Lohmann & Rauscher GmbH & Co.KG

The SLALOM Study

CLINICAL INVESTIGATION PLAN

Version 2.0

March 29, 2019

1 CLINICAL INVESTIGATION PLAN

Title : Comparative evaluation of the propertie**S** of the contact **LA**yer dressing **LOM**atuell Pro® versus UrgoTul® in the management of acute wounds

Short Title: SLALOM Study

Study Code: LR/RCTs/01_2017

Study design: Randomized, multicentric, parallel groups study, "Etude interventionnelle à risques minimes" according to French Regulation and non-inferiority study (main efficacy criterion: pain level at first dressing removal), ISO EN DIN 14155, MDD 93/42/EEC

Studied products: Contact layer dressings (Lomatuell Pro® and UrgoTul®). Class IIb medical devices.

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Table of contents

Table of illustrations

3 ABBREVIATIONS

AE	Adverse event
ADE	Adverse device effect
CI	Confidence interval
CIP	Clinical Investigational Plan
CL	Contact layer
CMC	Carboxymethylcellulose
CRF	Case Report Form
DD	Device deficiency
ET	Early Termination
HAS	Haute Autorité de Santé
ITT	Intent-to-treat
PDMS	Polydimethylsiloxane
PP	Per-protocol
PWS	Periwound skin
VAS	Visual analogue Scale
W.H.A.T.	Wound Healing Analysing Tool

4 STUDY SYNOPSIS

Title	Comparative evaluation of the propertieS of the contact LAyer dressing LOMatuell Pro® versus UrgoTul® in the management of acute wounds
Project Code/Number	LR/RCTs/01_2017 - 251
Version and Date	Version 2.0 – March 29, 2019
Name of Sponsor	Lohmann & Rauscher GmbH Co. KG
Device Description	Contact layer dressings (Lomatuell Pro® and UrgoTul®). Class IIb medical devices.
Intended Use	Lomatuell Pro® is intended to be used as a wound dressing for acute wounds according to "Etudes interventionnelles à risques minimes" in French regulation.
Study design	National, multicenter, prospective, randomized in parallel groups, non-inferiority, open-label investigation study.
• Study Objectives	• Main study objective • To document the non-inferiority of Lomatuell Pro® versus UrgoTul® on pain induced at first dressing removal in the management of acute wounds. • Secondary objectives • To compare between the two dressings: • Complete healing at day 21 • Condition of the wound (e.g. wound shift supporting moist wound healing during treatment) • Condition of the surrounding skin and efficiency of the CL to drain exudates (exudate management) • Global satisfaction of user • Subjects' global assessment • Safety
Inclusion criteria	• Acute wound: traumatic wound (dermabrasion, skin tears, other), small burns 1st and 2nd degree, requiring the use of dressings • Acute surgical wound • Acute wound size between 3 cm^2 and 24 cm^2 (wound could be covered by 2 investigational products maximum) • Wound whose duration is ≤ 3 days

	• Both gender with an age ≥ 18 years • Written confirmation from the study nurse that the patient was informed, orally agreed to participate and to comply with study treatment and planned visits • Subject able to follow the protocol
Exclusion criteria	• Infected, moderately to strongly exudative and haemorrhagic wound • Diagnosed underlying disease (e.g. diabetic neuropathy, stroke, etc.) which as judged by the investigator could interfere with the pain assessment • Known allergy/hypersensitivity to any of the components of the investigational products • Participation in other clinical investigation within one month prior to start of investigation • Pregnant or breast-feeding women • Person protected by a legal regime (tutorship or guardianship) • Patients unable to manifest an oral consent to participate (e.g. dementia) or to understand the use of the VAS tool • Patient not covered by health insurance/social security
Study Duration	24 months
Number of patients	168 patients (i.e. 84 per group)
Treatment duration and visits schedule	3 weeks: V1 (D0), V2 (D3±2) and V3 (D21+2 or earlier, as soon as the wound is epithelialized completely)
Endpoints	**Primary endpoint:** Percentage of wound dressing changes associated with a pain <30 mm on VAS at V2 (D3±2). **Secondary endpoint** • Complete healing at V3 (Day D21+2 or earlier, as soon as the wound is epithelialized completely): Percentage of epithelialization of the wound at V3 calculated based on a blind assessment from photographs using W.H.A.T. assessment • Condition of the wound: evaluation by the investigator of 6 condition items at V2 and V3 or Early Termination (ET): bleeding, inflammation, infection, maceration, ratio necrotic/ fibrinous /granulation/ epithelisation tissue, and tissue in-growth in the dressing holes

	• Condition of the surrounding skin and efficiency of the CL to drain exudates: assessment at V2 and V3 or ET regarding different conditions: inflammatory signs, irritation, allergic rash/eczema, blistering, skin stripping, maceration, dry, trauma to wound edges, product degradation on the skin and hematoma. • Global assessment of exudate management (efficiency of the CL to drain exudates to the secondary dressing) • Global assessment of the product will be performed by the investigator at V2 and V3 or ET by means of a specific questionnaire • Patient's global assessment of the product will be performed by the patient at V3 or ET by means of a specific questionnaire • Assessments from study nurse's booklet (at each dressing change) • Safety endpoint: frequency and character of device deficiencies (DDs), adverse events (AEs), serious adverse events (SAEs), adverse device effects (ADEs), serious adverse device effects (SADEs)
Participating Centers	100 study nurses will participate
Criteria for Early Study Termination	Patients may terminate participation in the study due to following reasons: • Consent withdrawal Identification of unacceptable risks, or incidents leading to an unacceptable benefit-risk assessment • Premature termination of the investigation decided by the Sponsor • Lost to follow-up • Occurrence or development of a condition described in the exclusion criteria (i.e. pregnancy, wound infection) throughout the investigation • Death
Ethical considerations	This protocol will be submitted to an Ethical Committee

5 STUDY RATIONALE

Contact layer (CL) dressings are primary dressings mainly adapted to the management of most non-complicated acute wounds or of chronic wounds at the proliferative stage. While numerous types of CL dressings are available, they all share a common basic structure composed of a thin non- or low-adherent layer which is impregnated with various compounds according to manufacturers. Their main objective is to protect the granulation tissue growth and re-epithelialization from external stresses in order to promote a smooth tissue repair process. They are furthermore expected to limit peri-wound skin irritation and, while not appropriate to manage strong exudation, to favor drainage of excessive wound fluids toward a secondary absorbent dressing which can be simple gauzes. In addition, CL dressings changes should be atraumatic for the viable tissue and as painless as possible.

This latter point was the main limitation of the first available CL dressings which were composed of a simple nylon or polyester layers impregnated with petrolatum or paraffin [1]. If left in place over 3-4 days or more, the compound impregnating the layer was absorbed by the secondary dressing and to a less extent by the wound bed itself [2]. The consequence was a drying of the dressing which then will adhere to the wound and to the skin around. Dressing removal was therefore frequently rather painful and might injured viable underlying tissues. Another disadvantage was that the meshes of the layer could be too large with a growth of granulation tissue through the mesh increasing possible risk of wound injury at removal.

One of the main technical developments that allowed limiting this possible problem, was the use of a mixture of carboxymethylcellulose (CMC) particles combined with lipidic particles. This mixture, when applied onto wound bed, makes a gel which will favour atraumatic removal and, on the other hand, will improve fluid management via the CMC water-absorbing properties. A largely used representative of this approach is represented by the UrgoTul® dressing [3, 4].

The Lomatuell Pro® dressing belongs to this category of CL and is rather similar to UrgoTul®. It might have additional useful properties such as a better conformability to wound and peri-wind anatomical shapes and it might help in regulating wound moisture (in particular of dry wounds) and prevent risk of maceration.

Due to the lack of controlled trials comparing these dressings, the choice by health professionals is primarily based on empirical evidences and personal experiences [5].

For these reasons, the main purpose of this study was to compare Lomatuell Pro® to UrgoTul® in order to confirm the non-inferiority on pain induced by dressing removal when managing acute wounds, an important clinical problem in daily care [6, 7]. This parameter reflects the potential of a dressing to become adherent to wound bed and is a major issue for French Health Authorities to provide reimbursement for this group of dressings [8].

6 STUDY OBJECTIVES

6.1 Main study objective

To document the non-inferiority of Lomatuell Pro® versus UrgoTul® on pain induced at first dressing removal in the management of acute wounds.

6.2 Secondary study objectives

To compare between the two dressings:

- Complete healing at day 21
- Condition of the wound at study end: overall and according to moisture status at inclusion (e.g. wound shift supporting moist wound healing during treatment)
- Condition of the surrounding skin and efficiency of the CL to drain exudates (exudate management)
- Global satisfaction of user
- Subjects' global assessment
- Safety

7 INVESTIGATION PLAN AND PROCEDURES

7.1 Overall Design and Flow Chart

This will be a national, multicenter, prospective, randomized in parallel groups, non-inferiority, open-label investigation conducted in France.

Approximately 100 study nurses are planned to participate in the investigation in order to enrol 168 subjects (i.e. 84 per group).

The subjects will be seen for maximum 21 (+2) days and will be followed by their investigator at 3 investigational visits (V): V1 at D0, V2 at D3±2 days and V3 at D21+2 days or earlier, as soon as the wound is epithelialized completely. In case the wound will not fully epithelialized within 23 days or the patient will preliminary discontinue the study treatment for any reason, he or she will receive further treatment of the investigators' choosing according to the actual wound condition and the national standards of care.

Between V2 and V3, additional dressing changes can be performed as often as necessary according to the instruction for use of the investigational product assigned. Lomatuell Pro® and UrgoTul® may be left in place up to 7 days.

7.2 Procedures and Assessments

7.2.1 Schedule of Assessments

All assessments of the investigation will be conducted as indicated in the following table which displays the frequency and timing of all measurements.

Table 1. Data collection schedule

	Inclusion visit	**Intermediate visit**	**Additional visits***	**Final visit**	**Early Termination visit****
Visit name (corresponding day)	V1 (D0)	V2 (D3±2)	Between V2 and V3	V3 (D21+2 or earlier, as soon as the wound is epithelialized completely)	ET
Oral consent of the patient to participate	☒				
Inclusion/exclusion criteria	☒				
Randomization	☒				
Demographics	☒				
Medical history	☒				
Wound/surrounding skin characteristics	☒	☒	☒	☒	☒
Investigational product application	☒	☒	☒		
Secondary dressing / fixation use	☒	☒	☒		
Dressing removal *(to follow the standardized removal procedure)*		☒	☒	☒	☒
Intake of analgesics	☒	☒		☒	☒
Pain assessment (VAS) after application of investigational product	☒				
Pain assessment (VAS) during removal		☒			

Amount of exudate	☒	☒	☒	☒	☒
Wound shift (ratio necrotic/ fibrinous/ granulation/ epithelisation tissue)	☒	☒		☒	☒
Complete healing assessment		☒	☒	☒	☒
Wound photograph	☒	☒		☒	☒
Photograph of the investigational product on the wound***	☒	☒		☒	☒
Adverse events/Adverse device effects	☒	☒		☒	☒
Global dressing investigator evaluation		☒		☒	☒
Global dressing subject's evaluation				☒	☒
Concomitant treatment	☒	☒		☒	☒
* optional, if required by wound's condition ** will be performed for the patients who discontinued the study preliminary for any reason, instead of the visit V3 ***after application of the product at V1, before removal of the product and after application of a new product at V2, before removal of the product at V3 or Early termination visit					

7.2.2 Investigation Procedures

7.2.2.1 Inclusion visit (V1, D0)

At the inclusion visit (V1, D0) the subject will receive complete information related to the investigation. Prior to any assessment, the oral consent of the patient to participate, according to the "Etudes interventionnelles à risques minimes" French regulations, will have to be obtained by the investigator. Inclusion and exclusion criteria will be checked by the investigator.

The subject will be consecutively allocated to a subject code providing they fulfil all inclusion and none of the exclusion criteria. The subject will be randomized to either receive Lomatuell Pro® or UrgoTul®.

The investigator will report the date of visit, and collect subject information in the case report form (CRF) such as demographic characteristics (gender, age, height, weight), significant medical history including the presence and type of disease which could interfere with the evolution of healing, concomitant therapy, intake of analgesics, characteristics of wound (type and duration of the wound, location, size, assessment of the wound bed (bleeding, maceration, inflammation, infection, ratio necrotic/ fibrinous/ granulation/ epithelisation tissue, and tissue in-growth in the dressing holes) and condition of the surrounding skin (inflammatory signs, irritation, allergic rash/eczema, blistering, skin stripping, maceration, dry, trauma to wound edges, product degradation on the skin, hematoma). Assessment of the amount of exudate (drainage) will be performed after removal of the dressing and before wound cleansing and it will be categorized as none, light, moderate, or heavy.

If applicable, the previous treatment or dressing used will be reported in the CRF. The investigator will also interview the subject about the use of analgesics since the wound occurrence including the frequency of use. These data will be reported in the appropriate form of the CRF.

The wound (with a millimetre ruler) will be photographed by the investigator before the first investigational product application according to the photography guidelines (*see Appendix*

17.1). A digital camera could be provided to the investigator participating in the investigation in case his/her camera does not meet the level of quality required to analyse wound on photographs or if they do not have any camera.

The investigator will apply the allocated investigational product on the wound. If required, 2 investigational products can be used to cover the wound.

A photograph of the wound with the investigational product in place (before the secondary dressing application) will be taken after dressing application according to the photography guidelines.

A secondary dressing could be applied over the investigational product. The type used will be indicated in the CRF by the investigator. The dressing confection will have to follow the condition mentioned in the protocol in section 7.5.

The pain after dressing application will be assessed by using the visual analogue scale (VAS). The investigator will ask the subject to assess his/her pain level during the care of his/her wound. The subject will be asked to rate the pain he/she felt using a VAS tool.

A specific ruler will be provided to the investigator in order to measure the VAS score. The subject will mark on the ruler the point that he/she feels represent his/her perception of his/her current pain. The VAS score will be directly measured by the investigator with a scale in millimetres. The VAS score will be filled in the CRF.

Adverse events (AEs) / Serious adverse events (SAEs) / Adverse device effects (ADEs) and Device deficiencies (DDs) occurring at/since the first application of the investigational product will be collected by the investigator. The investigator will also ensure that the subject continue the investigation.

The next visit (V2) will be scheduled with the subject three days after the inclusion visit at D3 (± 2 days).

7.2.2.2 Intermediate visit (V2, D3±2)

The intermediate visit must be planned three days after the first investigational product application. If appropriate, a window of two days before or after this expected visit is allowed to make sure that the patient will have the first dressing change as early as necessary according to their condition (i.e. already on the next day after V1).

Adverse events (AEs) / Serious adverse events (SAEs) / Adverse device effects (ADEs) and Device deficiencies (DDs) occurring since the previous visit will be collected by the investigator. Any changes to the concomitant therapy will also be collected. The investigator will also ensure that the subject continue the investigation.
The presence of complete healing status (100% of epithelialization, first epithelia layer) of the wound) will be assessed.
NB! In case of complete epithelialization all procedures, required for Visit 3 should be

performed, data is to be recorded in the CRF section Visit 3. Visit 2 should be marked as "Not performed due to early epithelialization" in the CRF.

Depending on the subject condition, analgesics may be concomitantly prescribed by the investigator. In this case, details on the type of prescribed treatments belonging to analgesic therapeutic class as well as hour of intake before removal (within 2 hours notably) will be recorded in the CRF.

A photograph of the wound with the investigational product in place will be taken before product removal (but after secondary dressing removal, if there was any), according to the photography guidelines *(see Appendix 17.1).*

The investigator will remove the investigational product by following the standardized removal procedure (*see Appendix 17.2*). Data about dressing soak will be collected in the CRF.

Pain at the first dressing removal will be assessed by using the visual analogue scale (VAS). The investigator will ask the subject to assess his/her pain level at the dressing removal. The subject will be asked to rate the pain he/she felt at the moment of dressing change using the VAS tool.

After product removal, a photograph of the wound will be taken according to the photography guidelines.

The investigator will assess the wound and surrounding skin condition:

- Wound size estimation
- Assessment of the wound bed (bleeding, maceration, inflammation, infection, ratio necrotic/ fibrinous/ granulation/ epithelisation tissue, and tissue in-growth in the dressing holes)
- Assessment of the surrounding skin (inflammatory signs, irritation, allergic rash/eczema, blistering, skin stripping, maceration, dry, trauma to wound edges, product degradation on the skin, hematoma)
- Global assessment of exudate management (efficiency of the CL to drain exudates to the secondary dressing)

The investigator will evaluate the use of the dressing regarding the following parameters:

- Ease of handling
- Ability to maintain its integrity
- Ease of application
- Ability to be repositioned during application
- Conformability
- Wound adhesion

- Ability of dressings to stay in place
- Transparency
- Ease / speed of removal,
- Overall impression,
- Absence of residue

The investigator will apply the allocated investigational product on the wound. If required, 2 investigational products can be used to cover the wound.

A photograph of the wound with the investigational product in place (before the secondary dressing application) will be taken after dressing application according to the photography guidelines.

A secondary dressing could be applied over the investigational product. The type used will be indicated in the CRF by the investigator. The dressing confection will have to follow the condition mentioned in the protocol in section 7.5.

7.2.2.3 Last visit (V3, D21+2 or earlier, as soon as the wound is epithelialized completely)

The last visit must be planned in 21 (+2) days after the first investigational product application (V1, D0), unless the wound is epithelized (one epithelial layer) earlier. In this case the visit should be scheduled shortly after the epithelialization (but not later as in 23 days after the first investigational product application).

Adverse events (AEs) / Serious adverse events (SAEs) / Adverse device effects (ADEs) and Device deficiencies (DDs) occurring since the previous visit will be collected by the investigator. Any changes to the concomitant therapy will also be collected.

Depending on the subject condition, analgesics may be concomitantly prescribed by the investigator. In this case, details on the type of prescribed treatments belonging to analgesic therapeutic class as well as hour of intake before removal (within 2 hours notably) will be recorded in the CRF.

A photograph of the wound with the investigational product in place will be taken before the investigational product removal (but after secondary dressing removal, if there was any), according to the photography guidelines *(see Appendix 17.1).*

The investigator will remove the investigational product by following the standardized removal procedure (*see Appendix 17.2*). Data about dressing soak will be collected in the CRF.

After product removal, a photograph of the wound will be taken according to the photography guidelines.

The investigator will assess the wound and surrounding skin condition:

- Wound size estimation
- Assessment of the wound bed (bleeding, maceration, inflammation, infection, ratio necrotic/ fibrinous/ granulation/epithelisation tissue, and tissue in-growth in the dressing holes)
- Assessment of the surrounding skin (inflammatory signs, irritation, allergic rash/eczema, blistering, skin stripping, maceration, dry, trauma to wound edges, product degradation on the skin, hematoma)
- Global assessment of exudate management (efficiency of the CL to drain exudates to the secondary dressing)

The presence of complete healing status (100% of epithelialization, first epithelia layer) of the wound) will be assessed.

The investigator will evaluate the use of the dressing regarding the following parameters:

- Ease of handling
- Ability to maintain its integrity
- Ease of application
- Ability to be repositioned during application
- Conformability
- Wound adhesion
- Ability of dressings to stay in place
- Transparency
- Ease / speed of removal,
- Overall impression,
- Absence of residue

The global assessment of the product by the patient will also be performed.

7.2.2.4 Additional visits

Between V2 and V3, additional dressing changes can be performed as often as necessary according to the instruction for use of the investigational product assigned. Lomatuell Pro® and UrgoTul® may be left in place up to 7 days. In this case, the data collected during these "in-between" visits will be collected in the Nurse Diary.

Data collected during these visits are:

- Number of the additional visit
- Date of the visit
- Reason for dressing change

- Presence of complete re-epithelialization (**NB!** In case of complete epithelialization all procedures, required for Visit 3 should be performed, data is to be recorded in the CRF section Visit 3 and not as an additional visit)
- Appearance of the dressing before removal
- Bleeding during dressing removal
- Appearance of the wound bed (bleeding, maceration, inflammation, infection, and tissue in-growth in the dressing holes)
- Appearance of the surrounding skin (inflammatory signs, irritation, allergic rash/eczema, blistering, skin stripping, maceration, dry, trauma to wound edges, product degradation on the skin, hematoma)
- Amount of exudate
- Wound moisture
- Local treatment
- Number of dressings used
- Application of dressing
- Secondary dressing
- Initials of person in charge for dressing change

7.2.2.5 Early termination visit

This visit will be registered for the patients who discontinued the study preliminary for any reason, including consent withdrawal, loss to FU or death, instead of the visit V3, and the list of the procedures should be if, to the extent possible, the same as for V3.
In case of consent withdrawal / lost to FU date of the patient's / nurse's decision to discontinue study participation should be entered in the CRF as the date of "early termination" visit with all other fields marked as NA. In case of patient's death date of the death should be entered as the date of this visit with all other fields marked as NA.

For the patient, who voluntary discontinued the treatment, Adverse events (AEs) / Serious adverse events (SAEs) / Adverse device effects (ADEs) and Device deficiencies (DDs) occurring since the previous visit should also be collected by the investigator, if patient agrees to provide this information. Any changes to the concomitant therapy should also be collected.

If the reason of the early termination is not: withdrawal of consent, patient lost to follow-up or death (cf §7.3.3); then the following data should be collected as possible:

- Depending on the subject condition, analgesics may be concomitantly prescribed by the investigator. In this case, details on the type of prescribed treatments belonging to analgesic therapeutic class as well as hour of intake before removal (within 2 hours notably) will be recorded in the CRF.

- A photograph of the wound with the investigational product in place will be taken before the investigational product removal (but after secondary dressing removal, if there was any), according to the photography guidelines *(see Appendix 17.1).*

- The investigator will remove the investigational product by following the standardized removal procedure (*see Appendix 17.2*). Data about dressing soak will be collected in the CRF.

- After product removal, a photograph of the wound will be taken according to the photography guidelines.

- The investigator will assess the wound and surrounding skin condition:
    - Wound size estimation
    - Assessment of the wound bed (bleeding, maceration, inflammation, infection, ratio necrotic/ fibrinous/ granulation/epithelisation tissue, and tissue in-growth in the dressing holes)
    - Assessment of the surrounding skin (inflammatory signs, irritation, allergic rash/eczema, blistering, skin stripping, maceration, dry, trauma to wound edges, product degradation on the skin, hematoma)
    - Global assessment of exudate management (efficiency of the CL to drain exudates to the secondary dressing)

- The presence of complete healing status (100% of epithelialization, first epithelia layer) of the wound) will be assessed.

- The investigator will evaluate the use of the dressing regarding the following parameters:
    - Ease of handling
    - Ability to maintain its integrity
    - Ease of application
    - Ability to be repositioned during application
    - Conformability
    - Wound adhesion
    - Ability of dressings to stay in place
    - Transparency
    - Ease / speed of removal,
    - Overall impression,
    - Absence of residue

- The global assessment of the product by the patient will also be performed.

7.3 Selection of population for investigation

7.3.1 Inclusion Criteria

Subjects must meet all criteria listed below to be included in the investigation:

1. Acute wound: traumatic wound (dermabrasion, skin tears, other), small burns 1st and 2nd degree requiring the use of dressings
2. Acute surgical wound
3. Acute wound size between 3 cm² and 24 cm² (wound could be covered by 2 investigational products maximum)
4. Wound whose duration is ≤ 3 days
5. Both gender with an age ≥ 18 years
6. Written confirmation from the study nurse that the patient was informed, orally agreed to participate and to comply with study treatment and planned visits
7. Subject able to follow the protocol

7.3.2 Exclusion Criteria

A subject will be excluded from the investigation if he/she meets any of the following criteria:

1. Infected, moderately to strongly exudative and haemorrhagic wound
2. Diagnosed underlying disease (e.g. diabetic neuropathy, stroke, etc) which as judged by the investigator could interfere with the pain assessment
3. Known allergy/hypersensitivity to any of the components of the investigational products
4. Participation in other clinical investigation within one month prior to start of investigation
5. Pregnant or breast-feeding women
6. Person protected by a legal regime (tutorship or guardianship)
7. Patients unable to manifest an oral consent to participate (e.g. dementia) or to understand the use of the VAS tool.
8. Patient not covered by health insurance/social security

Definitions:

Acute wound: wound without any local or general factor that could delay healing (unlike chronic wound). *For this investigation, only acute wound with a skin barrier break with loss of dermis will be included.*

Dermabrasion: skin lesions of traumatic origin (superficial abrasion) caused by tangential friction forces at the surface of the epidermis and the dermis.

Skin tears: traumatic injuries which can result in partial or full separation of the outer layers of the skin. These tears may occur due to shearing and friction forces or a blunt trauma, causing the epidermis to separate from the dermis (partial thickness wound) or both the epidermis and the dermis to separate from the underlying structures (full-thickness wound).

Burn: small burns of the 1st degree and light 2nd degree; dynamic injuries induced by traumatic destruction of the skin < 10%.
First degree burn and second degree superficial burn without any severity factor (as age > 60 years, vital/functional location, associated lesion, previous injuries/illnesses) are considered as benign burn.
For this investigation, only burn induced by a thermal process will be included.

7.3.3 Early Termination/ Withdrawal of subjects from treatment or assessment

Patients are free to withdraw from participation in the study at any time upon request and without any disadvantages for their further care.

An investigator may discontinue a patient from the study for the following reasons:

- The identification of unacceptable risks, or incidents leading to an unacceptable benefit-risk assessment
- Premature termination of the investigation decided by the Sponsor
- Lost to follow-up
- Occurrence or development of a condition described in the exclusion criteria (i.e. pregnancy, infection of the wound) throughout the investigation
- Death

The reason for patient discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF) in the early termination visit.

Subjects who discontinue the investigation should always be asked about the presence of any Adverse Events/Adverse Device Effects or Device Deficiencies and, if possible, be assessed by the investigator as per the list of the Early termination visit procedures. Serious Adverse Events/Adverse Device Effects should be followed up until the resolution of the event.

7.4 Investigational device

7.4.1 Description of Lomatuell Pro®

Lomatuell Pro® is a wound contact layer consisting of wide-meshed tulle, impregnated with a polymer matrix, which form a gel on contact with wound exudate to facilitate moist wound healing.

It offers a solution to the challenge of dressings/residue sticking to the wound or wound, which may cause pain and trauma on removal.

Key benefits

• Gel formation supports moist wound healing

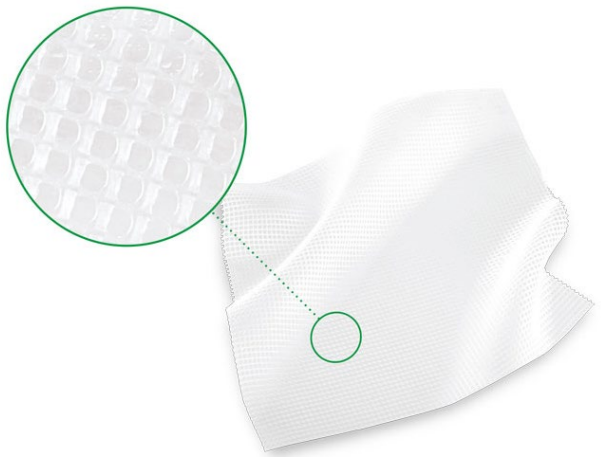
• Dressing changes are atraumatic and virtually painless

• Effective transfer of exudate into the secondary dressing

• Less disturbance of the wound bed: intervals between dressing changes may be extended

• Conforms well to the contours of the wound bed, meaning all the areas benefit from the moist properties

• Either side can be applied, eliminating concerns over incorrect application



Indications:

Wounds with no or low levels of exudate, or combined with an appropriate absorbant dressing for moderate to highly exuding wounds including:

- Chronic wounds e.g. leg ulcers, diabetic ulcers and pressure ulcers

- Acute wounds e.g. lacerations, cuts, abrasions and superficial epidermal and partial thickness burns

- Surgical wounds e.g. surgical wounds healing by secondary intention, toenail avulsions and skin graft and donor sites

Precautions:

Do not use if there is a known sensitivity to the product or any of its components

Wear time:

Average 2 to 4 days, and up to 7 days. Intervals between dressing changes must be determined by the clinician based on the condition of the wound, level of exudate and secondary dressing.

7.4.2 UrgoTul®

UrgoTul® is a flexible contact layer with TLC healing matrix comprised of a conformable polyester mesh impregnated with hydrocolloid and petroleum jelly particles.

Indications:

UrgoTul® is indicated for the treatment of non to low exuding wounds in the epithelialisation stage (burns, abrasions, traumatic wounds, post-operative wounds, leg ulcers, pressure ulcers, diabetic foot ulcers, epidermolysis bullosa).

Mode of action:

When in contact with wound exudate, UrgoTul® gels and creates a moist environment, promoting healing. UrgoTul® stimulates fibroblast proliferation and ensures non-adherence and pain-free dressing changes.

Wear time:

UrgoTul® should be changed every 2 to 4 days (up to 7 days) depending on the level of exudate and the clinical condition of the wound.

7.5 Secondary dressings and fixation

A secondary dressing could be applied on the investigational product. In case of exuding wound, secondary dressing should be applied. Investigational products could be used as protective layer only if the wound is not exuding.

List of possible secondary dressings and fixation (as an example):

Secondary dressings

- Hydrocolloid dressings

- Foam dressings
- Dry dressings with or without adhesive border (like Vliwasorb or Vliwazell, gauze)

Wound filler (if necessary)

- Alginate dressings
- Hydrofiber (CMC) dressings

Fixation

- Compresses
- Form dressings

7.6 Concomitant Treatment

All 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).

For analgesic treatment all data including type of analgesic, frequency of use before wound treatment (at D0 only) and hour of intake before dressing removal must be recorded in the appropriate form of the CRF.

7.7 Evaluation by W.H.A.T

The evaluation by the W.H.A.T. system will be performed by Lohmann & Rauscher with the photographs sent by RCTs on USB Keys.

For determination of the size of the wound area and recording of occurrence of necrotic/ fibrinous/ granulation/ epithelisation tissue the validated Wound Healing Analysing Tool (W.H.A.T.) will be used. The wound dressing should be removed from the lesion. The wound should be cleaned with isotonic saline solution and the rest of remedies should be removed. After cleaning the ruler must be placed close to the wound. To achieve a correct picture, the ruler with the square mark had to be placed in the same plane as the lesion. In the case the wound was not plane the ruler has to be applied in the same shape to allow an authenticable digital reproduction of the wound. One digital picture of the lesion will be taken at each visit (in total three pictures of the lesion for each patient for the whole duration of the study); a minimal resolution of 3.0 million pixels is required.

Also, four digital pictures of the investigational product on the wound should be taken during the study (two photographs will be taken after investigational product application before the secondary dressing application on V1 and V2, and two pictures of the wound with the investigational product in place will be taken before the investigational product removal at both visits V2 and V3 (or Early termination visit, if performed instead of V3).

Table 2. Photographs schedule

	Inclusion visit (V1)	Intermediate visit (V2)	Additional visits	Final visit, or earlier if epithelization (V3)	Early termination visit (whenever possible)
Picture of the wound with the investigational product in place before the investigational product removal (but after removing the secondary dressing)		x		x	x
Picture of the lesion (after cleaning)	x	x		x	x
Picture after investigational product application before the secondary dressing application	x	x			

The pictures should be saved on a USB Key and sent to Lohmann & Rauscher for assessment. Two shipments of the study pictures are planned:

- first shipment should be performed shortly after the V1 of the first patient at each site; this data will additionally serve for the quality assessment of the photos, performed by the particular site. If necessary, additional training for the nurse will be organised. (NB! No quality confirmation is to be awaited from L & R team; further pictures may be taken as soon as planned, study nurse will be contacted only in case of quality issues).
- all remaining pictures for the first site patient and all other patients should be sent after LPLV at the site.

For processing the pictures will be loaded on a personal computer, and evaluated by W.H.A.T. (Wild et al., 2008).

The pictures should be performed only on the study wound and there should be no possibility to identify the patient. While saving the pictures on the PC and USB Key, the investigator should make sure that the files' names do not contain any sensible information like patient's name or other personal data. Only patient's number, study timeline and date of the photo could be used for the authentication.

7.8 Efficacy and Safety

7.8.1 Subject Characteristics

- Demographic Data
- Medical History
- Wound and surrounding skin characteristics
- Secondary dressing and fixation characteristics

7.8.2 Efficacy Measurements and Variables

7.8.2.1 Main Objective

Variable

The main criterion corresponds to the percentage of non-painful dressing removals defined as the percentage of dressing removals associated with a value < 30 mm on a VAS assessing pain scale (0 to 100 millimeters) evaluated at the first dressing removal (V2, D3±2).
This 30 mm threshold is recognized to differentiate a weak pain (score <30 mm) from a moderate (score ≥30 mm) to severe (score >50 mm) one [9-12].

Measurement

Subjects will be asked by investigators to rate their pain intensity perceived at the first dressing removal (V2, D3±2). Pain assessment will be performed using a Visual Analog Scale (VAS). The VAS is a 100 mm straight line ranging from 0 to 100, on which the subject will indicate his/her pain. Subjects will beforehand be informed that the beginning of the scale refers to "no pain" (0) and the end to the most severe intensity of pain they can have (100). Painless dressing change is defined as pain < 30 mm on the VAS. The results obtained during the first dressing removal visit (V2, D3±2) will be filled in by the investigator in the CRF.

7.8.2.2 Secondary Objectives

Variables

Secondary efficacy criteria will be as follows:

- Complete healing at V3 (D21+2 or earlier, as soon as the wound is epithelialized completely).
- Wound condition assessment at V2 and V3 or ET
- Surrounding skin condition assessment at V2 and V3 or ET
- Global assessment of the dressing by the investigator at V2 and V3 or ET
- Global assessment of exudate management (efficiency of the CL to drain exudates to the secondary dressing)
- Global assessment of the dressing by the subject at V3 or ET
- Assessments from study nurse's booklet (at each dressing change)
- Adverse events (AEs), serious adverse events (SAEs), device effects (ADEs), serious device effects (SDEs), device deficiencies (DDs), occurring during the investigation

Measurements

Complete healing at V3

The evaluation of complete healing status (100% of epithelialization (first epithelia layer) of the wound) will be performed by the investigator at V3 (D21 ± 2 or earlier if the wound is

healed before D21), as the phenomenon of epithelialization is visible to the naked eye). Data on complete healing will be reported in the CRF.

In addition to the evaluation of complete healing status performed by the investigator at V3, a blind assessment of healing will be performed by an independent assessor - chosen prior to the start of investigation - on photographs taken by investigators at V1 and at the final visit (V3). All photographs will be taken of the wound site and adjacent intact skin under standardized conditions (*see Appendix 17.2*). The digital photographs will be captured and available to the independent assessor chosen. A blind assessment of these photographs will be performed using W.H.A.T. in order to evaluate the healing status.

Wound condition assessment

- **Bleeding of the wound bed**
  The investigator will have to report the possible occurrence and intensity of bleeding at each dressing removal (including V1).

- **Maceration of the wound**
  Maceration refers to the skin changes seen when moisture is trapped against the skin for a prolonged period. The investigator will evaluate this parameter at each dressing removal (including V1).

- **Inflammation**
  The investigator will evaluate the presence of inflammation at the V1 and at each dressing removal.

- **Infection**
  The investigator will evaluate the presence of infection at the V1 and at each dressing removal. (According to the investigation plan, presence of the infection is an exclusion criterion and the reason for the discontinuation of the patients from the study).

- **Necrotic/Fibrinous/Granulation/Epithelisation Tissue ratio**
  The investigator will assess wound necrotic/ fibrinous/ granulation/ epithelisation tissue ratio at the V1 and at each dressing removal.

- **In-growth in the dressing holes**
  The investigator will collect information on the wound tissue in-growth in the dressing holes at the V1 and at each dressing removal.

Surrounding skin condition assessment

Each of the following parameters will be evaluated at V1, V2 (D3±2) and V3 (D21+2 or earlier, as soon as the wound is epithelialized completely) or ET:

- Inflammatory signs
  (Inflammation is characterized by 4 main signs: erythema, oedema, warmth and pain)

- Infection
  (Deposition and multiplication of bacteria in tissue with an associated host reaction. The classic local signs of infection include: localised erythema, localised pain, localised heat, cellulitis and oedema; there may also be present specific exudation, smell, delayed healing, abscess, general symptoms. ***Presence of the infection is an exclusion criterion and the reason for the discontinuation of the patients from the study****)*
- Irritation
  (Irritation is synonymous of irritant contact dermatitis which is a secondary inflammation of the skin due to an irritant or caustic agent)
- Allergic rash/eczema
  (Cutaneous hypersensitivity reaction induced by a skin contact with an allergenic substance)
- Blistering
  (Uprising of a part of the epidermis, drawing a projection and thus achieving a bubble that contains a variable fluid)
- Skin stripping
  (Skin stripping is caused by the repeated application and removal of adhesive tapes and dressings from the skin. This process inflicts variable levels of damage to the layers of the stratum corneum, and may cause inflammatory skin damage, oedematous changes, skin soreness and a detrimental effect on skin barrier function)
- Maceration
  (Maceration refers to the skin changes seen when moisture is trapped against the skin for a prolonged period. The skin will turn white or grey and will soften and wrinkle)
- Dry
- Trauma to wound edges
  (Trauma corresponds to underlying lesions or to retraction of wound edges)
- Product degradation on the skin
- Hematoma
- Other

Global assessment of the dressing by the investigator

The dressing use will be evaluated by means of a specific questionnaire to be completed by the investigator at V2 and V3 or ET: ease of handling, ability to maintain its integrity, ease of application, ability to be repositioned, conformability, wound adhesion, ability of dressings to stay in place, transparency, ability to transfer wound fluid to the secondary dressing, ease/speed of removal, absence of residue, overall impression.

Global assessment of the dressing by the subject

The dressing use will be evaluated by means of a specific questionnaire to be completed by the subject at the end of the study (V3 or ET): ease of handling, ability to maintain its integrity, ease of application, ability to be repositioned, ability of dressings to stay in place, transparency, comfort of the patient, ability to transfer wound fluid to the secondary dressing,

ease/speed of removal, overall impression.

Assessments from the study nurse's booklet

For any additional dressing changes what will occur between V2 and V3, the study nurse will be asked to report at each dressing change in his/her booklet carefully and legibly: number of the additional visit, date of the visit, reason for dressing change, presence of complete re-epithelialization, appearance of the dressing before removal, bleeding during dressing removal, appearance of the wound bed, appearance of the surrounding skin, amount of exudate, wound moisture, local treatment, number of dressings used, application of dressing, secondary dressing, initials of person in charge of dressing change.

7.8.3 Safety Measurements and Variables

Safety measurements include AEs, ADEs, Serious Adverse Events (SAEs)/Serious Adverse Device Effects (SADEs), and Device Deficiencies (DDs) evaluations. The definition of AE, ADE, SAE, SADE, and DD and procedures for reporting SAEs, SADEs and DDs that could have led to a SADE are presented in section 8 of this Clinical Investigational Plan (CIP). All AEs, ADEs, SAEs, SADEs and DDs must be recorded in the appropriate form 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.

7.8.4 Anticipated ADEs

Anticipated local adverse events (e.g. events occurring at wound site) may be categorized as:

- Wound worsening secondary to wound infection or repeated traumatic injury.
- Device related such as contact dermatitis or dressing-induced skin irritation or wound bed injury at dressing removal.

Some examples of events which are not anticipated ADEs: bleeding, pain, adhesion to the dressing.
Pre-existing diseases (before application of the medical device) are not documented as adverse events but as medical history. New diseases and pre-existing diseases that worsen during the trial are documented as AEs.

7.9 Statistical methods and determination of sample size

7.9.1 Statistical Evaluation

The statistical analyses will be performed using the software SAS (version 9.4 or higher).

7.9.1.1 Population Analyses

Analyses will be performed on three populations as follows:

- The Safety population consists of all subjects allocated to treatment sample; and who had at least one investigational product applied.

- All randomized subjects with at least one exposure to either dressing will be included in the modified intent-to-treat (mITT) population. Subjects will be analysed in the treatment groups to which they will be randomly assigned (as per ITT principle).
- The per-protocol (PP) population consists of all enrolled subjects who satisfied the entry criteria of the investigation, who had an assessment of main criterion at V2 and who completed the treatment without major violations of the protocol.

7.9.1.2 Efficacy analyses

Analysis of the main criterion

The test for the non-inferiority of Lomatuell Pro® vs UrgoTul® for the main criterion will be carried out through a confidence interval (CI) approach. Non-inferiority will be established if the lower unilateral limit of the 97.5% CI in the PP population for the between-treatment difference (Lomatuell Pro® - UrgoTul®) in the percentage of wound dressing associated with a pain < 30 mm on VAS at V2 does not exceed -10%.

Considering that the studied population is “patients with an acute wound” and that the primary endpoint will be assessed at V2 (Day 3±2); we can expect very few drop-outs. We also expect few patients with a major protocol deviation. Therefore, we can conclude that an assumption of 10% attrition rate is acceptable for this study.

In order to unambiguously conclude to non-inferiority in agreement with most of guidelines, the same analysis will be performed on the mITT population. In case of missing data to evaluate the primary criterion, the subjects will be considered as failures. The trial will be considered positive if both approaches support noninferiority.

Adjustment

The frequency of analgesic intake will also be analysed. In case of a significant difference between the 2 dressing groups, the analysis of the primary criterion (painless dressing removals) will be adjusted using a Mantel-Haenszel test.

Analysis of the secondary criteria

The following statistical tests will be used to analyse the secondary criteria according to the criteria type:

- Qualitative nominal criteria will be compared using a Chi^2 test.
- Qualitative ordinal criteria will be compared using a Mann-Whitney-Wilcoxon test
- Quantitative criteria will be compared using an analysis of variance (ANOVA)

Degree of significance

The criteria for which the degree of significance of the bilateral test will not exceed 0.05 (statistically significant difference) will highlight the specificities between the 2 groups of dressing.

Percentage of complete healing at V3

A wound will be considered as completely healed when there is 100% of epithelialization (first epithelia layer) of the wound. The percentage of wounds healed will be calculated based on a blind assessment from photographs using W.H.A.T.

Assessment of the wound condition

The wound bed condition will be evaluated at V1, V2 and V3 or ET regarding 6 condition items - bleeding, maceration, inflammation, infection, ratio necrotic/ fibrinous/ granulation/ epithelisation tissue, and tissue in-growth in the dressing holes by means of the following 4-points scale: *none, mild, moderate, severe.* The percentage of each modality for each condition items will be calculated.

Assessment of the surrounding skin condition

The condition of the surrounding skin will be assessed at V1, V2 and V3 or ET regarding different conditions: inflammatory signs, irritation, allergic rash/eczema, blistering, skin stripping, maceration, dry, trauma to wound edges, product degradation on the skin, hematoma, other. These condition items will be assessed by means of the scale *Yes/No*. The percentage of each modality will be calculated.

Wound closure according to inclusion wound exudation status.

This will use a Cochran-Mantel-Haenszel test including treatment groups and baseline wound exudation status (none, light and moderate/heavy).

Global assessment of the dressing by the investigator

The global assessment of the dressing will be performed by the investigator at V2 and V3 or ET. Each item will be evaluated by means of the following scale: *very good, good, poor, and very poor*.

The percentage of each modality of each criterion (ease of handling, ability to maintain its integrity, ease of application, ability to be repositioned during application, conformability, wound adhesion, ability of dressings to stay in place, transparency, ability to transfer wound fluid to the secondary dressing, ease / speed of removal, overall impression, and absence of residue) will be calculated.

Global assessment of the dressing by the subject

A global assessment of the dressing will be performed by the subject at V3 or ET. Each item (ability to maintain its integrity, ability of dressings to stay in place, transparency, comfort of the patient, ability to transfer wound fluid to the secondary dressing, ease/speed of removal, overall impression) will be evaluated by means of the following scale: *very good, good, moderate, poor, very poor*. The percentage of each modality will be presented.

Assessments from the study nurse's booklet at each dressing change

The total number of dressing changes will be calculated and the mean value of dressing changes will be calculated.

For the other parameters (appearance of the dressing before removal, bleeding of the wound, condition of the wound, cleaning is required on or around the wound and type of solution used), the statistical unit is not the patient but the dressing change. The percentage of each modality of the other parameters will be calculated.

7.9.1.3 Safety analyses

Safety analyses will be descriptive overall and by dressing group. Any local and general adverse events occurring and those already present, but worsening, during the course of the investigation will be described on the safety population. Frequencies will be provided per dressing group and overall describing the type of event: device deficiency (DD), adverse event (AE), serious AE (SAE), adverse device effect (ADE), serious ADE (See Section 11).

7.9.2 Determination of Sample Size

A number of n = 75 subjects per group will allow a 80% power to demonstrate non-inferiority with a type I error of 2.5% one-sided considering 95% of dressing changes with a pain VAS value < 30 mm at D3 and a 10% non-inferiority margin, as recommended by the sponsor. Thus, considering an attrition rate equal to 10%, it is necessary to include n = 84 subjects per group to obtain the required power.

7.9.3 Randomization

Patients will be randomized in a 1:1 ratio to each treatment arm. A randomization list will be generated using a validated pseudo-random number generator, yielding reproducible and non-predictable results. Access to the randomization list will be controlled and documented. The method of permuted blocks will be used. The block size will be documented in the Study Report. Randomization will be centralized and performed by Interactive Web Response System (IWRS) at RCTs. Investigators will receive the result of the randomisation by email.

8 DATA MANAGEMENT

The sponsor provides all necessary technical equipment and documentation to the participating site or investigator, respectively. This includes study Clinical Investigation Plan, study nurses confirmation forms, CRFs, and contact details of the sponsor and monitor.

Data recording is conducted on paper-CRFs, except randomisation which is performed on IWRS.

All completed original CRF forms (as well as the study nurses diary) should be signed by the investigator and forwarded to RCTs within four weeks after completion at the latest. Additionally, pictures of wound will be provided to RCTs on an USB Key.

The data collected on the CRFs will be the data entered by RCTs and used for statistical analysis. Pictures of wound will be provided to RCTs on an USB Key for measurement by W.H.A.T, by Lohmann & Rauscher.

9 STUDY REPORT AND PUBLICATION POLICY

The data resulting from this study will be collected on behalf of Lohmann & Rauscher by RCTs and will be analyzed after all subjects have completed the study, and all data validation checks have been performed. RCTs will conduct the analysis of the clinical data and provide the results in a study report in cooperation with the sponsor. The study report will be submitted to the ethics committees involved.

It is planned to publish the trial results in a scientific journal and at German or international congresses. Publication of the results of the trial as a whole is also intended.

Any published data will observe data protection legislation covering the trial subject and investigators. Success rates or individual findings at individual trial sites are known only to the sponsor. By signing the contract to participate in this trial, the investigator declares that he or she agrees to submission of the results of this trial to national and international authorities for approval and surveillance purposes, and to the Federal Physicians Association, the Association of Statutory Health Fund Physicians and to statutory health fund organizations, if required. At the same time, the investigator agrees that his or her name, address, qualifications and details of his or her involvement in the clinical trial may be made known to these bodies.

The lead authorship of the manuscript of the whole clinical trial results and the co-authorships will be related to the amount of recruited patients. Lohmann & Rauscher staff will be included as co-authors.

The publication or presentation of the results of a single study center requires prior notice and prior comment and approval from the sponsor Lohmann & Rauscher. The support by Lohmann & Rauscher is to be mentioned in any publication. A copy of all publications will be sent to Lohmann & Rauscher.

10 QUALITY ASSURANCE

10.1 Quality assurance

All information about study subjects will be kept confidential. The CRFs will be pseudonymized. The CRFs will not contain any patient details like name, date of birth (only MM/YYYY will be collected), etc.

The CRF is the clinical data collection instrument for this study. All data requested on the CRF must be recorded. Missing data should be explained or filled in retrospectively by the respective investigator.

After data entry in the clinical data base (CDB), each data will be automatically checked and informatics queries may be issued.

These queries will be sent to the site in order to have them resolved in due time. The study nurses will have the help of RCTs within phone calls if necessary.

If any recording error has occurred on the CRF, straight line should be drawn through the incorrect entry and the correct data entered besides. The corrected information must be confirmed through initials and date by the investigator. Errors should not be blurred or erased.

The images gained during the course of the study will be evaluated by a blinded observer to reduce bias.

During the study, the study nurse coordinator will have regular contacts with the investigation site. It is planned to have also audit visits. Data in the CRF will be considered as source document, except for demographics and inclusion/exclusion criteria and randomisation reports. Moreover, the study nurse will have their own nursing record in which the main information regarding the care will be noted (i.e.: name, patient coordinates, date of care, act of care and comment).

It has to be verified the clinical study is conducted according the CIP, and subsequent amendments, and the applicable legal requirements.

All documents associated with the present study are archived for a period of 15 years at the sponsor´s site, study nurse site and at study nurse coordinator’s site.

10.2 Protocol Deviations

General definition: major protocol deviations are any protocol deviations that might significantly affect the completeness, accuracy, or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. Relevant major protocol deviations may include errors in treatment assignment, the use of excluded medication, poor compliance, loss to follow-up and missing data (cf. ICH E3. Questions and answers (R1). January 2013 and ICH E9).

In this trial, the following protocol deviations will be considered as major and will therefore lead to exclude patients from the PP set:

- Patient randomized while an inclusion criterion is not met
- Patient randomized while an exclusion criterion is met
- Patient not treated as per protocol between V1 (D0) and V2 (D3±2):
    - Patient randomized to Lomatuell Pro® but actually received UrgoTul® at D0
    - Patient randomized to UrgoTul® but actually received Lomatuell Pro® at D0
- Pain assessment (VAS) during removal at V2 (D3±2) is missing (i.e. primary endpoint is missing)
- Pain assessment (VAS) during removal at V2 performed out of the time-window (i.e. at D6 or later)

Further major protocol deviations may be defined during the conduct of the trial, if deemed relevant. The list of major protocol deviations will have to be finalized and documented (for example, in the data review minutes) prior to the database lock.

11 SAFETY AND EVENT HANDLING

The following definitions on the basis of DIN EN ISO 14155:2012-01 will be employed:

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.

Adverse device effect (ADE)

Adverse event related to the use of an investigational medical device.

Serious adverse event (SAE)

Adverse event that

a) led to death,

b) led to 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

Serious adverse device effect (SADE)

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

Device deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

a) if either suitable action had not been taken,

b) if intervention had not been made, or

c) if circumstances had been less fortunate,

shall be handled as specified for SADEs. These events are defined as device deficiencies with SADE potential.

Events that are assessed as SADE or device deficiencies with SADE potential by the investigators might match the definition of a reportable event.

Incidents

Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling **or** the instructions for use which might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health. (Directive 93/24 EEC)

An incident is a malfunction, failure or a modification of the features or performance or an inaccurate label or instruction manual for a medical device, which directly or indirectly caused, may have caused in the past, or may cause in the future, death or a serious aggravation of the state of health of a patient, a user or another person (MPSV § 2 (1)).

All SAEs, SADEs, device deficiencies with SADE potential or incidents according to the European Directive 93/42/EEG and national law **have to be immediately reported** to Lohmann & Rauscher GmbH & Co.KG, Irlicher Str. 55, 56567 Neuwied, Germany by fax to +49 2634 99 1566 or by E-mail to martin.abel@de.Lrmed.com.

12 REGULATORY ASPECTS AND PROTECTION OF SUBJECTS

The study will be conducted in accordance with French regulations applicable to the "études interventionnelles à risques minimes" at the date of approval of the Clinical Investigational Plan by the sponsor (Loi Jardé). The study will be submitted to a Committee for the Protection of Persons (CPP) with a notification to the National Agency for the Safety of Medicines and Health Products (ANSM) required by the texts.

The study will be conducted by Lohmann & Rauscher/RCTs in compliance with the regulations, the Helsinki Declaration and the applicable Good Epidemiological Practices including the recommendations of Ethics and Good Practices in Epidemiology (ADELF Version France - 2007) and the Guidelines for Good Pharmacology Practices (ISPE - 2008).

Lohmann & Rauscher/RCTs are committed to putting in place appropriate procedures to ensure the protection and well-being of subjects who will participate in this study. By agreeing to participate in the study, the study nurse agrees to abide by applicable regulations, protocol, applicable good practices and procedures for conducting the study.

13 BENEFITS AND RISKS

The study does not require any additional tests, consultations or treatments compared to the care patients would normally receive. Apart from the choice of the dressing, which will be made at random, the study will not change in any way the treatment patients receive from the nurse. There are no constraints for patients and no specific risks related to their participation. Patients' participation in the study will not prevent healthcare professionals from using other treatments or ordering further investigations as needed for patients' care. The main constraint related to the patients' participation will be to follow carefully the advice of the healthcare professionals who provide care for their wound. If, during the study, patients do not tolerate the dressing or if, based on the way their wound progresses, the dressing is not right for them, the healthcare professional will decide what treatment would be most suitable for the patient.

14 DECLARATION TO THE NATIONAL COUNCIL OF THE ORDER OF NURSES (CNOI) OF THE STUDY

The study nurses participating in this study are remunerated and the study Clinical Investigational Plan (or summary) and the financial agreements of the participating study nurses will be submitted to the National Council of the Study Nurses (CNOI, Article L.4113-6 of the Code of Public Health) by RCTs, on behalf of Lohmann & Rauscher.

Each participating study nurse will receive a copy of his/her contract with the opinion of the CNOI and any correspondence between RCTs and the CNOI or, if applicable, a letter from RCTs stating that the financial contract has been submitted to the CNOI and the period of 2 months having elapsed, the opinion of the CNOI shall be deemed to be favourable.

Each participating study nurse will have to send a copy of the CNOI's opinion or the letter of RCTs to its Departmental Council of the Order accompanied by a copy of its financial agreement (Articles L.4113-9, L.4113-10 and L.4163-10 of the Code of Public Health).

15 SUBMISSION TO THE COMMISSION NATIONALE DE L'INFORMATIQUE ET DES LIBERTES (CNIL)

Since this study requires collecting and processing personal data with the purpose of research in the field of health, it depends on chapter IX of the Modified Data Protection Act of January 6th, 1978.

As a "études interventionelles à risques minimes" organized and practised on/with human beings with the purpose of developing biological, medical or health knowledge in which all the acts are practised and products are used in a usual way, without any additional or unusual procedure of diagnosis, treatment or surveillance possibly related to databases and\or biological collections of samples which are pre-existing, legally established and have been the object of the necessary formalities of declaration and\or of authorization with competent authorities", it enters the perimeter of the Reference Methodology 001 (MR001). The data collected within the framework of the study are also in accordance with the MR001 and strictly limited to the necessary and relevant data with regard to the objectives of the research.

The necessity to collect indirectly personal data (identification of the subject by a number of inclusion with the following format: XX-YY, where XX is the site number and YY the number of patient included in the site) is justified by the necessity of being able to make requests for further information with the participating study nurses in the case of questionnaires, guarantee the quality of the data, be able to control in case of dispute during the computerization of the data and allow the study nurses to identify the subject that must be the object of a delayed collection of data.

The study nurse will have to fill in and keep a cross-reference table allowing them to return to the patient file according to its order number of inclusion in the study to be able to answer these requests.

Under the modified "Computing and Liberties" law of January 6th, 1978, the patient will be informed of his right of access, opposition and rectification regarding the data recorded on the occasion of this study, this right being applicable at any time with the study nurse.

Personal data relative to the participating study nurses will be declared and the study nurses will be informed within the framework of their financial agreement of their right of access, opposition and rectification of these information.

16 SCHEDULE

Study start: Enrolment of the first patient, defined as date of signing of the study nurse form

Study end: analysis and assessment of all collected clinical data is finalised, defined as time of finalisation of the study report

The expected study duration is 24 months.

The expected study duration per patient is 3 weeks.

17 REFERENCES

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18 APPENDICES

18.1 Photographic pictures

The photographic images are to be produced using a digital camera with a resolution of at least 3 million pixels and under the following standard conditions:

At visit V1, two photographs are to be taken: one after cleaning the wound and one after placement the product to the wound (before placement of a secondary dressing). At visit V2 three photographs are to be taken: one prior to removing the dressing (but after removing the secondary dressing, if any), one after cleaning the wound and one with the product on the wound (after placement the new product to the wound but before placement of the secondary dressing). At visit V3 (or Early termination visit, if performed instead) two photographs are to be taken: one prior to removing the dressing (but after removing the secondary dressing, if any) and one after cleaning the wound.

Instruction for the wound photography (without dressing):

1. Place the patient in a position that will ensure the best possible visibility of the wound.
2. Rinse the wound with a 0.9% saline solution and dry it with a sterile gauze pad.
3. Place the millimetre ruler above or below the wound. The patient's ID number and the date of the evaluation should be clearly visible on the ruler.
4. Hold the digital camera in a position perpendicular to the surface of the wound. Position the camera in such a way that the wound occupies as much of the visual field of the camera as possible. Ensure that the millimetre ruler provided by the Sponsor is in the visual field.

   Place the centre of the wound in the centre of the visual field.
5. Photograph the wound with the automatic settings of the camera and control the following features:
   - neutral background (do not use white fabric)
   - absence of external stray lighting
   - absence of fluid on the wound
   - absence of any objects in the visual field of the camera

18.2 Protocol for Removal of the Primary Dressing

Wound care is to comply with the reference text “Individualised dressing of clean wounds, whether sutured or not, septic wounds” issued by the CCLIN* Sud-Ouest (1997 revised).

The primary dressing is to be removed in accordance with the following instructions:

Before proceeding to remove the dressing, it is preferable to warn the patient that the dressing will be removed.

Use a sentence such as “Now we’re going to take care of your wound. Don’t hesitate to stop me if anything bothers you while I’m doing that”.

Do not use sentences like “This might hurt a little” or “I’m going to do my best to try not to hurt you”.

After removing the elastic compression strapping or other orthotics, if any, remove the secondary dressing.

Visually inspect the primary dressing.

If the dressing appears to be dry and is obviously adherent to the wound, it should be soaked with sterile saline solution.

Remove the dressing using sterile forceps or a non-sterile disposable glove.

Delicately peel back one of the edges and then gently remove the dressing all in one piece by pulling in the direction the hair grows. If you meet resistance, soak the dressing with saline solution.

Inspect the wound bed for bleeding, if any, and grade any bleeding you detect.

Assess the pain induced by removal using the visual analogue scale (VAS). Do not communicate the result to the patient.

* CCLIN is the Centre for coordination of the fight against hospital-acquired and care-related infections

18.3 Assessment of Pain using Visual Analogue Scale

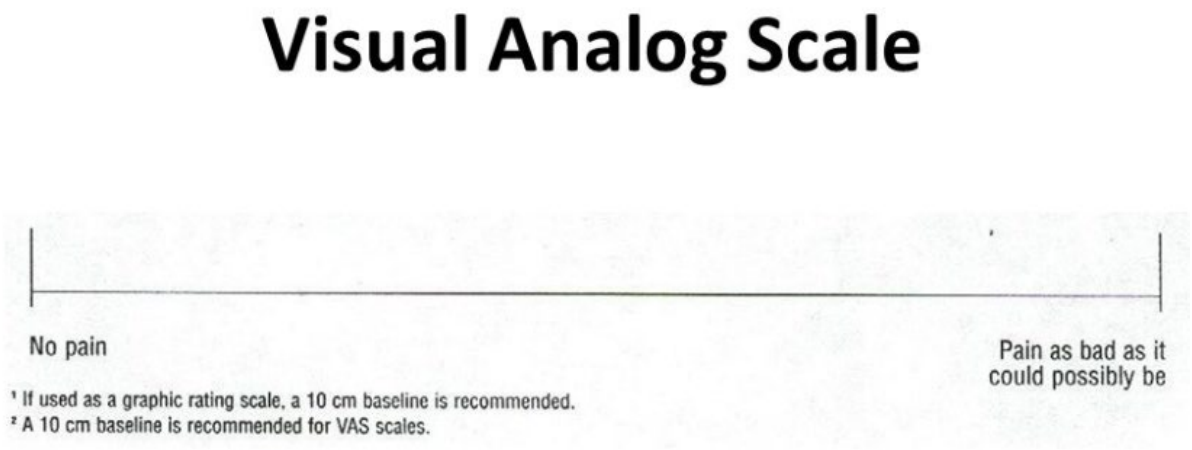
In all cases:

- Check the patient's visual acuity (provide correction, if needed)
- Check that the patient understands how the scale is used

18.3.1 Visual Analogue Scale

The VAS is used to grade the patient's pain and pain relief. It is a scale from 0 to 100 mm whitout any millimetter marks. The ends correspond to "0 = no pain" and "100mm = unbearable pain".

This specific ruler will be provided to the investigator in order to measure the VAS score. The subject will mark on the ruler the point that he/she feels represent his/her perception of his/her current pain. The VAS score will be directly measured by the investigator. The VAS score will be filled in the CRF.



When presented to the patient, the scale should be in the **horizontal position**. The patient should be asked to rate his/her pain in relation to a prior usual type of pain, for example, "When you have a headache, where would you say you are on the scale? And what is the pain like now? Stronger or not as strong?").

The **result in millimetres** is to be noted on the CRF form. It should not be **communicated to the patient**.

The method requires good motor coordination on the part of the patient, and it has other limitations, e.g. patients with limited capacity for abstract thought, those with poor eyesight and the elderly.

18.3.2 Evaluation of Pain on Removal of Dressing

The patient is placed in the most comfortable situation possible taking into account the constraints related to providing wound care and to the location of the wound.

If prior care was painful or if you are planning to perform debridement of the wound, it is possible to prescribe oral analgaesia. Note your prescription on the follow-up form.

Remove the secondary dressing. The primary dressing is then removed in accordance with the standardised protocol.

Immediately after removing the dressing and before performing any local wound care, assess the patient's pain using the VAS. If the VAS is not suitable in view of the patient's status, use the numerical scale.

Note the result on the CRF form, but do not communicate it to the patient.

Then, continue your assessment of bleeding, if any, and proceed with wound care.