

Evaluation of TLC-NOSF dressing with poly-absorbent fibres in exuding leg ulcers: two multicentric, single-arm, prospective, open-label clinical trials

Objective: To assess the efficacy, safety and acceptability of a new TLC-NOSF dressing with poly-absorbent fibres in the management of exuding leg ulcers, at the different stages of healing.

Method: This work presents the results of two prospective, multicentric clinical studies: NEREIDES and CASSIOPEE. Patients with a non-infected, moderate-to-strongly exuding leg ulcer of venous or mixed origin, were treated with the dressing and an appropriate compression system for 12 weeks. The wounds included in NEREIDES had to be in debridement stage, and those in CASSIOPEE at granulation stage. In both studies, the primary outcome was the relative wound area reduction (RWAR) at week 12. Main secondary outcomes included healing rate, time-to-reach wound closure, adverse events and acceptability of the dressing by patients and health professionals.

Results: There were 37 patients included in NEREIDES and 51 in CASSIOPEE. The two cohorts presented similar patient and wound characteristics, except from the percentage of sloughy tissue on wound bed at baseline (median: 75% NEREIDES and 30% CASSIOPEE). At week 12, the RWAR (60% NEREIDES and 81% CASSIOPEE), wound closure rates (18% NEREIDES and 20% CASSIOPEE) and mean times-to-reach wound closure (58±27 days NEREIDES and 55±23 days CASSIOPEE) supported the

beneficial outcomes of the treatment in both cohorts. In patients with a wound duration ≤6 months, the wound area reduction reached 85% in NEREIDES and 81% in CASSIOPEE, highlighting the importance to initiate adequate treatment as soon as possible. The nature and frequency of the local adverse events were similar in both studies and consistent with the good safety profiles of the poly-absorbent fibres and of the TLC-NOSF dressings. The acceptability of the dressing (easy to apply, conformable and non-adherent to the wound bed at removal, with no pain or bleeding at removal) has been judged 'very good' or 'good' at each stage of the healing process, by both nursing staff and patients.

Conclusion: These clinical results establish the new TLC-NOSF dressing with poly-absorbent fibres (UrgoStart Plus, Laboratoires Urgo) as an effective, safe and simple treatment for the local management of leg ulcers, at the different stages of healing and until wound closure.

Declaration of interest: This study was supported by a grant from Laboratoires Urgo. C. Tumba, S. Bohbot, and O. Tacca are employees of Laboratoires Urgo. ML. Sigal and S. Meaume have received monetary compensation as speakers for Laboratoires Urgo. Data management and statistical analyses were conducted independently by Altizem.

clinical trial • sucrose octasulfate dressing • TLC-NOSF dressing • UrgoStart • venous leg ulcers

Venous leg ulceration (VLU) is a common and serious medical condition, affecting 1% to 3% of the older population in Western countries.¹⁻³ These chronic wounds are known to be painful and distressing, with considerable impact on patients'

quality of life (QoL).⁴ Their management can be substantially expensive and time-consuming for both health-care systems and patients.⁵ Despite appropriate local and holistic management with effective compression therapy, 40–50% of VLUs still remain unhealed after 12 months,⁵ and the recurrence rate within three months of healing is around 70%.³ Moreover, the longer a leg ulcer remains unhealed, the less chance it has to close.⁶⁻¹⁰

VLUs are characterised by a continuous inflammatory state, cellular dysfunction and protease imbalance.¹¹ The elevated and prolonged expressions of matrix metalloproteinases (MMPs) found in the wound tissue and fluid have been correlated to the impaired healing and chronicity of VLUs, as in other types of chronic wounds, such as diabetic foot ulcers (DFU) and pressure ulcers (PU).¹² These high MMP levels are reported from VLU occurrence, and the highest levels seem to be reached during the inflammatory stage.^{12,13} To address

Michèle-Léa Sigal,¹ MD; Azeddine Addala,² MD; Hervé Maillard,³ MD; Maxime Chahim,⁴ MD; Florent Sala,⁵ MD; Sophie Blaise,⁶ MD; Sophie Dalac,⁷ MD; Sylvie Meaume,⁸ MD; *Serge Bohbot,⁹ MD; Clémence Tumba,¹⁰ PharmD; Olivier Tacca,¹⁰ PhD

*Corresponding author email: s.bohbot@fr.urgo.com

1 Dermatology Department, Victor Dupouy Hospital, Argenteuil, France. **2** Vascular Medicine Department, Edouard Herriot Hospital, Lyon, France. **3** Dermatology Department, Le Mans Hospital, Le Mans, France. **4** Department of Vascular Medicine, Corentin Célton Hospital, Issy Les Moulineaux, France. **5** Vascular Surgery Department, Montréal Polyclinic, Carcassonne, France. **6** Department of Vascular Medicine, Albert Michalon University Hospital, Grenoble, France. **7** Dermatology Department, Dijon University Hospital, Dijon, France. **8** Geriatric Department, Rothschild University Hospital, Paris, France. **9** Medical Affairs Department, Laboratoires Urgo, Paris, France. **10** Clinical Research Department, Laboratoires Urgo, Chenôve, France.

Table 1. Inclusion and exclusion criteria

Inclusion criteria*	Exclusion criteria
Male or female adult patient (≥18 years old) who has signed an informed consent	Minor or adult under guardianship with impaired capacity to provide informed consent
Inpatient or outpatient who can be monitored by the same investigation team throughout the duration of the study	Pregnant or breastfeeding woman or woman of childbearing potential not protected by an effective contraceptive method of birth control
Patient affiliated to the French Social insurance	Patient who participated in another ongoing clinical investigation
Patient with a leg ulcer of venous or mixed origin with an ankle-brachial pressure index (ABPI) between 0.7 and 1.3	Patient with known hypersensitivity to any component of the evaluated dressing or known allergy to carboxymethylcellulose
Patient who agrees to wear their compression therapy system with the studied dressing every day	Patient for who has a hyperbaric treatment planned in the 12 weeks after inclusion (not mentioned at the time of the NEREIDES study)
Moderate or highly exuding ulcer requiring the use of an absorbent dressing	Patient with a severe illness that might lead to a premature discontinuation of the trial
Covered by: ■ 70% or more of sloughy tissue (for NEREIDES) ■ 50% or more of granulation tissue (for CASSIOPEE) And with a wound duration ranging between: ■ 1 and 36 months (for NEREIDES)* ■ 3 and 18 months (for CASSIOPEE)† With a wound area ranging between: ■ 3 and 50cm ² (for NEREIDES) ■ 3 and 20cm ² (for CASSIOPEE)	Patient with an active neoplastic condition, treated by radiotherapy, chemotherapy, or hormone therapy Patient with a systemic infection not controlled by suitable antibiotic treatment Patient who has presented a deep venous thrombosis event within the previous three months Wound requiring a surgical treatment or for which a surgery is scheduled in the 12 weeks after inclusion
If a patient presented with several ulcers at the inclusion visit, the investigator selected one wound (the target ulcer) for the evaluation, which best met the selection criteria, distant from the edge of any other wound by a minimum of 3cm. The other wounds could be treated as per the investigating centre's standard procedures	Cancerous wound Ulcer whose surface is still totally or partially covered by dark necrotic tissue Ulcer clinically infected at initiation of the treatment

*The NEREIDES study also allowed amputation wounds with no revascularisation procedure scheduled in the 12 weeks following inclusion, and category III or IV pressure ulcers according to the European Pressure Ulcer Advisory Panel Classification, located on heel or pelvis (trochanter, ischium, sacrum area). †In CASSIOPEE study, it was expected that the included wounds would be of longer minimum duration (due to the debridement stage time), and of smaller maximum area (after a prior wound area reduction during the course of the debridement stage), as reflected by the specifications of the inclusion criteria

this imbalance, reducing levels of MMPs has been proposed to represent a possible therapeutic modality to improve ulcer healing.^{13,14}

Dressings including the Technology Lipido-Colloid with Nano Oligo Saccharide Factor (TLC-NOSF) are known for their protease inhibiting and healing enhancer properties.¹⁵ The superior efficacy on wound healing processes of these dressings, associated with good standard of care, has been previously demonstrated in the local treatment of chronic wounds, and their clinical evidence in DFUs and VLUs has been recently highlighted by the National Institute of Health Care Excellence (NICE) in its related evidence-base

guidance.¹⁶ In a double-blind, randomised controlled trial (RCT), Edmonds et al. have reported a significant higher closure rate of DFUs after 20 weeks of treatment with a TLC-NOSF dressing compared with the control dressing, alongside higher wound area reductions, higher magnitude of re-epithelialisation wave and shorter time-to-reach wound closure.¹⁷ In two other RCTs, one of them also with a double-blind design, significant higher wound area reductions and re-epithelialisation waves have been reported in patients with VLUs, respectively, after eight and 12 weeks of treatment with TLC-NOSF dressings, compared with a control dressing commonly used in this indication, and with another type of protease-inhibiting dressing.^{18,19} In real-life, the analysis of the pooled data from eight non-interventional studies, including more than 10,000 patients with VLUs, DFUs, or PUs, established similar favourable wound healing outcomes with substantial reduced times-to-reach wound closure, compared with that reported in the Social Health Insurance system database.²⁰ Moreover, in patients with venous and mixed ulcers, these outcomes were associated with a significant improvement of the patients' health-related QoL,²¹ and the cost-effectiveness of the TLC-NOSF treatment has been established.²² Finally, according to the clinical evidence, the TLC-NOSF dressings are well tolerated in patients with chronic wounds and well accepted by these patients and the health professionals.^{15,17-18}

However, as the guidelines from the European Wound Management Association (EWMA) and Wounds Australia point out, it is still important to select dressings that are appropriate, based on the wound bed and tissue characteristics, the specific ulcer stage and the amount and type of exudate.³ Most VLUs produce large amounts of exudate, containing high concentrations of proteases and inflammatory cytokines that may damage surrounding skin. The presence of slough and devitalised tissue on the wound bed also provides an ideal environment for further healing delay and bacterial proliferation.^{3,23} In particular, the presence of >50% of sloughy tissue has been shown to significantly slow down the healing process²⁴ and increase the risk of wound closure failure.⁶ Thus, the management of sloughy tissue and fibrin residues on the wound bed is crucial for optimal wound healing. Passing the debridement stage of the healing process can be time-consuming and delay the initiation of effective treatments that are more appropriate in the granulation stage. Poly-absorbent fibres ensure the absorption of exudate and the trapping of sloughy residues and the interest of these fibres in the management of exuding VLUs from the debridement stage has been previously established through a RCT.²⁵ The TLC-NOSF dressing range already included contact layers and foams, with or without silicone border. Combining the TLC-NOSF healing matrix with poly-absorbent fibres, the new dressing pad should offer an appropriate solution for the management of VLUs, whatever the level of sloughy tissue present at initiation of treatment. The purpose of

the two trials jointly presented in this paper was to evaluate the efficacy, safety and acceptability of this promising new dressing, in the local management of exuding leg ulcers, at the different stages of healing.

Material and methods

Study design

NEREIDES and CASSIOPEE are two multicentric, single-arm, prospective, open-label clinical trials. These two pilot studies differed essentially in the stage of the wound healing process of the included wounds: debridement or granulation stage, defined by the proportion of sloughy tissue present on the wound bed at baseline. In NEREIDES, patients were enrolled from 19 active centres, between September 2012 to January 2013. In CASSIOPEE, patients were enrolled between May 2017 and February 2018 from 16 active centers, of which half were common to those involved in CASSIOPEE. In both studies, the investigating centers

included dermatology and vascular medicine hospital wards, wards of private-practice physicians, angiologists and dermatologists located in France, and both hospitalised and ambulatory patients were enrolled.

Patients

The eligible participants were adult patients (≥ 18 years old) with an exuding leg ulcer of venous or mixed origin. The ulcer surface area had to be covered by 70% or more of sloughy tissue without dark necrotic plaque in NEREIDES (debridement stage at initiation of the treatment) and by 50% or more of granulation tissue without dark necrotic plaque in CASSIOPEE (granulation stage). All exclusion and inclusion criteria are outlined in Table 1.

Endpoints

The primary outcome of both studies was relative wound area reduction (RWAR) after 12 weeks of

Fig 1. Leg ulcer participant flow in the NEREIDES and CASSIOPEE studies (ITT—intention-to-treat; mITT—modified intention-to-treat)

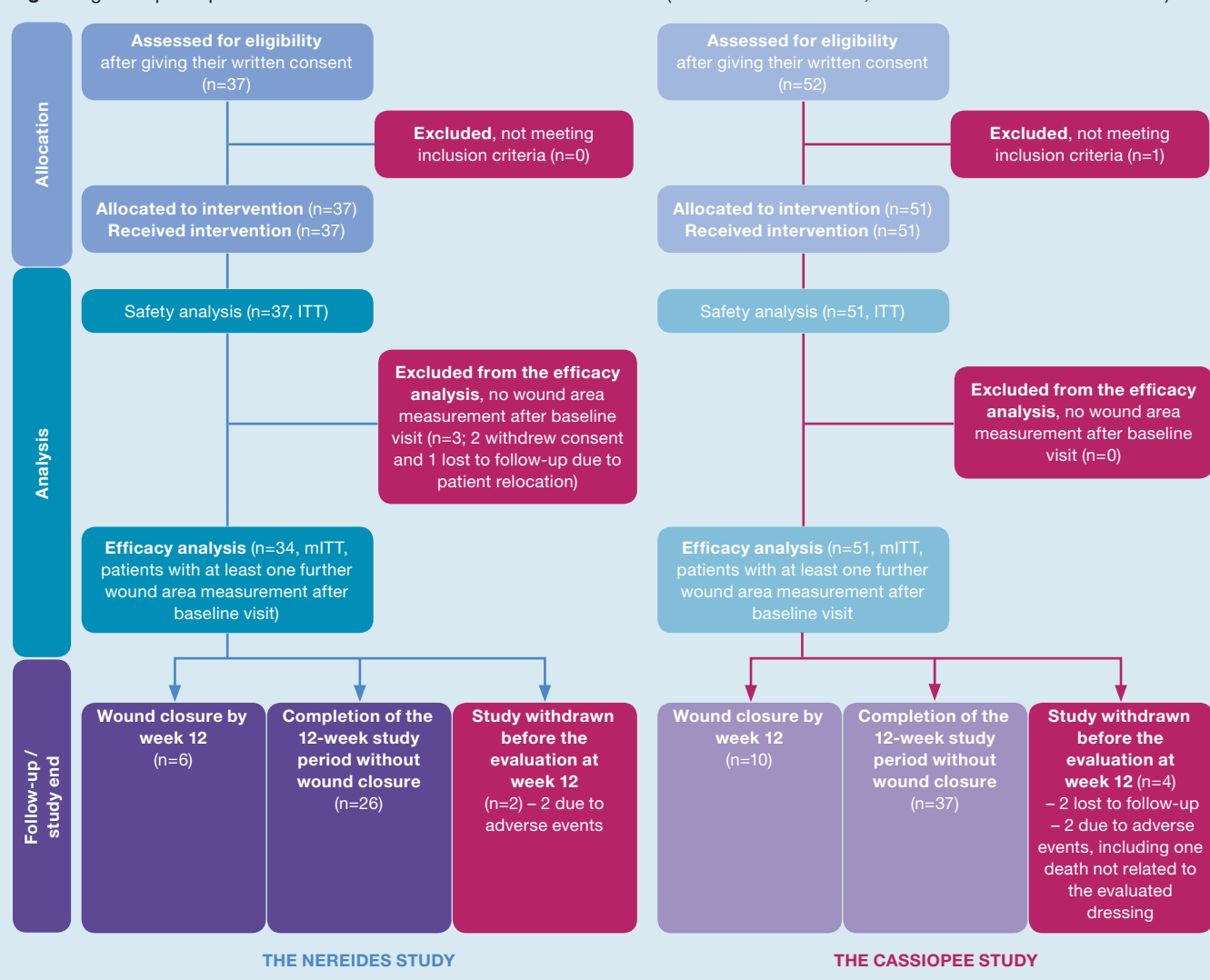


Table 2. Patient baseline characteristics

Patient characteristics	NEREIDES n=37	CASSIOPEE n=51
Sex (female, n (%)/male, n (%))	27 (73%)/10 (27%)	37 (73%)/14 (27%)
Age (years, mean±SD)	75.5±13.3	79.3±10.7
BMI (kg/m ² , mean±SD)	26.6±4.6	26.1±5.2
BMI >30kg/m ² (n, %)	7 (19%)	8 (16%)
Outpatient/hospitalised	36 (97%)/1 (3%)	46 (90%)/5 (10%)
Major medical condition and history*	36 (97%)	48 (94%)
High blood pressure (n)	21	31
Heart disease (n)	17	22
Diabetes (n)	10	12
History of allergy/hypersensitivity (n)	7	19
Other disorders (n)	34	43
Smoking habit (n)	3	4
Venous disease history*	33 (89%)	46 (90%)
History of deep vein thrombosis (n)	10	16
History of venous surgery (n)	14	21
History of venous ulcer (n)	24	26
Familial history of venous disease (n)	23	25
ABPI (mean±SD)	1.01±0.12	1.06±0.13

*Multiple answers possible. SD—standard deviation; BMI—body mass index; ABPI—ankle-brachial pressure index

treatment, expressed as a percentage. All wound areas were centrally measured from acetate tracings by two experienced operators, independent from the sponsor, using digital software (Universal Desktop Ruler).

Secondary outcomes included:

- The absolute wound area regression (AWAR) (in cm²)
- The number and percentage of participants with wound closure by week 12. Wound closure was assessed by investigators and defined as 100% re-epithelialisation without exudate, residual crust or anymore need for cutaneous protection
- The time-to-reach wound closure (from baseline visit to 100% re-epithelialisation, in days)
- The clinical change of the wound bed condition with the estimate by investigators of the percentage of wound area covered by sloughy tissue, granulation tissue or dark necrotic residues
- The clinical change of the periwound skin condition, assessed by investigators as healthy or not healthy (including erythematous, oedematous, irritated, eczematous or macerated skin)
- The safety profile of the evaluated dressing with the nature, incidence, imputability and severity of adverse events documented by the investigating physicians during the study period
- The acceptability of the evaluated dressing by the patient, nursing staff and investigating team through the evaluation, at each visit, of ease of application,

conformability, and ease of removal, without adherence to the wound bed, bleeding, pain or impact on the dressing integrity

- The Global Performance Score (on a 0–36 scale) of the evaluated dressing rated by the investigating physicians at the last evaluation visit. This subjective score, used in previous clinical studies, is calculated on the basis of nine parameters (efficacy, safety, preservation of granulation tissue, pain during dressing removal, management of exudate, handling, conformability of the dressing, patient comfort and acceptability of the dressing), using for each parameter a qualitative five-point scale ranging from 4:very good, 3:good, 2:fair, 1:poor, to 0:very poor.^{25,26} The higher the score, the better the dressing performance.

Data collection

Once written informed consent had been obtained, the ankle-brachial pressure index (ABPI) measurement performed (Dopplex D900, Huntleigh Healthcare, UK) and all the inclusion and exclusion criteria validated at the inclusion visit, the patients were included in the trials. Basic demographic information, relevant medical history of the patient and characteristics of the target ulcer (location, duration, clinical assessment) were recorded. Wound area tracing and photographs were made by the investigating physician before the initiation of the treatment.

Patients were treated with the evaluated dressing until wound closure or for a period of 12 weeks maximum. Patient evaluations were regularly scheduled until the end of the treatment period. In both studies, investigating visits were planned at least at week 2, week 4, week 8 and week 12. These evaluations performed by the investigating physicians included clinical examination with local tolerance assessment, wound-area tracing and photographs of the treated wound according to the standard procedure provided in the study protocols.

At each dressing change, compression therapy adherence, dressing acceptability, local practice such as debridement if performed, secondary dressing if applied and any treatment prescribed to the patient had to be documented in the patient's Case Report Form or the Nursing Care Diary. At the last clinical evaluation, the overall performance of the dressing was evaluated by the investigating physicians using the Global Performance Score.

Study dressing and intervention

The study dressing, UrgoStart Plus (Laboratoires URGO, Chenôve, France), is a sterile, non-woven pad made of cohesive poly-absorbent fibres, coated with a soft-adherent lipido-colloid healing matrix containing sucrose octasulfate (Technology Lipido-Colloid-Nano Oligo Saccharide Factor: TLC-NOSF, an enhancer of chronic wound closure).¹⁵ This primary dressing, designed to be in contact with the wound bed and the surrounding skin, is indicated in the local treatment of exuding chronic wounds.

The evaluated dressing (10x10cm in NEREIDES and 10x12cm in CASSIOPEE) was applied by the investigating physicians, hospital or community nurses, according to the manufacturer's instructions detailed in the trial protocols. At each visit, adequate wound debridement was done at the investigator and nurse's discretion. The use of 0.9NaCl solution was recommended for wound cleansing. Dressing changes were performed according to the judgment of the investigator, depending on the level of exudate and the clinical status of the wound. The use and nature of a secondary dressing covering the study dressing was left up to the investigator, but had to be documented. Leg ulcers were treated with appropriate compression therapy, as recommended by French Healthcare Authorities (i.e. applying the highest pressure borne by the patient, using multilayer bandages as first-line prescription).^{27,28} The compression system chosen was based on a full patient assessment, patient compliance and clinician preference.

Statistical analysis

Considering the non-comparative design of the trials, a formal sample size calculation was not performed. The statistical analyses of both trials were conducted by a contract research organisation (Altizem, Nanterre, France) according to a previously approved statistical analysis plan. Study data were entered into a SAS database (version 9.1.3). Analyses and dressing performance evaluations were only descriptive and no statistical tests were used. Continuous variables were described by number of observations (n), mean value, standard deviation (SD), median and range. Categorical variables were described in terms of number of patients and percentages.

All the patients for whom at least one follow-up wound area tracing was available were introduced in the efficacy and acceptability analyses (modified intention-to-treat basis, mITT) and all the included patients whose wounds were treated at least once with the evaluated dressing were taken into account in the safety analysis (intention-to-treat basis, ITT). For the analysis of the planimetry data, the last observation carried forward (LOCF) was used to compensate for missing data when necessary (when a patient was withdrawn before the week 12 treatment). Post-hoc analyses were performed in both studies to estimate mean times-to-reach wound closure using the Kaplan-Meier approach, and to determine relative wound area reductions and wound closure rates by week 12 in subgroups of patients classified according to their ulcer duration at initiation of the treatment.

Ethics approval

NEREIDES was performed before the dressing CE-marking, while CASSIOPEE was performed post-CE-marking. These two clinical investigations were conducted in accordance with Good Clinical Practice (GCP), with the principles laid down in the Declaration of Helsinki and with French law relative to the protection of persons. The authorisation from the French Healthcare Authorities

(ANSM) to conduct NEREIDES (RCB ID No 2012-A00491-42) was obtained in August 2012 and the approval of the French Ethics Committee in June 2012 (CPP Ile de France VIII). CASSIOPEE (RCB ID No 2016-A02071-50) was classified by the ANSM as not requiring an ANSM authorisation, and the approval of the French Ethics Committee for this clinical trial was obtained in March 2017 (CPP Ile de France X).

Results

Baseline characteristics of treated patients and leg ulcers

A total of 37 patients with leg ulcers were enrolled into NEREIDES, and 51 into CASSIOPEE. There were four

Table 3. Wound and periwound baseline characteristics

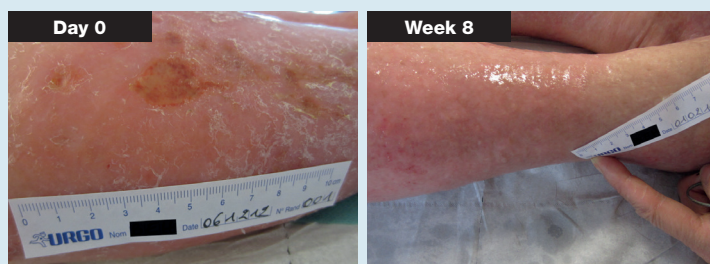
	NEREIDES n=37	CASSIOPEE n=51
Ulcer duration (months, mean±SD)	11±10	9±5
Median (range)	7 (1–36)	7 (3–18)
Duration >6 months (n, %)	19 (51%)	28 (55%)
Duration >12 months (n, %)	13 (35%)	12 (24%)
Compression therapy previously worn	28 (76%)	43 (84%)
Recurrence of a previous ulcer (n, %)	19 (51%)	20 (39%)
Initial wound area (cm ² , mean±SD)	9.1±7.6	9.8±7.0
Median (range)	7.1 (0.9–32.0)	7.8 (2.4–37.7)
Area >10 cm ² (n, %)	13 (35%)	20 (39%)
Wound bed aspect (% of wound bed covered)		
Sloughy tissue (mean±SD)	78±10	28±15
Median (range)	75 (70–100)	30 (0–49)
Granulation tissue (mean±SD)	22±10	72±15
Median (range)	25 (0–30)	70 (51–100)
Exudate levels		
Moderate	34 (92%)	37 (73%)
High	3 (8%)	14 (27%)
Periwound skin condition		
Healthy (n, %)	14 (38%)	8 (16%)
If not healthy*:	23 (62%)	43 (84%)
Erythematous (n)	18	30
Oedematous (n)	7	17
Irritated by the dressing (n)	5	4
Eczematous (n)	2	11
Macerated (n)	5	11
Other (n)	1	5
Pain between dressing changes		
None	17 (46%)	16 (31%)
Minor	7 (19%)	22 (43%)
Moderate	7 (19%)	8 (16%)
Severe	6 (16%)	5 (10%)

*Multiple answers possible; SD—standard deviation

Fig 2. Examples of wounds treated by the evaluated dressing in NEREIDES and CASSIOPEE trials



NEREIDES: Patient 17-02 at day 0 and week 12



NEREIDES: Patient 26-01 day 0 and week 8



CASSIOPEE: Patient 4-49 at day 0 and week 12



CASSIOPEE: Patient 11-35 at day 0 and week W12

others patients, treated for PUs (n=3) or amputation wounds (n=1) also included in NEREIDES, but as this work focuses on the management of leg ulcers, their data will not be reported here, and the following data only apply to the cohort of patients with VLUs.

The mean treatment period was of 75±27 days per

patient (median value: 85 days) in NEREIDES and 78±19 days (median value: 85 days) in CASSIOPEE. As illustrated in the leg ulcer participant flow chart (Fig 1), 86% (32/37 patients) of the NEREIDES cohort and 92% (47/51 patients) of the CASSIOPEE cohort were followed up until wound closure or week 12. All the patients included in CASSIOPEE and 34 of the 37 patients (92%) included in NEREIDES had a clinical evaluation follow-up and received at least two dressing applications, allowing the mITT analysis (efficacy) to be performed on 34 and 51 patients. In NEREIDES, two out of the 34 patients (6%) prematurely discontinued the study due to adverse events (one due to an allergic reaction and the other due to local pain). In CASSIOPEE, four out of the 51 patients (8%) withdrew before week 12: two due to adverse events (one death unrelated to the evaluated dressing and one secondary infection of the wound), and two were lost to follow-up.

The baseline characteristics of the patients and wounds included in NEREIDES and CASSIOPEE are presented in Table 2 and 3. The cohorts of patients from both studies were very similar. Included patients were mostly outpatients (>90%), predominantly female (73%), with a mean age of 76 (NEREIDES) and 79 years (CASSIOPEE) and an average Body Mass Index (BMI) of around 26kg/m² (overweight). More than half of the included patients had high blood pressure, a quarter of them had diabetes and most of them had a marked venous disease history, including previous VLU episode, history of venous surgery or deep vein thrombosis. The only marked difference between the two cohorts, in terms of medical history, was a higher proportion of patients with a reported history of allergy or hypersensitivity in CASSIOPEE (40% versus 19% in NEREIDES).

As for patient demographics and medical history, ulcer characteristics were very similar in both study cohorts (Table 3). The mean ABI values, respectively of 1.01±0.12 and 1.06±0.13 in NEREIDES and CASSIOPEE, testified the venous aetiology of the treated leg ulcers. At baseline, the included leg ulcers were present for seven months (median values) in both studies.

Compression therapy was documented as previously present in 76% of the patients in NEREIDES and in 84% of the patients in CASSIOPEE. The ulcers were recurrent in 51% of the cases in NEREIDES and in 39% of the cases in CASSIOPEE, highlighting the severity of the venous condition of the included patients. In both studies, the mean wound areas were similar at baseline (9.1±7.6cm² in NEREIDES and 9.8±7.0 in CASSIOPEE), with more than a third of the wounds being larger than 10cm² (35% in NEREIDES and 39% in CASSIOPEE). However, as requested by study protocol, in NEREIDES the treatment was initiated while ulcers were still in the debridement stage of their healing process with 78±10% of wound area covered by sloughy tissue, while in CASSIOPEE, ulcers were already in granulation stage, with 72±15% of wound area covered by granulation tissue.

In both studies, the level of exudate was moderate to

high, slightly more frequently important in the CASSIOPEE cohort (27% versus 8% in NEREIDES). At baseline, the periwound skin condition was generally poor, with a slightly lower proportion of patients with a healthy periwound skin in CASSIOPEE (16%) than in NEREIDES (38%). When periwound skin condition was not reported as healthy, it was mostly described as erythematous (78% and 70%, respectively in NEREIDES and CASSIOPEE), oedematous (30% and 40%), or macerated (22% and 26%). In both study cohorts, pain between dressing changes was reported by most of the patients (54% in NEREIDES and 69% in CASSIOPEE), and when reported, this pain was mainly described as intermittent (100% in CASSIOPEE and 85% of the patients in NEREIDES, the other 15% describing their pain as continuous). Photographs of VLU treated in NEREIDES and CASSIOPEE studies are given as examples in Fig 2.

Wound healing outcomes

After the 12-week treatment period with the evaluated dressing and the associated compression therapy system, the median relative wound area reduction was 60% compared with baseline in the NEREIDES cohort and 81% in the CASSIOPEE cohort (Table 4).

These RWARs were associated at the last evaluation by an AWAR of 2.8cm² in NEREIDES and of 4.7cm² in CASSIOPEE (median values). Additionally, by week 12, a wound closure was reported in 18% of the patients treated in NEREIDES (6/34) and in 20% of the patients treated in CASSIOPEE (10/51). For patients in whom a wound closure occurred, the mean time-to-reach wound closure was 58±24 days in NEREIDES and 55±23 days in CASSIOPEE. The first wound closure event occurred after 28 days of treatment in NEREIDES and after 23 days in CASSIOPEE. In both studies, an improvement or stabilisation of the wounds was reported for the majority of the patients (91% in NEREIDES and 90% in CASSIOPEE), as a relative wound area increase at week 12 was reported in only three patients in NEREIDES and in five patients in CASSIOPEE. According to the Kaplan-Meier approach, the estimated mean time-to-reach wound closure in the global cohort was 97±4 days in NEREIDES and 103±4 days in CASSIOPEE.

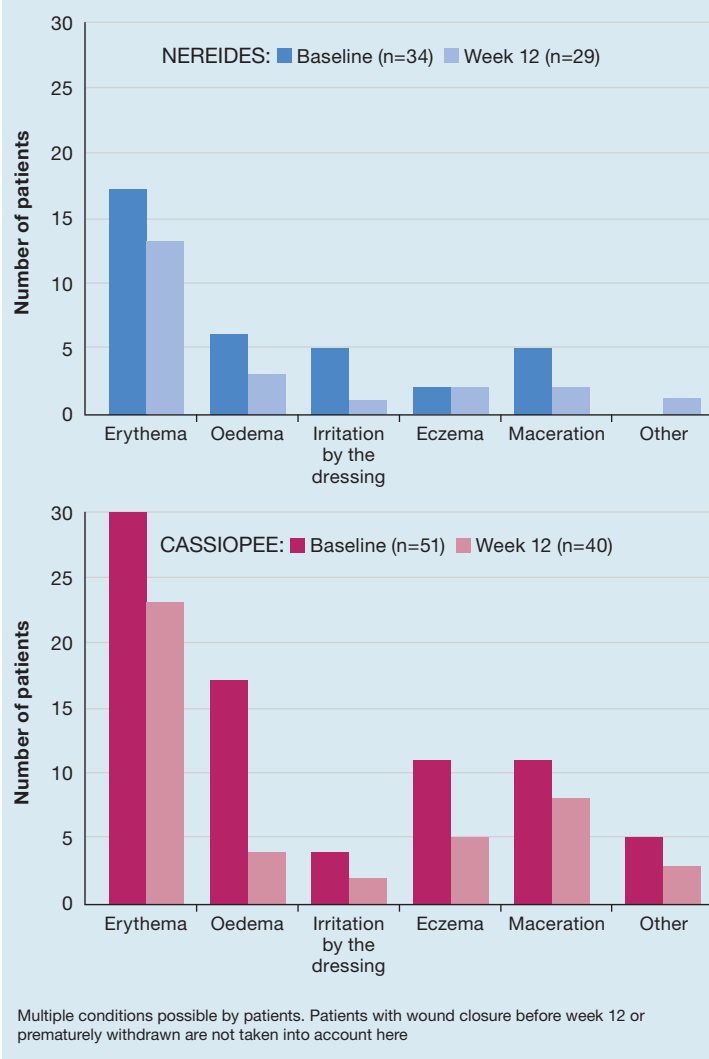
To test the impact of wound duration at baseline on the wound healing process, wounds ≤6 months and wounds >6 months were analysed. In NEREIDES, for the ulcers ≤6 months (n=16), the median RWAR at week 12 was 85% (range: -112–100%). For the wounds >6 months (n=18), the median RWAR was 43% (range: -65%–100%). In CASSIOPEE, the median RWAR was of 81% (range: -204–100%) in ulcers ≤6 months (n=23) and of 82% (range: -78–100%) in ulcers >6 months (n=28). In the NEREIDES cohort, the percentage of closed ulcers by week 12 were similar whatever the wound duration subgroups analysed (3/16, 19% versus 3/18, 17%), while in the CASSIOPEE cohort, wound closure occurred in seven patients with a wound duration ≤6 months (7/23, 30%) and only in three

Table 4. Wound healing outcomes

	NEREIDES n=34	CASSIOPEE n=51
Wound area at D0 (cm²)	7.0 (0.9–32.0)	7.8 (2.4–37.7)
Wound area at Week 12 (cm²)	2.5 (0.0–39.2)	2.0 (0.0–23.9)
RWAR at Week 12 (%)	60 (-112–100)	81 (-204–100)
AWAR at last evaluation (cm²)	2.8 (-20.7–11.8)	4.7 (-11.9–28.0)
Closed ulcers	6 (18%)	10 (20%)
Time to reach wound closure* (days, mean±SD)	58±24	55±23

Median values (range), n(%), otherwise specified; *For patients in whom a wound closure occurred during the 12 week study period, D0-day zero; RWAR—relative wound area reduction; AWAR—absolute area reduction; SD—standard deviation

Fig 3. Number of patients with non-healthy periwound skin at baseline and after 12 weeks of treatment with the evaluated dressing in NEREIDES and CASSIOPEE studies



patients with a wound duration >6 months (3/28, 11%). These outcomes illustrate the fact that wounds stuck for too long in the debridement stage will have a slower wound healing process (decreased median RWAR).

Table 5. Adverse events reported in NEREIDES and CASSIOPEE as unlikely, possibly, probably or certainly related to the evaluated dressing

	NEREIDES n=37	CASSIOPEE n=51
Patients with at least one adverse event related to the evaluated dressing	6 (16%)	9 (18%)
Number of adverse events related to the evaluated dressing*	10	9
Local pain	4 3 possibly, 1 certainly (5%) †	2 possibly (4%)
Cutaneous irritation	–	1 probably (2%)
Peri wound irritation + local pain	1 possibly (3%)	–
Peri wound erythema	1 probably (3%)	1 possibly (2%)
Eczema	1 possibly (3%)	2 possibly (4%)
Inflammatory reaction	1 possibly (3%)	–
Erythema + Oedema + local pain	1 possibly (3%)	–
Allergic reaction	1 possibly § (3%)	–
New wound	–	1 unlikely (2%)
Dermohypodermatitis	–	1 unlikely (2%)
Secondary infection	–	1 unlikely (2%)

The 'unlikely' category did not exist in the NEREIDES Case Report Form; †For each type of event, the corresponding percentage of concerned patients is given; ‡Three 'local pain' events were recorded in one patient. §No confirmation by patch test has been performed. The 'allergic reaction' was also notified as 'possibly' related to a fixation band

Table 6. Wound cares applied in NEREIDES and CASSIOPEE

	NEREIDES N=34	CASSIOPEE N=51
Median number of dressing applied per week	3 (1–7)	3 (1–7)
Dressing cut (yes, %)	490/864 (57%)	1239/1661 (75%)
Secondary dressing applied* (yes, %)	827/921 (90%)	1211/1603 (76%)
Gauze	614/921 (67%)	662/1603 (41%)
Superabsorbent	52/921 (6%)	249/1603 (16%)
Other	215/921 (23%)	339/1603 (24%)
Adherence to compression system (yes, %)	971/1001 (97%)	1662/1679 (99%)
Wound debridement (yes, %)	534/998 (54%)	691/1625 (43%)

* Multiple answers possible, (range)

Moreover, even when wounds pass into the granulation stage, the longer the wound duration was, the lower the wound healing rate will be. In NEREIDES similar outcomes (in terms of RWAR and wound closure rate) were also observed when considering wounds ≤3 months and >3 months, highlighting the fact that the sooner the adequate local management of the wounds, the higher wound healing outcomes obtained.

Changes of the wound bed and peri wound bed condition

In NEREIDES, the relative reduction of the sloughy tissue after 12-weeks of treatment was 83% (from 75% at baseline to 15% at week 12, median values). A similar

relative sloughy tissue reduction of 71% was observed in CASSIOPEE (from 30% to 10%, median values). The median time-to-reach 30% of sloughy tissue in the NEREIDES cohort was 28 days (range: 10–72 days).

A slight improvement in the condition of the peri wound skin was also observed throughout the investigation period in both studies. The number of patients with erythematous peri wound skin decreased from 17 patients at baseline to 13 patients at week 12 in NEREIDES and from 30 patients to 23 in CASSIOPEE. The numbers of patients with oedematous or macerated peri wound skin, as the numbers of patients with a peri wound skin irritated by dressing, also decreased in both cohorts, as represented in Fig 3.

Local tolerability (safety)

Throughout the 12 weeks of treatment, 10 adverse events in six patients were reported by the investigating physician as 'possibly', 'probably' or 'certainly' related to the evaluated treatment in NEREIDES (Table 5). Among these events, four 'local pain' events—the first one associated with peri wound irritation—occurred in one patient. There were two 'local pain' events, the 'inflammatory reaction' and the 'allergic reaction', which led to a definitive discontinuation of the evaluated dressing in four patients, but two of these patients were still followed until week 12, without wound closure, after a switch for another dressing. In CASSIOPEE, nine adverse events occurred in nine patients. These events were judged as 'unlikely', 'possibly' or 'probably' related to the evaluated dressing. The 'local pain' and 'secondary infection' events led to a definitive discontinuation of the evaluated dressing in three patients. For two of these patients, the evaluated dressing was switched for another dressing and patients had been followed until week 12, without wound closure.

As detailed in Table 5, the nature and frequency of these dressing-related events were quite similar in both cohorts, and none of them were serious.

Handling characteristics and Global Performance Score of the dressing according to investigators, nurses and patients' evaluations

Altogether, more than 2500 treatment episodes and dressing evaluations were documented by the investigating physicians and nursing staff during the two clinical trials (Tables 6 and 7). The median number of dressing changes was three per week (range: 1–7) in NEREIDES, as in CASSIOPEE. When the evaluated dressing had been cut (57% of the cases in NEREIDES and 75% in CASSIOPEE), it was usually still covering the peri wound skin (70% of the cases in NEREIDES and 81% in CASSIOPEE). Gauzes (or absorbent dressings) have been used as secondary dressings in 90% of the cases in NEREIDES and in 76% in CASSIOPEE. Patients' adherence to their compression therapy was high in both cohorts (97% NEREIDES and 99% CASSIOPEE). Despite lower sloughy tissue proportion at baseline in CASSIOPEE, wound debridement (mostly mechanical

debridement) was similarly performed in both trials, during approximately one out of two treatments.

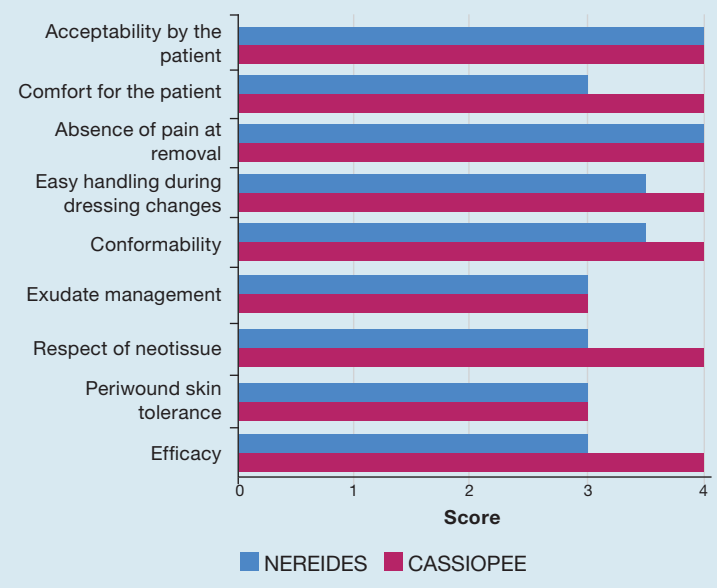
The evaluation of the handling characteristics of the dressing, reported in Table 7, revealed a high level of acceptance by both patients and nurses from the two studies: the evaluated dressing has been, during the large majority of the dressing changes and since the first evaluation, 'very easy' or 'easy' to apply, 'very conformable' or 'conformable' to the wound bed, and 'very easy' or 'easy' to remove, in one piece, without substantial dressing adherence to the wound bed or bleeding.

At the final visit, the Global Performance Score of the tested dressing was rated by the trial investigators at 29 in NEREIDES and 32 in CASSIOPEE (median values), on its 0–36 scale. As reported in Fig 4, all the nine items documented to calculate these Global Performance Scores had at least a value of three ('good') on their 0–4 point-scale. In particular, the comfort for the patient at wearing the dressing and the absence of pain at its removal were confirmed by a 'very good' acceptability of the treatment by the patients from both studies. Finally, the efficacy of the dressing, its exudate management and respect of neotissue and periwound skin were similarly judged by the investigators as 'good' or 'very good' in both cohorts, including when sloughy tissue was less present at initiation of the treatment.

Discussion

In NEREIDES, a 60% wound area reduction was obtained after 12 weeks of treatment, when the TLC-NOSF treatment was initiated on wounds covered by 70% or more of sloughy tissue at initiation. The wound area reduction reached 81% in CASSIOPEE when the treated wounds were covered by 50% or more of granulation tissue. Similar closure rates were also reported in both cohorts (18% and 20%, respectively). These healing outcomes and trajectories appear to be favourable regarding the patient and wound characteristics at baseline. In both studies, the included wounds presented a certain number of poor wound healing prognostic factors: ulcer duration >6 months, more than a third of the wounds with a wound area >10cm², high proportion of recurrence, and poor periwound skin condition. In NEREIDES, the proportion of sloughy tissue on the wound bed was an additional serious risk factor for wound delay and closure failure. Guidelines recommend initial and maintenance debridement in order to ensure formation of good quality granulation tissue and optimal wound healing.^{3,29–31} Indeed, the presence of 50% or more of sloughy tissue on the wound bed have been correlated to poorer wound healing outcomes with an increased risk of prolonged time-to-reach wound closure (adjusted odds ratio 8.89; 95% confidence interval (CI) 2.96–26.73; $p<0.01$),²⁴ and of wound closure failure within 24 weeks (adjusted odds ratio 3.42; 95% CI 1.38–8.45; $p=0.01$).⁶ However, in both NEREIDES and CASSIOPEE, wound area reductions, wound closure rates and time-to-reach wound closure

Fig 4. The Global Performance Score of the dressing as rated at the end of the 12-week treatment by the investigators in NEREIDES and CASSIOPEE (median values). Each item was scored according to the following scale: 4=very good, 3=good, 2=fair, 1=poor, to 0=very poor



were rather tightly consistent despite the marked sloughy tissue characteristics difference between the

Table 7. Acceptability of the handling characteristics of the dressing at application and removal according to the investigators, nurses and patients

	NEREIDES n=34	CASSIOPEE n=51
Ease of dressing application	947	1667
Very easy/easy	100%	99%
Difficult/very difficult	—	1%
Conformability during dressing application	899	1615
Very good/good	98%	97%
Poor/very poor	2%	3%
Ease of removal	970	1643
Very easy/easy	98%	98%
Difficult/very difficult	2%	2%
Loss of dressing integrity	889	1540
None/minor	97%	99%
Moderate/marked	3%	1%
Dressing adherence upon removal	961	1628
None/minor	89%	88%
Moderate/marked	11%	12%
Pain during dressing removal	956	1637
None/minor	87%	87%
Moderate/marked	13%	12%
Bleeding	946	1619
None/minor	97%	97%
Moderate/marked	3%	3%

Reflective questions

- What are the key local barriers to wound healing that a wound dressing should ideally address effectively?
- Describe the types of wounds and the stages of the healing process that can be treated with the TLC-NOSF dressing with poly-absorbent fibres.
- What benefits can be achieved by treating patient with TLC-NOSF dressing with poly-absorbent fibres?

wounds at baseline. When considering the treatment of wounds with the shortest duration, the results were even fully consistent with wound area reductions above 80% in both cohorts. The negative impact of wound duration on wound healing progress in chronic ulcers has long been established.^{7–10} In particular, the longer the debridement stage lasts, the higher risk for wounds to get stuck in a vicious inflammatory cycle. Hence, the sooner appropriate management is implemented, the higher the chance of success.

The poly-absorbent fibres of the new dressing absorbs and traps the wound exudates along with their deleterious residues while the TLC-NOSF healing matrix inhibits the proteases in excess accumulated from the beginning of the healing process. Furthermore, the TLC-NOSF healing matrix restores the impaired biological functions and stimulates angiogenesis through migration and proliferation of endothelial cells.¹⁵ This mode of action could explain how the dressing ensures the rapid transition from the debridement stage, to the granulation stage and to the wound closure. In both NEREIDES and CASSIOPEE, the times-to-reach wound closure in the global cohorts were estimated around 100 days, and consistent with evidence from real-life practice reporting similar closure times and substantial reductions of closure times with TLC-NOSF dressings.²⁰ As in NEREIDES and CASSIOPEE studies, Munter et al. had highlighted the importance of an early initiation of the TLC-NOSF treatment.²⁰ In their pooled analysis of routine practice data from thousands of patients, the shortest time-to-closure was obtained when patients were treated with first-line TLC-NOSF dressings, whatever the severity and nature of the chronic wound they suffered from (70 versus 104 days, $p < 0.001$).

In NEREIDES, as in CASSIOPEE, the global performances of the new TLC-NOSF dressing with poly-absorbent fibres has been judged 'very good' or 'good' in both debridement and granulation stages. Its efficacy on the wound healing process, the important and rapid debridement obtained, and the good management of exudate were reported along with the respect of neotissue and periwound skin, including when sloughy tissue were less present at initiation of the treatment. Despite the difficult condition of the treated patients, particularly prone to sensitisation reactions, the dressing was well tolerated, revealing a safety profile consistent with the good safety profiles of the poly-absorbent fibres and of the other TLC-NOSF dressings reported in the literature.^{15,17–20,25} The new TLC-NOSF dressing has been judged by both nursing staff and

patients easy to apply, conformable to wounds, non-adherent to the wound bed at removal, with no pain or bleeding at removal, and was well accepted at each stage of the healing process.

The management of chronic wounds can be complex, time consuming and very expensive. It is essential to find efficient and well-tolerated solutions, which would also be simple to use, without additional workload for caregivers. Estimation of the proportion of sloughy tissue on the wound bed can be tricky and may vary between evaluators. This estimation is not an issue in itself, unless a treatment is only effective below a certain sloughy tissue threshold and its chances of success are highly affected by it. Moreover, if the proportion of sloughy tissue on the wound bed tends to decrease throughout the wound healing process in some patients, this proportion can substantially vary over time and some wounds continuously fluctuate between debridement and granulation stages. Therefore, decisions regarding the strategy of local wound care could be greatly simplified by the use of dressings appropriate at these stages of the healing process, while further effort could be put on adherence to compression therapy and prevention of ulcer recurrence.

Limitations

The use of different compression therapy systems and the absence of a unique debridement technique suitable for all patients could be considered limitations of these studies. These decisions, however, were consistent with the EWMA guidelines that specify patient' preference and health professionals' experience and habits should be taken into consideration in leg ulcer management strategies.³ Leaving these details at health professionals' judgment is more representative of real-life practice but can generate heterogeneity of outcomes in relatively small sample size studies. Considering the positive outcomes reported here and the consistency of these results with those of the previous RCTs conducted with TLC-NOSF dressings, it would be interesting to corroborate the beneficial performances of this new TLC-NOSF dressing with poly-absorbent fibres within real-life practice studies of larger scale.

Conclusion

The clinical results from NEREIDES and CASSIOPEE studies corroborate the findings of previous clinical trials on TLC-NOSF dressings and confirm the clinical interest of this new TLC-NOSF dressing with poly-absorbent fibres in the local treatment of exuding chronic wounds, at their different wound healing stages and until wound closure. The promotion of the wound healing process, shown through substantial wound surface area reductions and a rapid decrease of the sloughy tissue, in addition to the good safety profile of the dressing and its high acceptability by both health professionals and patients, support the use of UrgoStart Plus in the context of accepted standard of wound care. **JWC**

Acknowledgment

We would like to thank all the patients and health-care professionals who contributed to make these trials possible and, in particular, the investigators for their commitment, time and effort— Jean-Charles Kerihuel, MD (Vertical, Paris) for the Kaplan-Meier estimation of time-to-closure in both studies, and Laetitia Thomassin, PhD (medical writer with Laboratoires Urgo) for her contribution throughout the writing process of this report.

References

- Graham ID, Harrison MB, Nelson EA et al. Prevalence of lower-limb ulceration: a systematic review of prevalence studies. *Adv Skin Wound Care* 2003; 16(6):305–316. <https://doi.org/10.1097/00129334-200311000-00013>
- Moffatt CJ, Franks PJ, Doherty DC et al. Prevalence of leg ulceration in a London population. *QJM* 2004; 97(7):431–437. <https://doi.org/10.1093/qjmed/hch075>
- Franks PJ, Barker J, Collier M et al. Management of patients with venous leg ulcers: Challenges and current best practice. *J Wound Care* 2016; 25(Sup6 Suppl 6):S1–S67. <https://doi.org/10.12968/jowc.2016.25.Sup6.S1>
- Joaquim FL, Silva RM, Garcia-Caro MP et al. Impact of venous ulcers on patients' quality of life: an integrative review. *Rev Bras Enferm* 2018; 71(4):2021–2029. <https://doi.org/10.1590/0034-7167-2017-0516>
- Guest JF, Fuller GW, Vowden P. Venous leg ulcer management in clinical practice in the UK: costs and outcomes. *Int Wound J* 2018; 15(1):29–37. <https://doi.org/10.1111/iwj.12814>
- Margolis DJ, Berlin JA, Strom BL. Risk factors associated with the failure of a venous leg ulcer to heal. *Arch Dermatol* 1999; 135(8):920–926. <https://doi.org/10.1001/archderm.135.8.920>
- Margolis DJ, Berlin JA, Strom BL. Which venous leg ulcers will heal with limb compression bandages? *Am J Med* 2000; 109(1):15–19. [https://doi.org/10.1016/S0002-9343\(00\)00379-X](https://doi.org/10.1016/S0002-9343(00)00379-X)
- Parker CN, Finlayson KJ, Shuter P, Edwards HE. Risk factors for delayed healing in venous leg ulcers: a review of the literature. *Int J Clin Pract* 2015; 69(9):967–977. <https://doi.org/10.1111/ijcp.12635>
- Yang GK, Cao S, Kayssi A et al. Critical Evaluation of Delayed Healing of Venous Leg Ulcers: A Retrospective Analysis in Canadian Patients. *Am J Clin Dermatol* 2016; 17(5):539–544. <https://doi.org/10.1007/s40257-016-0214-4>
- Parker CN, Finlayson KJ, Edwards HE. Predicting the likelihood of delayed venous leg ulcer healing and recurrence: development and reliability testing of risk assessment tools. *Ostomy Wound Manage* 2017; 63(10):16–33
- Raffetto JD. Pathophysiology of wound healing and alterations in venous leg ulcers-review. *Phlebology* 2016; 31(1_suppl Suppl):56–62. <https://doi.org/10.1177/0268355516632998>
- Lazaro JL, Izzo V, Meaume S et al. Elevated levels of matrix metalloproteinases and chronic wound healing: an updated review of clinical evidence. *J Wound Care* 2016; 25(5):277–287. <https://doi.org/10.12968/jowc.2016.25.5.277>
- Beidler SK, Douillet CD, Berndt DF et al. Multiplexed analysis of matrix metalloproteinases in leg ulcer tissue of patients with chronic venous insufficiency before and after compression therapy. *Wound Repair Regen* 2008; 16(5):642–648. <https://doi.org/10.1111/j.1524-475X.2008.00415.x>
- Raffetto JD. Which dressings reduce inflammation and improve venous leg ulcer healing. *Phlebology* 2014; 29(1_suppl suppl):157–164. <https://doi.org/10.1177/0268355514529225>
- White R, Cowan T, Glover D. Supporting evidence-based practice: a clinical review of TLC healing matrix (2nd edition). MA Healthcare Ltd, 2015
- National Institute for Health and Care Excellence. Medical technologies guidance [MTG42]. UrgoStart for treating diabetic foot ulcers and leg ulcers. 2019. <https://tinyurl.com/yyr93np9> (accessed 14 February 2019)
- Edmonds M, Lázaro-Martínez JL, Alfayate-García JM et al. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *Lancet Diabetes Endocrinol* 2018; 6(3):186–196. [https://doi.org/10.1016/S2213-8587\(17\)30438-2](https://doi.org/10.1016/S2213-8587(17)30438-2)
- Meaume S, Truchetet F, Cambazard F et al. A randomized, controlled, double-blind prospective trial with a Lipido-Colloid Technology-Nano-OligoSaccharide Factor wound dressing in the local management of venous leg ulcers. *Wound Repair Regen* 2012; 20(4):500–511. <https://doi.org/10.1111/j.1524-475X.2012.00797.x>
- Schmutz JL, Meaume S, Fays S et al. Evaluation of the nano-oligosaccharide factor lipido-colloid matrix in the local management of venous leg ulcers: results of a randomised, controlled trial. *Int Wound J* 2008; 5(2):172–182. <https://doi.org/10.1111/j.1742-481X.2008.00453.x>
- Münter KC, Meaume S, Augustin M et al. The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSF wound dressings. *J Wound Care* 2017; 26(Sup2 Suppl 2):S4–S15. <https://doi.org/10.12968/jowc.2017.26.Sup2.S4>
- Meaume S, Domp Martin A, Lok C. et al. Quality of life in patients with leg ulcers: results from CHALLENGE, a double-blind randomised controlled trial. *J Wound Care* 2017 2; 26(7): 368–379.
- Augustin M, Herberger K, Kroeger K et al. Cost-effectiveness of treating vascular leg ulcers with UrgoStart® and UrgoCell® Contact. *Int Wound J* 2016; 13(1):82–87. <https://doi.org/10.1111/iwj.12238>
- Percival SL, Suleman L. Slough and biofilm: removal of barriers to wound healing by desloughing. *J Wound Care* 2015; 24(11):498–510. <https://doi.org/10.12968/jowc.2015.24.11.498>
- Milic DJ, Zivic SS, Bogdanovic DC et al. Risk factors related to the failure of venous leg ulcers to heal with compression treatment. *J Vasc Surg* 2009; 49(5):1242–1247. <https://doi.org/10.1016/j.jvs.2008.11.069>
- Meaume S, Dissemmond J, Addala A et al. Evaluation of two fibrous wound dressings for the management of leg ulcers: Results of a European randomised controlled trial (EARTH RCT). *J Wound Care* 2014; 23(3):105–116. <https://doi.org/10.12968/jowc.2014.23.3.105>
- Dalac S, Sigal L, Addala A et al. Clinical evaluation of a dressing with poly absorbent fibres and a silver matrix for managing chronic wounds at risk of infection: a non comparative trial. *J Wound Care* 2016; 25(9):531–538. <https://doi.org/10.12968/jowc.2016.25.9.531>
- Haute Autorité de Santé. [Management of leg ulcers of predominantly venous origin (dressing excluded)]. *J Mal Vasc* 2007; 32(2):100–111. <https://doi.org/10.1016/j.jmv.2007.03.002>
- Haute Autorité de Santé. [Medical compression in chronic venous conditions]. *Ann Dermatol Venerol* 2013; 140(5):393–396. <https://doi.org/10.1016/j.annder.2013.03.004>
- Strohal R, Dissemmond J, Jordan O'Brien J et al. EWMA Document: Debridement: An updated overview and clarification of the principle role of debridement. *J Wound Care* 2013; 22(Sup1 1):S1–S49. <https://doi.org/10.12968/jowc.2013.22.Sup1.S1>
- O'Donnell TF Jr, Passman MA, Marston WA et al. Management of venous leg ulcers: Clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum. *J Vasc Surg* 2014; 60:2:5S–59S. <https://doi.org/10.1016/j.jvs.2014.04.049>
- Gethin G, Cowman S, Kolbach DN. Debridement for venous leg ulcers. *Cochrane Database Syst Rev* 2015; 9(9):CD008599

JWC NOW AVAILABLE ON MAG ONLINE LIBRARY

Sign up for an account and take advantage of these great benefits and features:

- Save JWC articles for quick access
- Save your searches: great if you frequently search for the same criteria
- Get citation alerts to track citations to specific articles

Once you've registered, you can sign up for table of contents alerts for JWC, delivered to you by email or RSS feed as soon as new content becomes available. Simply visit the journal and click 'TOC Alerts' in the menu.

www.magonlinelibrary.com/toc/hmed/current

