Multicenter, randomised in parallel groups, controlled study to compare performance and safety of Suprasorb®X+PHMB Pro with Suprasorb® X+PHMB dressing in treatment of infected venous leg ulcers

Protocol number: 2024-07

Post-Market Clinical Follow-up Plan

Final Version 1.1

14 August 2025

Sponsor:

Lohmann & Rauscher GmbH & Co. KG
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Document history

Protocol version		**Amendment reference**	
N°	**Date of approval/notification**	**Number**	**Classification**
1.0	21 May 2025	---	---
1.1	14 August 2025	1	Administrative incorporating also changes introduced by Memorandum no 1 version 1.0 dated 13.08.2025

Signatures

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Investigator‘s Agreement

I hereby certify that I have read the present study protocol and agree to conduct the study in accordance with the provisions of this study protocol.

Investigator

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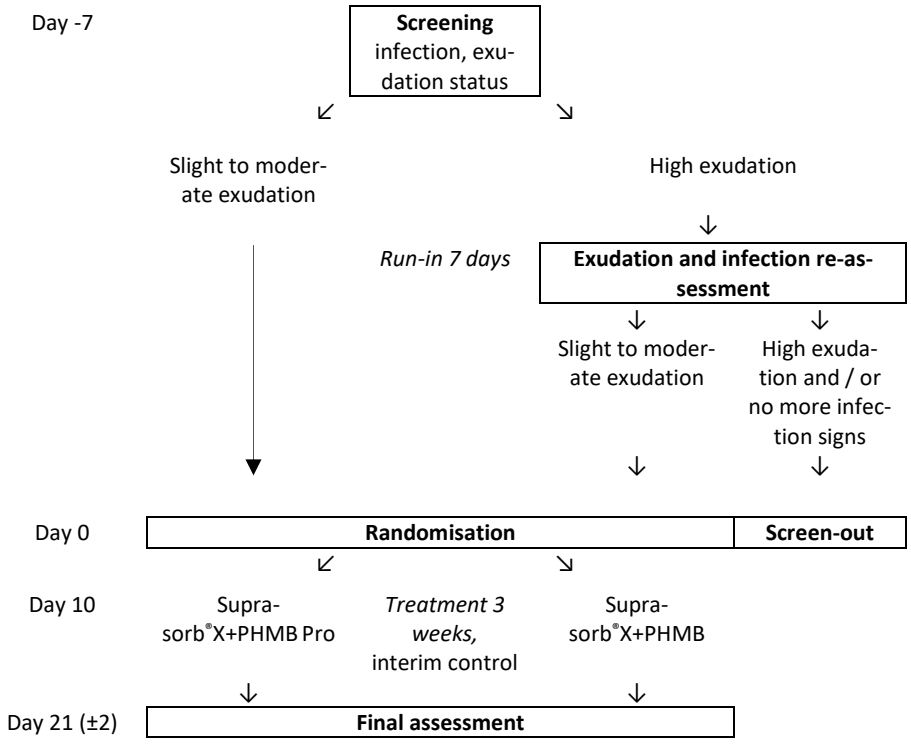
Date Signature

1. Table of contents

List of Abbreviations

ABPI	Ankle brachial pressure index
ADE	Adverse device effect
AE	Adverse event
BC	Bacterial cellulose
CDC	Centres for Disease Control and Prevention
e-CRF	Electronic Case report form
FAS	Full analysis set
ICF	Informed consent from
IFU	Instruction for use
NRS	Numeric rating scale
PMCF	Post-market Clinical Follow-up
PPS	Per protocol set
PHMB	Polyhexamethylene biguanide, Polyhexanide
QoL	Quality of Life
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety analysis set
TILI	Therapeutical Index for Local Infections
VLU	Venous leg ulcer

2. Synopsis

Name of the sponsor	**Lohmann & Rauscher GmbH & Co. KG**
Title of the study	Multicentre, randomised in parallel groups, controlled study to compare performance and safety of Suprasorb® X+PHMB Pro with Suprasorb® X+PHMB dressing in treatment of infected venous leg ulcers
Protocol number	2024-07
Version and date	Version 1.1, 14 Aug 2025
Study description	This clinical investigation will be conducted as a multicentre, open-label, randomised in parallel groups, controlled study on patients with infected venous leg ulcers. During the screening, all patients will be assessed for inclusion and exclusion criteria and wound exudation status. Eligible patients with slight or moderate wound exudation will be randomly assigned to treatment with either Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB. The patients who fulfil all other eligibility criteria but have high level of wound exudation will enter a 7-days run-in period, during which they will receive superabsorbent dressing (e.g. Vliwazell® Pro, Vliwasorb® Pro) and monitored compression therapy with Rosidal® 1C. During the run-in period they should receive appropriate treatment including systemic antimicrobial drug therapy if required. After this time, these patients should be re-assessed and in case they still fulfil all eligibility criteria, and the exudation decreased at least to a moderate level, they will be randomised to Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB. In case the exudation would not decrease within this period or other eligibility criteria are not met anymore, they will be screened out. 

	Upon randomisation, all patients will receive the assigned dressing for 21 (±2) days, or till the complete epithelialization, if it occurs earlier. The patients should also continue to receive adequate compression and, if necessary, systemic antimicrobial drug therapy. During the study participation, selected parameters of the wound will be assessed at Baseline, Interim Visit, and EOT visit. In addition, dressing changes may be performed in-between on as needed basis. After 3 weeks of treatment with Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB, all patients will complete the study. Their further treatment (if necessary), will not be the part of the study.
Objectives	Evaluation of performance and safety of Suprasorb®X+PHMB Pro in the treatment of infected venous leg ulcers in comparison to Suprasorb®X+PHMB.
Endpoints	Primary endpoint: Rate and severity of maceration after 3 weeks of treatment with Suprasorb®X+PHMB (Pro) (by the investigators' assessment as well as by an independent assessment of the wound photos) Secondary endpoints: – Wound area changes over time (by the investigators' assessment as well as by an independent assessment of the wound photos) – Change of necrotic & fibrinous / granulation tissue rate in the wound bed (by an independent assessment of the wound photos) – Change of wound infection status during the study (by a modified CDC definition, confirmed by a TILI score) – Product safety (assessed by rate of product-related complications) – Change of wound exudation and presence of peri-wound oedema (by the investigators' assessment) – Change in patient's pain (measured by NRS scale) – Product usability (assessed by means of user and patient questionnaire for both Suprasorb®X+PHMB (Pro) and Rosidal 1C) – Change in patient's quality of life (assessed by means of Wound QoL-17 scale) – Oedema reduction (by measurement of limb circumference) – Sub-bandage pressure levels retention (difference of the pressure levels, measured at the time of application and before the next dressing change)
Study population	Adult patients with infected venous leg ulcer. 150 patients will be randomised in the study (75 in each group), a drop-out rate of 5% is expected. To get this number, screening and inclusion of up to 200 patients is planned.
Study phase	IV (Post-marketing surveillance)

Study centres	6-8 sites in Poland
Study duration	Set up and preparation 3 months, recruitment 12 months, treatment 1 month, study closure and data analysis 9 months. Overall duration 24 months.
Participation duration	Each patient will participate for at least 21 (±2) days, or till the complete epithelialization, if it occurs earlier. In case a run-in period is necessary for a patient, maximal participation time will be 28 (±2) days.
Interim analysis	Planned upon randomisation of 75 patients (50% of the study population)
Inclusion criteria	– Age ≥ 18 years – Infected* venous** leg ulcer – Slightly to moderately exuding wound*** – Patient has signed informed consent * as per CDC definition, also TILI score ≥ 5 (see section 5.4.1) ** ABPI > 0.8 and < 1.2 (see section 5.4.2) *** patients with highly exuding wounds may be screened for a 7 days run-in period to receive superabsorbent dressing and monitored compression therapy and re-considered for enrolment in case the exudation level decreases (see section 5.4.3)
Exclusion criteria	– Participation in other interventional clinical trial that could interfere with the present study within 4 weeks of the randomisation and during the whole duration of this study – Wounds with exposed cartilage tissue (hyaline cartilage) – Contraindications to compression therapy (e.g.: advanced peripheral arterial occlusive diseases, decompensated cardiac insufficiency, septic phlebitis, phlegmasia coerulea dolens, sensation disorders of the skin) – Known allergy and/or hypersensitivity to any components of the study product or concomitant products (e.g. compression bandage) – Any other medical condition, which, by opinion of the investigator, may have impact of the success of the study treatment and / or interpretation of the study results.
Statistical methods	Study will be descriptive in nature. Outcome measures will be summarized using descriptive statistics by study arm, no formal comparisons between study arms will be performed. In assessment of primary endpoint (maceration at end of treatment, measured on 4-point scale) percentage of patients with maceration at each of 4 levels of the scale will be reported, by study arm, with corresponding two-sided 95% confidence intervals. A level of statistical significance alpha is set at 0.05, what corresponds to the two-sided 95% confidence intervals.
Sample size calculation	Enrolment of 150 patients, under assumption of 5% drop-out rate, will allow to estimate the percentage of patients with selected level of maceration at the end of treatment by the study arm with precision equal or greater (i.e. width of 95% confidence interval less than or equal to) 24 percentage points for

	percentage of 50% and increasing (i.e. decreasing width of 95% confidence interval) for percentages lower than and higher than 50%.
Insurance	Sponsor of the study will take over the insurance in accordance with the Polish Law.
Ethical considerations	Approval of the Ethics Committee(s) and the Regulatory Authority of Poland will be obtained before the study start.

3. Introduction and Justification

3.1 Medical and scientific background

Production of bacterial cellulose (BC) for the specific purpose of wound dressing dates back to the early 1980s. BC is a polymer produced by several bacteria species and its unique mechanical characteristic is a high surface area, which provides a great liquid loading capacity: water absorbency of BC was found to be more than 30% greater than for cotton gauze, and the drying time 33% longer.[1] BC also demonstrates high tensile strength, flexibility, pronounced permeability to gases and liquids, and a good skin compatibility.[1-4]

BC itself does not have antimicrobial properties to prevent infection in-growth and represents just a physical barrier against bacterial invention. One of the most actively utilized approaches used to introduce antimicrobial properties is impregnation of the BC with polyhexamethylene biguanide (PHMB).[1] PHMB is effective in both decreasing bacterial load and preventing bacterial penetration of the dressing, has low toxicity to human tissue and does not promote bacterial resistance.[5-7]

Suprasorb® X+PHMB Pro Antimicrobial HydroBalance wound dressing and its predecessor Suprasorb® X+PHMB Antimicrobial HydroBalance wound dressing are representatives of PHMB-impregnated BC dressings. Both dressings consist of cellulose, water and 0.3% polyhexamethylene biguanide (PHMB/polyhexanide), and the only difference is that the new (Pro) version is covered by a blue perforated polyethylene film on the side facing away from the wound, which acts as a moisture barrier during use and significantly slows down the evaporation of the fluid in comparison to the previous dressing version. This additional measure was intended to reduce the risk of wound dressing drying-out and attachment to the wound bed, which might cause wound bed injury by the dressing change. In the same time, it may be debated, if such change in the fluid management might potentially increase the risk of maceration. Possible effect of this difference on the maceration rate will be the main area of investigation within this clinical study.

3.2 Current clinical and preclinical data for both products

Suprasorb® X+PHMB Antimicrobial HydroBalance wound dressing and packing rope has been on a market since 2006 and demonstrated acceptable safety profile, also regarding maceration. Lenselink and Andriessen[8] do not report any cases of maceration for their cohort study of Suprasorb X+PHMB for the eradication of biofilms in non-healing wounds (28 adult patients suffering from non-healing locally infected and/or critically colonised wounds of various aetiologies. Eberlein and al.[9] compared treatment with Suprasorb X+PHMB versus silver dressings in patients with painful, critically colonised (wound-at-risk) or locally infected wounds (38 adult patients) and observed slight maceration in the Suprasorb®X+PHMB group at day 7 (mean score=1.2), which decreased during the study period to a mean score of 0.8 by day 28. Wild et al.[10] do not report cases of maceration in their study comparing Polyhexanide-Containing Cellulose Dressing (Suprasorb X+PHMB) with Polyhexanide Swabs in Eradication of Methicillin-Resistant Staphylococcus aureus in pressure ulcers; however, authors make a statement that “with the use of the HydroBalance dressing, changes to the wound edges may occur, which may be misinterpreted as maceration by less experienced clinicians. These whitish coatings on the peri-wound skin, however, can be easily removed by gentle wiping with a moist swab. Underneath it, the epidermis is intact and appears to be soft and more delicate as compared with the patient’s normal

skin (the ‘‘wipe’’ or ‘‘wave’’ effect). Therefore, effective monitoring of the wound bed evolution and peri-wound skin condition is required.” In the study by Nielsen and Andriessen[11] comparing Suprasorb X+PHMB and hydrophobic dressing with dialkylcarbamoyl-chloride (60 adult patients with surgical wounds healing by secondary intention), maceration of the peri-wound skin occurred by only 6% (n=2/30) patients in Suprasorb X+PHMB group vs 17% (n = 5/30) patients in comparator group.

Suprasorb X+PHMB Pro is not yet on the market but has been CE marked since 2018 and clinical data has been collected in the course of the pilot PMCF study[12] that has been conducted in 2019 / 2020 and an observational, international, multi-centric, 1-arm marketing study.[13]

- Pilot PMCF study: the acceptance criterion ‘vital without maceration for more than 75%’ was met; namely, 90.6% of the wounds demonstrated absence of maceration at V2. Only 5 cases of newly occurred maceration were recorded in the study totally by investigators and independent reviewer (the cases did not match), with 4 cases in the diabetic ulcer group and one case in the VLU group (rate 1/18 = 0,06).
- Observational, international, multi-centric, 1-arm marketing study: regarding maceration, mostly positive answers were received for retrospective comparison of Suprasorb X+PHMB Pro with Suprasorb X+PHMB (7 users were interviewed):

	Much better	Better	Similar	Worse	Much worse
Prevention of maceration	2	2	1	2	0

It appears that the risk of maceration of the peri-wound skin after use of Suprasorb X+PHMB Pro is not significantly different to that of Suprasorb X+PHMB. However, both studies involved only a limited population which does not allow to collect a statistically significant information, thus more investigation in clinical setting is necessary.

3.3 Justification of the study design

3.3.1 Primary study endpoint and selection of comparator

Due to the outer blue film of Suprasorb X+PHMB Pro dressing the drying of the product is slowed by a factor 10 in comparison to Suprasorb X+PHMB wound dressing. This additional measure was intended to reduce the risk of wound dressing drying-out and attachment to the wound bed, which might cause wound bed injury by the dressing change. In the same time, it may be debated, if such change in the fluid management might potentially increase the risk of maceration. Thus, this study was planned to investigate the performance and safety of Suprasorb®X+PHMB Pro, with a specific focus on the peri-wound skin maceration (both rate and severity of maceration will be evaluated).

Randomised controlled trial (RCT) design was selected as it represents the current standard of quality for the clinical trials, with randomisation allowing to reduce bias and to balance characteristics of the patients in the intervention and the control groups.[14-16]

Since the main focus of the study is the maceration risk change, which might be connected to the design change in comparison with the predecessor product Suprasorb®X+PHMB, the latter was selected as a comparator (control group).

3.3.2 Target study population

Venous leg ulcer (VLU) is the most common type of chronic wound.[17] The Society for Vascular Surgery and the American Venous Forum defines VLU as an open skin lesion of the leg or foot that occurs in an area affected by venous hypertension.[18] VLUs are caused by sustained venous hypertension, which results from chronic venous insufficiency or an impaired calf muscle pump. Risk factors include obesity, immobility, varicose veins, and deep vein thrombosis.[19, 20] Venous leg ulcers can also occur spontaneously or after minor trauma.[21]

Most venous leg ulcers produce large amounts of exudate. This fluid contains high concentrations of proteases and inflammatory cytokines that may damage surrounding healthy skin. Removal of wound drainage from the wound bed will reduce the inflammatory environment that prohibits wound healing. Even if there is insufficient evidence suggesting that a specific primary dressing that contacts the wound can result in a higher rate of wound closure, the Clinical Practice guidelines of the Society for Vascular Surgery and the American Venous Forum recommend use of dressings that will manage wound exudate and maintain a moist wound bed at the same time.[18] Primary dressings with high absorptive capabilities, including foams, alginates, and other specialty dressings, are often selected for the primary coverage layer for heavily exudative VLUs.[18] PHMB-impregnated BC dressings, such as Suprasorb X+PHMB (Pro) may also be recommended for treatment of VLUs since they can help managing wound exudate and decrease bacterial load at the same time.

Infected venous leg ulcer was selected as a target group for the study, since a) VLU is an indication prone to maceration due to generally high exudation level, especially if they are infected, and b) VLU is the most common type of chronic wound and thus the evidence collected on this etiology is of a great importance for the healthcare[16].

3.3.3 Secondary study endpoints and treatment duration

Twenty one day (3 weeks ±2 days window for possible logistic adjustments) seems to be enough to detect appearance and grade of maceration which may be reliably attributed to the use of the study dressing or comparator. Additional run-in period of seven days may be implemented for the patients with high levels of wound exudation to minimise the exudation and oedema levels. During this period, the patients will not receive the investigative product or comparator, but a superabsorbent dressing (e.g. Vliwazell® Pro, Vliwasorb® Pro) and monitored compression therapy with Rosidal® 1C.

It is generally not expected that venous leg ulcer will heal within 3 weeks. In the retrospective study of Läuchli et al.[22] healing rate, assessed for 355 patients with VLU composed 45.5% and 63.0% after 3 and 6 months, respectively. Kruszewska et al.[23] analysed the average ulcer healing time for 30 patients with VLU receiving antibiotic therapy, and it consisted 163.4 ± 97.1 (range 51.0 to 426.0) days and increased by 28 days with each additional bacterial strain in the ulcer ($p = 0.041$). Thus, in this study the wound area change will be assessed as a secondary endpoint, which, however, in combination with the level of pain and wound-related quality of life may represent an important patient-relevant benefit of the treatment.[16]

3.4 Study related risks

During the study participation the patients will be treated with CE-certified products within the intended purpose in both treatment arms. Also, only CE-certified products will be used as additional measures. Therefore, no additional study-related risks are expected for the participating patients.

3.5 Benefit-risk ratio of the study

All known potential risks that may occur during the study have been assessed. Suprasorb® X+PHMB Antimicrobial HydroBalance wound dressing and packing rope has been on a market since 2006 and demonstrated acceptable safety profile. Suprasorb® X+PHMB Pro is not yet on the market but has been CE marked since 2018. Clinical safety data on Suprasorb® X+PHMB Pro have been generated and are held by the manufacturer as part of a PMCF study, an observational study as well as usability (acceptance) tests. Also, PHMB-containing biocellulose dressings in general are clinically well-established dressings for infected wounds.

The study will not require any additional invasive tests or procedures, compared to the ones the patients would normally receive. There will be additional burdensome but non-invasive procedures: like continuous pressure measurement with a wireless pressure sensor; photographic wound documentation; completion of paper scales / wound questionnaires. In rare cases, continuous pressure measurement might cause non-severe and reversible skin irritation, local discomfort and / or pain. Other two procedures do not pose any additional risk to patients' health. Therefore, the benefit / risk ratio for this study may be assessed as positive.

4. Study devices

4.1 Suprasorb® X+PHMB Pro Antimicrobial HydroBalance wound dressings/ packing rope

Suprasorb® X+PHMB Pro Antimicrobial HydroBalance wound dressings consist of cellulose, water and 0.3% polyhexamethylene biguanide (PHMB/polyhexanide) and on the side facing away from the wound is covered by a blue perforated polyethylene film, which acts as a moisture barrier during use. Suprasorb® X+PHMB Pro Antimicrobial HydroBalance packing rope consists of cellulose, water and 0.3% polyhexamethylene biguanide (PHMB/polyhexanide). Both dressing and rope are additionally covered by arrow-printed release film made of PP. This protective sheet should be peeled off prior to the use of the devices.

The product is available in different sizes (5 × 5 cm, 9 × 9 cm, and 14 × 20 cm for the dressing, 2 × 21 cm for the rope), and can be additionally cut to size.

Due to the porous structure of the biocellulose and the content of water, Suprasorb X+PHMB Pro can absorb exudate and donate moisture. The principle of action of the HydroBalance effect is exchange of moisture: when the wound contains more moisture than the wound dressing, moisture migrates into the dressing. When there is more moisture in the wound dressing than in the wound (low level of exudation) the wound dressing can donate moisture to the wound. Water evaporates from the wound dressing into the surrounding air. The HydroBalance effect is therefore limited. Due to the outer blue film of Suprasorb X+PHMB Pro dressing the drying of the product is slowed by a factor 10 in comparison to Suprasorb X+PHMB wound dressing (predecessor product).

In addition to this PHMB inhibits microbial activity through specifically destroying bacterial cell membranes. Thus Suprasorb® X+PHMB Pro Antimicrobial HydroBalance wound dressings / packing rope have an antimicrobial effect against a broad spectrum of pathogens (see Table 1). A very rapid and almost complete release of polyhexanide (PHMB) from the dressing after 24 h has been demonstrated in vitro.

Table 1: Pathogen spectrum detected *in vitro*

Bacteria	Fungi	Anaerobe Organism
Bacillus subtillis	Aspergillus niger	Bacteroides fragilis
Enterobacter cloacae	Trichophyton mentagrophytes	Clostridium perfringens
Proteus vulgaris	Yeasts	Peptostreptococcus prevotii
Pseudomonas aeruginosa	Candida albicans	
Pseudomonas putida	Rhodotorula rubra	
Salmonella choleraesius	Saccharomyces cerevisiae	
Salmonella Typhimurium		
Staphylococcus aureus		
Staphylococcus aureus (MRSA)		
Enterococcus faecalis (VRE)		
Streptococcus lactis		
Escherichia coli		
Klebsiella pneumoniae		
Proteus mirabilis		
Serratia marcescens		
Staphylococcus epidermis		
Streptococcus pyogenes		

Changing the dressing is atraumatic. The material makes it easy to conform to the wound's particular shape and depth. The products are therefore especially suitable for areas of the body which are difficult to dress. The positive properties of the dressing resist adhesion to the wound or to the secondary dressing. The moist environment with a cooling effect is perceived by patients as pleasant and pain-relieving.

The products are packed individually and sterilised by irradiation.

Intended purpose

Antimicrobial HydroBalance Bio-Cellulose wound dressings / packing rope aid wound healing by donating moisture and absorbing exudate from lightly to moderately exuding superficial or deep, infected wounds or wounds at risk of infection, inhibiting microbial activity.

Indications

Suprasorb® X+PHMB Pro Antimicrobial HydroBalance wound dressings / packing rope are suitable for:

- arterial and **venous ulcers**
- diabetic ulcers
- pressure sores
- superficial 2nd degree burns
- postoperative surgical wounds
- skin grafts
- skin graft donor sites
- abrasions, lacerations

Contraindications

- 3rd degree burns
- wounds with exposed cartilage tissue (hyaline cartilage)
- known allergy and/or hypersensitivity to any of the product components

Side effects:

In very rare cases skin irritations and/or allergies may occur.

Isolated cases of anaphylactic shock or pain at the beginning of treatment have been described.

Warnings and precautions

Do not use if package is damaged or accidentally opened.

The continuation of treatment must be decided upon by a healthcare professional if any of the following symptoms should occur:

- change in colour and/ or odour of the wound
- stagnant wound healing
- clinical signs of infection

When treating infected wounds, the wound dressing should not be the only therapeutic measure used, but rather should be supplemented by drug therapy at the discretion of the treating physician in accordance with local clinical protocols.

Note that there might be interactions between cationic PHMB and anionic hyaluronic acid, as well as other anionic products, as the antimicrobial effect of the PHMB can be reduced by the binding of the ions.

Application during pregnancy, on breastfeeding women, and children up to two years of age is decided on by the treating physician. However, this is not recommended, as no documented clinical experience with the product in such cases is available.

Manufacturer
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4.2 Reference therapy

Suprasorb® X+PHMB Antimicrobial HydroBalance wound dressing and packing rope (predecessor products) will be used as a reference therapy. The only difference between the two dressings is that the new (Pro) wound dressing is covered by a blue perforated polyethylene film on the side facing away from the wound, which acts as a moisture barrier during use. Suprasorb® X+PHMB Pro Antimicrobial HydroBalance packing rope and Suprasorb® X+PHMB Antimicrobial HydroBalance packing rope (predecessor) are fully identical.

According to MDCG 2020-5 Suprasorb® X+PHMB Pro can be considered equivalent to Suprasorb X+PHMB regarding clinical, biological, and technical parameters. The main performance characteristics of the new (Pro) dressing are comparable to the predecessor product, with the exception of the drying out, which is slowed in Suprasorb X+PHMB Pro wound dressing by a factor 10 in comparison to Suprasorb X+PHMB wound dressing due to presence of the outer PE film. Possible effect of this difference of the change of maceration rate will be the main area of investigation within this clinical study.

Manufacturer
Lohmann & Rauscher International GmbH & Co. KG
Westerwaldstrase 4, 56579 Rengsdorf, Germany

4.3 Additional measures

Both Suprasorb® X+PHMB Pro and Suprasorb® X+PHMB should be additionally secured in place. The following options are proposed in the IFU of the products:

Suprasorb® X+PHMB Pro:[24]

“Secure the wound dressing with a suitable secondary dressing (Suprasorb® F film dressing, Curapor® sterile surgical wound dressing). For patients with lightly exuding wounds, other types of secondary dressings are not recommended (risk of drying out). For patients with moderately exuding wounds and a high risk of maceration, other types of secondary dressings (Suprasorb® P sensitive border foam dressing) should be used. Protruding edges in the combined dressing (blue perforated film and wound dressing) are not a matter for concern. The size of the secondary dressing should be big enough to overlap the wound dressing.”

Suprasorb® X+PHMB:[25]

“Secure with a suitable secondary dressing (Suprasorb® F film dressing, Suprasorb® P foam dressing).”

In addition, for both products controlled compression should be applied. Compression therapy is the most widely used treatment for venous leg ulcer.[26] Compression applied to the calf raises the local interstitial pressure and decreases the superficial venous pressure, thereby reducing the leak of solutes and fluid into the interstitial space. It also improves the venous return, which leads to decrease in venous hypertension and subsequently potentiates healing process.[27, 28, 29] According to Okan et al.,[30] clinicians must always remember to remove the causes of increased production of exudate through compression and elevation for venous and lymphoedematous leg ulcers.

Compression therapy (preferably multilayer) is directly recommended by the Society for Vascular Surgery and the American Venous Forum (SVS-AVF)[31] (See Table 2).

Table 2: Recommendations of Society for Vascular Surgery and the American Venous Forum for compression therapy by VLU

Treatment modality – compression therapy	**SVS-AVF guideline recommendation**
Compression therapy recommended over no compression in active VLU	GRADE 1A
Compression therapy to prevent recurrence in those with healed VLU	GRADE 2B
Multi-component or multilayer compression recommended over the use of single-component bandage for the treatment of active VLU	GRADE 2B

To unify the impact of compression on the study results, similar compression regime should be used for all study patients. One-component short-stretch bandage Rosidal® 1C should be used in combination with multi-point wireless pressure sensor (MPS) which allows to measure and control sub-bandage pressure during and after application.

Rosidal 1C bandage is a one-component system which includes short-stretch compression side and a soft side for padding. The bandage has a cross-elasticity of approx. 50%, which allows a comfortable application around joints, and a maximum lengthwise elongation of 100%, which ensures desired compression without a risk of excessive pressure ("safe-loc system"). For the application technique, please refer to the Instruction for use.[32] Recommended pressure levels at measurement point B1 (approximately 10 cm above the inner ankle, where the tendon merges into the calf muscle) lay between 40 and 60 mmHg.[33]

To additionally control the level of sub-bandage pressure, a small portable device (Tight Alright) will be used. Device consists of a pressure sensor and a battery-powered transmitter which wirelessly transfer the pressure data to a special software. The device should be applied above a non-compressive stockinette and appropriate padding, fixed by the included adhesive sheath, and then covered by the compression bandage. It should stay in place till the next dressing change or compression bandage adjustment. For the application technique, please refer to the Instruction for use.[34]

Systemic antimicrobial drug therapy is generally used by treatment of the infected VLUs.[23, 35] The selection of the exact treatment scheme should be done at the discretion of the treating physician in accordance with the local clinical protocols.

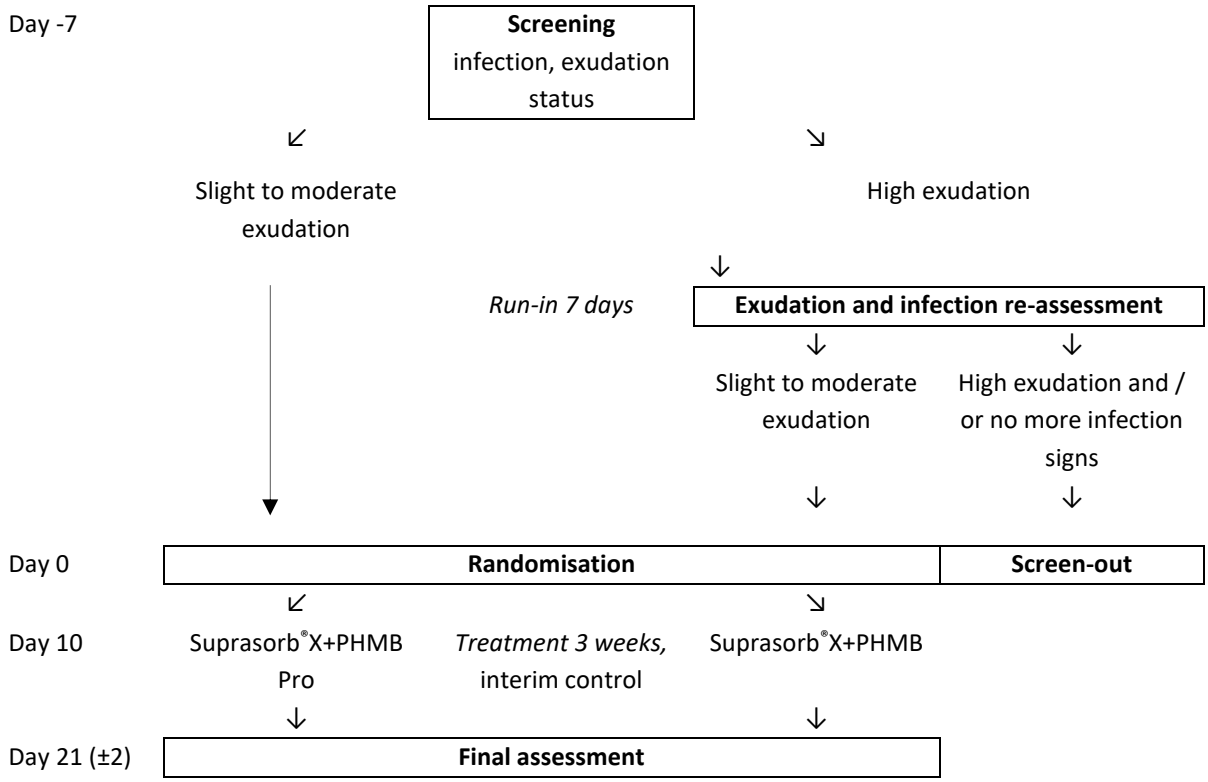
5. Study Details

5.1 Study Design

This clinical investigation will be conducted as a multicentre, randomised in parallel groups, controlled study on patients with infected venous leg ulcer.

During the screening, all patients will be assessed for inclusion and exclusion criteria and wound exudation status. Eligible patients with slight or moderate wound exudation will be randomly assigned to treatment with either Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB.

The patients who fulfil all eligibility criteria but have high level of wound exudation will enter a 7-days run-in period, during which they will receive superabsorbent dressing (e.g. Vliwazell® Pro, Vliwasorb® Pro) and monitored compression therapy with Rosidal® 1C. During the run-in period patients with infected venous leg ulcers should receive appropriate treatment including systemic antimicrobial drug therapy if required. After this time, these patients should be re-assessed and in case they still fulfil all eligibility criteria, and the exudation decreased at least to a moderate level, they will be randomised to Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB. In case the exudation would not decrease within this period or other eligibility criteria are not met anymore, they will be screened out.



Upon randomisation, all patients will receive the assigned dressing for 21 (±2) days, or till the complete epithelialization, if it occurs earlier. The patients should also continue to receive adequate compression and, if necessary, systemic antimicrobial drug therapy.

During the study participation, selected parameters of the wound will be assessed at Baseline, Interim Visit, and EOT visit. In addition, dressing changes may be performed in-between on as needed basis.

After 3 weeks of treatment with Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB, all patients will complete the study. Their further treatment (if necessary), will not be a part of the study.

5.2 Study endpoints

5.2.1 Primary endpoint

- Rate and severity of maceration during 3 weeks of treatment with Suprasorb®X+PHMB (Pro) (by the investigators' assessment as well as by an independent assessment of the wound photos)

5.2.2 Secondary endpoints

- Wound area change over time (by the investigators' assessment as well as by an independent assessment of the wound photos)
- Change of necrotic & fibrinous / granulation tissue rate in the wound bed (by an independent assessment of the wound photos)
- Change of wound infection status during the study (by CDC definition and a TILI score)
- Product safety (assessed by rate of product-related complications)
- Change of wound exudation and presence of peri-wound oedema (by the investigators' assessment)
- Change in patients' pain (measured by NRS scale)
- Product usability (assessed by means of user and patient questionnaire for both Suprasorb®X+PHMB (Pro) and Rosidal 1C)
- Change in patient's quality of life (assessed by means of Wound QoL-17 scale)
- Oedema reduction (by measurement of limb circumference)
- Sub-bandage pressure levels retention (difference of the pressure levels, measured at the time of application and before the next dressing change)

5.3 Study Population

Adult patients with infected venous leg ulcer. 150 patients will be included in the study (75 in each group), a drop-out rate of 5% is expected. To get this number, screening and inclusion of up to 200 patients is planned.

5.3.1 Inclusion criteria

- Age ≥ 18 years
- Infected* venous** leg ulcer
- Slightly to moderately exuding wound***
- Patient has signed informed consent

* as per CDC definition, also TILI score ≥ 5 (see section 5.4.1)
** ABPI > 0.8 and < 1.2 (see section 5.4.2)

*** patients with highly exuding wounds may be screened for a 7 days run-in period to receive superabsorbent dressing and monitored compression therapy and re-considered for enrolment in case the exudation level decreases (see section 5.4.3)

5.3.2 Exclusion criteria

- Participation in other interventional clinical trial that could interfere with the present study within 4 weeks of the randomisation and during the whole duration of this study
- Wounds with exposed cartilage tissue (hyaline cartilage)
- Contraindications to compression therapy (e.g., advanced peripheral arterial occlusive diseases, decompensated cardiac insufficiency, septic phlebitis, phlegmasia coerulea dolens, sensation disorders of the skin)
- Known allergy and/ or hypersensitivity to any of the study product or concomitant products (e.g. compression bandage) components
- Any other medical condition, which, by opinion of the investigator, may have impact of the success of the study treatment and / or interpretation of the study results.

5.4 Study methods

5.4.1 Modified CDC definition and TILI Score

To confirm the infection status of the wounds and its' change during the study, modified CDC SSI criteria,[36] confirmed by a TILI score,[37, 16] will be used.

Modification of the criteria implied exclusion of the "time after operative procedure" criteria since it is not relevant for the chronic wound, and change of the term "incision" to the term "wound". Otherwise, the criteria remained unchanged. To be included in the study, the patient /wound has to demonstrate *at least one* of the following criteria:

- a. purulent drainage from the wound;
- b. organism(s) identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or nonculture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing [ASC/AST])
- c. if culture or non-culture based testing of the superficial incision or subcutaneous tissue is not performed: patient has at least one of the following signs or symptoms: localized pain or tenderness; localized swelling; erythema; or heat
- d. diagnosis of a wound infection is confirmed by a physician or physician designee

Moreover, the infection should be confirmed by the TILI (Therapeutical Index for Local Infections) score, which is an objective scale considering six indirect signs of local wound infection:

- erythema to surrounding skin,
- heat,
- oedema, induration or swelling,

- spontaneous pain or pressure pain,
- stalled wound healing,
- increase and/ or change in colour or smell of exudate.

Each parameter costs 1 point and the score is a sum of the present points. TILI < 5 indicates a wound without infection, whereas TILI ≥ 5 means a local wound infection.

5.4.2 Grade of wound exudate

Suprasorb®X+PHMB (Pro) is intended for wounds with light to moderate exudation level. For the exudation grade, the following definition from the WUWHS Consensus Document[38] should be followed:

- **None:** Wound tissues are dry
- **Light**: Wound tissues are moist; no measurable exudate
- **Moderate**: Wound tissues are wet; moisture evenly distributed in wound; drainage involves <25% dressing
- **High**: Wound tissues are saturated; drainage may or may not be evenly distributed in the wound; the drainage involves > 25% to <75% dressing
- **Very high**: Wound tissues are bathing in fluid; drainage freely expressed; may or may not be evenly distributed in wound; drainage involves > 75% of dressing.

5.4.3 Assessment of vascular status

Before inclusion in the study, vascular status should be assessed by determination of the Anke Brachial Pressure Index (ABPI) which is the quotient of the highest blood pressure in the foot on which the ulceration exists divided by the highest blood pressure on any arm. Only patients with an ABPI > 0.8 and < 1.2 can be enrolled into the study.

5.4.4 Maceration score

Maceration score, proposed by Dini et al.[39] will be used in the study. This scoring system is based on the clinical degree of skin whiteness/redness and the numerical value of area involved in surrounding skin to the ulcer evaluated:

Clinical score	**Degree of Surrounding Skin maceration, area, cm^2**
0=absent	0
1=minimal	< 0,5
2=moderate	0,5 - 2
3=severe	> 2

This scoring will be done by the investigators and also confirmed by an independent review of the wound photos.

5.4.5 NRS

NRS (numeric rating scale) is a pain screening tool, commonly used to assess pain severity at that moment in time using a 0–10 scale, with zero meaning “no pain” and 10 meaning “the worst pain imaginable”.

According to Breivik at al.,[40] the NRS and the VAS have been shown to give almost identical values in the same patient at various times after surgery, whereas NRS is more practical than a VAS, easier to understand for most people, and does not need clear vision, dexterity, paper, and pen.

5.4.6 Wound-QoL-17

The Wound-QoL-17 is a clinical tool, which allows to measure the disease-specific, health-related quality of life (HRQoL) of patients with chronic wounds.[41] It was developed on the basis of three validated instruments assessing HRQoL in chronic wounds: the Freiburg Life Quality Assessment for wounds (FLQA-w),[42] the Cardiff Wound Impact Schedule (CWIS),[43] and the Würzburg Wound Score (WWS).[44]

The Wound-QoL is filled in by the patients themselves. The questionnaire is self-explanatory; yet, patients can be supported if they are not able to fill it in by themselves. In this case, the support has to be documented.

Validated translation of the Wound-QoL-17 in Polish will be used within this study.

5.4.7 Wound Photos

As the wound photos will be used for an independent assessment of the primary endpoint, as well as for the assessment of some secondary endpoints, their appropriate quality is crucial. The following rules should be considered by taking the wound photos for the study:

- photos are taken without wound dressing, after the wound cleaning, if necessary, but before debridement,
- uniform, bright illumination is necessary (flash may be used in case of insufficient room illumination, but there should be no glare on the photo),
- wound should cover at least 1/3 of the picture, pictures from the same wound should be done from the same angle,
- single use paper-based wound ruler should be present on every picture, it has to be placed on the same level as the wound itself. The square on the wound scale is used for later digital evaluation (the software recognizes the square and calculates the wound size and colour of the wound), hence, the square needs to be clearly visible on a photo and remain blank,
- all photos should be saved with patient’s number and date. Patient’s name or initials should NOT be visible anywhere on a photo or used in the file naming.

5.4.8 Pressure measurement

Tight Alright system consisting of wearable pressure sensing device and associated software programs (mobile app and web app) furnished by FeelTect Limited, will be used to measure and indicate the

pressure exerted by compression bandage. For the application technique, please refer to the Instruction for use.[34]

5.4.9 WHAT Tool

W.H.A.T. (Wound Healing Analysing Tool)[45] is a program for assessment of the wound photos, which allows objective evaluation and comparison over time. It is designed as a web-based documentation platform and needs only several simple and transparent steps (i.e. uploading an image, calibration with the calibration square and wound border tracing manually with the mouse) to obtain automatically-calculated results, such as circumference, area, dimensions, % of granulation or necrosis.

6. Study conduct

6.1 Study duration and time plan

The expected investigation duration is 24 months. Duration of the study active phase (from the first ICF till the closure of the last participating site – 18 months). Estimated enrolment period is 12 months.

The expected participation duration for each patient is maximum 3 weeks (21±2 days). In case a run-in period is necessary for a patient, maximal participation time will be 28 (±2) days (1 week of a run-in period and 3 weeks of the study treatment).

6.2 Patient recruitment

The investigator will inform all potentially eligible patients about the possibility to participate in the study. The study will be explained to interested patients in detail by the investigator. The patients will get ample time to consider their participation. By signing the informed consent form the patient is enrolled in the study.

6.3 Randomisation procedure

A computer-generated random sequence will be used to assign patients in a 1:1 ratio to the treatment arm. Randomisation will be stratified by maceration grade at the study entry. Block randomisation with randomly varying block sizes (2-6) will be employed to maintain allocation concealment and balance the number of patients across groups.

6.4 Visit schedule

During the screening, all patients will be assessed for inclusion and exclusion criteria and wound exudation status. Eligible patients with slight or moderate exudation will be randomly assigned to treatment with either Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB.

The patients who fulfil all eligibility criteria but have high level of wound exudation will enter a 7-days run-in period, during which they will receive superabsorbent dressing (e.g. Vliwazell® Pro, Vliwasorb® Pro) and monitored compression therapy with Rosidal® 1C. After this time, these patients should be re-assessed and in case they still fulfil all eligibility criteria, and the exudation decreased at least to a moderate level, they will be randomised to Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB. In case the exudation would not decrease within this period or other eligibility criteria are not met anymore, they will be screened out.

Upon randomisation, all patients will receive the assigned dressing for 21 (±2) days, or till the complete epithelialization, if it occurs earlier. There will be a Baseline visit (V1, D0), Interim visit (V2, D10±2) and a Final visit (V3, D21±2 or at the moment of the complete healing, if it occurs earlier). In addition, dressing changes may be performed in-between the study visits on as needed basis.

Table 3: Schedule of procedures and assessments

Procedure / Task	Screening	Baseline	Interim visit	Additional visits (VA1, VA2, etc.)	Final Visit / Early Termination Visit*
Timeline	(Day – 7)	Day 0	Day 10 ± 2	Each dressing change	Day 21 ± 2
Inclusion/exclusion criteria	✓	✓			
Informed consent	✓				
Assessment of wound exudation status ** +	✓	✓	✓		✓
Measurement of leg circumference **	✓	✓	✓	✓	✓
Optional, in case of a high-exuding wound: start of 7 days run-in period	✓				
Pressure data read-out **	✓	✓	✓	✓	✓
Demographics		✓			
Medical history		✓			
Wound history and previous treatment		✓			
Infection signs assessment (TILI and CDC score) **+	✓	✓	✓		✓
Maceration grade assessment #		✓	✓		✓
Pain assessment (NRS) after dressing removal +		✓	✓		✓
Wound cleaning / debridement **	✓	✓	✓	✓	✓
Wound photograph #		✓	✓		✓
Wound size and depth #		✓	✓		✓
Wound bed status #		✓	✓		✓
Surrounding skin assessment #		✓	✓		✓
Randomisation		✓			
Application of assigned study dressing		✓	✓	✓	
Adverse events	✓	✓	✓	✓	✓
Concomitant treatment***	✓	✓	✓	✓	✓
Device deficiency	✓	✓	✓	✓	✓
Wound Quality of Life **	✓	✓	✓		✓
Complete healing assessment			✓		✓
Global assessment investigator****					✓
Global assessment patient					✓

* Some of the activities may be not applicable for patients who have complete epithelialization

** If screening and baseline visits are performed on the same day, the procedure to be completed only once

*** Only concomitant medication which is prescribed for the wound treatment or may have effect on the wound treatment in general should be recorded (see Annex 1)

**** By an on-line questionnaire upon completion of the last patient at each site (see Annex 2)

+ To be assessed just after taking out the wound dressing

To be assessed after wound cleaning but before debridement

6.4.1 Screening visit (V0, Day -7)

During the screening visit, inclusion and exclusion criteria and wound exudation status should be assessed. The patients who fulfil all eligibility criteria (inclusion criterion "wound exudation level" may be not met at this time) will receive complete information about the investigation and will be provided with the informed consent form (ICF) for the familiarization. Patients should give their written informed consent prior to any further study activities. Upon ICF signature the patient is considered included into the trial.

Upon this, for the patients with light or moderate exudation the procedures of Baseline visit (Day 0) should be performed (see section 6.4.2).

The patients with high levels of wound exudation will enter the 7-days run-in period, during which they will receive superabsorbent dressing (e.g. Vliwazell® Pro, Vliwasorb® Pro) and monitored compression therapy with Rosidal® 1C. During this period, dressing changes and compression adjustment should be done by the investigator's discretion but following the IFU of Rosidal® 1C[32] and FeelTect.[34] Before application of the wound dressing leg circumference should be measured and saved in the application. Sub-bandage pressure data should be read-out in supine and standing position and saved in the application.

Registration of (S)AEs/ (S)ADEs/ device deficiencies /incidents for this study starts from the moment of the informed consent signature. Since the investigator product or comparator are not used during the run-in period, causal relationship to the study product should always be assessed as "unlikely" at this timepoint. However, assessment of possible causal relationship with actually used products / procedures should be provided.

6.4.2 Baseline visit (V1, Day 0)

Patients with run-in period after V0: before taking out the compression bandage at baseline visit, sub-bandage pressure data should be read-out and saved in the application.

Patients with light or moderate exudation: at the baseline visit wound type*, location and infection status will be assessed, and the patients, fulfilling the inclusion criteria without having any of the exclusion criteria will be randomly assigned to treatment with either Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB.

* only venous leg ulcer should be included in the study, i.e. with an ankle brachial pressure index (ABPI) > 0.8 and < 1.2.

The following procedures will be performed on this day:

- Just after taking out the existing wound dressing should be assessed:
  - ✓ pain level by NRS;
  - ✓ signs of infection (TILI and CDC score);
  - ✓ grade and character of exudation;
- Documentation of patient demographics, medical history, information about intake of relevant concomitant medications.
- Wound cleansing and debridement, according to the local standards.

- Documentation of wound type, location, history and local status, measurement of leg circumference. In case the patient has several wounds, only one of them should be described within the study. The following parameters should be assessed (after wound cleaning but before debridement, if necessary):
  - ✓ size (length, width, depth);
  - ✓ presence and grade of maceration;
  - ✓ wound bed status (% of necrotic & fibrinous tissue / granulation);
  - ✓ surrounding skin status;
  - ✓ wound photograph (see Section 5.4.7).
- Quality of life assessed by Wound QOL-17.
- Randomisation (including allocation of the study number).
- Application of the assigned study dressing, appropriate secondary dressing and controlled compression. Sub-bandage pressure data in supine and standing position should be read-out and saved in the application.
- Registration of (S)AEs / (S)ADEs / device deficiencies / incidents, if any should occur.

6.4.3 Interim visit (V2, D10 ±2)

During this visit, the dressing change should be performed. Before taking out the compression bandage, sub-bandage pressure data in supine and standing position should be read-out and saved in the application. Just after the removal of the study / comparator product, to be assessed: pain level assessment by NRS, signs of infection (TILI and CDC score) plus grade and character of exudation. Also, the main wound parameters should be assessed (after wound cleaning but before debridement, if necessary):

- ✓ presence of complete healing: in case the complete healing occurred, further data should be entered in the Final Visit (V3) form. If the wound is not healed yet:
- ✓ size (length, width, depth);
- ✓ presence and grade of maceration;
- ✓ wound bed status (% of necrotic & fibrinous tissue / granulation);
- ✓ surrounding skin status;
- ✓ wound photograph (see Section 5.4.7).

Also, any change in intake of relevant concomitant medications, as well as any (S)AEs / (S)ADEs / device deficiencies / incidents should be recorded. Before application of the wound dressing leg circumference should be measured and saved in the application.

The investigator should ensure that the patient receives the same study product as allocated at the Baseline visit (i.e. Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB). Appropriate secondary dressing and compression should be applied. Sub-bandage pressure data should be read-out in supine and standing

position and saved in the application. At the end of the visit, patient should also complete QoL-17 questionnaire.

6.4.4 Additional visits (VA1, VA2, etc., at each dressing change)

In-between the regular study visits, additional visit for dressing change should be performed. The number and frequency of such visits may vary depending on the wound condition, but it should be taken into account that both the study product and the comparator should not stay in a wound for more than 7 days. Thus, minimum 2 such visits (between V1 and V2 and V2 and V3) should be performed.

During these visits, dressing change (including wound cleansing and debridement, if necessary) should be performed. Before taking out the compression bandage, sub-bandage pressure data should be read-out in supine and standing position and saved in the application. Patient should also be asked about occurrence of any (S)AEs, device deficiencies plus any change in intake of relevant concomitant medications. Before application of the wound dressing leg circumference should be measured and saved in the application. The investigator should ensure that the patient receives the same study product as allocated at the Baseline visit (i.e. Suprasorb®X+PHMB Pro or Suprasorb®X+PHMB), appropriate secondary dressing and compression. Sub-bandage pressure data should be read-out in supine and standing position and saved in the application.

6.4.5 Final Visit (V3, Day 21±2 or the day the complete healing is achieved or Early Termination)

This visit should be conducted after 3 weeks of treatment, or on the day the complete healing is achieved, if it occurs earlier.

During this visit, the following activities should be performed:

- Before taking out the compression bandage, sub-bandage pressure data should be read-out in supine and standing position and saved in the application.
- Just after the study dressing / comparator removal to be assessed:
  - ✓ pain level assessment by NRS;
  - ✓ signs of infection (TILI and CDC score);
  - ✓ grade and character of exudation;
- Leg circumference should be measured and saved in the application.
- Documentation of wound status: presence of complete healing should be assessed.

If the wound is not healed yet: wound cleansing and debridement should be done, if necessary, according to the local standards. The following wound parameters should be assessed (after wound cleaning but before debridement, if necessary):

- size (length, width, depth);
- presence and grade of maceration;
- wound bed status (% of necrotic & fibrinous tissue / granulation);
- surrounding skin status

- wound photograph (see Section 5.4.7) should be taken and saved (also in case of complete wound healing).

- Any change in intake of relevant concomitant medications, as well as any (S)AEs / (S)ADEs / device deficiencies / incidents should be recorded.
- Also, the patient should complete QoL-17 questionnaire and the questionnaire about the product.

Further therapy, if still necessary, may now be selected by the investigator according to the local standards of the centre, the type of this therapy should be recorded.

No further patient data will be collected from this point on, except of the final data regarding SAEs/ SADEs which remained unresolved by the time the patient completed participation in the study. Such cases should be, whenever possible, followed up upon resolution or till the moment no further follow up is possible.

In case the patient has terminated the study participation earlier by any reason, the parameters listed above should be collected, whenever possible.

Also, the investigator should complete the on-line questionnaire about the study product and the compression bandage after the last patient at the site completed their participation (see Annex 2).

6.5 Termination Criteria

6.5.1 Individual

Patients may terminate their participation in the study at any time without providing reasons and without any disadvantages for their care. However, it is recommended to collect the reason for voluntary discontinuation in case the patient is ready to provide it.

Patients may be excluded from the study participation if violation of an inclusion or exclusion criteria is discovered after the enrolment (will be decided on a case-by-case basis, considering patient's safety).

Patients may be excluded from the investigation by the investigator if they violate the clinical investigation plan and if they are not compliant to treatment procedures.

6.5.2 Centre-specific

Centres may be excluded from the investigation by the sponsor if repeated major protocol deviations (see chapter 11.1) are observed at the site after re-training and reminder to stick to the protocol.

6.5.3 General

If unacceptable risks, or incidents leading to an unacceptable benefit-risk assessment are identified during the conduct of the PMCF, the study will be terminated immediately by the study sponsor.

7. Data Management

Clinical data will be collected via the certified eCRF System ResearchManager. Patient data will be entered into the electronic case report form (eCRF) directly at the study site. Data will be collected in pseudonymized way, patients that are enrolled in the study are assigned to an individual patient ID. The sites have to complete a patient identification log to ensure a secure assignment of data. By signing the informed consent form, the patient agrees with the collection of specified data during the study conduct and transmission of these data to the responsible clinical research organization Axcellant and the e-CRF provider ResearchManager.

7.1 Data Management procedures

The ResearchManager clinical database is qualified as certified clinical database to record clinical study data according to all regulatory requests (ICH E6 Good Clinical Practice (GCP), EU Annex 11, General Data Protection Regulation (GDPR), HIPAA (US) , ISO 27001, NEN 7510 and 21 CFR Part 11 compliant). ResearchManager allows the direct entry of the patient data at the site via a secure internet connection (using a registration request document with associate profile). Only authorized users with fixed roles have access to the clinical database. The access is controlled and maintained by the Data Management. Every access is automatically logged and changes of the clinical data are recorded in independent audit trails. Any changes of the data entries can be followed by reviewing the audit trails.

Validation procedures will be established as defined by the Data Validation Plan. Plausibility checks will be implemented to avoid or minimize data entry errors. Data cleaning will be performed prior to data transfer.

7.2 Procedures for data retention

After the last study activities have been completed the original study documents and their electronic copies will be stored in the archive of Lohmann & Rauscher GmbH & Co. KG for a period of 10 years (longer archiving periods for patient files as specified by legal regulations have to be observed if applicable). The archive provides storage conditions free from risk of fire, flood, theft and vermin. Access to the files is controlled.

8. Statistical Considerations

8.1 Biometrical aspects of trial design

This randomised double arm trial is designed to confirm the performance and safety of Suprasorb®X+PHMB Pro in comparison to the former product.

8.2 Measures against Bias

To avoid selection bias and to ensure structural comparability of groups the patients will be randomised in a 1:1 ratio to each treatment group. Block randomisation with randomly varying block sizes (2-6) will be employed to maintain allocation concealment and balance the number of patients across groups.

8.3 Primary Endpoint

Change in the grade of maceration during 3 weeks of treatment with Suprasorb®X+PHMB (Pro) (by the investigators' assessment as well as by an independent assessment of the wound photos).

8.4 Secondary endpoints

The secondary endpoints are:

- Wound area changes over time (by the investigators' assessment as well as by an independent assessment of the wound photos)
- Change of necrotic & fibrinous / granulation tissue rate in the wound bed (by an independent assessment of the wound photos)
- Change of wound infection status during the study (by a TILI and CDC score)
- Product safety (assessed by rate of product-related complications)
- Change of wound exudation and presence of peri-wound oedema (by the investigators' assessment)
- Change in patients' pain (measured by NRS scale)
- Product usability (assessed for both Suprasorb®X+PHMB (Pro) and Rosidal 1C by means of user and patient questionnaire)
- Change in quality of life (assessed by means of Wound-QoL-17 scale)
- Oedema reduction (by measurement of limb circumference)
- Sub-bandage pressure levels retention (difference of the pressure levels, measured at the time of application and before the next dressing change)

8.5 Sample size calculation

Enrolment of 150 patients, under assumption of 5% drop-out rate, will allow to estimate the percentage of patients with selected level of maceration at the end of treatment by the study arm with

precision equal or greater (i.e. width of 95% confidence interval less than or equal to) 24 percentage points for percentage of 50% and increasing (i.e. decreasing width of 95% confidence interval) for percentages lower than and higher than 50%.

8.6 Analysis population

Data will be evaluated according to the full analysis set, safety analysis set and per protocol set.

The **full analysis set** (FAS) includes all patients randomised independently of the real treatment they got – following the intent-to-treat principle.

The **safety analysis set** (SAS) includes all patients randomised and treatment started.

The **per protocol set** (PPS) includes all patients who were compliant to the procedures as defined by the PMCF plan.

The following patients will be excluded from the per-protocol analysis:

- Patients not meeting the inclusion/ exclusion criteria
- Initiation of study procedure prior to obtaining informed consent
- No available measurements of the primary variable/ endpoint
- Incomplete treatment, i.e. if treatment is discontinued due to complications or an undesirable event or for other medical reasons
- Change of assigned treatment to the other group without medical reason

8.7 Subgroups

As a part of exploratory analyses, efficacy analyses will be performed in subgroups by maceration grade at the study entry.

8.8 Statistical Analysis

All data available in the CRF and signed by the investigator will be transferred for analysis. Statistical analysis will be performed using descriptive and confirmatory statistical methods and no format comparisons between study arms will be performed. Statistical analyses will be described in detail in a separate document (SAP – Statistical Analysis Plan) once the study plan and the CRF are finalized.

All efficacy statistical analyses will be conducted for FAS and PP sets separately, and safety analyses will be conducted for SAS set.

The categorical data will be presented as number of non-missing observations, absolute and relative frequency, and count of missing observations. All results for continuous variables will be expressed as number of non-missing observations, count of missing observations, mean and standard deviation, median with range (min./max.).

Outcome measures will be summarized using descriptive statistics by study arm and by time point of assessment. If applicable, changes in relevant parameters (e.g. pain or questionnaires for user satisfaction) from baseline will be calculated.

In assessment of primary endpoint (maceration at end of treatment, measured on 4-point scale) percentage of patients with maceration at each of 4 levels of the scale will be reported, by study arm, with corresponding two-sided 95% confidence intervals.

Reported adverse events / incidences and known side effects will be summarized and presented as count of events and incidence per event type.

A level of statistical significance alpha is set at 0.05, what corresponds to the two-sided 95% confidence intervals

The analysis will be performed using the R version 4.1.3 or later (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

8.9 Handling of missing data

Missing data will be listed and documented in the final analysis.

8.10 Interim analysis

An interim analysis is planned upon inclusion of 75 patients (50% of the study population). The exact list of the analysed parameters will be described in the Statistical Analysis Plan (SAP).

8.11 Final analysis

The final analysis will be conducted after the end of study, when all observations of all sites were gathered, all data management procedures were completed and widely consistent data without discrepancies are available. The exact details of the final analysis will be described in the Statistical Analysis Plan (SAP).

9. Safety and Event Handling

9.1. Definitions

During the conduct of the PMCF adverse events as defined in ISO 14155:2020 shall be documented by the investigators. All adverse events will be evaluated by a medical expert with regard to device relation. If supplemental information is needed for the evaluation the investigators might be asked to provide further details. Any adverse event for which relation to the medical device cannot be excluded will be included in the safety assessment.

The following definitions on the basis of ISO 14155:2020 will be used:

Adverse event (AE)

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 1 to entry: This definition includes events related to the investigational medical device or the comparator.

Note 2 to entry: This definition includes events related to the procedures involved.

Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices.

Adverse device effect (ADE)

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

Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2 to entry: 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 led to any of the following

a) death,

b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic diseases, or

3) in-patient or prolonged hospitalization, or

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

c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

Note 1 to entry: 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.

Device deficiency

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

Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling.

Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator.

Also, the following definitions on the basis of MDR EU Regulation 2017/745 and German MPDG (Medizinprodukte-Durchführungsgesetz), as well as the German MPAMIV (Medizinprodukte-Anwendermelde- und Informationsverordnung):

(Serious) Incidents

- 'Incident' means any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect;
- 'Serious incident' means any incident that directly or indirectly led, might have led or might lead to any of the following: (a) the death of a patient, user or other person, (b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, (c) a serious public health threat

All SAEs, SADEs, device deficiencies with suspected SADE potential or suspected serious incidents according to MDR EU Regulation 2017/745 and national law **have to be immediately reported** to Lohmann & Rauscher GmbH & Co.KG

- by fax at +49 2631 99 1566 or
- by e-mail at Vigilance.int@de.LRMed.com, Martin.Abel@de.LRmed.com (Vigilance Officer L&R) and Daria.Trofimenko@de.LRMed.com (L&R Project Manager for the study)

9.2. Documentation of AEs/SAEs, device deficiencies and (serious) incidents

All AEs will be documented in the CRF including all information listed below. Exempted are the following conditions, which will be documented in other CRF sections:

- Occurrence or increase of infection signs
- Wound size increase
- Signs of maceration

- Injury to the wound ground during dressing change
- Increase of pain or exudation.

Also, pre-existing diseases and conditions (already present before the first application of the medical device) are not documented as adverse events but as concomitant diseases.

The AEs should be documented in the CRF including the following information:

- Date and time of onset and resolution
- Severity
- Causal relationship with a medical device / procedure
- Seriousness
- Measures taken in respect to AE, including interruption or withdrawal of investigation treatment
- AE status at the end of study

The investigator will classify the severity of AEs as follows:

- Mild: clinical symptoms or signs that are well tolerated and do not interfere with everyday activities
- Moderate: clinical symptoms or signs that are enough to impair everyday activities
- Severe: clinical symptoms or signs that markedly impair the trial subject and result in an inability to work or go about everyday activities

The investigator will assess for every AE whether a causal relationship with the medical device / study procedure can be assumed or not. The assessment includes consideration of the nature and type of reaction, the temporal relationship with the medical device, the clinical status of the trial subject, concomitant medication and other relevant clinical factors. If the event is considered to appear due to lack of efficacy or as a symptom or sign of the underlying disorder, no causal relationship should be assumed.

The following definitions are used to assess the causal relationship between all AEs and the medical device:

- Certain: clinical event, including laboratory test abnormality, occurring in a plausible time relationship to medical advice application or procedure, and which cannot be explained by concurrent disease or other measurements/ procedures. If the event disappears after interruption of treatment with the study product (or comparator) and reappears after its re-application (satisfactory rechallenge procedure), this event is to be regarded as certainly related to the product.
- Probable/likely: clinical event, including laboratory test abnormality, with a reasonable time sequence to medical advice application or procedure, unlikely to be attributed to concurrent disease or other measurements/procedures, and which follows a clinically reasonable response on withdrawal (rechallenge). Rechallenge information is not required to fulfil this definition.

- Possible: clinical event, including laboratory test abnormality, with a reasonable time sequence to medical advice application or procedure, but which could also be explained by concurrent disease or other measurements/procedures. Information on withdrawal of the study product (or comparator) may be lacking or unclear.
- Unlikely: clinical event, including laboratory test abnormality, with a temporal relationship to medical device application or procedure which makes a causal relationship improbable, and for which other drugs, measurements/procedures or underlying disease provide plausible explanations.
- Conditional/unclassified: clinical event, including laboratory test abnormality, reported as an adverse reaction, for which more data is essential for a proper assessment or the additional data are under examination.
- Unassessable/unclassifiable: report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Regardless of the assumed causal relationship, every SAE that occurs during the investigation (from the moment of ICF signature by the patient) must be documented in the appropriate part of the AE-CRF and sent to the sponsor within 24 hours. Non-serious AEs will be processed after the AE-CRF is collected and forwarded to the sponsor.

Regardless of whether a causal relationship between a SAE and the medical device is suspected, trial subjects who develop serious adverse events must be monitored until all symptoms have been subsided, pathological laboratory values have returned to pre-event levels, a plausible explanation is found for the SAE, the trial subject has died, or the investigation has been terminated for the trial subject concerned.

All device deficiencies and (suspected serious or serious) incidents, revealed during the study, should be directly reported to the sponsor's vigilance team. Prior to the reporting, the investigator should preliminary assess the event for the presence of seriousness criteria, according to MDR EU Regulation 2017/745 and the German and Polish law. In case the deficiency / incident met one of such criteria, expedited reporting (within 24 hours) is required. Also, in case the event is related to the study patient, corresponding SAE form should be completed and sent within 24 hours. Assessment and processing of the adverse events, device deficiencies and (suspected serious or serious) incidents will be performed by the sponsor.

10. Monitoring

During the conduct of the PMCF monitoring will be performed. A monitor will have regular contacts with the investigation sites.

A risk-based monitoring approach will be utilized for the study data.

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

The following visits will be performed during the study:

- Site qualification / selection visit;
- Initiation visit;
- Routine monitoring visits for data review and ongoing sites' assistance;
- Close out visit after the end of the documentation.

Detailed information about the amount and the scope of the monitoring will be presented in the monitoring plan.

11. Deviations from the study investigation plan

Protocol deviation is any noncompliance with the study protocol or requirements laid down in the EN ISO 14155:2020 (Clinical investigation of medical devices for human subjects — Good clinical practice). The noncompliance may be either on the part of the study patient, or the investigator / study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the investigator to identify and report deviations within 5 working days of the identification. All deviations must be addressed in study source documents and reported to the responsible LEC(s), if required by their policies. The site investigator is responsible for knowing and adhering to the reviewing LEC requirements.

11.1 Major deviations

The following deviations will be considered major deviations and will lead to the exclusion of the patients from the PP population:

- No informed consent form available for a patient or informed consent form was not signed by a patient themselves;
- Initiation of any study procedure prior to obtaining informed consent;
- Inclusion of non-eligible patient (deviation of the inclusion / exclusion criteria);
- Change of the initially assigned study product during the course of treatment.

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.

In case of repeated major protocol deviations at the site, study sponsor may make a decision of its closure.

12. Regulatory and Ethical Considerations

To fulfil requirements on medical device manufacturers, Lohmann & Rauscher GmbH & Co. KG conducts this multicentre, randomised in parallel groups, controlled study within the framework of Post-Market Clinical Follow-up (PMCF) in accordance with MEDDEV 2.12/2 rev. 2 and MDR EU Regulation 2017/745. Compliance with the applicable Polish legislation (Medical Devices Act of 7 April 2022) and MEDDEV 2.12-1 will be ensured.

The post-CE-mark randomised controlled study allows a continuous assessment of the benefit-risk profile for the given intended use with selection of patients according to the provided indications. Since additional examinations, which may be burdensome to the patients, are planned (continuous pressure measurement with a wireless pressure sensor; photographic wound documentation; completion of paper scales / wound questionnaires), the study will require notification to the Polish competent authority: The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products . Sponsor of the study will take over the insurance in accordance with the Polish Law.

The PMCF study will be conducted in accordance with the World Medical Association Declaration of Helsinki (Fortaleza, Brazil, October 2013), and as far as applicable with ISO 14155:2020 Clinical Investigation of Medical Devices for human subjects - Good Clinical Practice.

According to their professional regulations, consultation of the competent ethics committees is required by the participating physicians.

13. Study Report and Publication Policy

The data resulting from this study will be collected on behalf of L&R and will be analysed after all patients have completed the study, and all data validation checks have been performed. The results will be provided in a study report, which will be submitted to the involved ethics committee(s).

It is planned to publish the trial results in a scientific journal and to present them at German and / or international congresses. The order of authorship will be determined by the sponsor and will be based in part on the number of qualified and completing patients at each site.

Publication will be compliant with the document titled “Guidance on the publication of the clinical investigation reports and their summaries in the absence of EUDAMED”- MDCG 2024-15 dated November 2024.

Sponsor of the study will also fulfil Article 77 of Regulation (EU) 2017/745 titled “Information from the sponsor at the end of a clinical investigation or in the event of a temporary halt or early termination”.

Any published data will observe data protection legislation covering the study patients and investigators. Success rates or individual findings at individual trial sites will be known to the sponsor only. By signing the contract to participate in this trial, the investigator declares agreement 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 their name, address, qualifications, and details of their involvement in the clinical trial may be made known to these bodies.

The publication or presentation of the results of a single study centre requires prior notice and prior review and approval from the sponsor.

The support by L&R is to be mentioned in any publication. L&R staff will be included as co-authors as applicable. A copy of all publications should be sent to L&R.

14. Contact Information

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