



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

Sylvie Meaume, MD¹; François Truchetet, MD²; Frédéric Cambazard, MD³; Catherine Lok, MD⁴; Clélia Debure, MD⁵; Sophie Dalac, MD⁶; Isabelle Lazareth, MD⁷; Michèle-Léa Sigal, MD⁸; Anne Sauvadet, PhD⁹; Serge Bohbot, MD⁹; Anne Dompmartin, MD, PhD¹⁰; on behalf of the CHALLENGE Study Group

1. Dermatology & Geriatric Department, Rothschild University Hospital, Paris, France,
2. Dermatology Department, Beauregard Hospital, Thionville, France,
3. Dermatology Department, North University Hospital, Saint-Etienne, France,
4. Dermatology Department, South University Hospital, Amiens, France,
5. Department of Vascular Medicine, Corentin Celton Hospital, Issy-les-Moulineaux, France,
6. Dermatology Department, Bocage University Hospital, Dijon, France,
7. Department of Vascular Medicine, Saint-Joseph Hospital, Paris, France,
8. Dermatology Department, Victor Dupouy Hospital, Argenteuil, France,
9. Clinical Research Department, Laboratoires URGO, Chenôve, France, and
10. Dermatology Department, Clemenceau University Hospital, Caen, France

Reprint requests:

Dr. S. Meaume, Hôpital Rothschild,
Service de Gériatrie, 5 rue Santerre, 75571
Paris Cedex 12, France.
Tel: +33 1 4019 3306;
Fax: +33 1 4019 3057;
Email: sylvie.meaume@rth.aphp.fr

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ABSTRACT

Venous leg ulcers (VLUs) are the most prevalent chronic wounds in western countries with a heavy socioeconomic impact. Compression therapy is the etiologic treatment of VLU but until now no wound dressing has been shown to be more effective than another. The aim of this study was to assess the efficacy of a new dressing in the management of VLU. Adult patients presenting a noninfected VLU and receiving effective compression therapy were enrolled in this randomized, controlled, double-blind trial. The VLUs were assessed every 2 weeks for 8 weeks. The primary study outcome was the relative Wound Area Reduction (WAR, in %), and the secondary objectives were absolute WAR, healing rate, and percentage of wounds with >40% surface area reduction. One hundred eighty-seven patients were randomly allocated to treatment groups. Median WAR was 58.3% in the Lipido-Colloid Technology-Nano-OligoSaccharide Factor (TLC-NOSF) dressing group (test group) and 31.6% in the TLC dressing group (control group) (difference: -26.7%; 95% confidence interval: -38.3 to -15.1%; $p = 0.002$). All other efficacy outcomes were also significant in favor of the TLC-NOSF dressing group. Clinical outcomes for patients treated with the new dressing are superior to those patients treated with the TLC dressing (without NOSF compound), suggesting a strong promotion of the VLU healing process.

Venous leg ulceration is the most prevalent chronic wound in Western countries.¹ The reported prevalence rates of open ulcers, in studies with clinical validation, ranged from 0.12 to 1.1% of the population and that of open or healed ulcers was reported to be 1.8%.² These lesions are characterized by a cyclical pattern of healing and recurrence that is estimated to be in the range of 54–78% and has a significant socioeconomic impact in terms of both medical care and days off work³ in the United States alone; the treatment cost is estimated to be around one billion dollars per annum.⁴ Overall, these chronic wounds are responsible for a substantial impairment in quality of life.^{5,6}

The management of venous leg ulcers (VLUs) is based on its etiologic treatment, compression therapy, which is the

cornerstone of leg ulcer therapy.⁷ Despite appropriate care, 50–60% of VLU will take more than 20–24 weeks to heal.⁸

There is no evidence of differences in healing rates between the numerous types of available wound dressings when used with compression therapy.⁹ The objective of current management with dressings is to maintain an appropriate environment that favors the normal smooth tissue repair process.¹⁰

In chronic wounds, matrix metalloproteinases (MMPs) have been implicated by a number of studies as the major protease family responsible for the degradation of key factors critical to the ulcer's ability to heal.¹¹ The enhanced level of MMPs, whatever the etiology of the chronic wounds, is responsible for the lack of extracellular matrix compound

synthesis and the persistence of an inappropriate local inflammatory process.^{11–13} For this reason, MMP inhibitors have recently been developed and are expected to improve the local treatment of these chronic wounds.

Supported by *in vitro* studies showing its MMP modulation properties,^{14,15} a Nano-OligoSaccharide Factor (NOSF) was incorporated into a widely used, neutral, Lipido-Colloid Technology (TLC) dressing, providing its additional properties to promote the wound healing process in chronic wounds.

An initial randomized, controlled trial showed superior clinical benefits of the NOSF compound in the local management of VLU¹⁶ when compared with a collagen/regenerated, oxidized cellulose matrix designed to reduce the activity of MMPs in exudates and to protect local growth factors from degradation.^{17,18} The aim of this randomized, controlled, double-blind prospective trial was therefore to compare the clinical efficacy of a TLC dressing impregnated with NOSF with a neutral TLC dressing (without NOSF) to support the encouraging results from the first trial.

MATERIAL AND METHODS

Patients

Screened patients were of both sexes, over 18 years of age (with no upper age limit), and were being managed for a VLU, either as a hospital inpatient or outpatient. Participating patients had to give written consent after receiving full information from the investigating physician, agree to their ulcer being treated with an effective compression system therapy (monolayer or multilayer), and agree to be followed up over the whole study period by the investigators' team.

At inclusion, VLU area had to be between 5 and 50 cm², with between 6- and 36-month duration, despite appropriate treatment, according to the investigators' opinion. At baseline, the Ankle Brachial Pressure Index (ABPI) had to be between 0.8 and 1.3 and at least 50% of the leg ulcer wound bed had to be covered with granulation tissue without any black necrotic/devitalized tissue (colorimetric scale). If more than one ulcer was present, the ulcer that best met the selection criteria was selected (target ulcer) and had to be at least 3 cm away from any other wound.

The main exclusion criteria were the following: suspected clinical infection that could require systemic antibiotics, a known contact dermatitis to carboxymethylcellulose (CMC), a history of venous surgery within the previous 2 months, the occurrence of deep vein thrombosis in the previous 3 months, a concomitant severe comorbid disease or poor health status that could impair the expected 8-week follow-up, any known malignant wound degeneration, and concomitant treatment with immunosuppressive agents or high dose of oral corticosteroids.

Randomization

The randomization code was generated in blocks of two using a computer program and was stratified by center. Both dressings were identical in appearance, shape, color, and packaging. Prior to the start of the trial, an assessment team examined the two dressings and found no distinguishing features, indicating that they could be used in a double-blind trial.

Individual sterile dressings were packed in boxes of 35 dressings per patient. Each box and dressing was identified by a center identification number and patient number corresponding to the chronological patient inclusion number.

Because knowledge of the type of dressing was not necessary for patient management during any medical problems, the procedure to break the randomization code was not provided to the participating centers.

Treatments

The TLC-NOSF wound dressing (Urgostart[®], Laboratoires Urgo, Chenôve, France) is composed of a micro-adherent wound contact layer that includes sodium CMC particles, a NOSF, and polymers; this layer is attached to a hydrophilic polyurethane foam pad and the overall dressing is protected by a nonwoven polyurethane backing layer that allows gaseous exchange and provides a physical barrier to cover and protect the wound.

The control TLC dressing (Urgotul[®] Absorb, Laboratoires Urgo) has exactly the same composition but does not include the NOSF compound.

Dressing change was recommended at least every 2–4 days or more frequently, depending on the level of exudate and the clinical aspect of the wound.

During the study period, only sterile saline was used for wound cleaning during dressing change. The use of topical antibiotics, antimicrobial paste/cream, or antiseptics was not allowed. All other general and local treatments were allowed but had to be fully documented in the patients' case report forms.

Procedures

This was an 8-week French, prospective, multicenter, double-blind, randomized, controlled trial.

Any patient presenting with a VLU who met the selection criteria could be approached for inclusion in the study, irrespective of previous local treatment. After obtaining the patients' written informed consent to participate in the trial and the measurement of ABPI with a Doppler provided by the sponsor (Mini/Audio DOPPLEX[®] D900, Huntleigh Healthcare, Cardiff, UK), patients were enrolled and randomly allocated to either the test (TLC-NOSF) or control dressing (TLC). Demographic parameters and patient's medical, surgical, and leg ulcer history were documented. The previous treatment of the studied ulcer, location, and detailed wound description were recorded including periwound skin condition and colorimetric evaluation of the wound bed, *i.e.*, the presence of granulation tissue (red), slough (yellow), and necrosis (dark) was given as percentage of each color covering the wound area.

An acetate tracing (planimetric record) of the wound surface area was performed (according to a standardized protocol provided by the sponsor) and a photograph of the wound was taken (digital photographic image of at least 3 megapixels using a standardized protocol, after cleansing the wound with saline), both of which were identified by the individual patient number.

The target wound was cleaned and then the allocated dressing was applied. An appropriate compression therapy system, according to patient and ulcer status, was selected and applied by the investigating physician.

The VLU was evaluated by the investigating physician every 2 weeks until week 8, even if the tested dressing had been discontinued for whatever reason (except consent withdrawal or healing). At each visit, the wound evaluations were repeated (clinical assessment, acetate tracing, and wound photo). Investigators were required to notify any unexpected local adverse events whether dressing related or not. In the case of complete wound closure, an acetate tracing and a photo documenting complete epithelialization were to be taken.

Between the biweekly investigator's assessments, all local procedures were recorded by health-care professionals, including detailed information on dressing removal and application and the compression system applied. The parameters (ease of dressing application and removal, pain at removal, and between dressing changes and periwound maceration) were subjectively assessed using a four-level scale (from "very easy" to "extremely difficult" or "none" to "very important" depending on the parameter).

The EuroQol Quality of Life Questionnaire was documented by the patient at baseline and at week 8 (or before if a treatment discontinuation occurred), including five items representing the five following dimensions: mobility, autonomy, activity, pain–discomfort, and anxiety–depression, each one being assessed using a three-level scale. A visual analogic scale (VAS) was also associated to this patients' self-completed questionnaire.

Outcomes

Primary study outcome was relative Wound Area Reduction (WAR) calculated as $[\text{Area}_{\text{last}} - \text{Area}_{\text{t0}}] / \text{Area}_{\text{t0}} \times 100$ and expressed as a percentage (%). $\text{Area}_{\text{last}}$ was the last available wound tracing value. All acetate tracings were blinded and centrally measured by two nonparticipating clinicians using digital software (DeskTop Ruler™). Wound area and wound perimeter were recorded as the mean of both measurements. Neither of the measurements deviated by more than 5%. In addition, 10% of the tracings were randomly selected for a controlled evaluation using Scion Image™ program.

Secondary outcomes were absolute WAR ($\text{Area}_{\text{last}} - \text{Area}_{\text{t0}}$, expressed in square centimeter) and wound edge progression according to Gilman's formula. Wound edge progression is calculated as $2 \times (\text{Area}_{\text{last}} - \text{Area}_{\text{t0}}) / (P_{\text{t0}} + P_{\text{last}})$, where P represents the wound perimeter. This formula is expected to give a wound area evolution independent of the baseline surface area value.

Other efficacy outcomes were the wound healing rate $[(\text{Area}_{\text{last}} - \text{Area}_{\text{t0}}) / (t_{\text{last}} - t_0)]$, expressed in square millimeter per day of treatment, the percentage of wounds with a relative WAR $\geq 40\%$ (WAR40%) and $\geq 60\%$ (WAR60%) at last available tracing, and the mean time to reach the WAR $\geq 40\%$ goal.

Other end points included local tolerance (occurrence of local adverse events documented by the investigating physician) and the acceptability of the tested dressings (assessed by the nursing staff) at each dressing change during the 8-week follow-up.

Ethical considerations

This study was conducted according to European Good Clinical Practices recommendations, the principles of the Declara-

tion of Helsinki (1975), and current French regulations. Study protocol and documentation were submitted to the Comité de Protection des Personnes (French Ethics Committee) of Paris VIII (Ambroise Paré University Hospital), which gave its approval on January 21, 2009. The study was also approved by the French Competent Authority (Agence Française de Sécurité Sanitaire des Produits de Santé [AFSSAPS]) on January 13, 2009 (AFSSAPS Registration Number 2008-A1573-52).

At baseline, before being included in the trial, all patients received full information on the study objectives, potential harm, and benefits both verbally and in writing and gave their written consent to participate in the trial.

Statistics

Sample size was calculated to document the superiority of the TLC-NOSF dressing compared with the control TLC dressing, after 8-week follow-up.

A difference of 15% between the two groups had to be detected, on relative WAR, if standard deviation (SD) of the parameter is 34% maximum, on the basis of the previous trial, with a power of 80%. The alpha risk (bilateral) was fixed at 5%. Accordingly, 82 patients per group were required and it was decided to include a minimum of 180 patients in case of dropouts.

Analyses were conducted using SPSS 18.0 software on an unblinded database (allocated dressings were identified as A or B and treatment disclosure was performed after the final statistical report had been written).

Baseline comparability of the two groups was verified using adapted tests (Student's *t*-test, nonparametric Mann–Whitney test, and chi-square test), dependent on the distribution and the nature of the variables.

Knowing the large deviation of wound regression variable distributions from normal and the difficulties in normalizing these distributions, only nonparametric Mann–Whitney tests were used to compare the allocated dressing effects on primary and secondary efficacy outcomes.

For the other outcomes, chi-square tests were used and odds ratio (OR) was calculated with 95% confidence intervals (CIs). Time to reach relative WAR40% was evaluated using a Kaplan–Meier approach followed by log-rank test. Additionally, for WAR40%, a binary logistic regression was conducted with wound surface area at baseline, wound duration, and whether the ulcer was recurrent including in the model. Local tolerance analyses were described and the percentage of patients suffering from at least one adverse event was compared by using chi-square test.

All analyses were conducted on an "intent-to-treat" (ITT) population, defined as all randomized patients who received the allocated dressing at least once.

All tests were bilateral and a *p*-value < 0.05 was considered to be indicative of statistical significance.

Post hoc subgroup evaluations were performed to appreciate the magnitude of treatment differences according to baseline wound area (10 cm² cutoff), recurrent ulcer status, ulcer duration (one cutoff), and the nature of the compression system used during the study period (monolayer or multilayer compression therapy).

Scale variables are presented by their mean \pm SD, their median, and range. Median differences are given with 95% CIs according to the method proposed by Bonett and Price.¹⁹

Ordinal and nominal variables are presented by the number of patients involved and percentage.

At the end of the trial, the photographs taken during the trial were analyzed during a blind review. The photographs were reviewed independently of the sponsor by two experienced clinicians who had not participated in the trial as investigators and who were blinded to the dressing type. Each clinician rated their overall impression separately, on a seven-point scale (1: “strongly improved or healed” to 7: “strongly aggravated”), without knowing the results of the other clinician’s review. If the results of a photograph differed by more than one point, the clinicians discussed their decisions during a reconciliation meeting to achieve a consensus of opinion.

RESULTS

From March 2009 to July 2010, 187 patients were included and randomly allocated to either the test dressing (TLC-NOSF, *n* = 93) or the control dressing (TLC, *n* = 94) by 45 hospital investigators who were dermatologists, internal medicine specialists, or vascular medicine specialists.

The mean study participation time for each patient was 54.1 ± 9.2 days in the TLC-NOSF group and 53.2 ± 11.4 days in the TLC groups. As noted in the Figure 1 trial profile, 78 of the 93 patients (83.8%) in the test group and 77 of the 94 patients (81.9%) in the control group were treated until week 8 or until healing. Eleven of the 93 (11.8%) test patients and 11 of the 94 (11.7%) control patients were followed until week 8 having switched to another dressing during the trial,

mainly due to the occurrence of a local adverse event. Therefore, 94.6% of the whole tested population was followed up until week 8 or healing, whichever occurred first, and the total rate of withdrawn patients without any possible follow-up was 5.4% (including two deaths, one in each group, and three consent withdrawals, one in the test group and two in the control group).

All demographic data and ulcer characteristics were well balanced between the two groups at baseline (Tables 1 and 2), without any significant differences between their mean or median values.

Included patients were mostly outpatients (152 of the 187, 81.3%). The female sex was predominant (65.2% of total population) and the global population mean age was 73.5 ± 12.6 years with an average body mass index (BMI) of 30.3 ± 7.9 kg/m² (BMI ≥30 kg/m² in 42.8% of included population). Thirty of the 187 patients (16.0%) were diabetic (27 with type II diabetes). Most subjects (136 of the 187, 72.7%) had a previous history of VLU and the mean ABPI was 1.04 ± 0.13 mmHg (range: 0.8–1.50).

Fifteen patients (8.0%) had not been treated with a compression system therapy before baseline but all received compression therapy at randomization: the two groups being equally distributed to monolayer or multilayer compression systems.

A total of 103 leg ulcers (55.4%) had been present for 1 year or more (median: 12.0 months; range: 3–36 months) and 100 wounds (53.5%) were documented as a recurrent ulcer. All ulcers were appropriately debrided at inclusion (granulation tissue covering on average 72.1 ± 17.4% of wound area) and 38 ulcers (20.3%) had eczema lesions present at wound edges.

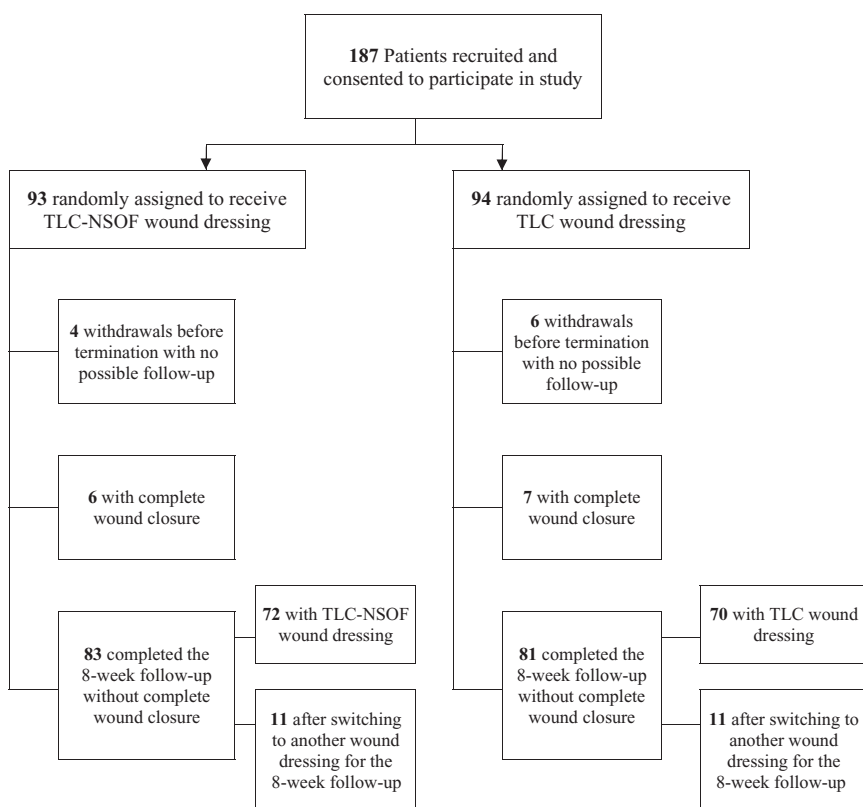


Figure 1. Trial intent-to-treat profile. TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor.

Table 1. Distribution at baseline of the patient's characteristics for the treatment groups (n = 187)

	TLC-NOSF n = 93	TLC n = 94
Females (n, %)	62 (66.7%)	60 (63.8%)
Age (year) (mean ± SD)	72.6 ± 13.0	74.4 ± 12.1
BMI (kg/m ²) (mean ± SD)	30.5 ± 8.7	30.1 ± 6.9
BMI >30 kg/m ² (n, %)	40 (43.0%)	40 (42.6%)
Diabetes (n, %)	13 (14.0%)	17 (18.1%)
Smoking (n, %)	10 (10.8%)	14 (14.9%)
History of deep venous thrombosis (n, %)	40 (43.0%)	32 (34.0%)
History of venous surgery (n, %)	32 (34.4%)	37 (39.4%)
History of VLU (n, %)	67 (72.0%)	69 (73.4%)
ABPI (mean ± SD) Median [range]	1.05 ± 0.14 1.00 [0.8; 1.5]	1.03 ± 0.12 1.00 [0.8; 1.3]
Patient status (n, %)		
• Outpatient	75 (80.6%)	77 (81.9%)
• Hospitalized	18 (19.4%)	17 (18.1%)
Ankle mobility (n, %)		
• Fully mobile	65 (69.9 %)	56 (59.6 %)
• Limited mobility	25 (26.9 %)	35 (37.2 %)
• Immobile	3 (3.2 %)	3 (3.2 %)
Autonomy of the patient (n, %)		
• Can easily walk	53 (57.0 %)	45 (47.9 %)
• Can walk with difficulty	39 (41.9 %)	48 (51.1 %)
• Confined to bed	1 (1.1 %)	1 (1.1 %)

ABPI, Ankle Brachial Pressure Index; BMI, body mass index; TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor; VLU, venous leg ulcer.

Mean ulcer area was 16.8 ± 15.7 cm² (median: 11.2 cm²; range: 2.3–86.9 cm²; wound area >10 cm² in 102 ulcers out of 187, 54.5%), without any difference between the two groups.

Efficacy outcomes

Patient compliance with the compression therapy prescribed at inclusion was very good with 98.9% of the patients seen at week 2, 96.6% at week 4, and 96.4% at week 6 still wearing compression. Between these visits, compression wearing was also checked by nurses during all the documented local procedures.

Table 2. Distribution at baseline of the VLU characteristics for the treatment groups (n = 187)

	TLC-NOSF n = 93	TLC n = 94
Duration of VLU (month) Median [range]	15.6 ± 9.1 12 [3; 35]	15.1 ± 8.7 12 [6; 36]
Duration >1 year (n; %)	54 (58.1%)	49 (52.7%)
Recurrent ulcer (n; %)	51 (54.8%)	49 (52.1%)
Healthy periwound skin (n; %)	35 (37.6%)	43 (45.7%)
Erythematous periwound skin (n; %)	34 (36.6%)	37 (39.4%)
Periwound eczema (n; %)	23 (24.7%)	15 (16.0%)
Wound bed aspect*		
% granulation Median [range]	71.4 ± 17.9 70 [30; 100]	72.8 ± 17.0 72 [30; 100]
% slough Median [range]	28.6 ± 17.9 30 [0; 70]	27.0 ± 16.8 27.5 [0; 70]
Wound size		
Wound area (cm ²) Median [range]	17.0 ± 15.6 12.9 [2.3; 86.9]	16.6 ± 15.8 10.5 [2.7; 85.3]
Wound perimeter (cm) Median [range]	19.3 ± 9.4 17.2 [6.5; 54.2]	19.8 ± 10.9 16.7 [7.7; 70.4]
Area >10 cm ² (n; %)	54 (58.1%)	48 (51.1%)

*Percentage of wound area covered by granulation tissue or sloughy tissue (colorimetric scale).

TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor; VLU, venous leg ulcer.

Concerning the primary outcome, the median relative WAR (Table 3) decreased by –58.3% in the test group and by –31.6% in the control group (difference: –26.7%; 95% CI for median difference: –38.3 to –15.1%; *p* = 0.002), as presented in Figure 2. Cumulative distributions of relative WAR are presented in Figure 3, showing a left shift of distribution for the test group compared with the control group.

By using the process of last-observed value carried forward to compensate for missing data, the profiles of relative WAR between-group differences over the 8-week period are presented in Figure 4; a superior effect of the test dressing was observed after only 2 weeks and increased steadily thereafter.

A highly statistically significant difference was observed in favor of the test dressing for absolute WAR (–6.1 cm² in the test group and –3.2 cm² in the control group) and healing rate (–10.81 mm²/day in the test group and –5.15 mm²/day in the control group) (Table 3).

Moreover, when considering the Gilman's formula (wound edge progression), which allows a calculation of the wound area independent of the baseline wound area value, the superiority of the test dressing can be confirmed (*p* = 0.001).

The WAR of more than 40% from baseline value (WAR >40%) was noted in 65.6% of patients receiving test dressing

Table 3. Efficacy outcomes in patients randomized to TLC-NOSF (*n* = 93) and TLC dressing (*n* = 94) on an ITT basis

		TLC-NOSF <i>n</i> = 93	TLC <i>n</i> = 94	<i>p</i> *
Last area (cm ²)	Mean ± SD	10.1 ± 15.4	14.0 ± 17.6	
	Median (range)	5.0 [0.0; 101.1]	6.1 [0.0; 87.4]	
Last perimeter (cm)	Mean ± SD	14.4 ± 10.3	17.9 ± 13.8	
	Median (range)	11.8 [0.0; 53.1]	13.2 [0.0; 75.8]	
Relative WAR (%)	Mean ± SD	-45.2 ± 47.9	-21.4 ± 81.0	0.002
	Median (range)	-58.3 [-100.0; 173.0]	-31.6 [-100.0; 571.0]	
Absolute WAR (cm ²)	Mean ± SD	-6.9 ± 11.4	-2.5 ± 11.9	0.003
	Median (range)	-6.1 [-55.5; 31.7]	-3.2 [-33.1; 74.4]	
Wound edge progression (mm) (Gilman)	Mean ± SD	-1.15 ± 1.20	-0.56 ± 1.19	0.001
	Median (range)	-1.15 [-3.96; 2.20]	-0.56 [-3.43; 6.97]	
Healing rate (mm ² /day)	Mean ± SD	-13.32 ± 24.56	-4.54 ± 23.20	0.005
	Median (range)	-10.83 [-158.32; 57.59]	-5.15 [-60.19; 132.87]	

*Mann-Whitney test.

ITT, intent to treat; SD, standard deviation; TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor; WAR, Wound Area Reduction.

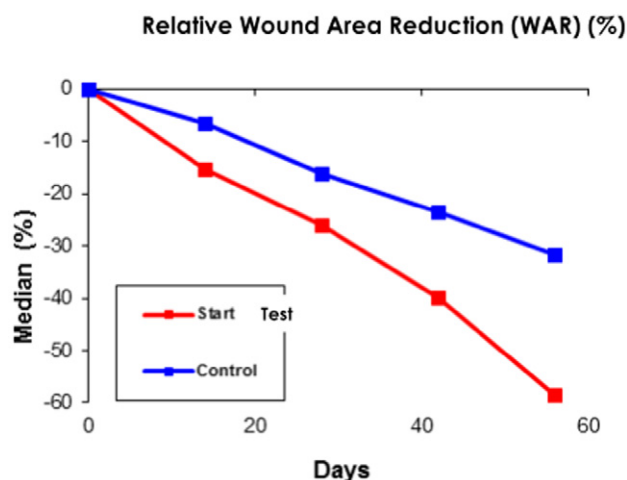


Figure 2. Relative Wound Area Reduction (WAR) calculated as $[(Area_{last} - Area_{10})/Area_{10}] \times 100$ ($Area_{10}$ is the baseline wound tracing value and $Area_{last}$ is the last available wound tracing value) and expressed as a percentage over the 8-week follow-up in patients randomized to TLC-NOSF (test) (*n* = 93) and TLC dressing (control) (*n* = 94) on an ITT basis. Values indicate median. ITT, intent to treat; TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor.

compared with 39.4% in the control group (OR: 2.9; 95% CI: 1.6; 5.3; *p* = 0.0003; Table 3) and the median time to reach WAR >40% was 43 days (95% CI: 37.2–48.8 days) in the test group and 63 days (95% CI: 57.8–68.1 days) in the control group, showing a statistically significant difference (*p* = 0.002; log-rank test).

When a more stringent criterion is used (relative WAR ≥60%), the OR is 2.2 (95% CI: 1.2; 4.0; *p* = 0.013). Figure 5

shows the percentages of patients presenting WAR ≥40% and WAR ≥60% in the TLC-NOSF group (A) and TLC group (B) at each investigator’s evaluation (weeks 2, 4, 6, and 8; Table 4).

By week 8, six and seven wounds had healed (with 100% reepithelialization and no further need of a primary dressing) in the test and control groups, respectively.

Complementary analyses were undertaken to document the relative WAR when considering parameters of poor healing prognosis such as the recurrence of the leg ulcer, the duration of the ulcer of more than 1 year, or an initial surface area greater than 10 cm² (Table 5). Whichever subgroup is considered, the superiority of the TLC-NOSF dressing is documented as having a very homogeneous effect, more marked when ulcers are of poor prognosis.

Finally, by using a binary logistic regression method that includes basal wound area (10 cm² cutoff), ulcer recurrence (yes/no), and duration (<1, 1–2, and >2 years) in the model, OR of WAR >40% is 3.3 (95% CI: 1.8–6.1; *p* < 0.001) in favor of the test dressing. Only the basal area was significant in this model (OR area <10 cm² vs. ≥10 cm²: 2.1; 95% CI: 1.1–4.0; *p* = 0.020).

At the end of the trial, the blind review, based on the photographs considered valuable by the two independent clinicians, was undertaken on 86 patients in the test group and 82 patients in the control group; 81.4% (70/86) ulcers were considered improved in the test group compared with 65.9% (54/82) in the control group, which is significantly different (*p* = 0.022). Thus, the blind review fully corroborates the evaluations made by the investigators during the course of the trial.

Dressing acceptability, adverse events, and local tolerance

Over the study period, a total of 3,547 local procedures were documented by the participating nurses (1,804 in the test group

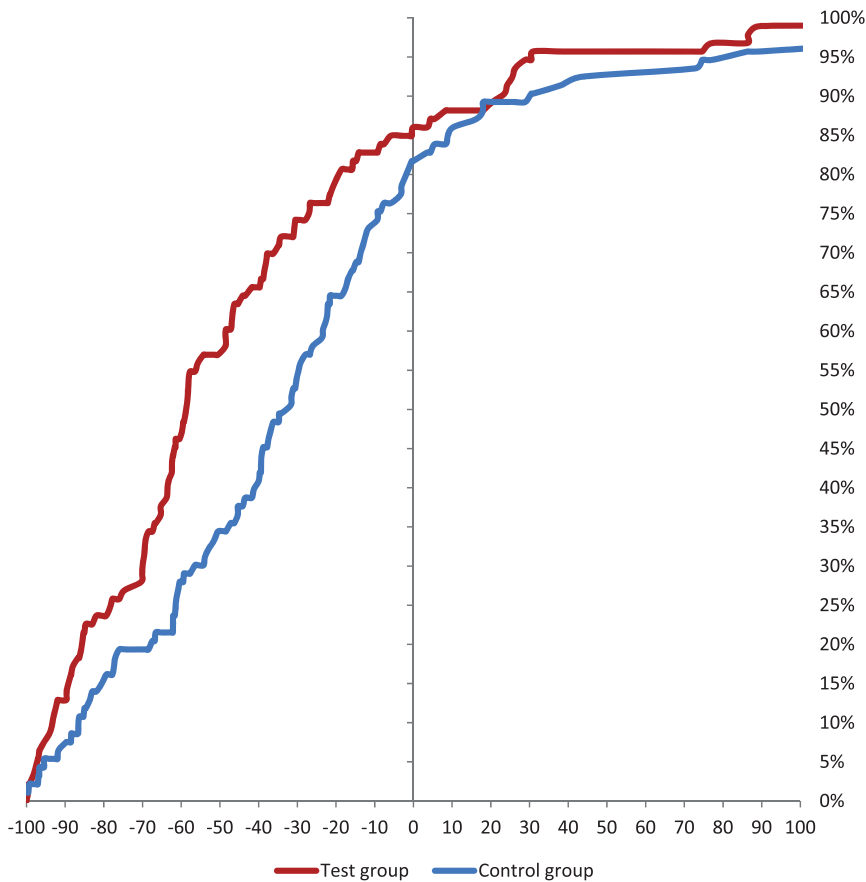


Figure 3. Cumulative distribution of relative wound area distributions. Horizontal bars represent median values: -58.3% for TLC-NOSF dressing (red curve) and -31.6% for TLC dressing (blue curve). TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor.

and 1,743 in the control group). Dressings were changed on average 6 ± 3 times every 2 weeks in both groups.

Dressing applications were considered easy or very easy in 98.4% of the cares, whatever group, test or control, and the dressing removals, easy or very easy in 97.1 and 98.0%,

in the test and control groups, respectively. These dressing removals were considered as totally painless in 84.7 and 86.8% of the documented cares in the test and control groups, respectively, and a periwound maceration was considered present in 15.3 and 16.9% of the cares in the TLC-

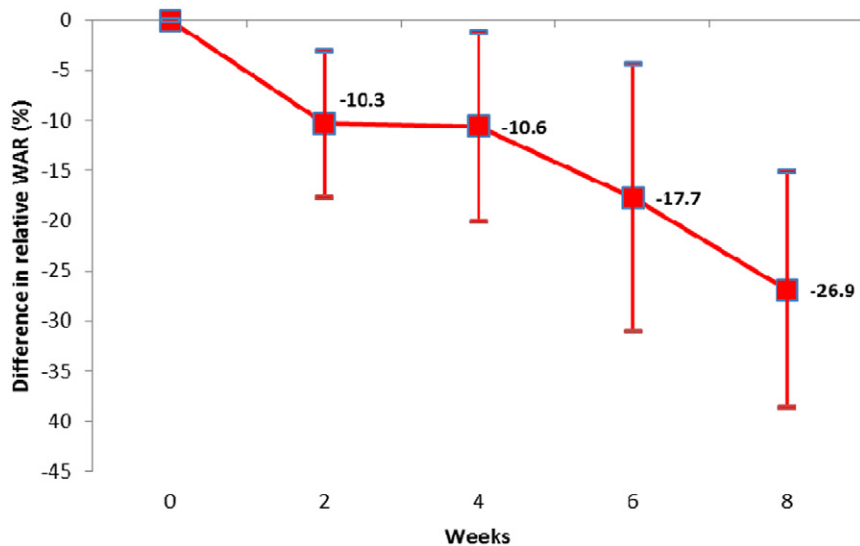


Figure 4. Differences in the median values of relative Wound Area Reduction (WAR) (TLC-NOSF dressing—TLC dressing) over 8 weeks (median of the differences; bars represent 95% CI of median difference). CI, confidence interval; TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor.

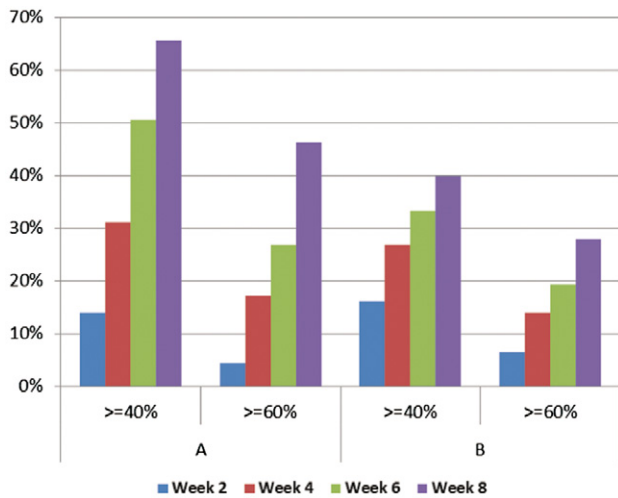


Figure 5. Percentages of patients presenting Wound Area Reduction (WAR) $\geq 40\%$ and $\geq 60\%$ in the TLC-NOSF group (A) and TLC group (B) at each evaluation (weeks 2, 4, 6, and 8). TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor.

NOSF and TLC groups. So, no difference between the two groups has been noted whatever acceptability parameter that was considered and documented by the nursing staff during the trial.

At least one local adverse event (emergent or already known at baseline) was reported in 29 patients allocated to the test dressing (31.2%; 95% CI: 22.0–41.6%) and in 27 allocated to the control dressing (28.7%; 95% CI: 19.9–38.0%).

A total of 66 local adverse events were noted (Table 6), with no obvious differences in event prevalence between the two groups. Periwound eczema was the most frequently reported problem (23 of the 187 patients, 12.3%), but this was already present in these patients at the time of randomization. Of the 66 local adverse events documented, 23 (10 in the test group and 13 in the control group) were considered by the investigators as most probably dressing related.

For 11 patients in the test group and 12 patients in the control group, the local adverse event was the reason justifying the discontinuation of the dressing before week 8.

Table 4. Percentage of wounds with a relative Wound Area Reduction $\geq 40\%$ (WAR $\geq 40\%$) and $\geq 60\%$ (WAR $\geq 60\%$) at last available tracing on an ITT basis

	Relative WAR $\geq 40\%$	Relative WAR $\geq 60\%$
TLC-NOSF (n, %)	61/93 (65.6%)	42/93 (45.2%)
TLC (n, %)	37/94 (39.4%)	26/94 (27.7%)
Odds ratio (95% CI)	2.9 [1.6; 5.3]	2.2 [1.2; 4.0]
<i>p</i>	0.0003	0.013

CI, confidence interval; ITT, intent to treat; TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor.

Table 5. Relative Wound Area Reduction (WAR). Subgroup analysis. Calculated with respect of the compression bandaging (monolayer or multilayer bandages), the ulcer duration (≤ 1 year or > 1 year), the recurrence, and the baseline wound area (≤ 10 or > 10 cm²). Expressed as a percentage over the 8-week follow-up in patients randomized to TLC-NOSF (test; *n* = 93) and TLC dressing (control; *n* = 94) on an ITT basis

	TLC-NOSF			TLC			Median difference	95% CI of median diff	
	<i>n</i>	Mean \pm SD	Median	<i>n</i>	Mean \pm SD	Median			
Compression bandaging*	Monolayer	57	-40.4 \pm 54.9	-58.3	61	-16 \pm 91.8	-31.7	-26.6	[-42.3; -11.0]
	Multilayer	27	-51.8 \pm 33.3	-58.2	26	-27.5 \pm 58.7	-32.7	-25.5	[-51.9; 0.9]
Ulcer duration	≤ 1 year	39	-55.9 \pm 37.5	-63.3	44	-34.2 \pm 49.8	-38.1	-25.3	[-49.5; -1.0]
	> 1 year	54	-37.4 \pm 53.1	-55.2	50	-10 \pm 100.0	-23.1	-32.0	[-48.7; -15.4]
Recurrent ulcer	Yes	51	-40.8 \pm 54.6	-58.2	49	-16.9 \pm 61.2	-26.1	-32.1	[-49.8; -14.5]
	No	42	-50.5 \pm 38.1	-61.8	45	-26.2 \pm 98.7	-39.3	-22.5	[-40.5; -4.6]
Baseline wound area	≤ 10 cm ²	39	-48.7 \pm 54.0	-61.7	46	-38.1 \pm 50.7	-40.6	-21.1	[-39.8; -2.3]
	> 10 cm ²	54	-42.6 \pm 43.3	-55.2	48	-5.3 \pm 100.0	-19.2	-35.9	[-54.5; -17.3]

*Patients with full concordance to prescribed compression therapy (84 in test and 87 in control group). CI, confidence interval; ITT, intent to treat; SD, standard deviation; TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor.

Table 6. Local adverse events (LAEs) categorized by randomization group

	Group					
	TLC-NOSF <i>n</i> = 93		TLC <i>n</i> = 94		Total <i>n</i> = 187	
	Number of LAE	% of patients	Number of LAE	% of patients	Number of LAE	% of patients
Contact dermatitis	1 (1)	1.08%	2 (1)	2.13%	3	1.60%
Pain	1 (0)	1.08%	0 (0)	0.00%	1	0.53%
Periwound eczema	14 (4)	15.05%	9 (5)	9.57%	23	12.30%
Increase of ulcer size	7 (1)	7.53%	4 (3)	4.26%	11	5.88%
Overgranulation	3 (2)	3.23%	2 (0)	2.13%	5	2.67%
Infection	7 (1)	7.53%	6 (0)	6.38%	13	6.95%
Inflammation/irritation	1 (1)	1.08%	2 (1)	2.13%	3	1.60%
Macerated periwound skin	0 (0)	0.00%	6 (2)	6.38%	6	3.21%
Apparition of dark tissue on wound bed	0 (0)	0.00%	1 (1)	1.06%	1	0.53%
Total	34 (10)		32 (13)		66	

Within parentheses: number of events considered as probably/certainly related to applied dressing by the investigators. TLC-NOSF, Lipido-Colloid Technology-Nano-OligoSaccharide Factor.

The Quality of Life Questionnaire was noted similar in the two groups at baseline when considering each of its five dimension scores. At the end of the trial, a significant difference between the two groups was observed in favor of the test group for two of the five items: scores of pain–discomfort (1.53 ± 0.53 vs. 1.74 ± 0.65 ; $p = 0.022$) and anxiety–depression (1.35 ± 0.53 vs. 1.54 ± 0.60 ; $p = 0.037$) were significantly lower in the TLC-NOSF group. At baseline, the two VAS scores were very similar (65.8 ± 17.7 and 65.6 ± 17.4 in the test and control groups, respectively) and both showed improvement at the end of the trial without reaching a significant level in favor of the test group (72.1 ± 17.5 vs. 67.3 ± 18.7 ; $p = 0.072$).

DISCUSSION

This randomized double-blind clinical trial clearly supports that the NOSF compound added to a neutral TLC wound dressing can significantly improve the healing process of VLU, whatever their prognosis, when associated with compression therapy.

As far as we know, this clinical trial, for which the objective was to demonstrate the potential benefit of a dressing impregnated with NOSF developed to favor the wound healing repair process when compared with the neutral dressing (without the NOSF compound), was the first to be conducted in a double-blind design. This approach had the advantage of allowing double-blind conditions, exceptional in the wound care field when comparing two wound dressings, which therefore renders the findings more relevant.

The neutral TLC dressing has been widely used by health-care professionals for a decade and its clinical benefits have been documented thoroughly in clinical trials undertaken in various indications, including pediatric wounds.^{20,21} In addition, in vitro data suggest that TLC can promote fibroblast

proliferation and the synthesis of extracellular matrix compounds although physical interactions with local wound environment are not yet fully elucidated.^{22,23}

In chronic wound exudate, the increased levels of MMPs result in the degradation of the extracellular matrix and inactivation of growth factors. This maintains the wound in an uncontrolled inflammatory state, delaying or stalling tissue repair, cellular proliferation, and angiogenesis.^{24,25} A dressing that is capable of sequestering excess MMPs from chronic wound exudate may therefore help to produce an anti-inflammatory effect and thus benefit healing.²⁶

If we consider the specific clinical status of the VLU, which is directly associated to the amounts of MMP-9 present in the wound fluid, a recent study suggests that higher levels of MMP-9 in chronic wound fluid correlate with a clinically worse wound.¹¹

Recent in vitro studies^{14,15,27} have shown that the TLC-NOSF dressing tested in the current trial reduces gelatinase (MMP-2 and MMP-9) and collagenase (MMP-1 and MMP-8) activities on a dermal equivalent (normal human dermal fibroblasts incorporated within a collagen matrix).

Thus, to ascertain whether the TLC-NOSF dressing, which interacts with the local MMPs present in chronic leg ulcers, was therapeutically more effective than the neutral TLC dressing, a prospective, randomized, double-blind, multi-center controlled clinical trial was undertaken, in compliance with the International Conference on Harmonisation GCP requirements.

In addition to venous origin, confirmed by the Doppler value documented at baseline, the main selection criterion was the presence of an open VLU with a duration of at least 6 months, prior to inclusion. This criterion was selected to favor the inclusion of leg ulcers, which would have an expected benefit from an active dressing and not just from compression therapy which still remains the cornerstone of VLU management. Lengthy ulcer duration, leg ulcer recur-

rence, and a wound size of 10 cm² or more are recognized as factors of poor healing prognosis despite appropriate compression therapy.^{26,28,29}

To confirm the clinical relevance of the detected effect with TLC-NOSF dressing, the best local treatment including compression therapy was strictly conducted in the two groups. Compression therapy is the main treatment for VLU but is often poorly tolerated by patients.^{7,30,31} In our study, patients were carefully instructed and regularly encouraged to wear their compression therapy so that patients' compliance with compression was very high throughout the whole trial.

Overall results clearly document a significant superiority and a sustained effect of the test dressing vs. the control when considering relative and absolute WAR over the 8-week treatment, as well as the healing rate of the treated leg ulcers. As basal wound area may influence its decreasing measurement over time, the formula proposed by Gilman³² allows a wound healing parameter to be derived, independent of the initial area; again, using this parameter, superiority of the test dressing was observed. Furthermore, the magnitude of this effect was still evident in all the subgroups stratified according to the type of compression therapy (monolayer or multilayer), the duration of ulcer (less or more than 1 year), the initial ulcer size (more or less than 10 cm²), and whether or not it was recurrent. A highly significant difference was observed in favor of the test dressing, whatever the prognosis of the treated leg ulcers.

The limitation of this trial might be the follow-up duration, which was too short to detect any difference on complete wound closure rate. However, numerous publications have shown that the initial change in wound area is highly predictive of a fully healed leg ulcer within 20–24 weeks and some authors consider that a 40% WAR at week 4 might be considered as a surrogate end point to complete closure.^{33–36} Here again, when using 40 or 60% WAR as an end point, a substantial and significant superiority of the TLC-NOSF dressing is observed with a 3-week reduced time in reaching this level of wound area change.

The superiority of this new dressing is supported by the main analysis and all the additional exploratory analysis, including those of the photographic blind review.

The addition of NOSF to the TLC dressing does not interact with the overall local tolerance and acceptability of this active dressing, as no differences between groups were documented. Furthermore, these acceptability and tolerance data are in accordance with those already documented in the literature, whatever dressing, TLC,^{20,21,37–39} or TLC-NOSF.¹⁶

The EuroQol Questionnaire was selected in this trial as already reported to explore the impact of VLUs on health-related quality of life,^{40–43} showing significant improvement in the test group for two of the five dimensions, the pain–discomfort and anxiety–depression.

The documented results in the present trial are in accordance with and reinforced by those obtained by Schmutz et al.¹⁶ who compared the TLC-NOSF dressing with a collagen/oxidized regenerated cellulose (ORC) matrix (Promogran®) in the management of VLU. This was a 12-week open prospective, randomized multicenter trial that was designed to document noninferiority of the test dressing compared with control dressing. Fifty-seven and 60 patients treated for their VLU were randomly allocated to the TLC-NOSF and ORC dressings, respectively. In the ITT population, medians of relative WAR were 54.4% in the test group

and 12.9% in the control group, and a conclusion of superiority of the test dressing was reached ($p = 0.0273$).

Our double-blind clinical trial is therefore the first one to clearly demonstrate that, combined with compression therapy, wound microenvironment modulation with a dressing is able to promote a favorable wound healing trajectory for VLU whatever their considered prognosis. This is dramatically new, as scientific literature reports that the type of wound dressing applied beneath compression does not affect ulcer healing.⁹ The literature also reports that there is no evidence that any of the modern dressings are better than another or better than saline or paraffin gauze in terms of general performance criteria¹⁰ even when considering growth factors that have not yet been established as clinically beneficial in the treatment of VLU.⁴

In conclusion, adding a TLC-NOSF wound dressing to the best local care for the management of VLU represents a new opportunity to promote the healing process of these chronic wounds that frequently remain unhealed for months or years with a high level of recurrence, despite adequate compression therapy.

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A. Sauvadet, employee of the sponsor as Clinical Study Manager, was responsible for the study monitoring supervision.

This paper was written only by the first and last authors, Sylvie Meaume, MD, and Anne Domp Martin, MD, without any participation of the sponsor's employees, and all the authors had full access to all data from the study.

All authors were involved in the planning and undertaking of the trial.

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