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Efficacy of two compression systems in the management of VLUs: results of a European RCT

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Efficacy of two compression systems in the management of VLUs: results of a European RCT

• **Objective:** To evaluate the efficacy, tolerance and acceptability an innovative two-layer system (KTwo; Laboratoires URGO) versus an established four-layer bandage system (Profore; Smith & Nephew) in the local management of venous leg ulcers.

• **Method:** A non-inferiority European randomised controlled trial, conducted in 37 centres, in three countries (France, UK and Germany), on patients presenting with venous leg ulcers (VLUs). Participants were adult, non-immunosuppressed patients who presented with non-infected, non-malignant leg ulcers, predominantly of venous origin (ABPI > 0.8), with a surface area of 2–50cm^2 and duration 1–24 months. Patients were followed-up every 2 weeks for a period of 12 weeks, or until full closure. Visits included a clinical examination, wound area tracings and photographic evidence. The primary endpoint was the percentage of leg ulcers healed after the 12 weeks, with secondary endpoints of relative wound area reduction (RWAR), absolute wound area reduction (AWAR) and the percentage of wounds with RWAR ≥ 40%.

• **Results:** In total, 187 patients were randomised to either the two-layer bandage (2LB, n=94) or four-layer bandage (4LB; n=93) system. The two groups were comparable, with regard to wound and patient characteristics, at baseline. By week 12, 44% of VLUs in the 2LB group and 39% in the 4LB group had healed (intention-to-treat [ITT] analysis). The per-protocol (PP) analysis showed that complete wound closure was obtained in 48% and 38% of the 2LB and 4LB groups, respectively. A non-inferiority margin within –10% is considered as demonstrating a 95% and 97.5% confidence interval (p=0.001). The AWAR was 6.6cm^2 in the test and 4.9cm^2 in the control group. The percentage of wounds with a RWAR ≥ 40% was 47% and 44% for the 2LB and 4LB systems, respectively. Pain between dressing changes was reported in 27% of the test and 40% of the control group, and the incidence of adverse events was 17% and 25%, respectively. The 2LB compression system was considered to be significantly easier to apply than the 4LB (p=0.038).

• **Conclusion:** The 2LB system (KTwo) was not seen to be any less effective than a well-known 4LB system (Profore) in the management of VLUs. Furthermore, the 2LB system was considered to be easier to apply, representing an alternative to the conventional treatment with 4LB currently available.

• **Declaration of interest:** This study was sponsored by a grant from Laboratoires URGO, manufacturers of KTwo. S. Bohbot and A. Sauvadet are employees of Laboratoires Urgo. S. Meaume has received monetary compensation as a speaker for Laboratoires Urgo. Data management and statistical analyses were conducted by Vertical (J.C. Kerihuel; Paris, France).

compression therapy; venous leg ulcer; randomised controlled trial; two-layer bandage

Chronic venous insufficiency in the lower extremities can result in venous stasis, venous hypertension and oedema, causing pain, discomfort and eventually the development of ulceration of the affected limb. Topical compression therapy provides a means to treat or prevent these adverse effects.[1]

High-compression bandaging is an effective treatment for leg ulceration, which affects 1.5–1.8% of adults in industrialised countries, healing the majority of new venous leg ulcers (VLUs) within 1 year.[2,3] Research has shown high compression devices to be more effective in healing VLUs than those exerting a lower pressure.[4] However, many of the sequaelae of ulceration affect a patient's ability to tolerate high pressures,[5] which makes application complex, requiring substantial skill and knowledge.

A better understanding of the pathophysiology underlying venous disease and the development of systems able to measure interface pressures in compression bandages, have led to the development of reliable and effective multilayer compression systems.[6] There are an increasing number of compression systems available for the topical treatment of VLUs, particularly multilayer compression systems (two to four layers). The use of any of these systems will depend on several parameters, including the choice and concordance of the patient, the acceptability and ease of application of the system used, and also the cost of each system.[2] Furthermore,

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research has shown that the proportion of patients to achieve full healing is related to their concordance with compression therapy,[7] which in turn is related to the ease and comfort while wearing the compression bandage.[8]

Several randomised clinical trials (RCTs), devoted to the management of VLUs, report that the efficacies of different compression systems are similar,[9–16] while other trials report multilayer bandage systems to be superior to short-stretch systems.[17–19]

Laboratoires URGO have developed a new two-layer compression system (2LB), KTwo, formed of two separated bandage components. This 2LB has been evaluated through an open clinical trial for the treatment of VLUs, which suggested it was effective, with a documented high level of patient concordance.[20] On healthy volunteers, this 2LB was shown to have similar bandage interface pressures to those observed with other multilayer compression systems, and has been shown to have good local tolerance.[21,22] Demonstrating two high-compression systems have the same level of clinical efficacy provides health professionals and patients with a greater choice as to these systems, which has the possibility to improve concordance.

The objective of this clinical RCT is to compare the therapeutic efficacy and the safety of two multilayer compression systems: KTwo and Profore (Smith & Nephew), a well–known four-layer system (4LB), in the treatment of VLUs.[13,17,23–26]

Method

This clinical, multicentre, controlled, randomised trial was conducted in two parallel groups in three European countries (France, United Kingdom and Germany). There were 37 active investigating centres, involving vascular physicians, dermatologists and tissue viability nurses.

Patients recruited for this clinical investigation were inpatients or outpatients, presenting with either a venous or mixed aetiology leg ulcer, confirmed by an ankle brachial pressure index (ABPI) of 0.8–1.3 in both legs, at baseline. Patients had to be ≥18 years receiving treatment for their leg ulcer with a multilayer compression system (two, three or four bandages), and be followed-up by the same investigating team throughout the 12-week treatment period. Additional criteria were:

- Ankle circumference 18–25cm
- Target ulcer surface area 2–5cm^2
- Ulcer duration 1–24 months.

If a patient presented with several ulcers located on the same limb at the inclusion visit, the investigator selected one wound for the evaluation (target ulcer), which best met the selection criteria. This ulcer had to be a minimum of 3cm from the edge of any other wound on the same limb. The other wounds were treated with the centre's standard protocol. Any ulcers located on the contralateral inferior limb were treated by the investigator with the same compression system, provided by the sponsor.

The primary exclusion criteria comprised:

- Suspected clinical infection of the ulcer
- Scheduled surgery for the ulcer during the 12 weeks following inclusion
- Ulcer surface totally covered with dry fibrinous tissue at inclusion, or a malignant ulcer (any known degeneration)
- History of deep or superficial venous thrombosis in the 3 months prior to inclusion.

Patients with a known hypersensitivity to one of the components of the tested compression systems were also excluded, as were those who presented with a neoplasic lesion being treated with radiotherapy or chemotherapy, patients being treated with immunosuppressive drugs or high-dose corticosteroids, and those confined to bed.

Study protocol

At the inclusion visit, written informed consent was obtained from each patient and the measurement of the ABPI confirmed, with a mini Doppler. Patients included in the trial were then randomised to either 2LB or 4LB systems, following a centralised randomisation list previously provided by the statistician.

Demographic parameters, the medical, surgical and leg ulcer history of the patient and a detailed wound description (location, duration, peri-lesional skin condition and state of the wound bed) were documented by the physician.

The compression systems were applied according to manufacturer instructions for 12 weeks, or until full healing, unless a serious adverse event occurred rendering patient follow-up impossible or if the patient withdrew consent. Dressing changes were conducted by the investigating team at the scheduled visits, and by private nurses between two visits. A specific letter and procedures were provided to the private nurse to explain the protocol and the Instructions for the application of the two compression systems. At every dressing change, the clinician documented which primary dressing was applied to the wound.

Investigator assessments were planned every 14±3 days, for 12 weeks (at weeks 2, 4, 6, 8, 10 and 12), including clinical examination, a planimetric record (wound area tracing) and a digital photograph following standard procedures provided by the sponsor. Visits also included evaluation of the tolerance (occurrence of local adverse events) and acceptability parameters (ease of application with a 4-point scale and pain on a visual analogue scale [VAS]).

Endpoints

The selected primary study endpoint for the two systems, 2LB and 4LB, was the number of ulcers to achieve complete closure (100% re-epithelialisation) after 12 weeks of treatment.

Secondary endpoints related to efficacy were the absolute wound area reduction (AWAR; in cm^2) over the 12-week period, relative wound area reduction (RWAR; in %), relative wound area reduction ≥40% versus baseline by week 4 (RWAR≥40%) and the time taken to reach complete re-epithelialisation. RWAR≥40% at week 4 can be considered as a substitute endpoint, predictive of complete wound closure in 20–24 weeks.[27–32] Acetate tracings were measured centrally by two non-participating, blinded clinicians, using digital software (DeskTop Ruler; AVPSoft).

Other secondary outcomes considered were local tolerance (occurrence of local adverse events), change frequency of the compression systems and acceptability parameters (pain experienced from one compression system change to the next and ease of application by the study compression system).

Interventions

The 2LB is composed of two separate bandage components: KTech (layer 1), a composite bandage formed of wadding and short-stretch compressive fabric, and KPress (layer 2), a cohesive long-stretch bandage made of acrylic, polyamide and elastane. Both layers are printed with pressure indicators designed to show when the bandages have been applied correctly (Fig 1), to reach the therapeutic level recommended to treat VLUs (approximately 40mmHg).[4]

The 4LB is comprised of four different bandages:

- Profore 1 (Softban natural), a natural wadding bandage
- Profore 2 (Softcrepe), a light conformable bandage
- Profore 3 (Litepress), a light compression bandage
- Profore 4 (Coplus), a flexible cohesive bandage.

The Profore kit also includes a Profore WCL (sterile wound contact layer), recommended by the manufacturer as a primary dressing for VLUs, and as a primary contact layer for other chronic and/or granulating skin wounds. The 4LB in the control group was selected as it is well-known and widely used worldwide.[9,13,17,23–26] Its therapeutic efficacy in the management of leg ulcers has been demonstrated in several meta-analyses.[19]

Investigators were asked to use a non-impregnated neutral primary dressing, the choice of which was left to the discretion of the clinician. If the clinical condition of the wound justified use of an antimicrobial dressing (clinical signs suggesting high bacterial colonisation), its use had to be authorised by the clinical investigator and used for a maximum of 4 weeks.

During the study period, only sterile saline was used for wound cleansing during dressing change, with dressing change frequency dictated by exudate level and the clinical aspect of the wound. However, other local treatments (pastes, corticosteroids) were permitted for application around the lesions, with their use documented in the case report form.

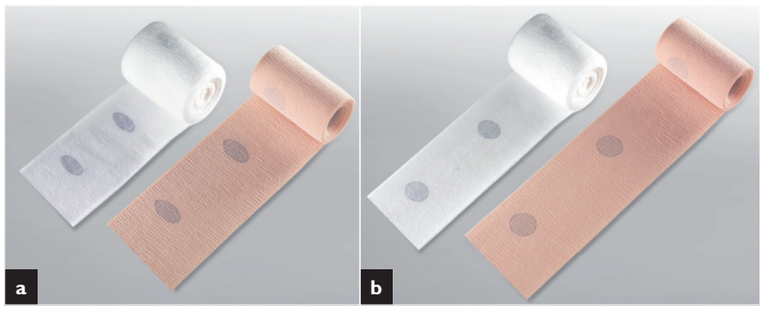

Fig 1. Two-layer bandage components with pressure indicators, both relaxed (a) and stretched to therapeutic levels (b)

Ethics

This trial was conducted according to the European good clinical practice (GCP) recommendations, the principles of the declaration of Helsinki (1975) and the specific regulations of the three countries involved. Laboratoires URGO commenced the trial after approval from the French Agency for the Safety of Health Products (AFSSAPS Registration no. 2009-A00815-52) and approval of the French Medical Ethics Committee of Paris Ile de France VIII (IDF8. No. 09 01 01). In the UK, the National Research Ethics Service, South East Research Ethics Committee, Kent (C-REC) issued a favourable opinion (No. 09/H1102/91) for the initiation of this clinical trial, which was sent to the individual local ethics committees (L-REC) of the investigating centres. In Germany, approval (no. 10-4479) was issued from the Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen.

At baseline and before inclusion, each patient received a full brief on the study objectives, its potential contraindications and benefits, both verbally and in writing, before giving their written consent to participate in the trial.

Statistical analysis

Data analyses were conducted by a company (Vertical), independent of the sponsor, in accordance with the statistical analysis plan, approved by the different parties involved in the trial. Non-inferiority analyses were done on the intention-to-treat (ITT) and per-protocol (PP) populations and conclusions could only be drawn if these two analyses yielded results of the same order. All analyses were performed using SPSS software (v18.0; IBM Inc.).

The comparability of the two groups at baseline was evaluated using Student's t-test or non-parametric test for continuous data, and Chi-squared test or Fisher's exact test for categorical. Treatment efficacy was evaluated by analysing the primary endpoint (100% re-epithelialisation) assessed at the last available evaluation. The last observed value carried forward (LOVCF) procedure was used to compensate for missing data relating to describe wound area

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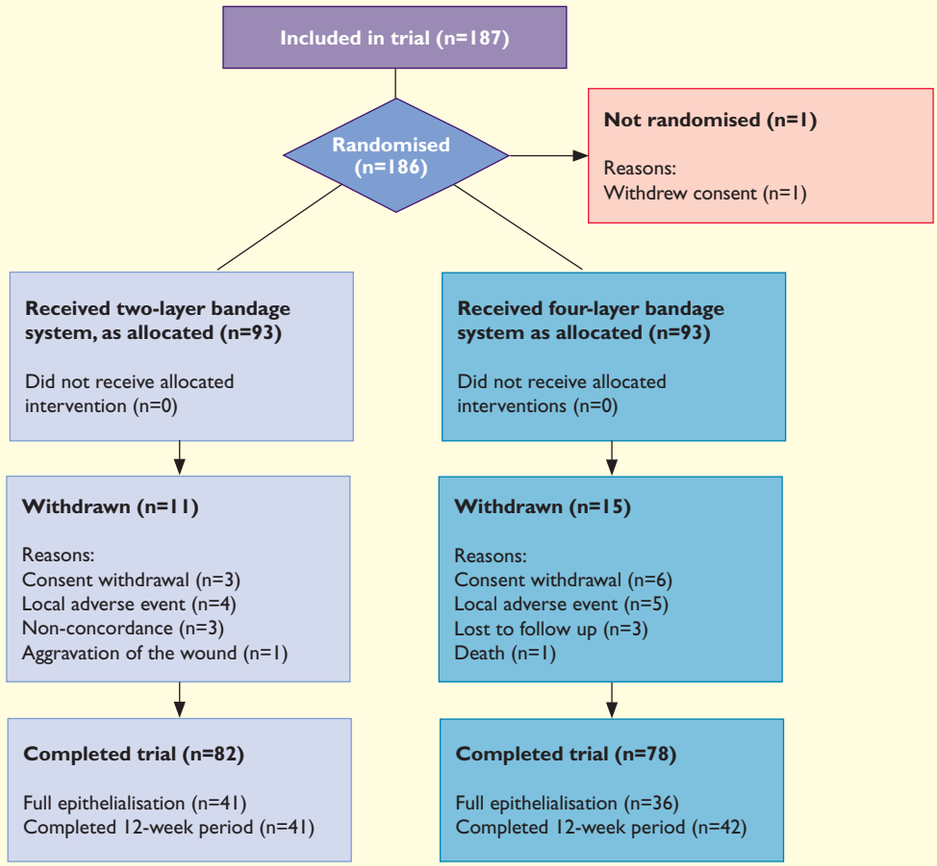
Fig 2. Flow of participants through each phase of the trial



regression (WAR) over time. AWAR and RWAR were calculated from the last available evaluation and compared by covariance analysis using the baseline value as covariant and the compression system and country as fixed factors.

The Kaplan-Meier test was employed, followed by the log-rank test to analyse the time taken to achieve complete wound closure. Prevalence of pain and ease of application were compared using the Chi-squared test. Any possible influence due to the country, due to different levels of clinical experience with the studied systems in the different countries, was analysed using a Mantel-Haenzel test on both parameters.

The percentage of patients experiencing at least one event was compared between the groups using Fisher's exact test. All other analyses on tolerance were purely descriptive.

Sample size

A non-inferiority (NI) margin of 15% was considered acceptable by the investigating coordinators to document the NI of the tested 2LB compared with the reference 4LB system on wound closure rate, following 12 weeks of treatment, as both multilayer compression systems provide a similar, effective interface pressure after application on inferior limbs.[20]

Based on published literature,[4,18,27,33–36] a wound closure rate of approximately 80% was expected after 12 weeks. Under these conditions, it was necessary to recruit a minimum of 88 patients into each treatment group (176 patients in total).

The NI margin initially decided in the protocol, corresponded to –15% and NI was concluded only if the one-sided 95% confidence interval (CI) for the difference in closure rates between the 2LB and 4LB groups did not include this limit (α=0.05; i.e. there is a 95% chance that the 2LB is at least 85% as good as the control 4LB). Given the results obtained, a stricter, supplementary approach (sensitivity analysis) was used to confirm the initial results. This analysis used a –10% NI margin and a one-sided 97.5%CI (α=0.025).

Results

A total of 187 patients were recruited into the study over a period of 15 months, from November 2009 to January 2011. One patient withdrew consent on the day of inclusion, before application of the compression system, leaving 186 patients (n=93 and n=93 in the 2LB and 4LB group, respectively).

Inclusion of patients by country showed a heterogeneous distribution. French investigators included 69% of participants (n=130), while investigators in the UK and in Germany included 19% (n=35) and

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Table 1. Baseline patient characteristics

	2LB (n=93)	4LB (n=93)
Female (n)	48 (52%)	54 (58%)
Age (years)*	72.9 ± 13.5	71.9 ± 12.1
BMI (kg/m²)*	27.6 ± 5.8	28.5 ± 5.9
Comorbidities (n)		
• High blood pressure	56 (60%)	59 (63%)
• Arthrosis	36 (39%)	36 (39%)
• Diabetes	12 (13%)	16 (17%)
• Contact dermatitis	18 (19%)	17 (18%)
• Smoking	12 (13%)	7 (7.5%)
• History of DVT	29 (31%)	26 (28%)
• History of venous surgery	12 (13%)	10 (11%)
ABPI*	1.06 ± 0.12	1.06 ± 0.13
• median	1.00	1.00
Patient status (n)		
• Outpatient	93 (100%)	89 (96%)
Ankle mobility (n)		
• Fully mobile	69 (74%)	67 (72%)
• Limited	21 (23%)	24 (26%)
• Immobile	3 (3.2%)	2 (2.2%)
Patient mobility (n)		
• Walking unaided	68 (73%)	66 (71%)
• Walking with aid	25 (27%)	26 (28%)
• Chairbound	0 (0.0%)	1 (1.1%)

* Results presented as mean ± SD;
BMI=body mass index; DVT=deep vein thrombosis;
ABPI=ankle brachial pressure index

Table 2. Baseline VLU characteristics

	2LB (n=93)	4LB (n=93)
Duration (months)*	6.42 ± 6.71	6.81 ± 6.66
• median [range]	4 [0.25–36]	3.8 [0.25–24]
Recurrent ulcer (n)	52 (56%)	48 (52%)
Wound surface area (cm²)*	9.75 ± 12.08	10.29 ± 10.22
• median [range]	5.94 [1.03–75.75]	6.08 [0.38–46.08]
Peri-lesional skin (n)		
• Healthy	35 (38%)	27 (29%)
• Erythematous	35 (38%)	43 (46%)
• Peri-wound eczema	17 (18%)	13 (14%)
Wound bed aspect (%)*†		
• Granulation median [range]	57.3 ± 33.1 60 [0–100]	63.0 ± 29.7 70 [0–100]
• Slough median [range]	42.7 ± 33.1 40 [0–100]	36.1 ± 29.1 30 [0–100]
Ulcer location (n)		
• Internal malleolus	39 (42%)	36 (39%)
• External malleolus	18 (19%)	23 (25%)
• Other	36 (39%)	34 (37%)

* Results presented as mean ± SD;
† Percentage of wound area covered by granulation tissue or sloughy tissue (colorimetric scale)

12% (n=22), respectively. This was due to fewer investigating centres (7 in the UK and 5 in Germany) being involved compared with France (25 centres) and the study starting later in these two countries (March–October 2010 in the UK, and October 2010 to January 2011 in Germany).

One-hundred and sixty patients (86%) were followed until week 12, or until complete re-epithelialisation of their wound (Fig 2). Twenty-six patients (14%; 11 in the 2LB group and 15 in the 4LB group) discontinued the study prior to week 12 for reasons other than complete closure of their wound.

The two groups were not significantly different in terms of either patient or wound characteristics at baseline. Mean age at baseline was 72.4±12.8 years, with a mean body mass index (BMI) of 28.0±5.9kg/m². The most common comorbidites were hypertension (62%) and cardiovascular disease (30%), which was possibly related to the age of the study population. Diabetes, if present (15%), was mainly type 2 (96%) and any previous allergy or hypersensitivity was noted in 19% of the study population (Table 1).

The majority of the participants (n=182; 98%) were treated as outpatients and were consulted for treatment of their leg ulcers; 72% were walking easily and had ankles that were fairly flexible (73%).

At baseline, mean ABPI was 1.06±0.13mmHg, with a median value for the circumference of the ankles, measured using a tape measure, of approximately 23cm for both groups.

Mean surface area of the target ulcers was 10.0±11.2cm² (median 6.0cm²) for both groups and the mean duration of the treated ulcers was slightly over 6 months (mean 6.6±6.7 months, median 4 months; Table 2). Target ulcers were most commonly located on the malleolar (62%) and they were primarily post-varicose (48%). The ulcers were also noted as being in the granulation phase of the healing process with peri-lesional skin being healthy in only a third of the patients, irrespective of the group.

There were no significant differences between groups with regard to the number of ulcers of >6 months duration (42% and 43% for the 2LB and 4LB groups, respectively; p=0.88), or for the number

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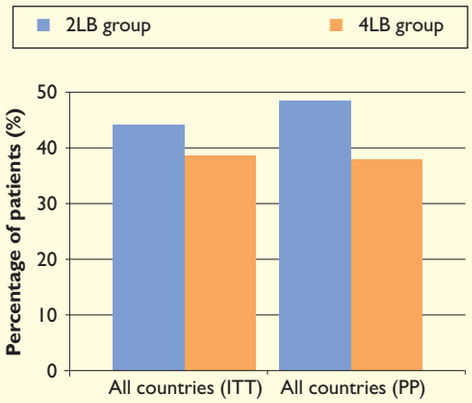
Table 3. Analysis of the primary endpoint in the intention-to-treat (ITT) and per-protocol (PP) populations

	ITT population		PP Population	
	$2LB_1$	$4LB_2$	$2LB_1$	$4LB_2$
No. of patients	93	93	62	66
Wound closure (n)	41 (44%)	36 (39%)	30 (48%)	25 (38%)
Difference (%)	5.38%		10.5%	
Lower limit of unilateral 95%CI	–6.52%		–3.94%	
Lower limit of unilateral 97.5%CI	–8.77%		–6.68%	
Non-inferiority				
• Margin –15%	p<0.005		p<0.001	
• Margin –10%	p=0.0165		p<0.001	

Fig 3. Complete wound closure rates



ITT=intention to treat population; PP=per-protocol population

of ulcers >10cm² (26% and 34% for the 2LB and 4LB groups, respectively; p=0.20) at baseline, both of which are known prognostic factors for healing.[27]

Prior to inclusion in the study, a venous compression system had already been applied to 84% of patients (n=157). The compression systems removed on the day of patient's inclusion, were mainly single-layer (43%), specifically long-stretch compression bandages in 24% of cases. Only 28% of the patients were receiving treatment with multilayer compression bandages (2LB, 3LB or 4LB).

The ITT population was defined as all randomised patients who received at least one application of the system allocated by randomisation (186 patients). The PP population was defined as all subjects who did not deviate from the protocol and who were treated with the allocated compression system for a period of at least 4 weeks (128 patients; 62 and 66 patients in the test and control groups respectively).

Primary endpoint: efficacy

Mean duration of follow-up was similar for both groups (66.6±25.2 days and 62.9±26.1 days in the test and control groups, respectively; p=0.332). In the ITT analysis, 41 ulcers (44%) in the 2LB group and 36 ulcers (39%) in the 4LB group were considered, by the investigators, to have complete re-epithelialisation (Fig 3).

A difference in complete closure rates of 5.38% was noted, with –6.52% being the lower margin of the one-sided 95%CI. The lower margin of the one-sided 97.5%CI was –8.77%. NI with a –10% margin was therefore accepted (p=0.0165; Table 3).

In the PP analysis, complete closure rates of 48% and 38% were obtained, giving a difference of 10.5% in favour of 2LB. The lower margin of the one-sided 95%CI was –3.94% and the lower margin of the one-sided 97.5%CI was –6.68%. NI with a –10% margin was therefore accepted (p<0.001; Table 3).

Wound closure rates in all three involved countries were also higher in the 2LB group (both in the ITT and PP populations), suggesting the NI conclusion to be homogeneous and country-independent.

Secondary endpoints

The planimetric area was documented by the investigator on a twice monthly basis during the 12 weeks of treatment. The last absolute wound area value available at week 12 was 0.48cm² versus 1.33cm² in the test and control groups, respectively (p=0.279; Fig 4), compared with 5.9cm² and 6.1cm² in the test and control groups, at baseline.

The last RWAR value available was –89.23% versus –81.82% in the test and control groups, respectively (p=0.353). The percentage of patients showing a RWAR of at least 40%, relative to baseline surface area by week 4, was also documented. The percentage of wounds showing a RWAR ≥40% at week 4 was 47% of the ulcers treated with the 2LB versus 44% with the 4LB (Fig 5).

Time to complete re-epithelialisation was also analysed between treatment groups, using the Kaplan-Meier test followed by the log-rank test. Mean time for complete re-epithelialisation was similar in both treatment groups with a median value of 91 days in both the ITT and PP analyses.

Local tolerance

Overall, 39 local adverse events (LAEs) were considered to be related to the study compression systems; 16 LAEs reported by 11 patients in the 2LB group (12%) and 23 LAEs by 16 patients (17%) in the control group (p=0.99; Table 4).

The two LAEs most often encountered were as a result of pain (5.4% vs 6.4% in the test and reference group, respectively) and the appearance of de novo ulceration (4.3% vs 6.4% in the test and reference group, respectively). Treatment was discontinued for two patients in both treatment groups due to the

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occurrence of LAE (eczema and de novo ulceration in the test group, and both due to pain in the control group) and due to temporary discontinuation of the 4LB in two patients.

With regard to the condition of the peri-lesional skin at the end of the treatment with the allocated compression systems (week 12 or discontinuation of treatment), the condition of the peri-lesional skin had improved slightly in both groups. It was considered to be 'healthy' in 44% vs 33% of the patients in the test and control groups, respectively, compared with 38% and 31% of the patients at baseline.

Acceptability

A total of 999 medical visits were documented in the 12-week study period; 519 compared with 480 visits in the test and reference groups, respectively. In addition, 1536 nursing treatments were carried out between the fortnightly investigator visits in the same time period.

Pain occurring between the dressing changes was documented by the physicians (intensity rated on a 4-point scale and on a 100mm VAS). Pain between dressing changes (VAS values) was seen to decrease from one physician evaluation to the next, in both treatment groups, with a more significant reduction in the 2LB than the 4LB group; however, this was not significant (Fig 6).

The intensity of the pain experienced was considered to be 'moderate' or 'marked' by 10% of patients in the test group compared with 20% of the patients in the control group. In addition, pain was noted to be 'intermittent' in 25% versus 36% of cases in the test and control groups, respectively.

The 2LB was considered to be significantly easier to apply than the reference compression system (p=0.038), with application of the 2LB considered to be 'very easy' in 62% of cases compared with 47% of cases with the 4LB. In addition, the 4LB was considered to be 'difficult' to apply in 4.3% of cases. This was particularly marked in France (46% vs 34% considered 'very easy' for the 2LB and 4LB , respectively; p=0.001, Mantel-Haenzel test).

Frequency of dressing changes

The median number of compression systems used per week in the two treatment groups for all countries together was 2.08 versus 2.13 in the test and control groups, respectively; however, variations were observed between countries. Although bandage change frequency was similar in France and Germany where elastic monolayer bandage and short-stretch compression are widely used, the frequency was lower in UK where non-removable multilayer compression is generally used, with 1.2 and 1.1 compression systems used per week in the test and the control group respectively.

Neutral dressings (hydrocellular, alginate, Hydrofiber, hydrogel or contact-layer dressings) were used in 87% versus 90% of cases in the test and control groups, respectively (Table 5). Active primary dressings were used in 13% versus 9.8% of ulcer care operations in the 2LB and 4LB groups and the majority of these were silver dressings (7.6% vs 9.0%).

Fig 4. Absolute wound surface area reduction (AWAR) over time

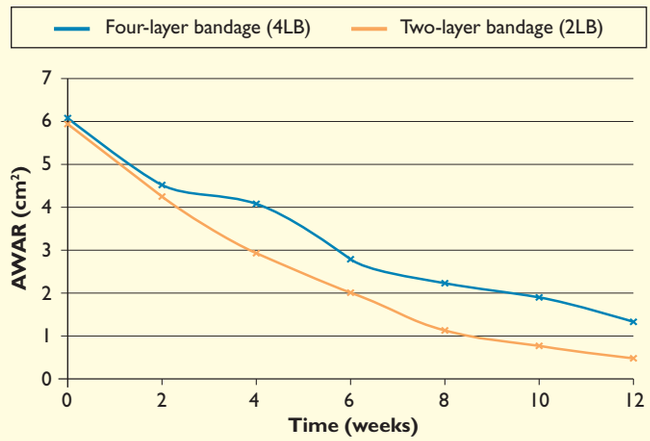
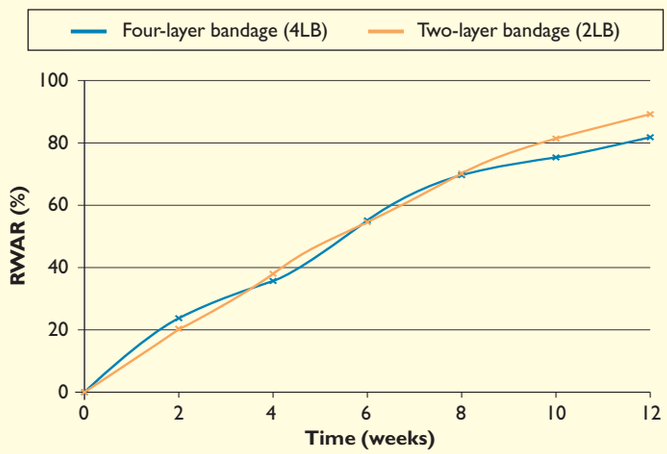


Fig 5. Relative wound surface area reduction (RWAR) over time

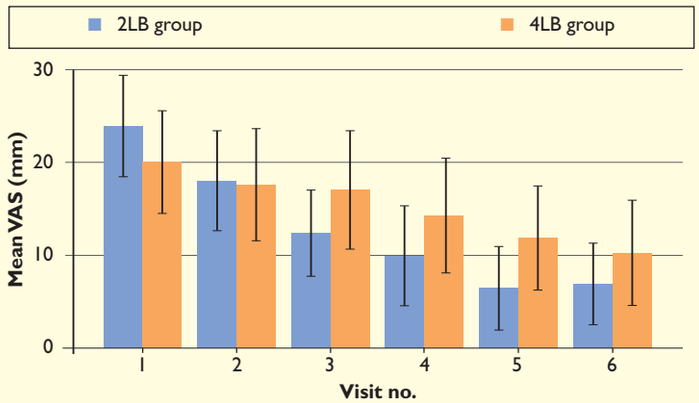


Discussion

The primary objective of this clinical trial (the Odyssey trial) was to evaluate the efficacy of two multilayer compression systems in the management of venous and mixed aetiology leg ulcers. This study involved 37 European investigating centres (25 centres in France, 7 in the UK and 5 in Germany). This multicentred approach was essential to account for any variations in closure rate due to the experience of the clinician.

The 2LB (KTwo) has previously been evaluated in

Fig 6. Changes in VAS pain values over time



Error bars represent 95% confidence interval

a non-comparative clinical trial for similar indications,[20] and has also been evaluated in studies involving healthy volunteers, to measure the level of interface pressure with different compression systems.[21,22] Previous clinical findings of the pilot study reported a median wound area reduction of 72.5% after 6 weeks (and a 24% wound closure rate).[20] Jünger et al.[21] reported similar interface pressure values for both KTwo and Profore compression systems following several days of application. This can be directly compared to those achieved by clinicians, unfamiliar with this two-layer system, where the interface pressure was 30–50mmHg in 85% of cases for the KTwo system and 65% of cases for the Profore system,[22] values deemed to be sufficient for the effective treatment of leg ulcers.[4]

Therefore, the Odyssey RCT was designed to provide a clinical demonstration of non-inferiority between the two systems. The Profore compression system was chosen as the control group as it is considered to be the reference system for this indication, due to several RCTs demonstrating its therapeutic advantages in the management of leg ulcers,[9,12,13,17,23,26] as underlined by the French National Authority for Health.[37]

The ITT analysis showed that complete wound closure was achieved in 44% of the patients in the 2LB group and 39% in the control group. As the difference corresponded to 5.38%, NI within a –10% margin may be considered as being demonstrated with a 95%CI and a 97.5%CI (p=0.0165). The PP analysis showed that complete wound closure was obtained in 48% of the patients in the 2LB and 38% in the control group, a difference of 10.5%. NI within a –10% margin can, therefore, be considered as being demonstrated with a 95%CI and 97.5%CI (p=0.001). These two analyses (strict ITT population and PP population) yielded very similar conclusions, thereby supporting the non-inferiority of the 2LB system in relation to the 4LB system.

Table 4. Number and nature of local adverse events

Local adverse event (n)	2LB (n=93)	4LB (n=93)
• Pain	5	6
• De novo ulceration	4	6
• Eczema	3	2
• Infection	2	5
• Skin Irritation	1	1
• Pruritus	—	2
• Bandage too tight	1	—
• Other	—	1
Total (n)	16	23
No. of patients with LAE(s)	11 (12%)	16 (17%)

Table 5. Primary dressings applied

Dressing type	Nursing operations (n)	
	2LB	4LB
Neutral contact layer	381 (52%)	331 (51%)
Neutral dressing	261 (36%)	259 (40%)
Silver dressing	56 (7.6%)	59 (9.0%)
NOSF dressing	36 (4.9%)	5 (0.8%)
Total	734 (100%)	654 (100%)

NOSF=nano-oligosaccharide factor

Wound closure in all three countries concerned was also consistently higher in the 2LB group (both in the ITT and PP populations, p=n/s), suggesting that the NI was homogeneous and independent of the evaluating country. Furthermore, for all other secondary efficacy endpoints tested (relative and absolute reductions in wound surface area at week 12, percentage of patients with ≥40% reduction in wound surface area by week 4), a value highly predictive of venous ulcer healing by week 20.[27–32] Similar results were obtained in both groups, but with a systematic trend in favour of the 2LB.

As neutral dressings were applied to the treated wounds in 87% and 90% of documented dressing changes during the study in the test and control groups, respectively, the healing rate observed for each group may reasonably be attributed to the two study compression systems. This is supported by analysis undertaken by certain health agencies in a number European countries (France, UK and Spain), which have recently reported that neutral dressings, of whatever class, have not yet demonstrated any differences between them in terms of efficacy, regarding the healing process.[37–40]

The secondary endpoints, including ease of appli-

cation, showed the 2LB to be considered significantly easier to apply than the 4LB by investigators at the inclusion visit (p=0.031). These results recorded for patients with leg ulcers, are consistent with those recorded on healthy volunteers,[21] where KTwo was considered 'very easy' to apply in 63% of cases compared with 47% of cases with Profore.

Regarding the tolerance profiles of the study compression systems, 16 and 23 LAEs, either possibly or definitely related to the study systems, were reported in 11 and 16 patients in the 2LB and 4LB groups, respectively. Pain was reported by five and six patients in the 2LB and 4LB groups, respectively, with one patient in the 2LB group and five in the 4LB considering it to be 'severe'. This led to premature withdrawals from the trial for two patients in the control group (and none in the test group).

VAS values expressing the pain experienced by the patient between two compression system changes, appeared to decrease more markedly over the follow-up period for the 2LB group than the control group; however, the difference was not significant.

Similar pain was reported by the Moffatt et al.,[9] where 53% of the patients (n=9) withdrew from the study prematurely because of intolerance to the same 4LB. More recently, an evaluation of the same 4LB system on healthy volunteers was discontinued because of pain experienced by 25% of the patients, whereas no study withdrawals were noted in the 2LB group.[21] Furthermore, it has been documented that pain generated by a compression system may affect patient compliance with this aetiological treatment for venous disease.[33]

The results provided by the Odyssey trial are consistent with those in previous literature; however, care must always be taken when comparing the results of one clinical trial with those of another, particularly when the trials are conducted in different countries.

For the primary efficacy endpoint, the wound closure rate observed with the Profore system may be considered to be similar to that observed in other studies evaluating this compression system with other four-layer systems.[10,18,34,35] Similarly, the median time to closure of 91 days with 4LB was identical to that observed with all four-layer systems in a study Nelson et al.,[18] which evaluated wounds with a more positive prognosis (smaller and more recent VLUs).

Although the clinical data available today for venous trophic disorders are in favour of using multilayer compression, they do not specify whether the efficacy of such systems increases with the number of layers.[36] Some published data, both the study by Ukat et al.[17] with Profore and the study by Nelson et al.[18] with several four-layer compression systems, tend to show that four-layer compression systems are significantly superior in the management of VLUs compared to short-stretch compression systems, with healing rates documented at week 12 and week 24 being higher with the multilayer systems.

This clinical data is consistent with those provided by a meta-analysis by O'Meara et al.,[19] which included five RCTs (797 patients). It concluded that multilayer bandage systems are superior to short-stretch bandages as they result in more rapid healing of leg ulcers, despite the fact that other clinical studies for the same indication have reported these two compression systems as showing similar efficacy.[9,10,12–14,23]

Conclusion

Both analyses (ITT and PP populations) support the non-inferiority of the 2LB system (KTwo) compared with the 4LB system (Profore), with a very high level of confidence. The Odyssey clinical trial did not demonstrate the 2LB to be any less effective than the 4LB system in the therapeutic treatment of leg ulcers; however, it was considered easier to apply and was shown to be well-tolerated in all countries taking part in the evaluation. The 2LB also showed good local tolerance, particularly with regard to pain, representing an alternative to the conventional treatment with 4LB currently available. ■

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