journal of wound care JWC
VOLUME 30. NUMBER 10 OCTOBER 2021

Quality of life improvement in patients with hard-to-heal leg wounds treated with Prontosan wound irrigation solution and wound gel

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Objective: This study evaluated the impact of four weeks of treatment with Prontosan Wound Irrigation Solution and Prontosan Wound Gel (B. Braun Medical Inc., US) on adults with hard-to-heal leg wounds. Overall change (weeks 1–5) in the Global Quality of Life scale (GQOL), changes in body, psyche and everyday life (EDL) quality of life (QoL) subscores, and changes in wound appearance and size after treatment were assessed.

Method: In this prospective, open-label, single-arm, five-centre study, non-hospitalised patients with no more than two wounds below the knee were recruited into the study; wounds were ≥5cm^2 and ≤50cm^2 and present for ≥4 weeks. The investigator or a designee applied the wound solution and gel to the wounds at clinic visits, and patients/caregivers applied the wound solution and gel at home. Wound-QoL questionnaires were completed at the initial screening and at each week of treatment. Wound size and photographs were obtained at pre- and post-treatment during clinic visits.

Results: A total of 43 patients were enrolled in the study. Mean GQOL scores decreased by 1.11 (46.1%). Body, psyche and EDL decreased by 1.17 (60.0%), 1.26 (41.8%) and 1.00 (42.2%), respectively. Wounds also showed improvement in odour, appearance and size. Adverse events were mild in intensity and transient in nature.

Conclusion: This study demonstrated marked improvement in the QoL of patients with hard-to-heal leg wounds below the knee during four weeks of treatment with the wound solution and gel. Wounds also showed improvement in odour, appearance and size, and the treatment solution and gel were well tolerated.

Declaration of interest: B. Braun Medical Inc. funded the research and preparation of this article. AK, DV, CRC and WC are employees of B. Braun Medical Inc. AO and RS declare no conflict of interest.

chronic • gel • Global quality of life • hard-to-heal • Prontosan • quality of life • solution • wound • wound care • wound gel • wound healing • wounds • wound solution • Wound-QoL questionnaire

Hard-to-heal leg wounds are those that do not progress through the normal healing process in a timely manner. In the US alone, these wounds are estimated to affect between 2.4–4.5 million patients.[1] Hard-to-heal wounds are typically classified as vascular ulcers (venous and arterial ulcers), diabetic ulcers and pressure ulcers. While there is no defined length of time that classifies a wound as hard-to-heal, the range of four weeks to three months is often used in the literature.[2] On average, hard-to-heal wounds last much longer, approximately 12–13 months, and recur in up to 60–70% of patients. Hard-to-heal wounds can lead to a loss of function, decreased quality of life (QoL), and increased morbidity. Primarily a condition of older people, hard-to-heal wounds are becoming more prevalent as populations in developed countries age.[3]

In caring for hard-to-heal wounds, the concurrent management of both the underlying systemic problem (for example, diabetes, peripheral arterial disease) and the wound bed preparation encourages the proper environment in which autolytic tissue repair can take place. The basic tenets of wound bed preparation have been described by the TIME acronym:[4]

- Tissue assessments and management
- Infection/inflammation management
- Moisture imbalance management
- Edge of wound observation and management.

For tissue management, repetitive and maintenance debridement and wound cleaning are recognised as essential throughout the healing period.

Almost all hard-to-heal wounds are thought to contain biofilms, a barrier to the natural progression of wounds towards healing. Biofilms act as a mechanical barrier between the wound and external environment, reducing the antimicrobial contact with bacteria and increasing the chance of critical bacterial colonisation and infection. Furthermore, biofilms adhere to wound bed tissue and are highly resistant to cleansing by irrigation with isotonic solutions.[5] Biofilms are reported to be abundant in hard-to-heal wounds; a study by James et al.[6] demonstrated that biofilms are

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present in 60% of hard-to-heal wounds compared with only 6% of acute wounds. Topical antiseptics are commonly used to control bioburden in wounds. Excessive or insufficient wound exudate can be addressed with a wide range of dressings to regulate moisture balance, to protect periwound skin and to optimise healing. At the edge of the wound, therapies such as negative pressure wound therapy (NPWT) may be used to help improve epithelial advancement and wound closure.[7]

There are many topically applied agents for debridement, cleaning, and moistening acute and hard-to-heal wounds.[4,5,8] In this study, we evaluated Prontosan Wound Irrigation Solution and Prontosan Wound Gel (B. Braun Medical Inc., US), wound cleansing agents containing purified water, polyaminopropyl biguanide (polyhexanide, PHMB) (0.1%) and betaine (0.1%). PHMB is a synthetic compound similar to naturally occurring antimicrobial peptides that is believed to work by breaking down the lipopolysaccharide layer of a bacterial cell wall to kill bacteria. Betaine is a mild surfactant with a hydrophilic head and a hydrophobic tail that repels water and attracts dirt and debris.[9] Additionally, betaine helps remove proteins coating the wound and disrupts the cell-to-cell communication of biofilms via the signalling molecule homoserine lactone.[10] Studies have shown that the combination of PHMB and betaine are able to more effectively penetrate difficult-to-remove wound coatings, lift debris, and clear bacteria and biofilm from a wound.[9]

Rationale

Improving health-related QoL is recognised as a strong outcome measure for an intervention, especially for patients living with chronic conditions. In patients with hard-to-heal wounds, the physical symptoms of these wounds, especially pain, can affect activities of daily living and mobility. Additionally, sleep disturbance from pain impacts work and social activities. Having a hard-to-heal wound has been documented as causing frustration and anxiety.[11]

To evaluate the QoL of patients with hard-to-heal wounds in this study, a validated instrument (Wound-QoL questionnaire) was used to assess the health-related QoL of patients with hard-to-heal wounds and for showing measurable changes with interventions. This Wound-QoL questionnaire has 17 items for patients to indicate the impact of their wounds on their activities and thoughts. The Wound-QoL questionnaire yields a

Table 1. Key study-related procedures

Period	Screening visit	Treatment period				
		Baseline visit				Final visit/ EOS
Week	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5
Visit	Clinic	Clinic	Clinic	Home	Home	Clinic
Informed consent	X					
Demographics	X					
Inclusion/exclusion criteria	X	X				
Medical history/wound history	X	X				
Concomitant medication review	X	X	X	X	X	X
Vital signs	X					X
Physical examination	X					X
Collect blood for clinical laboratory tests	X					X
Wound-QoL questionnaire*	X	X	X	X	X	X
Wound assessment†	X	X	X			X
Wound measurement	X	X‡	X‡			X‡
Wound photographs		X‡	X‡			X‡
Dispense diary		X	X			
Administer study treatment		X	X	X	X	X
Provide/review instructions on treatment and diary		X	X	X	X	X
Dispense study treatment		X	X			
AE assessment		X	X	X	X	X

EOS—end of study; AE—adverse events; *Patients completed the Wound-QoL (quality of life) questionnaire before any other study-related procedure, including any dressing change (with the exception of consenting the patient at screening). Patients were given several blank Wound-QoL questionnaires at the Week 2 visit to fill out on specific days during Weeks 3 and 4 before study treatment on those days; †The Investigator or designee assessed the wounds for appearance, granulation tissue, exudate, drainage, surrounding erythema and/or swelling, and any signs of infection; ‡Conducted pre-treatment and post-treatment

Fig 1. Wound-Quality of Life questionnaire

	In the last 7 days...	Not at all	A little	Moderately	Quite a lot	Very much
1	...my wound hurt	○	○	○	○	○
2	...my wound had a bad smell	○	○	○	○	○
3	...the discharge from the wound has upset me	○	○	○	○	○
4	...the wound has affected my sleep	○	○	○	○	○
5	...the treatment of the wound has been a burden to me	○	○	○	○	○
6	...the wound has made me unhappy	○	○	○	○	○
7	...I have felt frustrated because the wound is taking so long to heal	○	○	○	○	○
8	...I have worried about my wound	○	○	○	○	○
9	...I have been afraid of the wound getting worse or of getting new wounds	○	○	○	○	○
10	...I have been afraid of hitting the wound against something	○	○	○	○	○
11	...I have had trouble moving around because of the wound	○	○	○	○	○
12	...climbing stairs has been difficult because of the wound	○	○	○	○	○
13	...I have had trouble with everyday activities because of the wound	○	○	○	○	○
14	...the wound has limited my recreational activities	○	○	○	○	○
15	...the wound has forced me to limit my contact with other people	○	○	○	○	○
16	...I have felt dependent on help from others because of the wound	○	○	○	○	○
17	...the wound has been a financial burden to me	○	○	○	○	○

The Wound-QoL questionnaire measures the health-related QoL of patients with hard-to-heal wounds.[12,17] Subscores 'Body' applies to items 1–5; subscores 'Psyche' applies to items 6–10; and subscores 'everyday life' applies to items 11–16. Item 17 does not belong to any of the subscores

global score to describe the overall impact and three subscores (body, psyche and everyday life (EDL)) to capture the specific QoL issues that contribute to this impact.[12] The Wound-QoL questionnaire is intended to be completed by the patients at 7-day intervals.

The Wound-QoL questionnaire was used to assess patient QoL at baseline and after each week of treatment with the wound solution and gel, with the primary endpoint being the change from baseline to week five (end of study, EOS) in the global score. In addition to the global score, the three Wound-QoL subscore outcomes, and the change from baseline in wound appearance and size were also examined.

This study will use a validated tool to show the improvement in the overall QoL as well as the body, psyche and EDL subscores in patients with hard-to-heal leg wounds who used the wound solution and gel for treatment of their hard-to-heal leg wounds.

Objectives

The primary objective of this study was to assess the overall change in the Global QoL after four weeks of treatment with the wound solution and gel in patients with hard-to-heal leg wounds. The secondary objectives were to assess the changes in the body, psyche and EDL subscores of the Wound-QoL questionnaire after four weeks of treatment with the wound solution and gel.

The exploratory objective was to assess the change in the appearance and size of the wounds by direct evaluation and photographic measurements after four weeks of treatment with the wound solution and gel. All objectives were achieved by evaluating changes from baseline (week one) to week five (EOS).

Methods

Study design

This was a prospective, open-label, single-arm, multisite study (involving five centres) to evaluate the change from baseline (week one) in Wound-QoL after four weeks of treatment with the wound solution and gel in adult patients with hard-to-heal leg wounds. Enrolment was competitive across all five study sites in the US, i.e., no minimum number of patients was required by each site.

The investigator or designee applied the wound solution and gel to the wounds during clinic visits at weeks one, two and five. Patients applied the wound solution and gel themselves (or had them applied by a caregiver) at home in between clinic visits (weeks three and four). The frequency and method of treatment applications were per institutional guidelines and the manufacturer's instructions for use (IFU) for the individual patient wound(s).[13,14] Patients were given diary cards to document their use of the wound solution and gel while at home, and to record any AEs.

The study consisted of a screening period (Week 0), a baseline assessment (Week 1), and 4 weeks of treatment (Week 1 to Week 5). A safety follow-up was performed only if there were unresolved AEs. A detailed description of the key weekly study procedures is displayed in Table 1.

Ethical approval and patient consent

All Clinical Study sites participating in this study received approval from an institutional review board before the study began at their location.

Each patient was informed about the nature of the study and all patients signed an informed consent form before any study-related procedures were performed. This consent also gave approval to take photographs of their wounds.

Table 2. Demographics

Characteristic	Enrolled/safety population n=43	Evaluable population n=40	Completer population n=36
Mean age, years (standard deviation, SD)	64.1 (14.7)	63.9 (15.2)	63.2 (15.3)
Sex, n (%)			
Male	22 (51.2)	20 (50.0)	17 (47.2)
Female	21 (48.8)	20 (50.0)	19 (52.8)
Race, n (%)			
Asian	1 (2.3)	1 (2.5)	1 (2.8)
Black/African American	16 (37.2)	16 (40.0)	15 (41.7)
White	23 (53.5)	20 (50.0)	17 (47.2)
Not available	3 (7.0)	3 (7.5)	3 (8.3)
Hispanic or Latino ethnicity, n (%)	9 (20.9)	9 (22.5)	8 (22.2)
Mean body weight, kg (SD)	96.4 (23.3)	96.5 (23.2)	95.3 (21.5)
Mean height, cm (SD)	169.1 (10.9)	168.6 (10.9)	169.3 (10.9)
Mean body mass index, kg/m^2 (SD)	33.7 (7.02)	33.9 (7.1)	33.3 (6.8)
Mean systolic blood pressure, mmHg (SD)	138.6 (17.5)	138.8 (17.9)	138.0 (18.1)
Mean diastolic blood pressure, mmHg (SD)	79.7 (11.6)	80.2 (11.9)	80.3 (12.4)

Table 3. General characterisation of the wounds at baseline (Week 1) for all study populations

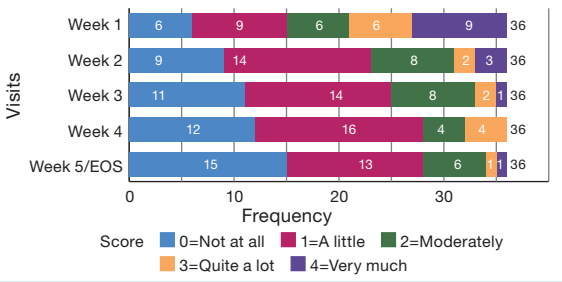
	Enrolled/safety population n=43		Evaluable population n=40		Completer population n=36	
	Wound 1* n=43	Wound 2 n=11	Wound 1* n=40	Wound 2 n=11	Wound 1* n=36	Wound 2 n=9
Wound type, n (%)						
Venous ulcer	30 (69.8)	8 (72.7)	27 (67.5)	8 (72.7)	25 (69.4)	6 (66.7)
Diabetic ulcer	7 (16.3)	0	7 (17.5)	0	5 (13.9)	0
Cellulitis	0	1 (9.1)	0	1 (9.1)	0	1 (11.1)
Neuropathic ulcer	2 (4.7)	1 (9.1)	2 (5.0)	1 (9.1)	2 (5.6)	1 (11.1)
Traumatic ulcer	4 (9.3)	1 (9.1)	4 (10.0)	1 (9.1)	4 (11.1)	1 (11.1)
Wound age, weeks						
Mean (SD)	115.7 (282.6)	62.9 (79.2)	120.4 (292.4)	62.9 (79.2)	96.9 (267.7)	41.8 (49.7)
Median	20.0	20.0	19.5	20.0	18.5	20.0
Min–max	4–1613	1–260	4–1613	1–260	4–1613	1–156
Wound location, n (%)†						
Left leg	16 (37.2)	5 (45.5)	15 (37.5)	5 (45.5)	15 (41.7)	5 (55.6)
Right leg	21 (48.8)	5 (45.5)	19 (47.5)	5 (45.5)	17 (47.2)	3 (33.3)
Left foot	3 (7.0)	0	3 (7.5)	0	2 (5.6)	0
Right foot	3 (7.0)	1 (9.1)	3 (7.5)	1 (9.1)	2 (5.6)	1 (11.1)
Past complications, n (%)						
Infection	10 (23.3)	4 (36.4)	10 (25.0)	4 (36.4)	10 (27.8)	4 (44.4)
Recurrent hospitalisations	3 (7.0)	1 (9.1)	3 (7.5)	1 (9.1)	3 (8.3)	1 (11.1)
Other	1 (2.3)	0	0	0	0	0
Calculated wound surface area, cm^2						
Mean (SD)	17.7 (12.8)	27.5 (41.1)	18.1 (13.1)	27.5 (41.1)	18.3 (12.9)	16.3 (28.7)
Median	12.50	3.40	13.05	3.40	13.75	2.30
Min–max	5.0–48.0	0.6–123.2	5.0–48.0	0.6–123.2	5.0–48.0	0.6–75.0

*Wound 1 was considered the primary wound for the assessment of the study objectives; †A patient's wound was classified into more than one category.
Min—minimum; max—maximum; SD—standard deviation

Fig 2: Representative stacked bar charts for Wound-Quality of Life (QoL) questionnaire responses from each of the three subscores: body, psyche and QoL

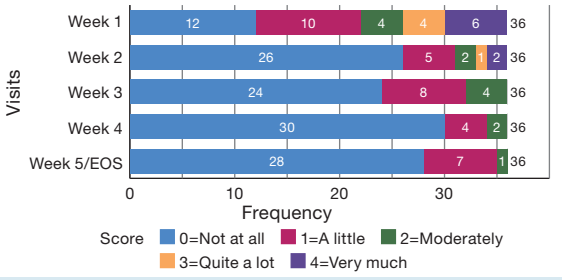
Body subscore

Wound-QoL Question 1: My wound hurts



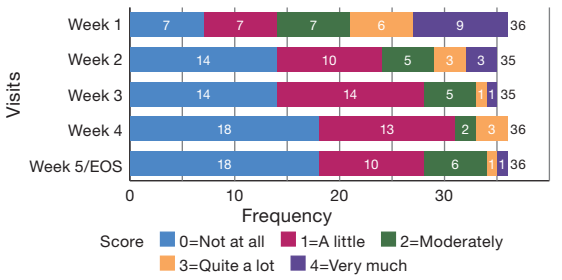
Note: The % change from baseline based on the numerical response was 57.3% with a p-value of <0.0001

Wound-QoL Question 2: My wound has a bad smell



Note: The % change from baseline based on the numerical response was 83.3% with a p-value of <0.0001

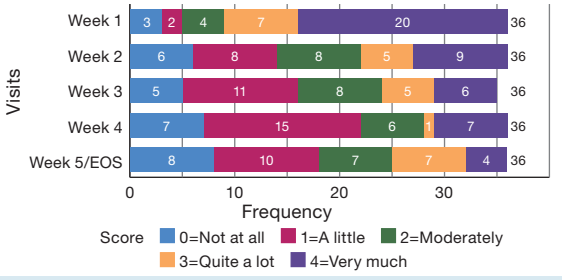
Wound-QoL Question 4: The wound has affected my sleep



Note: The % change from baseline based on the numerical response was 61.3% with a p-value of <0.0001

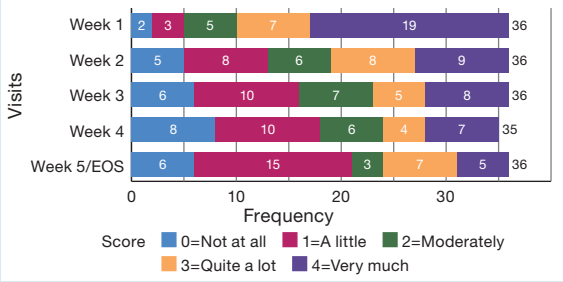
Psyche subscore

Wound-QoL Question 6: The wound has made me unhappy



Note: The % change from baseline based on the numerical response was 45.1% with a p-value of <0.0001

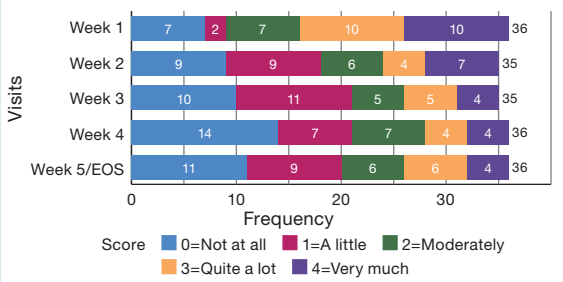
Wound-QoL Question 9: I have been afraid of the wound getting worse or of getting new wounds



Note: The % change from baseline based on the numerical response was 43.7% with a p-value of <0.0001

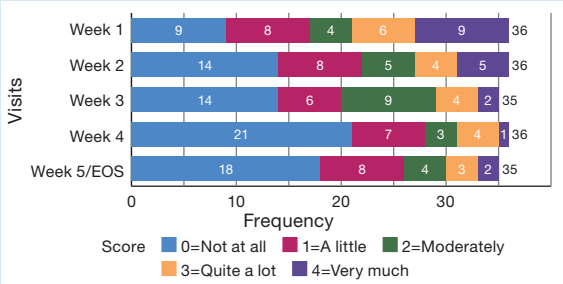
EDL subscore

Wound-QoL Question 11: I have had trouble moving around because of the wound



Note: The % change from baseline based on the numerical response was 36.0% with a p-value of <0.0007

Wound-QoL Question 15: The wound has forced me to limit my contact with other people



Note: The % change from baseline based on the numerical response was 51.5% with a p-value of <0.0001

The completer population was used for these analyses. Wound-QoL questions 1, 2, and 4 contributed to the body subscore, Wound-QoL questions 6 and 9 contributed to the psyche subscore, and Wound-QoL questions 11 and 15 contributed to the EDL subscore. The Wound-QoL questionnaire is presented in Fig 1. EOS—end of study; EDL—everyday living

Table 4. Summary of the mean quality of life (QoL) statistical results at Week 5 in the completer population

Score/subscore	n	Baseline mean	Week 5 mean	Numerical change from baseline	% change from baseline	p-value	95% CI
Global QoL score	36	2.413	1.301	–1.112	46.1%	<0.0001	–1.425 to –0.799
Body QoL subscore	36	1.956	0.783	–1.172	60.0%	<0.0001	–1.583 to –0.761
Psyche QoL subscore	36	3.017	1.756	–1.261	41.8%	<0.0001	–1.647 to –0.875
Everyday life QoL subscore	36	2.375	1.372	–1.003	42.2%	<0.0001	–1.339 to –0.668

Baseline is defined as the assessment at Week 1. Percent change from baseline was calculated as: [(Mean Week 1 – Mean Week 5)/(Mean Week 1)] × 100. A negative value indicates improvement in the score. CI—confidence interval

Study device and data tools

The wound solution used in this study is a clear, colourless liquid containing purified water, 0.1% undecylenamidopropyl betaine as a surfactant, 0.1% polyaminopropyl biguanide (polyhexanide (PHMB)) as a preservative and sodium hydroxide for pH adjustment. The device is cleared by the US Food and Drug Administration (FDA) for prescription and over-the-counter use for cleaning wounds and moistening and lubricating absorbent wound dressings for the management of cuts, lacerations, ulcers, burns, post-surgical wounds and abrasions.[15,16]

The wound gel used in this study is a clear, colourless gel containing glycerol, hydroxyethylcellulose, 0.1% undecylenamidopropyl betaine, 0.1% PHMB and purified water. The device is cleared by the FDA for prescription and over-the-counter use for cleaning and moistening the wound bed for the management of cuts, abrasions, lacerations, ulcers, first- and second-degree burns, partial- and full-thickness wounds, and surgical incisions. It can be used during wound dressing changes to soften encrusted wound dressings.[17,18]

The wound solution and gel were stored under controlled room temperature (20–25°C) with allowed excursions between 15–30°C.

A validated Wound-QoL questionnaire was used to assess changes in QoL and an example is provided in Fig 1.[12,19] The validated 'clock' method was used to measure wound size.[20] Patients were supplied with a diary card to record their treatment use and any adverse events (AEs) while at home. Additionally, photographs were taken by study site staff during inpatient visits with a sponsor-supplied digital camera to document wound size and appearance only.

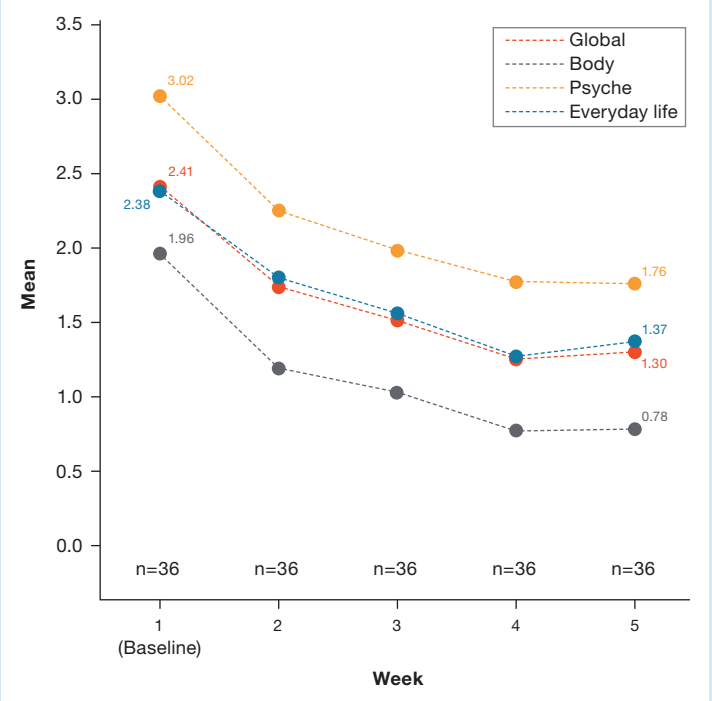
Patient selection

The planned sample size of 52 patients had an 80% power to detect a change from baseline to week five of at least 0.35 points in the Wound-QoL global score, assuming an estimated standard deviation (SD) of differences of 0.88, using a paired t-test with a 0.05 two-sided significance level. Patient enrolment was planned to be six months; however, enrolment was below expectations and even though the enrolment period was extended to 18 months, the study was terminated before achieving 52 patients.

There were four possible statistical study populations:

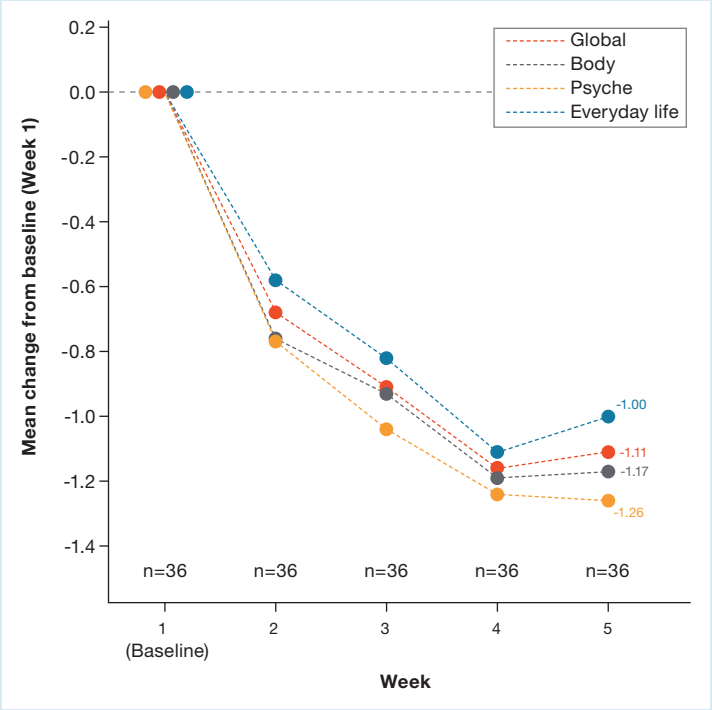
- The enrolled population included all patients who signed the informed consent form at the initial screening visit, met the inclusion/exclusion criteria and participated in the week one (baseline) visit
- The evaluable population included all patients who

Fig 3. Mean values of the Global Wound-QoL (quality of life) score and the body, psyche and everyday life subscores at baseline and during four weeks of treatment for the completer population



Baseline is defined as the assessment at Week 1

Fig 4. Absolute mean changes in the Global Wound-QoL (quality of life) score and the body, psyche and everyday life subscores from baseline to week five for the completer population



Baseline is defined as the assessments at Week 1

received at least two weeks of study treatment and completed the week three Wound-QoL questionnaire

- The safety population included all patients who received at least one study treatment administration. All patients in the enrolled population successfully completed screening and baseline assessments. Therefore, the enrolled and safety populations were the same.
- The completer population included all patients who completed the four-week treatment period.

Thus, 43 patients were actually enrolled in week one (evaluable/safety population), 40 patients completed the study at week three (statistical population) and 36 patients completed the week five study activities (completer population).

Patients were 18 years of age or older with either two wounds on one leg, one wound on each leg, or only one wound. All wounds were located below the knee and for any given patient at least one wound had to have a surface area ≥5cm^2 and ≤50cm^2 and had to be present for ≥4 weeks to be enrolled. Patients were required to have a mean global QoL score of ≥1.18 on the Wound-QoL questionnaire at screening (week 0). Patients were also excluded from the study if they had prior treatment with either the wound solution and/or gel.

Statistical analysis

The statistical analysis focused on clinical outcome assessments: patient-reported Wound-QoL questionnaire, and investigator-reported wound size and wound characteristics.

The global score of the Wound-QoL questionnaire was summarised in a paired t-test analysis of the mean global score at baseline and after four weeks of treatment. Secondary analyses included the changes from baseline in subscores of the Wound-QoL questionnaire for body, psyche, and EDL QoL dimensions. Exploratory analyses included the change from baseline in the appearance and size of the wounds. All endpoints were summarised using descriptive statistics. All safety assessments were conducted using the enrolled/safety population.

Results

Demographics and baseline characteristics

A total of 43 patients were enrolled into week one and had study procedures performed including receiving their first applications of the wound solution and gel, with no dropouts between successful screening and completion of baseline (week one) assessments (enrolled/safety population). Demographic and baseline characteristics of patients in the enrolled/safety, evaluable, and completer populations are shown in Table 2. There were approximately equal numbers of male and female patients in all three populations. The age of patients in the Completer Population was a mean 63.2 years and ranged from 34–85 years. Most patients in the completer population were white (47.2%) or African American (41.7%). Characteristics of patients in the enrolled/safety population and in the evaluable population were essentially similar.

Table 3 shows characteristics of patients' wounds for the three analysis populations. In the Completer Population, three-quarters (75.0%) had only one wound that was treated and assessed (referred to as primary wounds), while the remaining 25.0% had both a primary and secondary wound that were treated and assessed. Venous ulcers were the most common primary wound type in the study and accounted for more than two-thirds (69.4%) of study wounds. Diabetic ulcers were the next most common primary wound type in the completer population (13.9%), followed by traumatic ulcers (11.1%) and neuropathic ulcers (5.6%).

Evaluation of overall change in quality of life

Representative individual Wound-QoL questions from each of the three subscores are presented in Fig 2. An average of statements 1–17 was used to calculate global Wound-QoL; an average of statements 1–5, 6–10, and 11–16 were used to calculate QoL subscores for body, psyche and EDL, respectively. The percent change from baseline and corresponding p-values of the paired t-test indicate statistically significant

Table 5: Detailed characterisation of the wounds in the completer population

	Baseline (Week 1)		Week 2		Week 5/EOS	
	Wound 1 n=36 n (%)	Wound 2 n=9 n (%)	Wound 1 n=36 n (%)	Wound 2 n=9* n (%)	Wound 1 n=36 n (%)	Wound 2 n=9* n (%)
Surrounding erythema						
Yes	8 (22.2)	1 (11.1)	5 (13.9)	0 (0.0)	3 (8.3)	0 (0.0)
No	28 (77.8)	8 (88.9)	30 (83.3)	7 (77.8)	33 (91.7)	7 (77.8)
Swelling						
+1	16 (44.4)	5 (55.6)	14 (38.9)	2 (22.2)	10 (27.8)	1 (11.1)
+2	9 (25.0)	1 (11.1)	8 (22.2)	3 (33.3)	10 (27.8)	3 (33.3)
+3	1 (2.8)	0 (0.0)	3 (8.3)	0 (0.0)	2 (5.6)	0 (0.0)
None	10 (27.8)	3 (33.3)	10 (27.8)	2 (22.2)	14 (38.9)	3 (33.3)
Odour						
None	32 (88.9)	9 (100.0)	34 (94.4)	7 (77.8)	36 (100.0)	6 (66.7)
Mild	3 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Foul	1 (2.8)	0 (0.0)	1 (2.8)	0 (0.0)	0 (0.0)	1 (11.1)
Strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Granulation tissue						
Yes	35 (97.2)	7 (77.8)	32 (88.9)	5 (55.6)	31 (86.1)	5 (55.6)
Mild	11 (30.6)	3 (33.3)	7 (19.4)	1 (11.1)	4 (11.1)	2 (22.2)
Moderate	19 (52.8)	3 (33.3)	18 (50.0)	4 (44.4)	21 (58.3)	3 (33.3)
Abundant	5 (13.9)	1 (11.1)	7 (19.4)	0 (0.0)	6 (16.7)	0 (0.0)
No	1 (2.8)	2 (22.2)	3 (8.3)	2 (22.2)	5 (13.9)	2 (22.2)
Exudate						
Yes	29 (80.6)	6 (66.7)	29 (80.6)	5 (55.6)	23 (63.9)	4 (44.4)
Scant	12 (33.3)	2 (22.2)	17 (47.2)	2 (22.2)	13 (36.1)	2 (22.2)
Moderate	13 (36.1)	3 (33.3)	9 (25.0)	3 (33.3)	8 (22.2)	1 (11.1)
Copious	4 (11.1)	1 (11.1)	3 (8.3)	0 (0.0)	2 (5.6)	1 (11.1)
No	7 (19.4)	3 (33.3)	6 (16.7)	2 (22.2)	13 (36.1)	3 (33.3)
Drainage						
Yes	31 (86.1)	7 (77.8)	27 (75.0)	3 (33.3)	21 (58.3)	4 (44.4)
No	5 (13.9)	2 (22.2)	8 (22.2)	4 (44.4)	15 (41.7)	3 (33.3)

EOS—end of study; *In the Wound 2 category, the wounds of two patients healed at Week one and so are not counted under Week two or Week 5/EOS

improvement in mean scores from baseline to week five/EOS (Fig 2).

There was a marked and gradual improvement in the global QoL score as seen by a decrease in mean scores after baseline (week one). Mean global QoL scores consistently decreased week after week from baseline until and including week four, with no further changes apparent at week five/EOS. Mean at week five/EOS was 1.301 with the 95% confidence interval (CI) being −1.425–−0.799. There was a 46.1% percent improvement in global Wound-QoL between baseline and week five/EOS. Corresponding p-values of the paired t-test ranged from 0.0001– <0.0001, indicating statistically as well as clinically, significant improvement in mean scores from baseline to week five/EOS (Table 4).

Evaluation of changes in the quality of life subscores body, psyche and EDL

Mean changes from baseline are also shown in Table 4 for the subscores of body, psyche and EDL among patients in the completer population, respectively.

There were clear improvements in all three Wound-QoL subscores, as seen by decreases in mean scores over time. These improvements were gradual until week four; mean changes in scores of the three subscores from baseline to week five differed only slightly from the mean changes in scores of the three subscores from baseline to week four. Corresponding p-values of the paired t-test indicate statistically and clinically significant improvement in mean scores from baseline to week five/EOS.

Fig 3 and Fig 4 graphically display the mean values

Table 6. Wound measurements for the completer population

	Week 5/End of study	
	Wound 1 n=36	Wound 2 n=9
Pre-treatment		
Change from baseline (cm^2)		
n	36	7
Mean (SD)	–6.63 (18.30)	12.11 (41.78)
Median	–3.35	0.20
Min–max	–87.0–34.5	–17.1–105.7
Post-treatment		
Change from baseline (cm^2)		
n	31	6
Mean (SD)	–8.22 (19.17)	16.98 (43.54)
Median	–3.50	0.80
Min–max	–87.0–34.5	–5.4–105.7

Min—minimum; max—maximum

Table 7. Overview of patients with treatment-emergent adverse events (TEAE) and adverse device (ADE) reactions

Patients with:	n=43 n (%) [number of events]
Any TEAE	**29 (67.4) [156]**
Any TEAE causally related to treatment	14 (32.6) [113]
Any TEAE leading to discontinuation of treatment	3 (7.0) [3]
Maximum severity for any TEAE	
Mild	20 (46.5)
Moderate	6 (14.0)
Severe	3 (7.0)
Any serious TEAE	3 (7.0%) [7]
Any ADE	**14 (32.6) [113]**
Any ADE leading to discontinuation of treatment	1 92.30 [1]
Maximum severity for any ADEs	
Mild	14 (32.6)
Moderate	0 (0)
Severe	0 (0)
Any serious ADEs	0 (0)

and absolute mean changes of the global and body, psyche and EDL subscores at baseline and during four weeks of treatment in the completer population, respectively. Absolute mean changes in global, body, psyche, and EDL Wound-QoL ranged from −1.00–−1.26 between baseline (week one) and week five/EOS.

Changes in wound appearance and size

As an exploratory objective, wound appearance and wound size were assessed at baseline (week one) and at weeks two and five/EOS. Overall, the appearance of the wounds improved from baseline (week one) to week five. The percentage of patients presenting with erythematous surroundings of primary wounds gradually decreased from 22.2% at baseline (week one) to 13.9% at week two and 8.3% at week five (Table 5).

In regard to swelling, 69.4% of patients in the completer population had primary wounds of swelling grade one or two, and 27.8% had no swollen primary wounds at baseline (week one). The percentage of patients without swollen primary wounds increased from 27.8% at baseline to 38.9% at week five. At baseline, 88.9% of patients' primary wounds had no odour, and odour of the remaining primary wounds was either mild (8.3%) or foul (2.8%). The percentage of primary wounds with no odour increased to 100.0% at week five/EOS.

Granulation tissue was observed in 80.6% of primary wounds at baseline, with the majority (36.1%) having moderate amounts of granulation tissue. The percentage of primary wounds with granulation tissue decreased to 63.9% at week five, while the percentage of primary wounds with no granulation tissue increased from 19.4% at baseline (week one) to 36.1% at week five/EOS. Similarly, the percentage of patients with drainage decreased from 86.1% at baseline (week one) to 58.3% at week five/EOS.

Pre-treatment and post-treatment mean changes from baseline to week five in the completer population are shown in Table 6. Mean primary wound sizes were not materially different between pre-treatment and post-treatment measurements at each of the three visits. Mean pre-treatment primary wound size at baseline among patients in the completer population was 18.44cm^2. Changes in wound size from baseline to week five/EOS varied from a decrease of 87.0cm^2 to an increase of 34.5cm^2; mean change was –6.63cm^2 and median change was –3.35cm^2. Post-treatment wound size in the same population changed between baseline and week five/EOS by a mean of –8.22cm^2.

Adverse events

A total of 156 treatment-emergent adverse events (TEAEs) were recorded in 29 patients (67.4%). In 14 (32.6%) patients, 113 TEAEs that occurred were found to be causally related to treatment and were classified as adverse drug reactions (ADEs). The number and percentage of patients experiencing TEAEs and ADEs are presented in Table 7. Adverse drug reactions with ≥10 events included the following: burning sensation (62 events), paraesthesia (18 events), pain (13 events) and skin pain (10 events). Adverse drug reactions for the 43 patients in the enrolled/safety population are presented in Table 8. There were five patients who together experienced 11 serious adverse events (SAEs); four SAEs occurring in two patients occurred before the first administration of the wound solution and gel, and the other seven SAEs were not

Table 8: Adverse device reactions in the enrolled/ safety population

Primary system organ class preferred term	n=43 n (%) [number of events]
At least one ADE	14 (32.6) [113]
General disorders and administration site conditions	**11 (25.6) [76]**
Burning sensation	11 (25.6) [62]
Pain	3 (7.0) [13]
Paraesthesia	1 (2.3) [1]
Skin and subcutaneous tissue disorders	**8 (18.6) [37]**
Burning sensation	1 (2.3) [1]
Pain	1 (2.3) [1]
Pain of the skin	1 (2.3) [10]
Paraesthesia	4 (9.3) [18]
Pruritis	1 (2.3) [4]
Sensitive skin	1 (2.3) [1]
Skin disorder	1 (2.3) [1]
Skin irritation	1 (2.3) [1]

associated with the treatment wound solution and gel. Overall, treatment with the wound solution and gel was well tolerated by the study patients.

Discussion

There is a clear correlation between physical improvements to the condition of a wound (pain, odour, discharge) and improvements to a patient's general wellbeing and QoL (mood, sleep, mobility).[21] Enduring and recalcitrant pain is a common concern in patients with hard-to-heal wounds such as venous leg ulcers, pressure ulcers, diabetic neuropathic foot ulcers and malignant wounds.[22,23] There is a wealth of evidence that shows psychological stress has an adverse effect on wound healing via depressed immune function and elevated levels of proinflammatory cytokines.[24,25] Chronic pain also contributes to delayed healing through psychosocial impacts including behavioural changes, social isolation, mobility issues due to pain, and behavioural stressors such as poor diet and little exercise.[25] To achieve the best outcomes in the management of hard-to-heal wounds, providers must address the wound cause and patient-centred concerns.

Although time-to-healing is an important measure for wound care, QoL may be equally or more important for people living with non-healable or hard-to-heal wounds. Thus, a validated Wound-QoL was used in this study to evaluate physiological factors that contribute to health related QoL including body, psyche and EDL.[12,19]

Malodour, or wound odour, is typically the result of necrotic tissue or bacterial colonisation of the wound. Problems typically associated with wound odour include social isolation, loss of appetite, intimacy issues, and distress for the patient and caregivers. These odours can induce a vomit or gagging reflex and are often described as acrid. The impact on patients is particularly devastating, as they live with the consequences of the foul-smelling, discharging wound, which can negatively impact body image.[26] The psychological effects of wound odour also impact relatives and caregivers. Treating the underlying infection or debridement of the devitalised tissue may help improve the odour, and ultimately improve odour-associated problems, body image and QoL.

The wound solution and gel treatment used in this study are FDA approved for cleaning and moistening wounds, helping with removing devitalised tissue, rebalancing the bioburden, and reducing exudate to prepare the wound for closure.[9] They also soften encrusted wound dressings, making wound dressing changes easier and less painful for the patient. These cleaning and moistening actions reduce the amount of odour-causing necrotic tissue, thus encouraging the healing process. In this study, there was significant improvement (83.3%; $p<0.0001$) in QoL regarding smell (i.e., 'my wound has a bad smell') (Fig 2).

Although the enrolment period was extended to 18 months (initial plan was for six months), the study was halted in September 2019, which resulted in the enrolment of 43 of the planned 52 patients. The observed improvement in global score of the Wound-QoL was nevertheless statistically significant in this smaller sample of patients ($p<0.0001$). This was because the mean global-QoL score improved considerably more than the minimum clinically meaningful change of 0.35. In fact, the required sample size to detect the actually observed mean change of –1.10 points (SD 0.90) would have been approximately 10 patients.

Wound infection, pain and odour are factors known to affect mobility, sleep and social interactions, and reduce QoL.[7,27] Some patients have also reported emotional and psychological effects such as lower self-confidence, guilt, anger and worry about the wound.[27,28] Additionally, there can be significant limitations in daily living activities, coupled with increased dependency on family members or caregivers. These data demonstrate the strong impact of psychological factors and perception of their medical condition on a patient's overall QoL and wound healing.[28]

In the present study, improvements in pain and odour were correlated with an increase in the patient's mobility and decrease in his/her dependence on others for help. This is likely due to an improvement in confidence while interacting with others, thus greatly improving their QoL (Fig 4).

The improvement in overall QoL was demonstrated by reductions in global Wound-QoL scores, with the mean score decreasing consistently week by week in the first three weeks of treatment, then appearing to stabilise after patients had their fourth week of treatment. The reductions in global wound-QoL ranged from a mean of –0.99 in patients who received

at least one round of treatment to a mean of –1.11 in patients who completed all four weeks of therapy. These findings indicate clinically meaningful improvements in QoL.

Visual inspection of the wounds showed a decrease during the study in wound size and in the proportion of patients with erythematous wound surroundings. Wounds also improved over time with respect to swelling. In addition to the known safety and efficacy profiles, this study demonstrates that the wound solution and gel used in this study improved patient QoL and was well tolerated.

Limitations

The primary objective was to assess the changes in the QoL of the patients after treatment with the wound solution and gel. It was not designed to primarily assess the change in the wound size and appearance. Thus, we could not clearly quantify the significance in the change in the size and appearance of the wound. In addition, a longer study may have been able to determine if the observed improvement in the QoL plateaus after four weeks of treatment or if the patient's QoL continues to improve over time.

Conclusions

This study demonstrates a marked improvement in the QoL of adult patients with one or two hard-to-heal leg wounds below the knee after four weeks of treatment with the wound solution and gel. This improvement in QoL was seen together with improvements in wound appearance and wound size. Treatment with the wound solution and gel was well tolerated, and is a promising treatment in wound healing. **JWC**

References

1 Richmond NA, Maderal AD, Vivas AC. Evidence-based management of common chronic lower extremity ulcers. Dermatol Ther 2013; 26(3):187–196. https://doi.org/10.1111/dth.12051
2 de Moya N, Montero P, Ho H et al. Non-healing wounds. ACS/ASE Medical Student Core Curriculum. https://tinyurl.com/5ahmjv29 (accessed 27 Spetember 2021)
3 Canadian Agency for Drugs and Technologies in Health. Optimal care of chronic, non-healing, lower extremity wounds: a review of clinical evidence and guidelines. Ottawa (ON), Canada, 2013
4 Frykberg RG, Banks J. Challenges in the treatment of chronic wounds. Adv Wound Care 2015; 4(9):560–582. https://doi.org/10.1089/wound.2015.0635
5 Bellingeri A, Falciani F, Traspedini P et al. Effect of a wound cleansing solution on wound bed preparation and inflammation in chronic wounds: a single-blind RCT. J Wound Care 2016; 25(3):160–168. https://doi.org/10.12968/jowc.2016.25.3.160
6 James GA, Swogger E, Wolcott R et al. Biofilms in chronic wounds. Wound Repair Regen 2008; 16(1):37–44. https://doi.org/10.1111/j.1524-475X.2007.00321.x
7 Leaper DJ, Schultz G, Carville K et al. Extending the TIME concept: what have we learned in the past 10 years?. Int Wound J 2012; 9(2 Suppl 2):1–19. https://doi.org/10.1111/j.1742-481X.2012.01097.x
8 Romanelli M, Dini V, Barbanera S, Bertone MS. Evaluation of the efficacy and tolerability of a solution containing propyl betaine and polihexanide for wound irrigation. Skin Pharmacol Physiol 2010; 23(1 Suppl):41–44. https://doi.org/10.1159/000318266
9 Bradbury S, Fletcher J. Prontosan made easy. Wounds International 2011; 2(2). https://tinyurl.com/fhf998j5 (accessed 29 September 2021)
10 Andriessen AE, Eberlein T. Assessment of a wound cleansing solution in the treatment of problem wounds. Wounds 2008; 20(6):171–175
11 Price P, Krasner DL. Health-related quality of life and chronic wounds: evidence and implications for practice. In: Chronic wound care: the essentials; a clinical source book for healthcare professionals. Vol. 1 (5th edn). Krasner DL. Rodeheaver GT, Sibbald RG, Woo KY (eds). HMP Communications, 2014
12 FDA.report. Prontosan wound irrigation solution. Part of a premarket notification filed by B.Braun Medical, Inc., with the FDA for Prontosan Wound Irrigation Solution. 510(k) K072876. 2008. https://fda.report/PMN/K072876 (accessed 28 September 2021)
13 B. Braun Medical, Inc., Prontosan Wound Irrigation Solution Instructions for Use, 350-mL bottle, revised April 2011. https://tinyurl.com/4kh6dxwd (accessed 27 September 2021)
14 B. Braun Medical, Inc., Prontosan Wound Gel Instructions for Use, 30-mL bottle, revised January 2011. https://tinyurl.com/yhy6mewt (accessed 27 September 2021)
15 FDA letter of issuing substantial equivalence (for over-the-counter use): 501(k) K110744 (Prontosan Wound Irrigation Solution), dated 06 April 2011. https://tinyurl.com/rwyvca3j (accessed 27 September 2021)
16 US Food and Drug Administration. 510(k) K090141. Premarket notification. Prontosan Antimicrobial Wound Gel. 2009. https://tinyurl.com/tkszc3kn (accessed 28 September 2021)
17 FDA letter issuing substantial equivalence (for over-the-counter use): 501(k) K101882 (Prontosan Wound Gel) dated 03 November 2010. https://tinyurl.com/9nhehrt (accessed 28 September 2021)
18 Blome C, Baade K, Sebastian Debus E et al. The 'Wound-QoL': a short questionnaire measuring quality of life in patients with chronic wounds based on three established disease-specific instruments. Wound Repair Regen 2014; 22(4):504–514. https://doi.org/10.1111/wrr.12193
19 Wound-QoL Short Manual. March 2016. https://tinyurl.com/5hechw4r (accessed 28 September 2021)
20 Clinical Solutions. A joint publication of the Illinois Health Care Association and CE solution, May 2014. https://tinyurl.com/259xpyc8 (accessed 5 October 2021)
21 Valenzuela RA, Perucho SN. [Effectiveness of a 0.1% polyhexanide gel.] [in Spanish.]. Rev ROL Enf 2008; 31(4):247–252
22 Finlayson K, Miaskowski C, Alexander K et al. Distinct wound healing and quality-of-life outcomes in subgroups of patients with venous leg ulcers with different symptom cluster experiences. J Pain Symptom Manage 2017; 53(5):871–879. https://doi.org/10.1016/j.jpainsymman.2016.12.336
23 Woo KY, Sibbald RG. Chronic wound pain: a conceptual model. Adv Skin Wound Care 2008; 21(4):175–188. https://doi.org/10.1097/01.ASW.0000305430.01413.2e
24 Soon K, Acton C. Pain-induced stress: a barrier to wound healing. Wounds UK 2006; 2(4):92–101
25 Wynn M, Holloway S. The impact of psychological stress on wound healing: a theoretical and clinical perspective. Wounds UK 2019; 15(3):20–27
26 Wound Source. Wound odor. https://tinyurl.com/rdcf8px2 (accessed 27 Spetember 2021)
27 Fagervik-Morton H, Price P. Chronic ulcers and everyday living: patients' perspective in the United kingdom. Wounds 2009; 21(12):318–323
28 Hareendran A, Bradbury A, Budd J et al. Measuring the impact of venous leg ulcers on quality of life. J Wound Care 2005; 14(2):53–57. https://doi.org/10.12968/jowc.2005.14.2.26732

Reflective questions

- What criteria were used to evaluate patient quality of life?
- What quality of life and physical improvements were seen after four weeks of treatment with the treatment wound solution and gel?
- How were the safety and tolerability of the treatment wound solution and gel monitored throughout the study?