical signs of local infection
- Apply the IP and measuring (proximal cm, distal cm, sinister cm and dexter cm) the length between the wound edges and film edges according to the Figure 2
- Photo
- Pain (VAS)
- Change and removal of the IP
- Investigator/Nurse and subject evaluation
- AE/ ADE/ SAE/SADE/DD

Only one target wound per patient will be included in this investigation.
* Evaluation of the skin se Appendix E

Figure: 2



Only one target wound per patient will be included in this investigation.

Additional wound care material used will be documented on the dressing log.
Photos will also be taken if extra dressing changes are required. AE´s/ADE´s/unexpected events with the device may be documented by relevant photos at time. All photos shall include a sticker marked with subject code, visit number/date and time. All photos will be checked by monitor.

3.2.1 Schedule of Assessment

Day	Visit 1	**Visit 2**	Visit 3	Visit 4	Visit 5	**Termination End of treatment**
Visit (number)	1	2	3	4	5	Termination
Subject demography	✓					
Inclusion and Exclusion Criteria	✓					
Inform Consent	✓					
Vital Signs	✓				✓	✓
Medical and surgical history	✓					
Skin assessment	✓	✓	✓	✓	✓	✓
Wound History	✓					
Randomization	✓					
Cleansing and/or Debridement	✓	✓	✓	✓	✓	
Signs of symptoms of infection	✓	✓	✓	✓	✓	✓
Pain (VAS)	✓	✓	✓	✓	✓	✓
Wound status after (cleansing, debridement)	✓	✓	✓	✓	✓	
Dressing application	✓	✓	✓	✓		
Dressing removal		✓	✓	✓	✓	✓
Photo	✓	✓	✓	✓	✓	✓
Investigator/nurse evaluation	✓	✓	✓	✓	✓	✓
Subject evaluation		✓	✓	✓	✓	✓
Medication log	✓	✓	✓	✓	✓	
AE/ADE/DD	✓	✓	✓	✓	✓	✓
SAE/SADE	✓	✓	✓	✓	✓	✓
Dressing Log	✓	✓	✓	✓	✓	✓

3.3 Selection of Population for Investigation

3.3.1 Inclusion Criteria

Inclusion Criteria

1. Exuding wound indicated for treatment with NPWT therapy
2. In case of multiple wounds, target wound must be ≥ 10 cm distant from other wounds. Selection of target wound is according to the investigator's preference
3. Peri-wound skin assessable and 5 cm of peri-wound skin present around the wound
4. Male or female, 18 years of age and above
5. Signed Informed Consent

3.3.2 Exclusion Criteria

1. Dressing sizes does not fit the target wound
2. Unexplored blind tunnels or non-enteric fistula
3. Untreated osteomyelitis
4. Malignant wounds
5. Wounds with necrotic tissue or eschar (if not adequately debrided)
6. Bleeding wounds
7. Subject not suitable for the investigation according to the investigator's judgment
8. Subject included in other ongoing clinical investigation which could interfere with this investigation, as judged by the investigator
9. Known allergy/hypersensitivity to any of the components included into the investigation.

3.3.3 Withdrawal of Subjects from Treatment or Assessment

Subjects are free to discontinue participation in the investigation at any time, and without prejudice to further treatment. Subjects who discontinue the investigation should always be asked about the reason(s) for their discontinuation and about the presence of any AE/ADE or DD and, if possible, be assessed by an investigator. AE/ADE should be followed up.

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

Incorrectly enrolled or randomized 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).

3.4 Investigational Device

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

Treatment

System

All subjects will receive treatment with the Avance® Negative Pressure Wound Therapy System consisting of:

- Avance® Pump
- Avance® View Pad
- Avance® Foam
- Film sealant (either the **Investigational device,** Avance Film® with Safetac®Technology or the **Comparator,** V.A.C. Drape,)

Pump settings (pressure and mode (intermittent or constant pressure) and size of the foam and the film must be registered in the relevant section of the CRF.

Other materials

Actual use of supporting and/or protecting materials must be registered in the relevant section in the CRF.

- *Skin fixatives*
  Mepiseal® will be available for use in combination with the Avance film with Safetac, according to investigators preference.
  Mepiseal is a flexible sealant intended to use on the surrounding skin of wounds or stomas that are difficult to dress due to uneven skin surfaces, location or mobility. Mepiseal helps prevent leakage and premature loosening of the wound dressing, NPWT or ostomy systems. Mepieseal can also be used as a filler uneven surrounding skin.

- *Wound contact layers*
  Non-adherent dressing materials Mepitel can be used to protect fragile tissue such as bones, tendons and nerves. It can also be used to cover sharp edged or bones to prevent puncture of blood vessels or organs..

- *Skin protection*
  In this investigation, use of additional film (other transparent film), Cavilon or hydrocolloids is **not allowed** to be used as protection of the peri-wound skin as this could potentially interfere with the measurement of the primary objective.

All medical devices are CE marked and used according to intended use, with the exception of the overlapping Avance Film® with Safetac with V.A.C. Drape and V.A.C. Drape together with Avance System and Avance Foam, which is used outside intended use. Based on product risk management for the investigational device, it can be concluded that there are no unacceptable risks of harm for subject, the user nor third party involved.
The investigational device meets all relevant essential requirements except for those being investigated in the clinical investigation, as declared separately.

3.4.2 Labeling

MHC will provide the investigational medical devices to the investigation sites for free. 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 each participating country.

3.4.3 Accountability

The Principal Investigator is responsible for establishing routines for correct handling of investigational medical device, to ensure that:

- The Principal Investigator or his/she's designee correctly receives deliveries of such device from MHC.
- Accurate records are maintained, accounting for the receipt of the investigational medical device (a delivery note for this purpose will be provided) and for the disposition of the device
- Investigational medical device is to be handled and stored safely, properly and in agreement with the given storage instructions.
- The investigational medical device is to be prescribed only by the investigator or by a person authorized to do so by the Principal Investigator
- Under no circumstances will the investigator allow the investigational device to be used for other purposes than as directed by the CIP.
- When dispensing investigational medical device to subjects, this must be noted in the accountability form investigation device per subject. Recorded information includes identification of the subject to whom the investigational medical device is dispensed, the investigational medical device and quantity dispensed, date of dispensing, and documentation of returned device (if any) from the subject. This record must be kept in the Central Site File (CSF).
- Returned and unused devices is accounted for and returned to MHC for destruction, or destroyed locally upon agreement with, and approval from MHC. All returned devices should be documented for on a specific form supplied by MHC.

3.4.4 Storage conditions

The device should be stored under normal condition.

3.4.5 Method of Assigning Subjects to Treatment Groups

The investigation is randomized, open, controlled pilot study. All subjects who fulfil all inclusion and none of the exclusion criteria and have signed a written inform consent form will be randomly assigned in a 1:1 ratio, within each arm on day 1, to one of the two treatment groups provided by the electronic eCRF system (Viedoc) as indicated below:

Treatment group 1:
Film A (subject right side) = Avance Film with Safetac
Film B (subject left side) = V.A.C. Drape

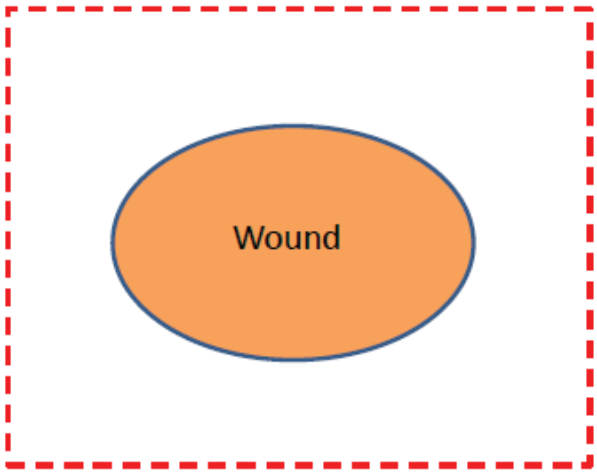
Treatment group 2:
Film A (subject right side) = V.A.C. Drape
Film B (subject left side) = Avance Film with Safetac

The investigation center will be numbered 01 and the subject will be consecutively allocated to the treatment and given a subject code e.g. 0101,0102 etc

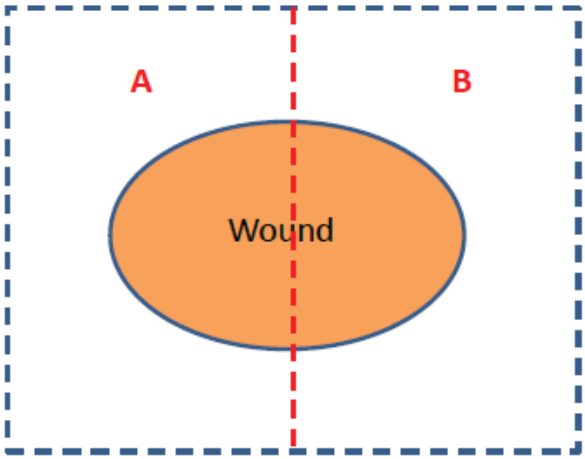
Randomization

Eligible subjects will have the investigated wound randomly divided into two halves. One half of the wound will be dressed with Avance Film with Safetac while the other half on top of the Avance Film with Safetac will be dressed with V.A.C. Drape.

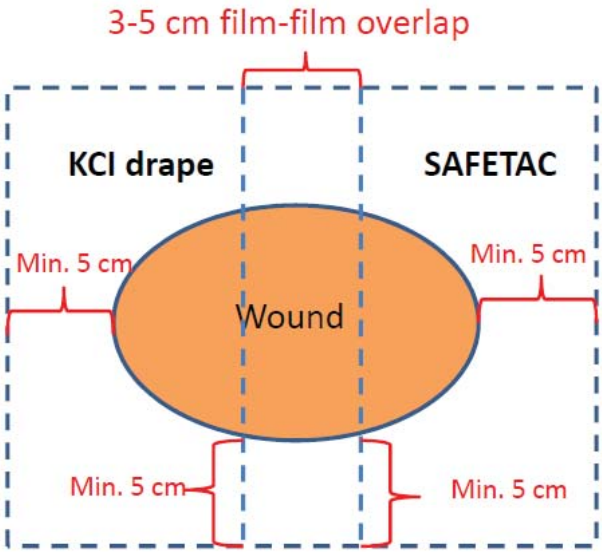
1. The area which is intended to be covered with film will be drawn on the subject's skin with a semi-permanent marker pen:



2. This skin area will be divided into two approximately equal halves and A or B will be written on each half (to allow for correct positioning of new films in connection with dressing changes). The intended direction of film application will be according to the location of the wound, anatomy of the relevant body part and the investigators best judgment for how the best seal can be obtained.



3. Instruction about the film-film overlap and the overlap from wound edge on dry peri-wound skin to ensure an optimal vacuum is described in the application step-by-step guide.



3.5 Concomitant Treatments

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

3.6 Performance and Safety

3.6.1 Subject Characteristics

See Appendix C

3.6.2 Performance and Safety Measurements and Variables

Primary outcome variable:

Primary performance variable will be change in total score of Condition of peri-wound skin, the sum of scores (0-3) of redness/irritation, rash, peri-wound dermatitis or eczema, maceration, blistering and skin tear from baseline to last visit

Secondary outcome variables:

Secondary performance variables will be change in the following variables from baseline to last visit:

- Redness/irritation
- Rash, periwound dermatitis or eczema
- Maceration
- Blistering

- Skin tear
- Damage to peri-wound skin caused by Avance Film
- Damage to peri-wound skin caused by KCI Film
- Overall peri-wound condition changes by the Avance Film
- Overall peri-wound condition changes by the KCI film

Investigator/Nurse evaluation

Film

- Overall ease of application
- Overall ease of removal
- Adherence to healthy, intact skin
- Conformability
- Overall satisfaction
- Sticking to the wound bed
- Sticking to the surrounding skin
- Retention of dressing pieces in the wound

Foam

- Overall ease of application
- Overall ease of removal
- Conformability
- Overall satisfaction
- Sticking to the wound bed
- Foam adhering to tissues
- Foam imbedded in the wound
- Foam fragmentation
- Disintegration of the foam
- Foam retention, needing for sharp debridement

Patient reported outcome (PRO)

- VAS before removal of the covering film
- VAS before removal of the foam filler,
- VAS during removal of the covering film,

- VAS during removal of the foam filler
- VAS after removal of the covering film,
- VAS after removal of the foam filler

Saftey

- Incidence of AE, ADE, DD and SAE
- Incidence of AE:s,ADE:s, DD:s and SAE:s leading to withdrawal

For details see Appendix C

3.6.3 Safety Measurements and Variables

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

3.6.4 Anticipated ADEs

The following events have been identified as anticipated effects in the Product Risk Management Record:

- Wound dry out
- Maceration
- Infection
- Pain and discomfort
- Skin irritation
- Skin stripping
- Skin tears

The conclusion of the Product Risk Management Record is as following:
Based on this risk management record it can be concluded that for the investigational devices there are no unacceptable risks of harm for subject, the user nor third party involved in this investigation when used under normal condition.

3.7 Data Quality Assurance

3.7.1 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 (MHC) personnel will be available between visits if the investigator or other staff at the site needs information and/or advice.

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

3.7.2 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.

3.7.3 Data Management

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

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

Viedoc, a web based electronic CRF system, will be used to capture data in this investigation. The eCRF system complies with FDA Title 21 CRF 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 help for consistency and validation of the data.

Pharma Consulting Group will support with a helpdesk function taking care of system user questions regarding Viedoc.

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

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

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

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

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

3.8 Statistical Methods and Determination of Sample Size

3.8.1 Statistical populations

ITT Population

The Intention to Treat (ITT) population will include all randomised subjects with at least one post-randomisation performance measurement. The final definition of the ITT population will be made at the clean-file meeting.

Per Protocol Population
The Per Protocol (PP)-Population will include all subjects in the ITT-population without significant protocol violations. Subjects identified as protocol violators will be documented and agreed between MHC and the principal investigator at the clean-file meeting before the database lock.

Safety Population

The safety population will include all subjects with at least one treatment with at least one of the study films.

3.8.2 General statistical methodology

The design of the study is paired since both treatments are applied on each side of the same wound. This implies that all statistical analyses will be paired.
For comparison of change in continuous variables (e.g. total score) between the two treatments Wilcoxon Signed Rank test will be applied on the differences of the changes from baseline to last visit between the two treatments.
For comparison of change in ordered categorical variables (e.g. each of the conditions of peri-

wound skin) between the two treatments Wilcoxon Signed Rank test will be applied on the differences of the changes from baseline to last visit classified as worse (-1), equal (0) and better(1) between the two treatments.

For comparison of change over time within groups Wilcoxon Signed Rank will be used for continuous variables and sign test for ordered categorical variables.

Continuous variables will be described with mean, SD, median and minimum and maximum and categorical variables will be described with number and percentage.

All variables will be described per treatment film and with distributions of the differences between the two treatment films.

All the main performance analyses will be performed on the ITT-population. Complementary performance analyses will be performed on the PP-population.
All safety analyses will be performed on the safety population.

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

3.8.3 Performance Analyses

Primary Performance Analysis
Primary performance analysis will be the analysis of the difference in primary performance variable, change in total score, the sum of scores (0-3) of redness/irritation, rash peri-wound dermatitis or eczema, maceration, blistering and skin tear on the skin from baseline to last visit between the Avance Film with Safetac and V.A.C Drape with two-sided Wilcoxon Signed Rank on the ITT-population at the 5% significance level.

Secondary Performance Analyses
Secondary performance analyses will be the analyses between the Avance Film with Safetac and V.A.C Drape film of all the secondary performance variables given above in section 3.6.2 according to the statistical methods given above in section 3.8.2 General statistical methodology on both the ITT population and PP population.

3.8.4 Safety analyses

All safety variables given above in section 3.6.2 will be analyzed descriptively by treatment film on the safety population.

3.8.5 Baseline analysis

All variables measured at baseline will be summarized for the ITT population and for the PP population using appropriate descriptive statistics.

3.8.6 Statistical Analysis Plan (SAP)

Before the database is locked a statistical analysis plan (SAP) will be written and signed with all details in the statistical analyses given, together with a listing of all Tables, Figures and Listings to be produced.

3.8.7 Determination of Sample Size

In order to find a mean difference in change of primary performance variable, total sum score (0-15) of 1 unit between Avance Film with Safetac and V.A.C Drape with Wilcoxon Signed Rank test with power 80% at 5% significance level 7-23 evaluable subjects are needed. From a pilot study the SD of the change in corresponding score (0-5) was 0.647. The SD for change in total sum score (0-15) was then estimated to be 1.94. In the sample size analysis it is assumed a correlation of 0.70 between the change in Avance Film with Safetac and change in V.A.C Drape.

3.9 Changes to the Clinical Investigation Plan

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

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

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

4. STATEMENTS OF COMPLIANCE

4.1 Ethics

4.1.1 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 investigation plan as per local requirements.

4.1.2 Ethical Conduct of the Investigation

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

4.1.3 Patient Information and Consent Form

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

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

4.2 Regulatory and standards

4.2.1 Regulatory 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 a CA before enrolment of any subject into the investigation. MHC is responsible for informing the CA of any amendment to the investigation plan as per local requirements.

4.2.2 Standards and other

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

4.2.3 Subject Data Protection

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

4.3 SUBJECT PROTECTION PROCEDURES

4.3.1 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.

4.3.2 Insurance

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

5. INVESTIGATION TIMETABLE AND TERMINATION

Investigation start: Q4 2015

Inclusion completed:Q2 2016

Last subject out:Q2 2016

The investigation could be prematurely discontinued if the dropout rate is high and/or the investigation site is unable to fulfil the inclusion period according to the Clinical Investigation Agreement.
The Sponsor, Ethics Committee or Regulatory Authority may prematurely terminate or suspend the Clinical Investigation as a whole or at an individual investigation site for significant and documented reasons. The Principal Investigator may also prematurely terminate or suspend the Clinical Investigation at his/her site, for significant and documented reasons. Reasons for premature termination or suspension by any party include, but are not limited to safety, inadequate recruitment, Principal Investigator issues, and device related problems, alignment with business strategy or administrative issues.
If suspicion of an unacceptable risk to subjects arises during the Clinical Investigation, or when instructed by an Ethics Committee or Regulatory Authority, the Sponsor shall suspend the Clinical Investigation at all active sites while the risk is assessed. The Sponsor shall terminate the Clinical Investigation if an unacceptable risk is confirmed, or resume the Clinical Investigation following appropriate communication and approval from the Ethics Committee and Regulatory Authority as required.
In terminating the clinical investigation, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subject's interests.
After the clinical investigation has been successfully completed the participating subject will continue to receive standard care according the institute's routine practice.

6. 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. Sussia, D., Danino, A., & Nikolis, A. (2011). Negative-pressure therapy versus standard wound care: a meta-analysis of randomized trials. Plastic and reconstructive surgery, 128 (5) 498 e-503e doi:10.1097/PRS.2b013e31822b675c
2. Rafter, L., Use of soft silicon based film dressing in negative pressure wound therapy. Wounds UK (2013), Volume 9; Number 4 :107-113
3. Upton, D., Andrew, A., Pain and trauma in negative wound therapy: a review. International Wound Journal 2013, March, doi:10.1111/iwj.12059

7. 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 labeling.

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

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

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

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

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

Serious Adverse Event (SAE)
Adverse Event that:

a) led to death,
b) led to a serious deterioration in the health of the subject, that either resulted in
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, or

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

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

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

Serious Adverse Device Effect (SADE)

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

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

The investigator must inform Mölnlycke Health Care (MHC), within 1 day of awareness of the event by sending the Serious Adverse Event/Serious Adverse Device Effect form by email to: Clinical_Investigations_Event_Reporting@molnlycke.com, of any SAE that occurs in the course of the investigation. All SAE have to be reported, whether or not they are considered causally related to the investigation product. When a SAE 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 and a separate report are therefore not required when eCRF is used.

Device Deficiencies that could have lead 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 and/or the Competent Authority of the SAE/SADE as per local requirements.

PROCEDURES FOR DD REPORTING

All DD needs to be reported to MHC as soon as possible, without unjustified delay. If the DD could have lead 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. The completed DD report form must be sent by email to Clinical_Investigations_Event_Reporting@molnlycke.com

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.

Causality Assessment

The investigator is required to assess the causal relationship to the investigation product for each AE/SAE according to the following classifications:

1. **Definite:**

   Event with plausible time relationship to device application

   No other explanation - current disease, concomitant drugs and/or other devices

   Response to withdrawal plausible

   Event definitive - localized, specific

   Rechallenge positive

2. **Probable:**

   Event with reasonable time relationship to device application

   No other explanation current disease, concomitant drugs and/or other devices

   Response to withdrawal clinically reasonable

   No rechallenge

3. **Possible:**

   Event with reasonable time relationship to device application

   Could also be explained by disease or other drugs and/or devices

   Information on device withdrawal lacking or unclear

   No rechallenge

4. **Unlikely:**

   Event with duration to onset that makes a relationship improbable (but not impossible)

   Diseases other drugs or devices provide plausible explanations

   Symptoms do not resolve on withdrawal

   Nature of event unrelated to action or properties of device

   No rechallenge

5. **Unable to determine**

   Event occurred but there is insufficient information

Investigation Code Avance 02 **Final Version** **CIP Approval date** 2015-09-11

Amendment Final Version **Amendment Approval date** 2016-03-07

CLINICAL INVESTIGATION PLAN (CIP) Central AMENDMENT no 01

Substantial

INVESTIGATIONAL DEVICE:

Avance® Negative Pressure Wound Therapy System

INVESTIGATION TITLE:

A randomized open, controlled pilot investigation comparing trauma to the peri-wound skin and Pain during treatment with Avance NPWT system when using two different fixations

SITES AFFECTED BY THE AMENDMENT:

The amendment affect all in the study

THE CLINICAL INVESTIGATION PLAN (CIP) IS TO BE AMENDED AS FOLLOWS:

FROM:

1. Title: Randomized, Intra-patient, Open Controlled Pilot Investigation

2. Comparing trauma to the peri-wound skin

3. Patient included 7-23 evaluable subjects

4. Eligible subjects will have the investigated wound randomly divided into two halves. One half of the wound will be dressed with Avance Film with Safetac while the other half on top of the Avance Film with Safetac will be dressed with V.A.C. Drape.

5. Each subject will be followed in the investigation for a maximum of five (5) dressing changes or until treatment with NPWT is no longer indicated

6. Investigational Device
Treatment
System
All subjects will receive treatment with the Avance® Negative Pressure Wound Therapy System consisting of:

- Avance® Pump
- Avance® View Pad
- Avance® Foam
- Film sealant (either the **Investigational device,** Avance Film® with Safetac®Technology or the **Comparator,** V.A.C. Drape)

7. Inclusion/Exclusion Criteria

Inclusion Criteria

1. Exuding wound indicated for treatment with NPWT therapy

2. In case of multiple wounds, target wound must be _ 10 cm distant from other wounds.

Selection of target wound is according to the investigator's preference

3. Peri-wound skin assessable and 5 cm of peri-wound skin present around the wound

4. Male or female, 18 years of age and above

5. Signed Informed Consent

Exclusion Criteria

1. Dressing sizes does not fit the target wound

2. Unexplored blind tunnels or non-enteric fistula

3. Untreated osteomyelitis

4. Malignant wounds

5. Wounds with necrotic tissue or eschar (if not adequately debrided)

6. Bleeding wounds

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

8. Subject included in other ongoing clinical investigation which could interfere with this investigation, as judged by the investigator

9. Known allergy/hypersensitivity to any of the components included into the investigation

TO:

1. Title: Randomize, Open Controlled Pilot Investigation.

2. Comparing trauma to the peri-wound skin and pain during treatment with Avance NPTW system.

3. Patient included 32 evaluable subjects.

4. Subjects will be randomized using optimal allocation (minimization) balancing baseline variables age and type of skin (normal/dry/flaky/oily/moist). Eligible subjects will be randomized to receive Avance® Film with Safetac® Technology or Avance® Transparent film in a ratio of 1:1 provided by the electronic eCRF system (Viedoc).

5. Each subject will be followed in the investigation for a maximum of six (6) dressing changes or until treatment with NPWT is no longer indicated

6. Investigational Device

Treatment

System

All subjects will receive treatment with the Avance® Negative Pressure Wound Therapy System consisting of:

- Avance® Pump
- Avance® View Pad
- Avance® Foam
- Film sealant (either the **Investigational device,** Avance ® Film with Safetac®Technology or the **Comparator,** Avance® Transparent film.)

7. Inclusion/Exclusion Criteria

Inclusion Criteria

1. Traumatic, surgical or dehisced wounds, Venous Leg Ulcer or Pressure Ulcer indicated for treatment with NPWT therapy

2. In case of multiple wounds the target wound must be ≥ 10 cm distant from other wounds. Selection of the target wound is according to the investigator's preference

3. Peri-wound skin assessable and 5 cm of peri-wound skin present around the wound

4. Male or female, 18 years of age and above

5. Signed Informed Consent

Exclusion Criteria

1. Dressing sizes does not fit the target wound
2. Unexplored blind tunnels or non-enteric fistula
3. Untreated osteomyelitis
4. Malignant wounds
5. Wounds which needed extra skin protection such as Cavilon, Zink pasta, ointment, or other type of skin protections.
6. Subjects treated with systemic immunosuppressive or glucocorticosteroids, except subjects taking occasional doses or doses less than 10mg prednisolone/day or equivalent.
7. Subjects with decreased sensation, as judged by the investigator
8. Wounds with exposed blood vessels, anastomotic sites, organs or nerves.
9. Previous NPWT treatment on the target wound ≤ 3 months at inclusion
10. Wounds with necrotic tissue or eschar
11. Significantly bleeding wounds, as judged by the investigator
12. Subject not suitable for the investigation according to the investigator's judgment
13. Subject included in other ongoing clinical investigation which could interfere with this investigation, as judged by the investigator
14. Known allergy/hypersensitivity to any of the components included into the investigation.
15. Previous treatment of the target wound with acrylic film ≤ 1 week at inclusion

Investigation Code	**Avance 02**	**Final Version**		**CIP Approval date**	**2015-09-11**
Amendment Final Version			**Amendment Approval date**		**2016-03-07**

REASON FOR MAKING THE AMENDMENT:

The Medical Products Agency (MPA) recommendation was to do the study on a CE approved design. The purpose of the previous design was neither CE mark V.A.C Drape for use in combination with the Avance NPWT system nor to CE mark V.A.C Drape overlapping Avance Film.

ACTIONS TO BE TAKEN:

Investigator at the site will be provided with the amendment and signature will be collected.

The Amendment will be sent to the Ethic committee for approval according to local procedures.

Investigation Code	**Avance 02**	**Final Version**	**CIP Approval date**	**2015-09-11**
Amendment Final Version		**Amendment Approval date**	**2016-03-07**	

CLINICAL INVESTIGATION PLAN (CIP) SYNOPSIS

Investigation title:

A randomized open, controlled pilot investigation comparing trauma to the peri-wound skin and Pain during treatment with Avance NPWT system when using two different fixations

Objectives

Primary objective

- Changes on Peri-Wound* Skin from baseline to termination during treatment with Avance System and Avance Foam.

  * Redness/Irritation, Flaky, Maceration, Blistering, Skin tears (None, Mild/Moderate/Severe)

Secondary objectives

- Changes in Pain measured by the Visuell analog scale (VAS) from baseline to termination
- AE,SAE,SADE, ADE and DD

Overall Design

This investigation is designed as a randomized controlled open clinical investigation. The outcome will be used to guide the manufacture to the design and implementation of a larger scale randomized study. In order to compensate for a drop-out rate of 5 %, this clinical investigation will include 17 subjects per group across one (1) site in Sweden to yield a total of 32 evaluable subjects.

All subjects who has not previously been treated with NPWT and fulfill all inclusion, none of the exclusion criteria and have signed a written inform consent will be enrolled. Subjects will be randomized using optimal allocation (minimization) balancing baseline variables age and type of skin (normal/dry/flaky/oily/moist). Eligible subjects will be randomized to receive Avance® Film with Safetac® Technology or Avance® Transparent film in a ratio of 1:1 provided by the electronic eCRF system (Viedoc).

This investigation is comparing pain at dressing change and trauma and/or other changes to the peri-wound skin during treatment with Avance NPWT system when using two different fixation films, Avance® Film with Safetac® Technology or Avance® Transparent film. Since the investigation is comparing films with clear visual differences, it is not possible to blind neither the investigator nor the subject.

Dressing change

Dressing change will be performed at the investigation site and the frequency of dressing change will be depending on the condition of the wound and the peri-wound skin. Recommended dressing change frequency is every 48-72 hours.

A record (dressing log) will be completed for every dressing change.

Investigation Visit frequency and subject participation

Eligible subjects will be enrolled at the baseline visit (Visit 1), where the first dressing applications take place. From Visit 2 and onwards, one dressing application is considered as one study visit, e.g. the study visits are flexible and depending on the dressing changing frequency of the individual subject. The total treatment time for a subject may vary, depending on the wound type and condition. Each subject will be followed in the investigation for a maximum of six (6) dressing changes or until treatment with NPWT is no longer indicated. After termination from the investigation, subjects will be treated according to standard clinical practice at the investigation site. No additional data (except follow up information on ongoing safety events) will be collected after termination.

Subjects will be recruited at the investigation site, which have experience in managing the investigation population with NPWT and have access to a suitable number of subjects (based on historic data).

Following variables should be considered (Appendix C):

At visit 1

- Informed consent
- Subject demographic details
- Inclusion and exclusion criteria
- Vital signs
- Care (Inpatient/ Outpatient)
- Medical and surgical history
- Wound history
- Skin assessment*
- Concomitant medication
- Photo
- Pain (VAS)
- Adverse Event (AE)/ Adverse Device Effect (ADE)/ Serious Adverse Event (SAE) /Serious Adverse Device Effect (SADE)/Device Deficiency (DD)
- Apply the Investigational Product (IP)
- Randomization

At visit 2-6

- Skin assessment*
- Concomitant medication
- Photo
- Pain (VAS)
- Change and removal of IP
- AE/ ADE/ SAE/SADE/DD

Only one target wound per patient will be included in this investigation.

* Evaluation of the skin se Appendix D

Schedule of Assessment

Day	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Termination End of treatment
Visit (number)	1	2	3	4	5	6	Termination
Subject demography	✓						
Inclusion and Exclusion Criteria	✓						
Inform Consent	✓						
Vital Signs	✓					✓	✓
Medical and surgical history	✓						
Skin assessment	✓	✓	✓	✓	✓	✓	✓
Wound History	✓						
Randomization	✓						
Pain (VAS)	✓	✓	✓	✓	✓	✓	✓
Dressing application	✓	✓	✓	✓	✓		
Dressing removal		✓	✓	✓	✓	✓	✓
Photo	✓	✓	✓	✓	✓	✓	✓
Medication log	✓	✓	✓	✓	✓	✓	✓
AE/ADE/DD	✓	✓	✓	✓	✓	✓	✓
SAE/SADE	✓	✓	✓	✓	✓	✓	✓

Inclusion/Exclusion Criteria

Inclusion Criteria

1. Traumatic, surgical or dehisced wounds, Venous Leg Ulcer or Pressure Ulcer indicated for treatment with NPWT therapy

2. In case of multiple wounds the target wound must be ≥ 10 cm distant from other wounds. Selection of the target wound is according to the investigator's preference

3. Peri-wound skin assessable and 5 cm of peri-wound skin present around the wound

4. Male or female, 18 years of age and above

5. Signed Informed Consent

Exclusion Criteria

1. Dressing sizes does not fit the target wound
2. Unexplored blind tunnels or non-enteric fistula
3. Untreated osteomyelitis
4. Malignant wounds
5. Wounds which needed extra skin protection such as Cavilon, Zink pasta, ointment, or other type of skin protections.
6. Subjects treated with systemic immunosuppressive or glucocorticosteroids, except subjects taking occasional doses or doses less than 10mg prednisolone /day or equivalent.
7. Subjects with decreased sensation, as judged by the investigator
8. Wounds with exposed blood vessels, anastomotic sites, organs or nerves
9. Previous NPWT treatment on the target wound ≤ 3 months at inclusion
10. Wounds with necrotic tissue or eschar (if not adequately debrided)
11. Significantly bleeding wounds, as judged by the investigator
12. Subject not suitable for the investigation according to the investigator's judgment
13. Subject included in other ongoing clinical investigation which could interfere with this investigation, as judged by the investigator
14. Known allergy/hypersensitivity to any of the components included into the investigation.
15. Previous treatment of the target wound with acrylic film ≤ 1 week at inclusion

Investigational Device

Treatment

System

All subjects will receive treatment with the Avance® Negative Pressure Wound Therapy System consisting of:

- Avance® Pump
- Avance® View Pad
- Avance® Foam
- Film sealant (either the **Investigational device,** Avance ® Film with Safetac®Technology or the **Comparator,** Avance® Transparent film.)

All medical devices are CE marked.

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LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
ADE	Adverse Device Effect
CA	Competent Authorities
CDM	Clinical Data Manager
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRA	Clinical Research Associate
CRF	Case Report Form
CRM	Clinical Research Manager
DCF	Data Clarification Forms
DD	Device Deficiency
FSI	First subject in
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
ID	Investigational Device
ITT	Intention to Treat
LSO	Last subject out
MHC	Mölnlycke Health Care AB
PI	Principal Investigator, a person responsible for the conduct of the clinical investigation at the investigational investigation site. Every investigational investigation site has a principal investigator.
PIC	Patient Information and Consent Form
RA	Regulatory Authority
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SDV	Source Data Verification

INTRODUCTION

Negative pressure wound therapy (NPWT) also referred to as topical negative pressure (TNP), negative pressure therapy (NPT), sub-atmospheric pressure wound therapy, and sealed surface wound suction is a modality that has found significant use in complex acute surgical, delayed healing surgical and hard to heal chronic wounds, including those with elevated bacterial contamination. Negative pressure wound therapy manages exudate, combats peri-wound oedema, increases blood flow to the wound, maintains optimal moist wound conditions and encourages the formation of wound bed granulation tissue. A meta-analysis reported a significant reduction in time to healing for wounds treated with NPWT when compared to those treated with standard care (1). The Avance NPWT System comprises a range of CE marked products which are used collectively as a NPWT system. The Avance NPWT System has been marketed by Mölnlycke Health Care AB since May 2010.
Despite the research support for its effectiveness in wound healing, fewer studies have considered the impact of NPWT on the patient in terms of the pain that can be experienced. Wound care and dressing changes can be very painful for patients, and this pain can also cause patients to feel stressed or anxious, thus impacting negatively on both their physical and psychological well-being. Such factors need to be considered in any evaluation of NPWT or other treatment (2).
Trauma and pain caused by the removal and reapplication of the NPWT dressings and/or removal of the foam has been identified as a major contributor to wound pain (2). Film-based dressings with adhesive skin contact layers are used to keep NPWT system in place and skin stripping may occur because the film can adhere to aggressively to the peri-wound skin, resulting in trauma and pain (2). Trauma may also occur when tissue grows into the foam on the dressing and this tissue becomes torn during dressing change (3). Damage to the wound and surrounding skin can involve bleeding, blisters, skin stripping and other skin damage, leading to a higher frequency of dressing changes, a greater level of pain and a longer time taken for the wound to heal (3). Despite the importance of minimizing trauma during NPWT and other wound care, few researchers have focused on this area (3)
Although not focusing on NPWT specifically, a study by Upton and Solowiej also demonstrated how dressing type can affect the level of pain experienced during dressing change. In 49 patients with chronic wounds, the authors explored differences in pain and stress levels between those who received conventional dressings ($n = 39$) and those who were given atraumatic dressings with Safetac technology. Physiological and psychological measures of pain and stress were taken. It was found that self-reported pain and stress were significantly lower in those who were given atraumatic dressings as part of their care routine (2).

In the literature there are numerous supporting articles reporting effectiveness of NPWT treatment. However, information regarding choice of dressing materials are lacking. Should for example the adhesive material of the dressing have a protecting effect on the surrounding skin around the NPWT treated wound?

What is known from other studies in other stages of the wound healing is that skin trauma such as bleeding, redness, irritation, skin stripping and blisters might occur when a film dressing is removed. Such trauma can lead to delayed healing and prolonged treatment of the patient.

In a study made by Upton in 2013, half of the participating patients reported skin trauma or irritation.The purpose of this study is to compare with two different types of film dressings one with silicon adhesive (Avance® Film with Safetac®Technology) and one with acrylic adhesive (Avance® Transparent film) to see if there is a difference in peri-wound skin damage and pain at dressing removal.

1. OBJECTIVES

Primary objective

- Changes on Peri-Wound* Skin from baseline to termination during treatment with Avance System and Avance Foam.

  * Redness/Irritation, Flaky, Maceration, Blistering, Skin tears (None, Mild/Moderate/Severe)

Secondary objectives

- Changes in Pain measured by the Visuell analog scale (VAS) from baseline to termination
- AE,SAE,SADE, ADE and DD

2. CLINICAL INVESTIGATOR(S) AND INVESTIGATION ADMINISTRATIVE STRUCTURE

2.1 Staff at Investigation site(s)

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

2.2 Mölnlycke Investigation Personnel

Tina Kjellén, Clinical Study Manager

Lennart Wäne, Clinical Data Manager

2.3 Other Participants

Pharma Consulting Group
Kungsängsvägen 19, 1 tr
753 23 Uppsala, Sweden

Statistiska Konsultgruppen
Nils-Gunnar Pehrsson, Biostatistician
Stigbergsliden 5
SE-414 63 Göteborg

3. INVESTIGATION PLAN AND PROCEDURES

3.1 Overall Design and Flow Chart

This investigation is designed as a prospective, randomized controlled open clinical investigation. The outcome will be used to guide the manufacture to the design and implementation of a larger scale randomized study. In order to compensate for a drop-out rate of 5 %, this clinical investigation will include 17 subjects per group across one (1) site in Sweden to yield a total of 32 evaluable subjects.

All subjects who has not previously been treated with NPWT and fulfill all inclusion and none of the exclusion criteria and have signed a written inform consent will be enrolled. Subjects will be randomized using optimal allocation (minimization) balancing for baseline variables age and type of skin (normal/dry/flaky/oily/moist). Eligible subjects will be randomized to receive Avance® Film with Safetac® Technology or Avance® Transparent film in a ratio of 1:1 provided by the electronic eCRF system (Viedoc).

An evaluable subject is defined as a subject that is enrolled and has data for at least one visit after baseline visit.
The target populations are male or female, 18 years and above, which have exuding wounds indicated for treatment with NPWT therapy. The subject should not previously been treated with NPWT, previous treatment, may have an bias on the skin evaluation.
The study visits are flexible and depending on the dressing changing frequency of the individual subject. The total treatment time for each subject may vary depending on the wound type and condition of the wound. Each subject will be followed for a maximum of six (6) dressing changes or until treatment with NPWT is no longer indicated (withdrawal criterion). After termination from the investigation, subjects will, if necessary, be treated according to standard clinical practice at the investigation site. No additional data (except for follow up information on ongoing safety events) will be collected after termination.

3.2 Procedures and Assessments

<u>Following variables should be considered (Appendix C):</u>
At visit 1

- Informed consent
- Subject demographic details
- Inclusion and exclusion criteria
- Vital signs
- Care (Inpatient/ Outpatient)
- Medical and surgical history
- Wound history
- Skin assessment*
- Concomitant medication
- Photo
- Pain (VAS)
- Adverse Event (AE)/ Adverse Device Effect (ADE)/ Serious Adverse Event (SAE) /Serious Adverse Device Effect (SADE)/Device Deficiency (DD)
- Apply the Investigational Device (ID) Apply the IP
- Randomization

At visit 2-6
- Skin assessment*
- Medication
- Photo
- Pain (VAS)
- Change and removal of the IP
- AE/ ADE/ SAE/SADE/DD

Only one target wound per patient will be included in this investigation.
* Evaluation of the skin se Appendix D
Photos will be taken before and after application of the film fixations and also if extra dressing changes are required. All unexpected events with the device may be documented by relevant photos at time. All photos shall include a sticker marked with subject code, visit number/date and time. All photos will be checked by monitor.

3.2.1 Schedule of Assessment

Day	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Termination End of treatment
Visit (number)	1	2	3	4	5	6	Termination
Subject demography	✓						
Inclusion and Exclusion Criteria	✓						
Inform Consent	✓						
Vital Signs	✓					✓	✓
Medical and surgical history	✓						
Skin assessment	✓	✓	✓	✓	✓	✓	✓
Wound History	✓						
Randomization	✓						
Pain (VAS)	✓	✓	✓	✓	✓	✓	✓
Dressing application	✓	✓	✓	✓	✓		
Dressing removal		✓	✓	✓	✓	✓	✓
Photo	✓	✓	✓	✓	✓	✓	✓
Medication log	✓	✓	✓	✓	✓	✓	✓
AE/ADE/DD	✓	✓	✓	✓	✓	✓	✓
SAE/SADE	✓	✓	✓	✓	✓	✓	✓

3.3 Selection of Population for Investigation

3.3.1 Inclusion Criteria

1. Traumatic, surgical or dehisced wounds, Venous Leg Ulcer or Pressure Ulcer indicated for treatment with NPWT therapy

2. In case of multiple wounds the target wound must be ≥ 10 cm distant from other wounds. Selection of the target wound is according to the investigator's preference

3. Peri-wound skin assessable and 5 cm of peri-wound skin present around the wound

4. Male or female, 18 years of age and above

5. Signed Informed Consent

3.3.2 Exclusion Criteria

1. Dressing sizes does not fit the target wound

2. Unexplored blind tunnels or non-enteric fistula

3. Untreated osteomyelitis

4. Malignant wounds

5. Wounds which needed extra skin protection such as Cavilon, Zink pasta, ointment, or other type of skin protections.

6. Subjects treated with systemic immunosuppressive or glucocorticosteroids, except subjects taking occasional doses or doses less than 10mg prednisolone /day or equivalent.

7. Subjects with decreased sensation, as judged by the investigator

8. Wounds with exposed blood vessels, anastomotic sites, organs or nerves

9. Previous NPWT treatment on the target wound ≤ 3 months at inclusion

10. Wounds with necrotic tissue or eschar

11. Significantly bleeding wounds, as judged by the investigator

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

13. Subject included in other ongoing clinical investigation which could interfere with this investigation, as judged by the investigator

14. Known allergy/hypersensitivity to any of the components included into the investigation.

15. Previous treatment of the target wound with acrylic film ≤ 1 week at inclusion

3.3.3 Withdrawal of Subjects from Treatment or Assessment

Subjects are free to discontinue participation in the investigation at any time, and without prejudice to further treatment. Subjects who discontinue the investigation should always be asked about the reason(s) for their discontinuation and about the presence of any AE/ADE or DD and, if possible, be assessed by an investigator. AE/ADE should be followed up.

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

Incorrectly enrolled or randomized 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).

3.4 Investigational Device

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

Treatment

System

All subjects will receive treatment with the Avance® Negative Pressure Wound Therapy System consisting of:

- Avance® Pump
- Avance® View Pad
- Avance® Foam
- Film sealant (either the **Investigational device,** Avance® Film with Safetac®Technology or the **Comparator,** Avance® Transparent film)

All medical devices are CE marked.

3.4.2 Labeling

MHC will provide the investigational medical devices to the investigation sites for free. 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.

3.4.3 Accountability

The Principal Investigator is responsible for establishing routines for correct handling of investigational medical device, to ensure that:

- The Principal Investigator or his/she's designee correctly receives deliveries of such device from MHC.
- Accurate records are maintained, accounting for the receipt of the investigational medical device (a delivery note for this purpose will be provided) and for the disposition of the device.

- Investigational medical device is to be handled and stored safely, properly and in agreement with the given storage instructions.
- The investigational medical device is to be prescribed only by the investigator or by a person authorized to do so by the Principal Investigator.
- Under no circumstances will the investigator allow the investigational device to be used for other purposes than as directed by the CIP.
- When dispensing investigational medical device to subjects, this must be noted in the accountability form investigation device per subject. Recorded information includes identification of the subject to whom the investigational medical device is dispensed, the investigational medical device and quantity dispensed, date of dispensing, and documentation of returned device (if any) from the subject. This record must be kept in the Central Site File (CSF).
- Returned and unused devices is accounted for and returned to MHC for destruction, or destroyed locally upon agreement with, and approval from MHC. All returned devices should be documented for on a specific form supplied by MHC.

3.4.4 Storage conditions

The device should be stored according to instruction for use (IFU:n).

3.4.5 Method of Assigning Subjects to Treatment Groups

The investigation is a prospective randomized, controlled open clinical investigation .All subjects who fulfil all inclusion and none of the exclusion criteria and have signed a written inform consent form will be randomized using optimal allocation (minimization) balancing for baseline variables age and type of skin (normal/dry/flaky/oily/moist). Eligible subjects will be randomized to receive Avance® Film with Safetac® Technology or Avance® Transparent film in a ratio of 1:1 provided by the electronic eCRF system (Viedoc).

The investigation center will be numbered 01 and the subject will be consecutively allocated to the treatment and given a subject code e.g. 0101,0102 etc.

3.5 Concomitant Treatments

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

3.6 Performance and Safety

3.6.1 Subject Characteristics

See Appendix C

3.6.2 Performance and Safety Measurements and Variables

Primary outcome variable:

Primary performance variable will be change in total score of Condition of peri-wound skin, the sum of scores (0-3) of redness/irritation, flaky, maceration, blistering and skin tear from baseline to last visit.

Secondary outcome variables:

Secondary performance variables will be change in the following variables from baseline to last visit:

- Redness/irritation
- Flaky
- Maceration
- Blistering
- Skin tear

Patient reported outcome (PRO)

- Pain before application
- Pain before removal of the covering film
- Pain before removal of the foam filler,
- Pain during removal of the covering film,
- Pain during removal of the foam filler
- Pain direct after removal of the covering film,
- Pain direct after removal of the foam filler

Safety

- Incidence of AE, ADE, DD, SADE and SAE
- Incidence of AE:s, ADE:s, DD:s, SADE and SAE:s leading to withdrawal

For details see Appendix C

3.6.3 Safety Measurements and Variables

AE/ADE, SAE/SADE and 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 7 of this CIP. All AE, ADE, SAE, SADE and DD must also be recorded in the appropriate section of the CRF. It is of utmost importance that all staff involved in the investigation is familiar with the content of section 7. It is the responsibility of the Principal Investigator to ensure this.

3.6.4 Anticipated ADEs

The following events have been identified as anticipated effects in the Product Risk Management Record:

- Wound dry out
- Maceration
- Infection
- Pain and discomfort
- Skin irritation
- Skin stripping
- Skin tears

The conclusion of the Product Risk Management Record is as following:
Based on this risk management record it can be concluded that for the investigational devices there are no unacceptable risks of harm for subject, the user nor third party involved in this investigation when used under normal condition.

3.7 Data Quality Assurance

3.7.1 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 (MHC) personnel will be available between visits if the investigator or other staff at the site needs information and/or advice.

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

3.7.2 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.

3.7.3 Data Management

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

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

Viedoc, a web based electronic CRF system, will be used to capture data in this investigation. The eCRF system complies with FDA Title 21 CRF part 11 (ER/ES) and the Swedish 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 help for consistency and validation of the data.
Pharma Consulting Group will support with a helpdesk function taking care of system user questions regarding Viedoc.

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

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

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

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

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

3.8 Statistical Methods and Determination of Sample Size

3.8.1 Statistical populations

ITT Population

The Intention to Treat (ITT) population will include all randomized subjects with at least one post-randomization performance measurement. The final definition of the ITT population will be made at the clean-file meeting.

Per Protocol Population

The Per Protocol (PP)-Population will include all subjects in the ITT-population without significant protocol violations. Subjects identified as protocol violators will be documented and agreed between MHC and the principal investigator at the clean-file meeting before the database lock.

Safety Population

The safety population will include all subjects with at least one treatment with at least one of the study films.

3.8.2 General statistical methodology

The design of the study is a two parallel group design. The main analyses will be a comparison between the two randomized treatments regarding change from baseline to last visit.
For comparison between the two groups Mann-Whitney U-test will be used for continuous variables, Mantel-Haenszel chi-square test for ordered categorical variables, Fisher's exact test for dichotomous variables and chi-square test for non-ordered categorical variables. For comparison of changes within groups Wilcoxon Signed Rank test will be used for continuous variables and sign test for dichotomous variables and ordered categorical variables.
Continuous variables will be described with mean, SD, median and minimum and maximum and categorical variables will be described with number and percentage.

All variables will be described per randomized treatment.
All the main performance analyses will be performed on the ITT-population. Complementary performance analyses will be performed on the PP-population.
All safety analyses will be performed on the safety population.
In the main analysis missing values will be replaced using last observation carried forward (LOCF).

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

3.8.3 Performance Analyses

Primary Performance Analysis
Primary performance analysis will be the analysis of the difference in primary performance variable, change in total score, the sum of scores (0-3) of redness/irritation, flaky, maceration, blistering and skin tear on the skin from baseline to last visit between the Avance® Film with

Safetac®Technology and Avance® Transparent film with Mann-Whitney U-test on the ITT-population at the 5% significance level.

Secondary Performance Analyses
Secondary performance analyses will be the analyses between the Avance® Film with Safetac® Technology and Avance® Transparent film of all the secondary performance variables given above in section 3.6.2 according to the statistical methods given above in section 3.8.2 General statistical methodology on both the ITT population and PP population.

3.8.4 Safety analyses

All safety variables given above in section 3.6.2 will be analyzed descriptively by treatment film on the safety population.

3.8.5 Baseline analysis

All variables measured at baseline will be summarized for the ITT population and for the PP population using appropriate descriptive statistics by randomized treatment and analyzed by treatment group according statistical methods given above in section 3.8.2 General statistical methodology

3.8.6 Statistical Analysis Plan (SAP)

Before the database is locked a statistical analysis plan (SAP) will be written and signed with all details in the statistical analyses given, together with a listing of all Tables, Figures and Listings to be produced.

3.8.7 Determination of Sample Size

In order to find a mean difference in change of primary performance variable, total sum score (0-15) of 1 unit between Avance® Film with Safetac® Technology and Avance® Transparent film with Mann-Whitney U-test test with power 80% at 5% significance level 16 evaluable subjects are needed in each group. From a pilot study the SD of the change in corresponding score (0-5) was 0.647. The SD for change in total sum score (0-15) was then estimated to be 1.94. In the sample size analysis it is assumed a correlation of 0.70 between the baseline values and last observation. In order to compensate for a drop-out rate of 5% we need to randomize 17 to each group.

3.9 Changes to the Clinical Investigation Plan

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

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

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

4. STATEMENTS OF COMPLIANCE

4.1 Ethics

4.1.1 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 before enrolment of any subject into the investigation. The Principal Investigator is responsible for informing the EC of any amendment to the investigation plan as per local requirements.

4.1.2 Ethical Conduct of the Investigation

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

4.1.3 Patient Information and Consent Form

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

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

4.2 Regulatory and standards

4.2.1 Regulatory review

Not applicable.

4.2.2 Standards and other

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

4.2.3 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 MHC and/or a CA and/or EC/IRB, require direct access to those parts of the hospital/practice records relevant to the investigation, including medical history, for verification of data. All data computerized by MHC will be identified by subject number only.

4.3 SUBJECT PROTECTION PROCEDURES

4.3.1 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.

4.3.2 Insurance

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

5. INVESTIGATION TIMETABLE AND TERMINATION

Investigation start: Q2 2016

Inclusion completed:Q4 2016

Last subject out:Q42016

The investigation could be prematurely discontinued if the dropout rate is high and/or the investigation site is unable to fulfil the inclusion period according to the Clinical Investigation Agreement.
The Sponsor, Ethics Committee or Regulatory Authority may prematurely terminate or suspend the Clinical Investigation as a whole or at an individual investigation site for significant and documented reasons. The Principal Investigator may also prematurely terminate or suspend the Clinical Investigation at his/her site, for significant and documented reasons. Reasons for premature termination or suspension by any party include, but are not limited to safety, inadequate recruitment, Principal Investigator issues, and device related problems, alignment with business strategy or administrative issues.
If suspicion of an unacceptable risk to subjects arises during the Clinical Investigation, or when instructed by an Ethics Committee or Regulatory Authority, the Sponsor shall suspend the Clinical Investigation at all active sites while the risk is assessed. The Sponsor shall terminate the Clinical Investigation if an unacceptable risk is confirmed, or resume the Clinical Investigation following appropriate communication and approval from the Ethics Committee and Regulatory Authority as required.
In terminating the clinical investigation, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subject's interests.
After the clinical investigation has been successfully completed the participating subject will continue to receive standard care according the institute's routine practice.

6. 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. Sussia, D., Danino, A., & Nikolis, A. (2011). Negative-pressure therapy versus standard wound care: a meta-analysis of randomized trials. Plastic and reconstructive surgery, 128 (5) 498 e-503e doi:10.1097/PRS.2b013e31822b675c
2. Rafter, L., Use of soft silicon based film dressing in negative pressure wound therapy. Wounds UK (2013), Volume 9; Number 4 :107-113
3. Upton, D., Andrew, A., Pain and trauma in negative wound therapy: a review. International Wound Journal 2013, March, doi:10.1111/iwj.12059

7. 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 labeling.

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

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

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

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

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

Serious Adverse Event (SAE)
Adverse Event that:

a) led to death,
b) led to a serious deterioration in the health of the subject, that either resulted in
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, or

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

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

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

Serious Adverse Device Effect (SADE)

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

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

The investigator must inform Mölnlycke Health Care (MHC), within 1 day of awareness of the event by sending the Serious Adverse Event/Serious Adverse Device Effect form by email to: Clinical_Investigations_Event_Reporting@molnlycke.com, of any SAE that occurs in the course of the investigation. All SAE have to be reported, whether or not they are considered causally related to the investigation product. When a SAE 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 and a separate report are therefore not required when eCRF is used.

Device Deficiencies that could have lead 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 and/or the Competent Authority of the SAE/SADE as per local requirements.

PROCEDURES FOR DD REPORTING

All DD needs to be reported to MHC as soon as possible, without unjustified delay. If the DD could have lead 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. The completed DD report form must be sent by email to Clinical_Investigations_Event_Reporting@molnlycke.com

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.

Causality Assessment

The investigator is required to assess the causal relationship to the investigation product for each AE/SAE according to the following classifications:

1. **Definite:**

   Event with plausible time relationship to device application

   No other explanation - current disease, concomitant drugs and/or other devices

   Response to withdrawal plausible

   Event definitive - localized, specific

   Rechallenge positive

2. **Probable:**

   Event with reasonable time relationship to device application

   No other explanation current disease, concomitant drugs and/or other devices

   Response to withdrawal clinically reasonable

   No rechallenge

3. **Possible:**

   Event with reasonable time relationship to device application

   Could also be explained by disease or other drugs and/or devices

   Information on device withdrawal lacking or unclear

   No rechallenge

4. **Unlikely:**

   Event with duration to onset that makes a relationship improbable (but not impossible)

   Diseases other drugs or devices provide plausible explanations

   Symptoms do not resolve on withdrawal

   Nature of event unrelated to action or properties of device

   No rechallenge

5. **Unable to determine**

   Event occurred but there is insufficient information

Title: CIP Amendment 02

Investigation Code	**Avance 02**	**Final Version**	**CIP Approval date**	**2015-09-11**
Amendment Final Version		**Amendment Approval date**	**2016-05-31**	

CLINICAL INVESTIGATION PLAN (CIP) Central AMENDMENT no 2

Substantial

INVESTIGATIONAL DEVICE:

Avance® Negative Pressure Wound Therapy System

INVESTIGATION TITLE:

A randomized open, controlled pilot investigation comparing trauma to the periwound skin and Pain during treatment with Avance NPWT system when using two different fixation

SITES AFFECTED BY THE AMENDMENT:

ALL

Investigation Code Avance 02 Final Version CIP Approval date 2015-09-11

Amendment Final Version Amendment Approval date 2016-05-31

THE CLINICAL INVESTIGATION PLAN (CIP) IS TO BE AMENDED AS FOLLOWS:

Section and page in the Clinical Investigation Plan:

SYNOPSIS, Section : Overall Design, Page:2

Section 3.1 Overall design and Flow Chart, page 14

From:

This pilot study will include 23-30 subjects across 1sites in Sweden to yield a total of 7-23 evaluable subjects, all subjects who has not previously been treated with NPWT and fulfill all inclusion and none of the exclusion criteria and have signed signed a written inform consent will be enrolled.

To:

This pilot study will include 23-30 subjects across 2 sites in Sweden to yield a total of 7-23 evaluable subjects, all subjects who has not previously been treated with NPWT and fulfill all inclusion and none of the exclusion criteria and have signed signed a written inform consent will be enrolled

Information och samtycke, Section: Bakgrund och syfte, Page 1

From:

Totalt kommer 32 patienter med sår som kräver vakuumassisterad sårbehandling att ingå i studien som genomförs på en klinik i Sverige och omfattar både män och kvinnor över 18 år.

To:

Totalt kommer 32 patienter med sår som kräver vakuumassisterad sårbehandling att ingå i studien som genomförs på två kliniker i Sverige och omfattar både män och kvinnor över 18 år.

REASON FOR MAKING THE AMENDMENT:

Add an additional center.

ACTIONS TO BE TAKEN:

Investigators at all centres will be provided with the amendment and their signatures will be collected.

This Amendment will be sent to the Ethic committee for approval, according to local procedures.

Investigation Code Avance 02 **Final Version** **CIP Approval date** 2015-09-11

Amendment Final Version **Amendment Approval date** 2016-12-16

CLINICAL INVESTIGATION PLAN (CIP) Central AMENDMENT no 3

Substantial

INVESTIGATIONAL DEVICE:

Avance® Negative Pressure Wound Therapy System

INVESTIGATION TITLE:

A randomized, intra-patient, open, controlled pilot investigation comparing trauma to the peri-wound skin after treatment with Avance NPWT system when using two different fixations

SITES AFFECTED BY THE AMENDMENT:

The amendment affect all in the study

THE CLINICAL INVESTIGATION PLAN (CIP) IS TO BE AMENDED AS FOLLOWS:

Section and page in the Clinical Investigation Plan:

Page 6, Synopsis, Overall Design

From:

This investigation is designed as a randomized controlled open clinical investigation. The outcome will be used to guide the manufacture to the design and implementation of a larger scale randomized study. In order to compensate for a drop-out rate of 5 %, this clinical investigation will include 17 subjects per group across two (2) sites in Sweden to yield a total of 32 evaluable subjects.

All subjects who ~~has not previously been treated with NPWT and~~ fulfill all inclusion, none of the exclusion criteria and have signed a written inform consent will be enrolled. Subjects will be randomized using optimal allocation (minimization) balancing baseline variables age and type of skin (normal/dry/flaky/oily/moist). Eligible subjects will be randomized to receive Avance® Film with Safetac® Technology or Avance® Transparent film in a ratio of 1:1 provided by the electronic eCRF system (Viedoc).

This investigation is comparing pain at dressing change and trauma and/or other changes to the peri-wound skin during treatment with Avance NPWT system when using two different fixation films, Avance® Film with Safetac® Technology or Avance® Transparent film. Since the investigation is comparing films with clear visual differences, it is not possible to blind neither the investigator nor the subject.

<u>Dressing change</u>
Dressing change will be performed at the investigation site and the frequency of dressing change will be depending on the condition of the wound and the peri-wound skin. Recommended dressing change frequency is every 48-72 hours.

A record (dressing log) will be completed for every dressing change.

<u>Investigation Visit frequency and subject participation</u>
Eligible subjects will be enrolled at the baseline visit (Visit 1), where the first dressing applications take place. From Visit 2 and onwards, one dressing application is considered as one study visit, e.g. the study visits are flexible and depending on the dressing changing frequency of the individual subject. The total treatment time for a subject may vary, depending on the wound type and condition. Each subject will be followed in the investigation for a maximum of ~~six (6)~~ dressing changes or until treatment with NPWT is no longer indicated. After termination from the investigation, subjects will be treated according to standard clinical practice at the investigation site. No additional data (except follow up information on ongoing safety events) will be collected after termination.
Subjects will be recruited at the investigation site, which have experience in managing the investigation population with NPWT and have access to a suitable number of subjects (based on historic data).

To:

This investigation is designed as a randomized controlled open clinical investigation. The outcome will be used to guide the manufacture to the design and implementation of a larger scale randomized study. In order to compensate for a drop-out rate of 5 %, this clinical investigation will include 17 subjects per group across two (2) sites in Sweden to yield a total of 32 evaluable subjects.

All subjects who fulfill all inclusion, none of the exclusion criteria and have signed a written inform consent will be enrolled. Subjects will be randomized using optimal allocation (minimization) balancing baseline variables age and type of skin (normal/dry/flaky/oily/moist). Eligible subjects will be randomized to receive Avance® Film with Safetac® Technology or Avance® Transparent film in a ratio of 1:1 provided by the electronic eCRF system (Viedoc).

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Subjects will be recruited at the investigation site, which have experience in managing the investigation population with NPWT and have access to a suitable number of subjects (based on historic data).

Page 7, Synopsis, Overall Design &

Page 16, Section:3.2, Procedures and Assessments

From:

Following variables should be considered (Appendix C):

At visit 2-~~6~~

To:

Following variables should be considered (Appendix C):
At visit 2- 4

Page 8, Synopsis, Schedule of Assessment &
Page 16, Section: 3.2.2, Scheduled of Assessment

From:

Day	Visit 1	Visit 2	Visit 3	Visit 4	~~Visit 5~~	~~Visit 6~~	Termination End of treatment
Visit (number)	1	2	3	4	~~5~~	~~6~~	Termination
Subject demography	✓						
Inclusion and Exclusion Criteria	✓						
Inform Consent	✓						
Vital Signs	✓					~~✓~~	✓
Medical and surgical history	✓						
Skin assessment	✓	✓	✓	✓	~~✓~~	~~✓~~	✓
Wound History	✓						
Randomization	✓						
Pain (VAS)	✓	✓	✓	✓	~~✓~~	~~✓~~	✓
Dressing application	✓	✓	✓	~~✓~~	~~✓~~		
Dressing removal		✓	✓	✓	~~✓~~	~~✓~~	✓
Photo	✓	✓	✓	✓	~~✓~~	~~✓~~	✓
Medication log	✓	✓	✓	✓	~~✓~~	~~✓~~	✓
AE/ADE/DD	✓	✓	✓	✓	~~✓~~	~~✓~~	✓
SAE/SADE	✓	✓	✓	✓	~~✓~~	~~✓~~	✓

To:

Day	Visit 1	Visit 2	Visit 3	Visit 4	Termination End of treatment
Visit (number)	1	2	3	4	Termination
Subject demography	✓				
Inclusion and Exclusion Criteria	✓				
Inform Consent	✓				
Vital Signs	✓				✓
Medical and surgical history	✓				
Skin assessment	✓	✓	✓	✓	✓
Wound History	✓				
Randomization	✓				
Pain (VAS)	✓	✓	✓	✓	✓
Dressing application	✓	✓	✓		
Dressing removal		✓	✓	✓	✓
Photo	✓	✓	✓	✓	✓
Medication log	✓	✓	✓	✓	✓
AE/ADE/DD	✓	✓	✓	✓	✓
SAE/SADE	✓	✓	✓	✓	✓

Page 8, Synopsis, Inclusion and Exclusion Criteria &
Page 17, Section: 3.3.1, 3.3.2, Inclusion and Exclusion criteria.

From:
Inclusion Criteria

1. Traumatic, surgical or dehisced wounds, Venous Leg Ulcer or Pressure Ulcer indicated for treatment with NPWT therapy

2. In case of multiple wounds the target wound must be ≥ 10 cm distant from other wounds. Selection of the target wound is according to the investigator's preference

3. Peri-wound skin assessable and 5 cm of peri-wound skin present around the wound

4. Male or female, 18 years of age and above

5. Signed Informed Consent

Exclusion Criteria

1. Dressing sizes does not fit the target wound
2. Unexplored blind tunnels or non-enteric fistula
3. Untreated osteomyelitis
4. Malignant wounds
5. ~~Wounds which needed extra skin protection such as Cavilon, Zink pasta, ointment, or other type of skin protections.~~
6. Subjects treated with systemic immunosuppressive or glucocorticosteroids, except subjects taking occasional doses or doses less than 10mg prednisolon/day or equivalent.
7. ~~Subjects with decreased sensation, as judged by the investigator~~
8. ~~Wounds needed, wound contact layer to protect veins and nerves~~
9. ~~Previous NPWT treatment on the target wound ≤ 3 months at inclusion~~
10. Wounds with necrotic tissue or eschar (if not adequately debrided)
11. Significantly bleeding wounds, as judged by the investigator
12. Subject not suitable for the investigation according to the investigator's judgment
13. Subject included in other ongoing clinical investigation which could interfere with this investigation, as judged by the investigator
14. Known allergy/hypersensitivity to any of the components included into the investigation.
15. ~~Previous treatment on the target wound with acrylic film ≤ 1 week at inclusion~~

To:

Inclusion Criteria

1. Traumatic, surgical or dehisced wounds, Venous Leg Ulcer, Diabetic Foot Ulcer or Pressure Ulcer indicated for treatment with NPWT therapy
2. In case of multiple wounds the target wound must be ≥ 10 cm distant from other wounds. Selection of the target wound is according to the investigator's preference
3. Peri-wound skin assessable and 5 cm of peri-wound skin present around the wound
4. Male or female, 18 years of age and above
5. Signed Informed Consent

Exclusion Criteria

1. Dressing sizes does not fit the target wound
2. Unexplored blind tunnels or non-enteric fistula
3. Untreated osteomyelitis
4. Malignant wounds
5. Subjects treated with systemic immunosuppressive or glucocorticosteroids, except subjects taking occasional doses or doses less than 10mg prednisolon/day or equivalent.
6. Wounds with necrotic tissue or eschar (if not adequately debrided)
7. Significantly bleeding wounds, as judged by the investigator
8. Subject not suitable for the investigation according to the investigator's judgment
9. Subject included in other ongoing clinical investigation which could interfere with this investigation, as judged by the investigator
10. Known allergy/hypersensitivity to any of the components included into the investigation.

Page 14, Section 2.2 Mölnlycke Investigation Personnel

From:
Tina Kjellén, Clinical Study Manager

~~Lennart Wäne, Clinical Data Manager~~

To:

Tina Kjellén, Clinical Study Manager

Henrik Ahlbom, Clinical Data Manager

Sven Anders Benjegård, Clinical Operation Manager

Page 15, Section 3.1 Overall Design and Flow Chart Synopsis

From:

This investigation is designed as a prospective, randomized controlled open clinical investigation. The outcome will be used to guide the manufacture to the design and implementation of a larger scale randomized study. In order to compensate for a drop-out rate of 5 %, this clinical investigation will include 17 subjects per group across two (2) sites in Sweden to yield a total of 32 evaluable subjects.
All subjects who has ~~not previously been treated with NPWT and~~ fulfill all inclusion and none of the exclusion criteria and have signed a written inform consent will be enrolled. Subjects will be randomized using optimal allocation (minimization) balancing for baseline variables age and type of skin (normal/dry/flaky/oily/moist). Eligible subjects will be randomized to receive Avance® Film with Safetac® Technology or Avance® Transparent film in a ratio of 1:1 provided by the electronic eCRF system (Viedoc).

An evaluable subject is defined as a subject that is enrolled and has data for at least one visit after baseline visit.
The target populations are male or female, 18 years and above, which have exuding wounds indicated for treatment with NPWT therapy. ~~The subject should not previously been treated with NPWT, previous treatment, may have an bias on the skin evaluation.~~
The study visits are flexible and depending on the dressing changing frequency of the individual subject. The total treatment time for each subject may vary depending on the wound type and condition of the wound. Each subject will be followed for a maximum of ~~six (6)~~ dressing-changes or until treatment with NPWT is no longer indicated (withdrawal criterion). After termination from the investigation, subjects will, if necessary, be treated according to standard clinical practice at the investigation site. No additional data (except for follow up information on ongoing safety events) will be collected after termination.

To:

This investigation is designed as a prospective, randomized controlled open clinical investigation. The outcome will be used to guide the manufacture to the design and implementation of a larger scale randomized study. In order to compensate for a drop-out rate of 5 %, this clinical investigation will include 17 subjects per group across two (2) sites in Sweden to yield a total of 32 evaluable subjects.
All subjects who has fulfill all inclusion and none of the exclusion criteria and have signed a written inform consent will be enrolled. Subjects will be randomized using optimal allocation (minimization) balancing for baseline variables age and type of skin (normal/dry/flaky/oily/moist). Eligible subjects will be randomized to receive Avance® Film with Safetac® Technology or Avance® Transparent film in a ratio of 1:1 provided by the electronic eCRF system (Viedoc).
An evaluable subject is defined as a subject that is enrolled and has data for at least one visit after baseline visit.
The target populations are male or female, 18 years and above, which have exuding wounds indicated for treatment with NPWT therapy.
The study visits are flexible and depending on the dressing changing frequency of the individual subject. The total treatment time for each subject may vary depending on the wound type and condition of the wound. Each subject will be followed for a maximum of four (4) dressing changes or until treatment with NPWT is no longer indicated (withdrawal criterion). After termination from the investigation, subjects will, if necessary, be treated according to standard clinical practice at the investigation site. No additional data (except for follow up information on ongoing safety events) will be collected after termination.

Page 26, Section 5, Investigation Timetable and Termination

From:

Investigation start: ~~Q2~~2016

Inclusion completed: ~~Q4 2016~~
Last subject out: ~~Q4 2016~~

To:

Investigation start: Q3 2016

Inclusion completed: Q3 2017
Last subject out: Q3 2017

REASON FOR MAKING THE AMENDMENT:

The reason to add one inclusion criteria, and removing five exclusion criteria's are to be more align with the majority of the patients group, who are visiting the two participated sites. Participated sites are located in the northern region of Sweden with a large, patient uptake area. The majority of the patients are elderly and have long way to travel to the hospital by decreasing the number of visits from 6 to 4, will this lead to a decreased traveling for the potential study patients. This will hopefully do it easier for the clinics to include patients to the study. We have considered that the update will not lead to any bias.

ACTIONS TO BE TAKEN:

Investigator at the sites will be provided with the amendment and signatures will be collected.

The Amendment will be sent to the Ethic committee for approval according to local procedures.