Evaluation of fluorescence biomodulation in the real-life management of chronic wounds: the EUREKA trial

Objective: Fluorescence biomodulation (FB), a form of photobiomodulation (PBM) that is also known as low energy level light (LELL), has become an increasingly used clinical tool to induce wound healing in wounds that remain recalcitrant to treatment. In a real-life clinical setting, the aim of the EUREKA (EvalUation of Real-lifE use of Klox biophotonic system in chronic wound mAnagement) study was to confirm the efficacy and safety of LumiHeal, a system based on FB, in the treatment of chronic wounds such as venous leg ulcers (VLUs), diabetic foot ulcers (DFUs) and pressure ulcers (PUs). The effects of this FB system on the modulation of wound healing in chronic ulcers through FB induction were previously examined in an interim analysis of this study.

Method: A multicenter, prospective, observational, uncontrolled trial in 12 clinical sites in Italy. The wound was cleansed with saline and a 2mm thick layer of a chromophore gel was applied to the affected area in a biweekly regimen. The area was then illuminated with the LED activator for five minutes at a distance of 5cm. Treatment was used in combination with standard of care specific to each type of chronic wound (VLU, DFU, PU). Wound area evaluation was assessed using the Silhouette Imaging System and quality of life (QoL) with the Cardiff Wound Impact Schedule (CWIS). A seven-point evaluation of the clinicans' view was also examined.

Results: We enrolled 100 subjects, with the final analysis including 99 patients/ulcers consisting of 52 VLUs, 32 DFUs and 15 PUs. Total wound closure at the end of the study was achieved in 47 patients by aetiology: 26 VLUs (50% of VLUs); 16 DFUs (50% of DFUs); and five PUs (33.3% of PUs). The mean wound area regression at last study assessment was significant for VLUs (41.0%; $p<0.001$) and DFUs (52.4%; $p<0.001$). After four weeks of treatment, it was possible to significantly predict if the ulcer would respond (defined as a decrease of wound size) to the study treatment. Adherence was high (95.2%) and no related serious adverse events were reported during the study. QoL significantly improved, with an increase of 15.4% of the total score, using the CWIS ($p<0.001$).

Conclusion: The study confirmed a positive efficacy profile of the FB system in inducing the wound healing process in three different types of hard-to-heal chronic wounds. The treatment was shown to be safe and well tolerated by the patients, with a significant improvement in patient QoL. This approach offers an effective modality for the treatment of hard-to-heal chronic ulcers.

Declaration of interest: S. Fauverghe is senior director of Clinical and Medical Affairs at KLOX Technologies. M. Romanelli, G. Scapagnini, V. Dini, C. Scarpa and F. Bassetto are medical consultants for KLOX Technologies.

biophotonics • diabetic foot ulcers • fluorescence biomodulation • photobiomodulation • phototherapy • pressure ulcers • venous leg ulcers

Chronic wounds, frequently linked to older age, vary in aetiology and include venous leg ulcers (VLUs), diabetic foot ulcers (DFUs) and pressure ulcers (PUs).[1] They represent a clinical challenge for physicians worldwide. There has been considerable attention given to low energy level light (LELL) treatments as novel therapy for non-healing human wounds. Several experimental and well-controlled studies observed that LELL stimulates a cascade of reactions which, in turn, intensifies physiologic activities involved in essential cellular steps of the wound healing process.[2–5] LELL, frequently referred to as photobiomodulation (PBM), including fluorescence biomodulation (FB), is a treatment for chronic wounds.[6,7]

Studies in chronic wounds found that the use of PBM led to a significant increase in blood flow and Falanga[8] wound bed score versus untreated controls in patients with or without diabetes.[9] Similarly, studies in leg ulcers in patients with diabetes found that PBM promoted rapid granulation and healing in wounds that had failed to respond to other forms of treatment,[10] while studies in chronic venous ulcers found improved healing with PBM, particularly for medium and large-sized ulcers.[11]

A review highlighted the benefits of PBM to accelerate healing and reduce inflammation in a variety of dermatologic procedures including skin resurfacing, vascular and benign pigmented lesions, and chemical peels.[12] According to the European Wound Management Association (EWMA) guidelines on wound management,

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PBM has accumulated evidence of a positive effect on all phases of wound repair from the inflammatory to the remodelling phase.[13] A reference to the Eureka interim results is included in the guidelines, concluding on the positive effects of the biophotonic treatment on healing rates in chronic wounds.[13]

Data collected in clinical trials demonstrated that the two-part FB system, consisting of a topical photo-converter wound gel and a blue LED activator lamp, possesses the ability to modulate biological responses in both healthy and disease-affected tissues, and its stimulatory properties have been proven in the treatment of skin and soft tissue pathological conditions, such as acne and chronic wounds.[14–18]

We previously showed that FB is an effective treatment to enhance the wound healing process.[6] The reported early interim analysis of the EUREKA study was based on the first 33 subjects (13 VLUs, 17 DFUs, 3 PUs) who completed the trial. These results suggested that the FB system may offer a safe, new option in the management of hard-to-heal chronic wounds. Here, we report on the final analysis of the EUREKA study based on the 99 subjects (52 VLUs, 32 DFUs, 15 PUs).

Aim

The primary aim of the EUREKA study was to confirm the efficacy and safety of a system based on FB, known as LumiHeal (KLOX Technologies Inc., Canada). Secondary aims were to examine quality of life (QoL) in subjects who received the treatment and collect feedback from health professionals on the usability of the FB System in the management of chronic wounds.

Methods

Study design and patients

This was a multicentre, prospective, observational, uncontrolled trial. We enrolled patients >18-years old with VLUs, DFUs or PUs. There were few restrictions in the inclusion criteria and the trial was designed as a real-life study. If the investigator believed, based on clinical data, that the FB treatment would be an appropriate option, the patient could be included. Exclusion criteria included pregnant subjects, patients with conditions known to induce severe photosensitivity (such as porphyria) and patients with known skin hypersensitivity.

Patients were treated until wound closure, or up to a maximum period of 16 weeks for VLUs and PUs, and 24 weeks for DFUs. Patients were seen three times over an eight-week period post-wound closure to confirm persistence of closure. PUs were categorised according to the European Pressure Ulcer Advisory Panel/National Pressure Ulcer Advisory Panel/Pan Pacific Pressure Injury Alliance (EPUAP/NPUAP/PPPIA) system.[19] DFUs were graded according to the University of Texas Wound Classification System.[20] For VLUs, the presence of a diagnosed open leg ulcer with the presence of a venous disease was required.

Although pain intensity was not assessed, investigators evaluated the presence or absence of wound pain at each treatment visit through a specific questionnaire. The trial was conducted in compliance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice.[21,22] Protocol, informed consent and all procedures were approved by the local ethics committees of the 12 Italian clinical sites involved in the study (Table 1), while the study was registered with Clinicaltrials.gov (NCT03021811). All patients signed an informed consent form.

Table 1. List of ethics committees

1 Comitato Etico Sperimentazione Clinica CEAVNO	No. 631
2 Comitato Etico Sperimentazione Clinica CEAVNO	No. 630
3 Comitato Etico Regionale Liguria	No. 226REG2015
4 Comitato Etico per la Sperimentazione clinica della Provincia di Padova	No. 3528/AO/15
5 Comitato Etico Regionale Liguria	No. 266REG2015
6 Comitato Etico Interaziendale AOU San Luigi Gonzaga di Orbassano	No. 120/2015
7 Comitato Etico Regionale Unico (CERU)	No. 77/2015
8 Comitato Etico IRST-IRCCS AVR (CEIIAV)	No. 1412
9 Comitato Etico IRST-IRCCS AVR (CEIIAV)	No. 1412
10 Comitato Etico Regionale delle Marche	No. 20150345OR
11 Comitato Etico Interaziendale A.O.U. Citta della Salute e della Scienza di Torino	No. 0117610
12 Comitato Etico per la Sperimentazione clinica (CESC) delle provincie, di Verona e Rovigo	No. 49357

Treatment with the FB system

The gel used in the system is a topical photo-converter wound gel containing specific chromophores which are illuminated by a LED activator, which is a device delivering photons with wavelengths between 440nm and 460nm, and a power density between 55mW/cm^2 and 129mW/cm^2, at a distance of 5cm from the light source.

Upon illumination by the LED activator, the chromophores produce fluorescence in the visible range with a broad spectrum of wavelengths. The system was proven to be non-irritating for the skin, and safe to use on wounds according to *in vitro* and *in vivo* studies performed in rabbits, rats and pigs, along with previous clinical trials realised with the same or similar FB-based products.[14–18,23] The topical chromophore is presented in two jars, which must be mixed together before application. The biweekly regimen was used in combination with standard of care (SoC) specific to each type of chronic wound (VLU, DFU, PU). Typically, any excess fibrin or necrotic tissue was debrided if judged necessary by the investigator. The wound was cleansed with saline and a 2mm thick layer of the chromophore gel was applied on the affected area. The area was then illuminated with the LED activator for five minutes at a distance of 5cm. Once the illumination was completed, the chromophore gel, which had changed in colour from a deep orange to a transparent

pink, was removed from the wound with saline irrigation. A non-adherent standard dressing was then applied to prevent any contact between the wound and the external environment. SoC specific to each ulcer was then followed, including: compression bandage systems, offloading, pressure redistribution, management of a moist wound environment, use of barrier creams and nutritional assessment.

The EUREKA study was designed to assess the following endpoints:

- Confirmation of the efficacy and safety of the treatment
- Improvement of the QoL in treated subjects
- Usability of the system by health professionals.

The efficacy of the treatment was estimated through the following criteria:

- Rate of complete wound closure (defined as: skin re-epithelialisation without drainage or dressing requirements)
- Time to complete wound closure
- Wound area reduction over time
- Incidence of wound breakdown following closure
- Impact of treatment on QoL.

Wound area evaluation (mean change in wound area over time) was performed with the Silhouette Imaging System (ARANZ Medical, New Zealand), a device allowing wound pictures and assessments of key characteristics as previously reported by Romanelli et al.[24] In addition, ulcers were characterised as non-responders to the system if their size did not decrease during the study. The safety analysis was performed considering the following parameters: adverse events (AE), serious adverse events (SAE), device incidents, clinical laboratory parameters, vital signs, physical examinations, pain, and proportions of subjects with a clinically infected wound requiring systemic antimicrobial therapy. The QoL measurements were performed using the Cardiff Wound Impact Schedule (CWIS), which is a wound-specific questionnaire designed and validated for subjects affected by chronic ulcers.[25] The CWIS was administered at baseline and at the first follow-up visit. It includes three main domains or 'subscores': 'social life', 'wellbeing' and 'physical symptoms and daily living'.

Ease of use of the system was assessed by the investigators, at first and last treatment visit, through specific questionnaires designed by the study sponsor. For each question, investigators had to assess their satisfaction by selecting on a seven-point scale their satisfaction, from 'very unsatisfied' to 'very satisfied'.

Statistical analysis

There was no formal sample size calculation. Sample size was based on clinical considerations and no statistical power calculations. Clinical endpoints and safety analyses were carried out on the intent-to-treat (ITT) population and consisted of all patients having received at least one treatment. Absolute wound area regression, relative wound area regression (RWAR) and CWIS scores were analysed using paired t-tests and Wilcoxon signed-rank test, and a $p<0.05$ was considered statistically significant.

Table 2. Wounds characteristics at study entry, all wounds (n=99)

	VLU	DFU	PU	All wounds
Gender F:M %	44.2 : 55.8	21.9 : 78.1	13.3 : 86.7	32.3 : 67.7
Age, mean±SD years	70.80±11.03	69.27±11.58	60.18±14.56	68.70±12.23
Size at entry, mean±SD cm²	10.96±11.39	3.03±3.40	4.29±5.36	7.39±9.47
Median duration at entry, months	9.30	3.90	12.50	8.90

Source: ORS-K1002-P001 database; VLU—venous leg ulcer; DFU—diabetic foot ulcer; PU—pressure ulcer; F—female; M—male; SD—standard deviation

Table 3. Prognostic factors of poor healing at study entry, all wounds (n=99)

	VLU	DFU	PU	All wounds
None	19.2%	43.8%	33.3%	29.3%
***One**	51.9%	46.9%	60.0%	51.5%
***Two (both factors present)**	28.8%	9.4%	6.7%	19.2%
Total	100.0%	100.0%	100.0%	100.0%

*Area>10cm² (or 5cm² for DFU), or duration >6 months Source: ORS-K1002-P001 database; VLU—venous leg ulcer; DFU—diabetic foot ulcer; PU—pressure ulcer

Results

The mean age of the population was 68.7 years and the participants were all Caucasian. There were 99 subjects who received at least one treatment—only one patient decided to withdraw from the study before treatment. Among the 99 ulcers, 52 were VLUs, 32 were DFUs (14 of stage 1a and 18 of stage 2a), and 15 were PU (six category II and nine category III). The mean duration of the chronic ulcers was 35.5 months at screening (VLU: 42.9 months; DFU: 10.2 months; PU: 64.1 months). Median duration at screening was 8.9 months (all wounds). The mean VLU area was 10.96±6.85cm² (mean±standard deviation) at screening, while the average area of DFU and PU was 3.03±1.60cm² and 4.29±1.90cm², respectively. Table 2 summarises the main wound characteristics at study entry. The method of prognostic factors of poor wound healing developed by Margolis et al.[26–29] was used to identify the healing prognostic of leg ulcers and DFUs based on two criteria: area >10cm² for VLUs and PUs (5cm² for DFUs) and the ulcer age at study entry (>6 months). Results showed that 19.2% of the wounds (all wounds combined) had two prognostic factors of poor wound healing and 70.7% at least one factor. As shown on Table 3, the worst prognostic at study entry was for VLUss which showed that 28.8% of the wounds had two prognostic factors of poor wound healing and 80.8% at least one factor.

Clinical endpoints

Table 4 shows the clinical response of the 99 patients who completed the study. We found a high rate of wound closure in the VLU and DFU groups, reporting

Table 4. Comparison of wound closure rate between interim and final analysis

	Interim results on 33 patients		Final results on 99 patients	
	n	Mean (%)	n	Mean (%)
VLU	7	53.8%	26	50.0%
DFU	9	52.9%	16	50.0%
PU	1	33.3%	5	33.3%
Total	**17**	**51.5%**	**47**	**47.5%**

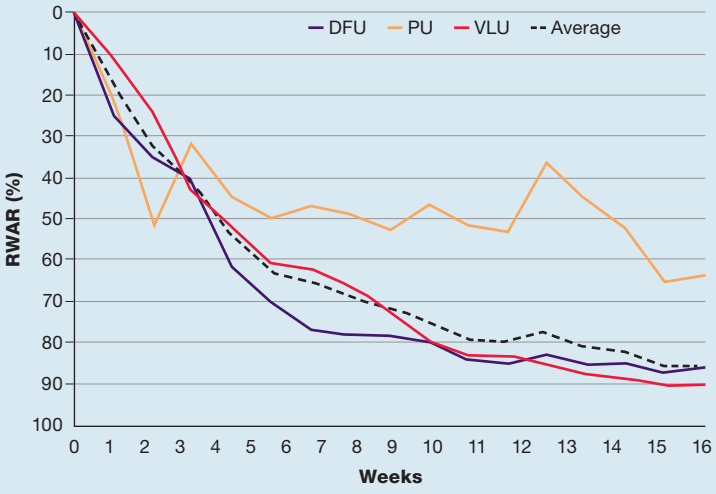
VLU—venous leg ulcer; DFU—diabetic foot ulcer; PU—pressure ulcer

Table 5. Median wound area regression versus baseline (n=99)

Wound type	Median wound area regression at last visit	p-value
VLU	94.2%	<0.001
DFU	78.1%	0.001
PU	36.8%	0.268

Source: ORS-K1002-P001 database; VLU—venous leg ulcer; DFU—diabetic foot ulcer; PU—pressure ulcer

Fig 1. Mean relative wound area reduction within the 'responders' group, all wounds (n=81)



Source—EUREKA study database; VLU—venous leg ulcer; DFU—diabetic foot ulcer; PU—pressure ulcer; RWAR—relative wound area reduction;

Mean RWAR at week 4: 54.4%; Mean RWAR at week 10: 79.2%

that 50% of VLUs and DFUs reached a 100% wound closure by the end of the study. Similarly, the interim analysis on 33 patients had shown a VLU closure rate of 53.8%, a DFU closure rate of 52.9% and a PU closure rate of 33.3%.[6] The mean time to reach total closure was 70.3 days, with a minimum of two days and a maximum of 209 days. The variation of the mean time of closure was dependent on the type of wound; DFUs showed a faster closure (41.3 days) compared with VLUs (82.3 days) and PUs (81.2 days).

Wound breakdown occurred during the two-week follow-up period after wound closure in only two cases (4.2% of closed wounds).

Table 5 shows the median wound area regression over time. Although patients with VLUs initiated the study with a higher mean wound area, they responded well to the treatment with the FB system, with a median wound area reduction of 94.2% (6.85cm^2 at screening to 0.40cm^2; p<0.001). DFUs demonstrated a similar favourable outcome, with a median wound area regression of 78.1% (p=0.001). Although PUs demonstrated a wound area regression of 36.8% during the study period, it was non-statistically significant (p=0.268), possibly due to the smaller sample size (15 patients).

There were 18 wounds (18.2%) that did not respond to treatment as their wound size area increased during the trial. Among these wounds, 10 (19.2%) were VLUs, four (12.5%) were DFUs, and four (26.6%) were PUs.

An additional post-hoc analysis was performed for the 'responder' group, which included 81.8% of the treated wounds that had a decrease of the wound size area during the study. This group included 42 VLUs (80.8% of VLUs), 28 DFUs (87.5% of DFUs) and 11 PUs (73.3% of PUs), representing a total of 81 wounds. Approximately 58% of the responding wounds closed during the study period. VLU wounds continued to show the highest level of wound closure (62%) followed by DFUs (57%) and PUs (45%). As shown in Fig 1, the mean RWAR over time of the responders group showed a mean RWAR of 54.4% compared with screening at week four. Results continued to progress, with a mean RWAR compared with screening of 79.2% at week 10: (VLU: 82.8%; DFU: 83.8%; PU: 51.8%). The heterogeneity of the SoC practices between the clinical sites might be a factor explaining the differences between the non-responder and responder groups. Regular ulcer debridements were, for example, less frequent in the non-responder group

After four weeks of treatment, the wound size decreased an average of 51.4% for VLUs, 61.5% for

Table 6. CWIS results over time in all type of wounds (n=73)

	Screening			Follow-up visit 1			Variation		
Parameters	**Mean score**	**(n)**	**SD**	**Mean score**	**(n)**	**SD**	**Mean score**	**%**	**p-value**
Social life	78.3	(73)	23.3	87.0	(73)	16.9	+8.7	+11.1%	<0.001
Wellbeing	52.8	(73)	19.7	67.5	(73)	20.3	+14.7	+27.9%	<0.001
Physical symptoms and daily living	77.7	(73)	18.4	86.5	(73)	16.3	+8.8	+11.3%	<0.001
Total score	208.9	(73)	53.8	241.0	(73)	48.1	+32.2	+15.4%	<0.001

Source: ORS-K1002-P001 database; SD—standard deviation

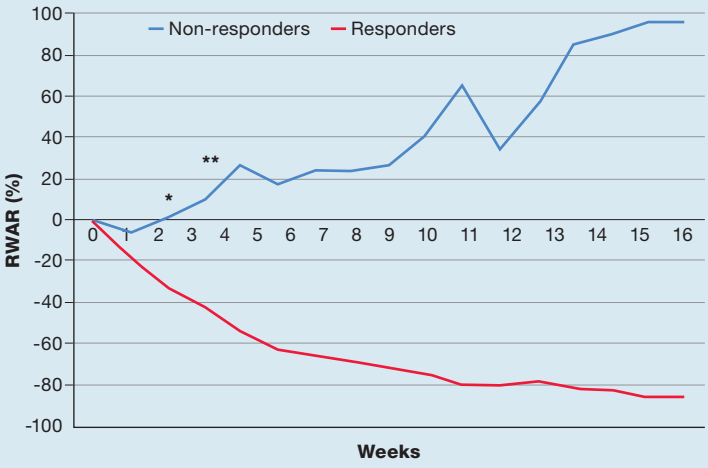
DFUs and 44.8% for PUs in the responder group. Conversely, the wound size in the non-responder group increased an average of 16.05% for VLUs, 8.5% for DFUs and 72.5% for PUs during the same period.

Mean RWAR after each week of treatment was analysed in the responder and the non-responder groups. By week two of treatment, there was a statistically significant difference (p=0.001) between the two groups in terms of change in wound size area (mean increase in the non-responder group and a mean decrease in the responder group). By week three, and every visit thereafter, this statistical significance increased (p<0.001). The mean RWAR for non-responders and responders are presented in Fig 2.

A questionnaire was used by investigators to assess if wounds became ready for skin grafting during the treatment period. According to investigators, 69.2% of VLUs, 68.8% of DFUs, and 40% of PUs became ready for skin grafting at one point during the study. The mean and median time for 100% of the wounds to become graft-ready was estimated using the Kaplan-Meir method. Overall, the mean time was 95.7 days, with a median time of 86.0 days, with a large difference between the wounds. The fastest were the DFUs (mean time of 79.0 days and median time of 41.0 days), followed by VLUs (mean: 94.0; median: 89.0 days) and then by PUs (mean: 116.4; median: 140.0 days).

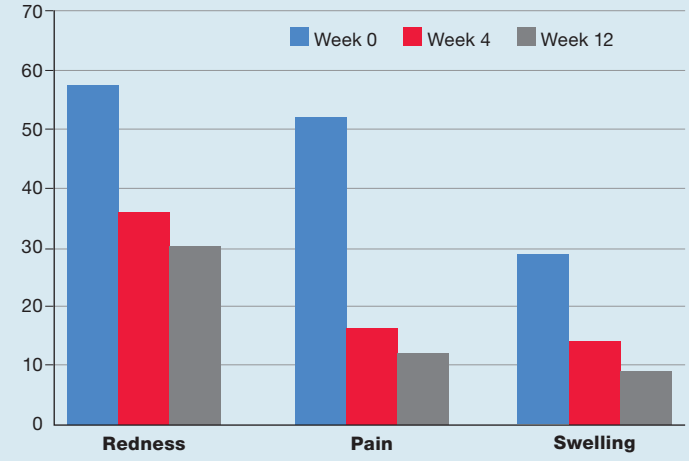
Clinical signs generally observed during wound colonisation were evaluated by investigators at every treatment visit. The VLU group was the population of patients most affected by these clinical signs (including redness, pain and swelling) among all chronic ulcer subjects of the study. VLU patients showed a rapid decrease in all these clinical signs after the treatment initiation, as shown in Fig 3. Pain, present at baseline, decreased progressively once the first treatment was initiated, from 27 patients (51.9%) at week zero to eight patients (16.3%) at week four, and four patients (12.1%) at week 12, meaning a decrease of 70.4% by week four and of 85.2% by week 12.

Fig 2. Mean relative wound area regression, 'non-responders' and 'responders' groups, all wounds (n=99)



Source: EUREKA study database; RWAR—relative wound area reduction
*Week 2: p=0.001; **Week 3 and following weeks: p<0.001

Fig 3. Presence of redness, pain and swelling during the study period (percentage of evaluations of VLUs) (n=52)



Source: EUREKA study database

Safety endpoints

There was a total of 47 AEs reported on 32 subjects and the highest frequency was in the category 'skin and subcutaneous disorders'. The majority of these AEs were not related to the study treatment and considered as expected in a population affected by chronic wounds. Most of the AEs (87.2%) were reported as mild or moderate and only six AEs (12.8%) were classified as severe. The six severe AEs were not related to the study

Table 7. CWIS results over time in venous leg ulcers (n=41)

	Screening			Follow-up Visit 1			Variation		
Parameters	**Mean score**	**(n)**	**SD**	**Mean score**	**(n)**	**SD**	**Mean score**	**%**	**p-value**
Social life	83.0	(41)	27.3	90.1	(41)	15.4	+7.0	+8.4%	<0.001
Well-being	50.5	(41)	18.7	70.1	(41)	20.2	+19.6	+38.8%	0.001
Physical symptoms and daily living	78.8	(41)	16.4	88.1	(41)	18.0	+9.2	+11.7%	0.015
Total score	212.4	(41)	44.9	248.2	(41)	49.3	+35.8	+16.9%	<0.001

Source: ORS-K1002-P001 database; SD—standard deviation

Table 8. Overall satisfaction by site. Response to question: 'Would you recommend LumiHeal to your colleagues?'

	No	Yes	Total	Mean percentage
Visit 1	10	89	99	89.9%
Follow-up	5	94	99	94.9%
Total	**15**	**183**	**198**	**92.4%**

Source—EUREKA study database

treatment but to the patients' comorbidities: cardiac disorders (three), intestinal occlusion (one) and gastrointestinal neoplasms (two). Considering the mean age of the study population, the number of severe AEs may be considered as low and expected. There were three AEs (representing 6.4% of the total number of AEs) related to the treatment, with patients reporting mild and moderate intermittent erythema. Only one patient discontinued from the study following a related AE. No related serious adverse events (SAEs) were observed during the study. Eight cases of SAEs were reported; cardiac disorders (two), neoplasms (two), intestinal occlusion (one), erysipelas (one), fracture of ribs (one) and genital infection (one), but none of these SAEs were considered as related to the treatment.

During the study period, only three infections of the wound and/or periwound skin were observed (one in each wound type). None were considered as related to the study treatment. Lastly, no clinically significant abnormal values in biochemical, haematological or urine analyses were observed.

The overall safety profile reported, based on these results, was similar to results observed in the interim analysis and previous studies using the system in patients with chronic wounds.[15,16] Adherence data showed that patients were present at 95.2% of the expected visits.

QoL outcomes

Table 6 shows the results of patients who completed the questionnaire between screening and first follow-up visit. A total score increase of 15.4% during the study period for all wounds ($p<0.001$) confirmed the statistically significant impact of the treatment on QoL in subjects affected by chronic wounds. This significant result was also observed in the three subscores: 'social life' (+11.1%; $p<0.001$), 'wellbeing' (+27.9%; $p<0.001$) and 'physical symptoms/daily living' (+11.3%; $p<0.001$). This data indicates that the system induced an improvement in QoL of the patients throughout the study period. The positive action on the 'wellbeing' component, which increased of 38.8% for VLUs only (Table 7) might be linked to the results observed on pain reduction.

Usability of the FB system

A total of 198 investigator questionnaires (two per patient) were collected to assess the satisfaction of the investigators on the use of the FB system. Overall, the system was considered as very easy to use, and 92.4% of the questionnaires reported that investigators would recommend the system to their colleagues (Table 8). The number of positive recommendations increased during the study period, from 89.9% of the investigators at the first treatment visit, to 94.9% at the last treatment visit. Mean reasons given to investigators to explain this high level of satisfaction were the ease of use and the efficacy of the treatment.

Discussion

The population affected by chronic wounds is a continuing challenge that requires innovative approaches.[13] Standard treatments appear ineffective and often reduce QoL for patients.[30–32] There is growing interest in light-based therapies such as FB, which addresses the pathophysiological processes involved in wound healing.[33–35] They induce changes in the redox state of the cell that are known to induce several intracellular signalling pathways, regulate nucleic and protein synthesis, and stimulate enzymes and cell cycle progression.[36] These biochemical and cellular changes improve the healing of chronic wounds.[37] Moreover, PBM and FB differ from other light-based therapies as they are not based on the generation of heat and do not cause a temperature increase in treated tissues.[38,39]

This final analysis of the EUREKA study was conducted to confirm the clinical results previously reported in our published interim analysis[14] and in several studies.[14–18,23] The results of this clinical evaluation confirm the use of FB system as a possible treatment to manage chronic wounds. Despite the chronicity and heterogeneity of the different wounds treated in this study, the overall clinical profile is considered promising. The study results revealed the interesting clinical potential of the system in terms of rate of wound closure, mean time to reach wound closure, extremely low rate of wound breakdown and mean RWAR.[40,41]

The ability for health professionals to assess the effect of the treatment as early as four weeks is interesting. Based on the results obtained within the EUREKA study, if a wound does not respond with a decrease in wound size at four weeks, after the initiation of the treatment, the therapeutic strategy should be changed, as there is a higher probability that the treatment alone is not an appropriate therapeutic strategy. Among the population of responding ulcers, the RWAR quickly reached 50%, and the wound size continued then to decrease progressively.

The system showed an excellent safety profile, while reporting a total of 47 AEs during the study, with only three (6.4%) of them considered as possibly related to the study treatment. This safety profile was confirmed in other clinical trials using a similar medical device but in different cohorts of patients.[15–18,23] Tolerability was also evaluated through the assessment of pain. Standard treatments for chronic ulcers are generally considered as painful and/or uncomfortable, particularly in patients affected by VLUs.[42,43] The results showed that pain started to decrease as soon as the first treatment was initiated in the VLU group,

with a decrease of the number of patients reporting pain of 70.4% by week four and 85.2% by week 12. Compared with existing treatment approaches, this is an important benefit of the system, improving both safety and QoL. Effective healing of chronic wounds relies largely on patient adherence and this aspect may be an issue in populations with hard-to-heal chronic wounds.[44] We observed a high rate of adherence in this final study, confirming the results showed in the interim analysis.[14] There were three cases of infection observed during the study but none of these was considered as severe or related to the treatment. The low rate of wound infection might be associated with the effects of the treatment to positively control the proliferation of key bacteria involved in the colonisation of wound surfaces. This aspect is particularly important as wound colonisation/infection is often responsible for delayed wound healing and wound breakdown.[45]

A crucial factor in the treatment of chronic wounds is its impact on QoL for patients.[46] The overall QoL index significantly rose by 15.4% ($p<0.001$) from screening to follow-up. This increase was observed not only with the wounds that closed, but also for most of wounds that had their size decreased during the study. Therefore, even though the wound did not close completely, the treatment had a positive impact on QoL. A positive impact of the system on the 'wellbeing' score, especially for VLUs, is probably linked to its action on pain reduction. Investigators also reported a high level of satisfaction, confirming the results already reported in the interim analysis.[14] Most important, this satisfaction increased with the use of the treatment throughout the study period.

Limitations

There are limitations in this study that should be noted. Since the purpose of this study was to confirm the efficacy of the system in a real-life setting, there was no formal sample size calculation for each group, no randomisation and no control group.

There was also a limited number of inclusion and exclusion criteria, which resulted in a heterogeneity of wound characteristics, particularly in terms of wound size. However as can be noted with the mean ulcer age at study entry (35.5 months), most of the recruited ulcers failed multiple treatments before their inclusion.

Conclusion

The results obtained in this final analysis confirm the preliminary data observed in the EUREKA study's interim analysis, which demonstrate that the system is extremely effective in promoting wound healing in different hard-to-heal chronic wounds, while being safe and well tolerated. The system also demonstrated an improved QoL with high patient adherence and investigator satisfaction on the overall usability of the system, and a positive action on pain reduction in VLUs.

These results confirm that the studied system based on FB offers an important and innovative approach in the management of chronic hard-to-heal wounds. JWC

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Reflective questions

- How does fluorescence biomodulation (FB) impact wound healing according to the results reported here?
- Is there a high incidence of wound breakdown once a chronic wound is closed with FB?
- How can FB have an impact on the patients' quality of life when used in the management of chronic wounds?
- How is compliance important in the management of chronic wounds?

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