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ORIGINAL ARTICLE

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Use of a purified reconstituted bilayer matrix in the management of chronic diabetic foot ulcers improves patient outcomes vs standard of care: Results of a prospective randomised controlled multi-centre clinical trial

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Abstract

Diabetic foot infections continue to be a major challenge for health care delivery systems. Following encouraging results from a pilot study using a novel purified reconstituted bilayer matrix (PRBM) to treat chronic diabetic foot ulcers (DFUs), we designed a prospective, multi-centre randomised trial comparing outcomes of PRBM at 12 weeks compared with a standard of care (SOC) using a collagen alginate dressing. The primary endpoint was percentage of wounds closed after 12 weeks. Secondary outcomes included assessments of complications, healing time, quality of life, and cost to closure. Forty patients were included in an intent-to-treat (ITT) and per-protocol (PP) analysis, with 39 completing the study protocol (n = 19 PRBM, n = 20 SOC). Wounds treated with PRBM were significantly more likely to close than wounds treated with SOC (ITT: 85% vs 30%, $P = .0004$, PP: 94% vs 30% $P = .00008$), healed significantly faster (mean 37 days vs 67 days for SOC, $P = .002$), and achieved a mean wound area reduction within 12 weeks of 96% vs 8.9% for SOC. No adverse events (AEs) directly related to PRBM treatment were reported. Mean PRBM cost of healing was $1731. Use of PRBM was safe and effective for treatment of chronic DFUs.

KEYWORDS

advanced wound care, advanced wound matrix, diabetic foot ulcers, standard of care, wound healing

Key Messages

- patients with non-healing DFUs randomised to treatment with an advanced wound matrix, PRBM, demonstrated a significantly improved healing rate

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and shorter time to heal compared with patients randomised to standard of care treatment over a 12-week period
- the mean PRBM product cost to *closure* was $1731 per healed wound
- PRBM demonstrated a statically significant improvement in percent area reduction over 12 weeks vs standard of care

1 | INTRODUCTION

The prevalence of diabetes in the United States continues to rise, with the disease now affecting 34.2 million, with an estimated additional 84 million at risk of progressing to diabetes in the coming years.[1] The lifetime incidence of DFUs among diabetics is 19% to 34%, with recurrent ulceration reported as approximately 40% at 1 year and 60% at 3 years.[2] Management is challenging and associated with substantial socio-economic burden approaching $40 billion annually in direct costs.[3] Approximately 70% of DFUs resolve with standard wound care therapies. However, the natural healing cascade is arrested in the remaining 30%, which ultimately become chronic wounds.[4,5] Patients with chronic wounds typically suffer loss of function, recurrent infection, and significant morbidity.[6] Amputations are reported in up to 20% of cases with an associated mortality of 70% at 5 years post-amputation.[2] Successful treatment of non-healing wounds is challenging and not generally accomplished using a 'one size fits all' approach. Often, multiple therapies over an extended course are necessary to achieve complete closure.[7]

Ongoing focus on development of new modalities to improve diabetic wound healing has produced numerous advanced biomaterials. Presently, 76 commercially available skin substitutes for chronic wounds are recognised by the Centers for Medicare & Medicaid Services (CMS).[8] The majority are extracellular matrix (ECM) grafts derived from human and animal tissues. Whether produced from allogeneic or xenogeneic sources, decellularised grafts purport to preserve the essential ECM structure and biochemical functions for wound healing. Numerous products have been described as capable of enhancing chronic wound healing, however only a limited number have been rigorously studied.

Recently, a novel porcine-derived, purified reconstituted bilayer wound matrix (PRBM, Geistlich Derma-Gide, Geistlich Pharma AG, Switzerland) was evaluated in a series of 10 patients with chronic DFUs and was found to safely support rapid healing in 90% of wounds at a relatively low product cost to achieve closure.[9] PRBM is processed using proprietary extraction and purification methods to remove cells, lipids, undesired proteins, and antigens and also to inactivate potential viruses. The purified, tissue-derived components are reconstituted into a non-cross-linked 3-dimensional bilayer ECM with a structure similar to human dermis[9,10] (Figure 1). In in vitro experiments, PRBM supported the attachment, proliferation, and migration of fibroblasts and keratinocytes, the binding of growth factors, and the

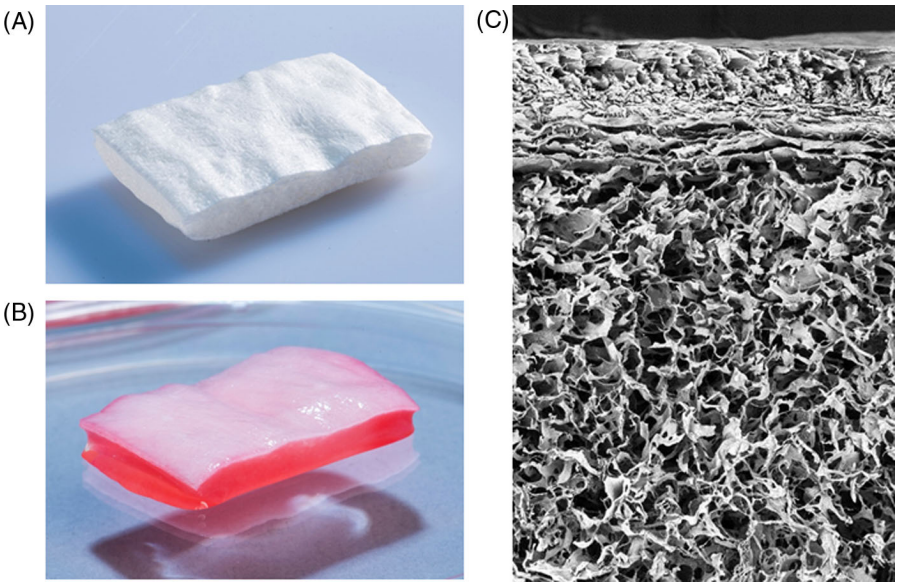

FIGURE 1 Purified reconstituted bilayer matrix (PRBM). (A) The image of PRBM in its dry state and (B) in its hydrated state. The pores of PRBM allows drainage of wound fluid, up to nine times of its own mass. (C) Scanning electron micrograph of cross section of PRBM. The electron microscopy image shows the bilayer structure of the PRBM. The upper compact layer is more densely packed forming a barrier to microbe entry and to loss of wound fluid, and it guides reepithelialisation. The lower porous layer mimics dermis and provides a structure for cellular ingrowth

modulation of excessive MMPs typically found in the chronic wound microenvironment.[10]

Following these initial clinical and bench-top assessments, a randomised trial to compare the safety, effectiveness, and cost of PRBM vs standard of care (SOC) was performed.

TABLE 1 Study protocol schedule

Wk 1-2 screening phase
• Informed consent, inclusion/exclusion criteria assessment • Medical history and physical, vital signs and labs • Assessment of diabetic wounds; DFU history • Assessment of current wound therapies • 10-point monofilament test • X-ray • ABI, SPP, TCOM TBI measurement or arterial Doppler study • Patient completes Wound-QoL and pain assessment • Selection of index ulcer; measurement of surface area and digital imaging • Index Ulcer Assessment of exudate and infection • Treatment of index ulcer with SOC protocol • Wound improvement over 14 d • Confirm eligibility to continue enrolment into study
Wk 3-14 treatment phase
• Medical history and physical, vital signs and blood sugar • Assessment of any adverse events • Pain and neuropathy assessments • Index ulcer assessment (exudate and infection), cleaning and debridement • Measurement of surface area, depth, and digital imaging of index ulcer • Assessment of offloading • Randomisation (wk 3) ○ If randomised to SOC: Apply SOC therapy with Fibracol and outer dressing ○ If Randomised to PRBM: Apply SOC therapy with PRBM and outer dressing • Weekly assessment of index ulcer, measurement, cleaning, debridement, and repeat dressings (wk 4-14) ○ If index ulcer is healed, no further treatment ○ After six treatment visits, if wound <50% healed, treatment phase ended; treatment failure
Wk 15-16: end of study/confirmation visit
• Medical history and physical vital signs and labs/blood sugar • Assessment of any adverse events • Assessment of offloading • Assessment of index ulcer (exudate and infection); complete epithelialization or if wound has re-opened • Measurement of surface area and digital imaging of index ulcer • Assessment of infection • Cleaning, debridement, and dressing of index ulcer if applicable • Patient completes Wound-QoL and pain assessment

2 | METHODS

2.1 | Study design

A multi-centre, prospective, parallel-group, randomised, controlled trial (RCT) evaluating treatment of full-thickness, non-infected non-ischaemic (Wagner Grade 1/University of Texas 1A) DFUs with PRBM or SOC was approved by Western IRB (Protocol #20190130) and conducted in compliance with United States FDA and ISO standards and in conformance with the ethical guidelines of the Declaration of Helsinki. The trial was performed at multiple specialty wound care centres between February 2019 and September 2020. Table 1 summarises the protocol schedule. Patients were provided written consent prior to any study-related activities.

TABLE 2 Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age 18 or older • Type 1 or type 2 diabetes • DFU Wagner Grade 1 • No clinical signs of infection • Study ulcer present >4 wk unresponsive to SOC prior to screening visit • Study ulcer size ≥1.0 cm^2 and <25 cm^2 • Serum creatinine <3.0 mg/dL and HbA1c <12% • Other ulcers, if present on the same foot, are >2 cm distant from the study ulcer • Adequate circulation to the affected foot: TCOM or SPP of ≥30 mm Hg, or ABI between 0.7 and 1.3 within 3 mo of screening or biphasic Doppler of dorsalis pedis and posterior tibial vessels at the level of the ankle or TBI of >0.6 • Offloading of target ulcer ≥14 d prior to randomisation • Able and willing to provide consent and comply with weekly visits	• Ulcer(s) deemed to be caused by conditions other than diabetes • Known or suspected malignancy of index ulcer • Index wound duration >1 y • Patients taking COX-2 inhibitors, immune system modulators • Patients on any investigational drug(s) or therapeutic device(s) within 30 d • History of radiation at the ulcer site or requirement of chemotherapy • Osteomyelitis of the affected foot within 30 d prior to randomisation. • Diabetes with poor metabolic control (HbA1c > 12.0) within 90 d of randomisation • End-stage renal disease • Wounds improving >20% over 14 d run-in with standard of care treatment and offloading prior to randomisation visit • History of poor adherence with medical treatment or inability to complete study

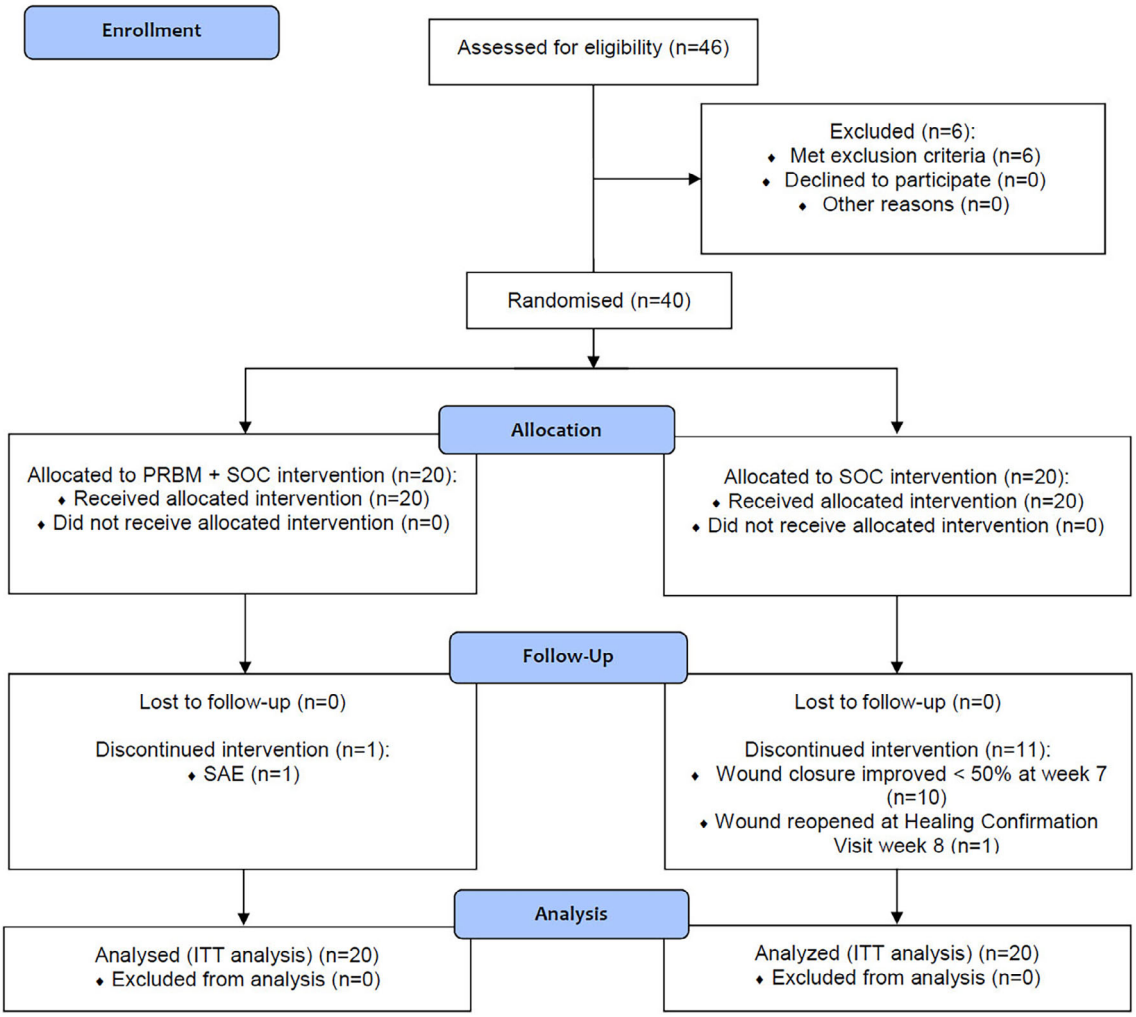

FIGURE 2 Consort flow diagram

2.2 | Treatments

2.2.1 | Purified reconstituted bilayer matrix

Sterile, shelf-stable PRBM (Geistlich Derma-Gide; Wolhusen Switzerland) was provided in individual dry packaging in sizes from 1.1 to 12 cm^2. PRBM was manually trimmed to match the size of each wound and placed dry with the porous lower layer facing down, directly onto the wound bed, allowing for uptake of wound fluids. If the PRBM was not completely hydrated by wound fluid, sterile saline was added for complete hydration, allowing the graft to conform to the wound bed before application of a routine topical dressing.

2.3 | Standard of care (SOC)

A moisture-retentive, conformable collagen alginate dressing (FIBRACOL Plus Dressing, KCI, San Antonio, TX) was the primary wound dressing in the SOC study arm. This dressing has been rigorously tested with favourable results and was chosen as a well-known, clinically accepted SOC product readily available in wound clinics.[11]

2.4 | Study endpoints

The primary study endpoint was a comparison of wound closure rates at 12 weeks. Secondary endpoints included comparisons of time to heal at 6 and 12 weeks, percentage wound area reduction at 6 and 12 weeks, and patient-reported quality of life outcomes. Cost to closure was calculated for PRBM based on product list prices and the total number and size of grafts used.

2.5 | Patient screening

After obtaining informed consent, participants were screened over a 14-day run-in period to determine

TABLE 3 Patient characteristics

Variable	PRBM	SOC	*P* value
Age (years)	59.3 (13.35)	66.5 (11.26)	**.073**
Race			
Caucasian	20 (100)	19 (95)	**1.0**
African American	0 (0)	1 (5)	
Gender			
Male	13 (65)	12 (60)	**.74**
Female	7 (35)	8 (40)	
BMI	33.0 (7.68)	31.8 (7.14)	**.49**
Smoking			**.072**
Never	8 (40)	12 (60)	
Former	8 (40)	8 (40)	
Current	4 (20)	0 (0)	
HbA1c (screening)	7.2 (1.20)	6.9 (1.83)	**.19**
HbA1c (end study)[a]	6.7 (1.17)	6.6 (1.71)	**.92**
Creatinine	1.1 (0.51)	1.2 (0.39)	**.27**
Blood glucose	160 (57.47)	174 (71.0)	**.51**
History of significant foot deformities	9 (45)	6 (30)	**.33**
Age when first DFU appeared (years)	52.3 (12.77)	60.3 (10.80)	**.037**
Prior DFU count	4.7 (3.48)	6.1 (5.29)	**.63**
History of DFU recurrence	13 (65)	12 (60)	**.74**
Amputation			**.35**
Minor (1)	5 (25)	1 (5)	
Major (1)	1 (5)	1 (5)	
Both (1)	0 (0)	1 (5)	
Other concurrent DFUs (at screening)	3 (15)	4 (20)	**.68**

Note: Subject-related demographics. Categorical variables reported as numbers and percentages in parentheses; continuous variables reported as means and SD in the parenthesis.
[a]Conditional statistical power using beta curve parameters (mean/SD) to estimate a Mann-Whitney approximation with bootstrap: 95%-99%.

eligibility according to inclusion and exclusion criteria (Table 2). The run-in preceded randomisation to eliminate those patients in whom a short course of routine therapy would demonstrate effectiveness as measured by a >20% reduction in wound area. A review of each patient's medical history and a complete physical examination were performed including visual assessment of all foot ulcers with attention to signs of infection. The index ulcer was selected, imaged, and measured for area and depth. All wounds were managed during run-in using a standard protocol including cleaning, appropriate sharp debridement, infection management, dressing, and offloading using a diabetic offloading boot or when the patient's foot could not be accommodated with the offloading boot, a total contact cast was used. Subjects were instructed to keep the wound site dry and informed on the importance of offloading. They received education on infection indicators and asked to contact the clinic with concerns. Patients completed the wound quality-of-life (Wound-QoL) questionnaire[12,13] and scored their pain intensity on a scale of 0 to 10 using a visual analogue scale (VAS). After failing sufficient progress during the 2-week run-in period, subject eligibility was reconfirmed, and all eligible patients proceeded to randomisation.

2.6 | Randomisation and measures to minimise bias

Subjects were randomised to either the PRBM Arm or SOC arm. To assure a balanced randomisation, envelopes were created with a random allocation sequence in block sizes of 10. Wound assessment at conclusion of treatment

TABLE 4 Wound-related characteristics

Variable	PRBM	SOC	*P* value
Wound area (cm^2)[a]	2.5 (2.16)	3.5 (2.85)	**.21**
	Median: 1.7; IQR: 1.4	Median: 3.0; IQR: 3.8	
Initial depth (mm)[a]			**.18**
<2	15 (75)	11 (55)	
≥2	5 (25)	9 (45)	
Wound age (weeks)[a]	12.1 (8.21) Median: 9; IQR: 8	15.6 (12.92) Median: 8; IQR:17	**.74**
Plantar location	14 (70)	14 (70)	**1.0**
Wound position			**.74**
Lateral	7 (35)	8 (40)	
Medial	13 (65)	12 (60)	
Wound location			**.34**
Toe	5 (25)	2 (10)	
Forefoot	4 (20)	7 (35)	
Midfoot	9 (45)	6 (30)	
Heel	1 (5)	4 (20)	
Ankle	1 (5)	1 (5)	
Offloading duration at screening (weeks)	11.6 (11.09)	18.7 (23.77)	**.67**
Mean % of time wound offloaded during study	83.5 (13.56)	84.7 (9.32)	**.89**

Note: Summary of wound-related characteristics. Categorical variables are reported as numbers and percentages in parentheses, continuous variables are reported as means and SD in parentheses. For continuous variables that are relatively non-normal in distribution (eg, wound area), medians and interquartile ranges and IQR are included.
[a]At randomisation.

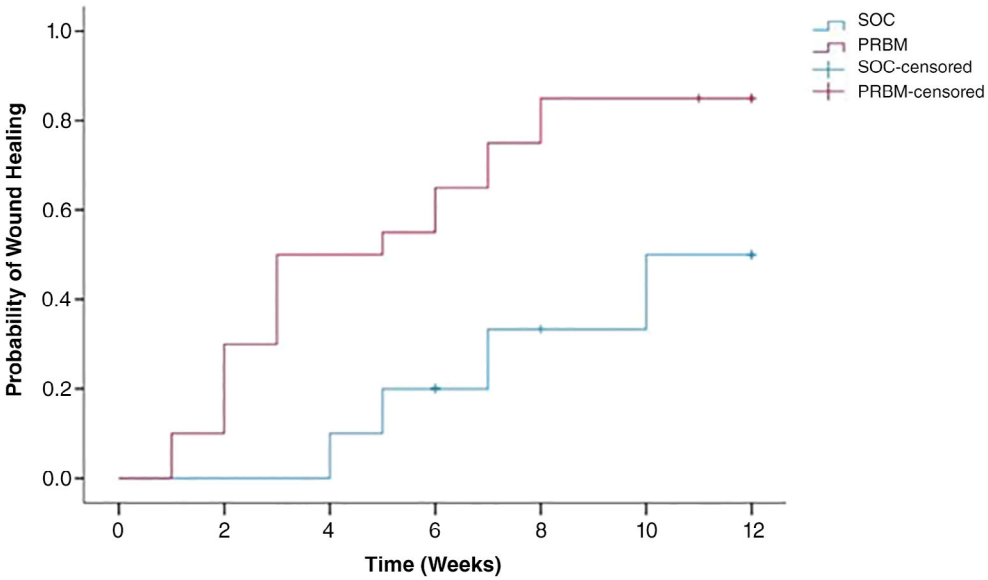

FIGURE 3 Kaplan-Meier plot of probability of wound healing by treatment group. Unadjusted time depicted after randomisation. Censor marks indicate subject exit prior to 12 weeks. A superior healing trajectory is demonstrated in the PRBM treatment group with a divergence apparent after about 1 week

was performed by a clinician, other than the investigator, who was blinded to the treatment. Additionally, confirmation of wound healing was overseen by an independent adjudication committee of experts.

2.7 | Treatment phase

Regardless of the study arm, wounds were managed with accepted routine SOC practices, including weekly

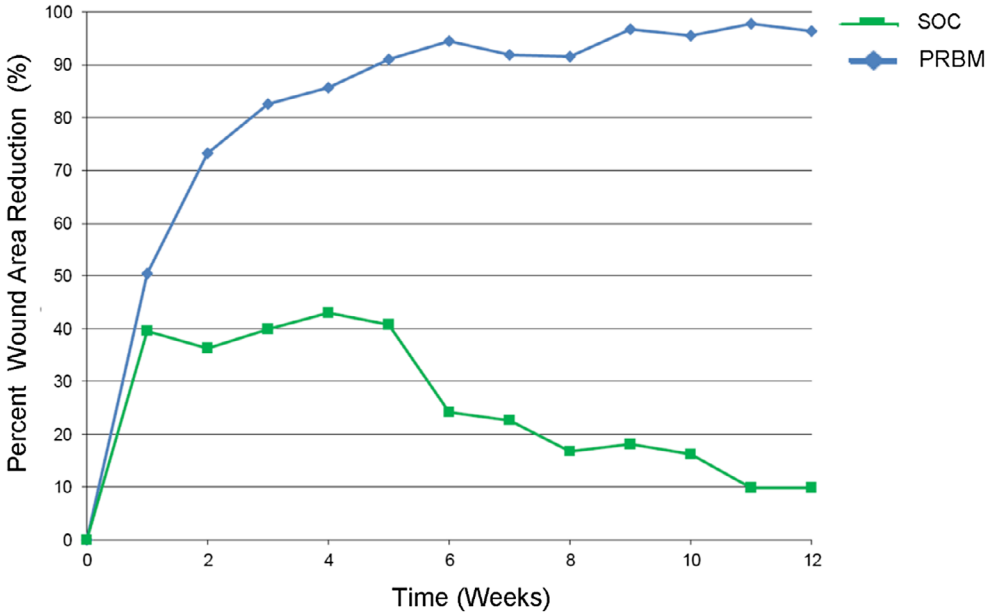

FIGURE 4 Weekly percent wound area reduction by treatment group. Weekly mean percent reduction of ulcer surface area by treatment group. After 1 week, healing trajectories diverge considerably, with PRBM-treated wounds demonstrating greater, more rapid area reduction compared to wounds treated with SOC alone

sharp debridement as indicated. Patients randomised to PRBM arm were treated with a PRBM graft followed by a silicone non-adherent dressing (Adaptic Touch, 3 M/KCI Minneapolis, MN or equivalent), and those randomised to SOC arm were treated with calcium alginate dressing (FIBRACOL Plus). All wounds received an outer dressing comprised of a padded 3-layer dressing (Dynaflex, 3M/KCI Minneapolis, MN or equivalent).

Study visits were performed weekly until either complete healing of the index ulcer or for 12 weeks, whichever came first. At each visit, the subject's overall health, glucose control, and offloading were assessed, and closure of the index ulcer was gauged by a blinded investigator. If the index ulcer was not completely reepithelialised, the wound was evaluated for signs of infection, cleaned, imaged, and measured. When the index ulcer was deemed to be 100% reepithelialised, further treatment ceased, and the patient was scheduled for two consecutive visits 1 week apart. Final wound area measurement and conclusive imaging were performed, and patients completed the Wound-QoL questionnaire at the final visit. Subjects whose index ulcer did not improve by 50% after 6 weeks were designated per protocol as a treatment failure and were allowed to receive alternative treatments outside of the study. Details specific to PRBM including trimmed size and handling characteristics were noted. Any adverse events (AEs) were identified, investigated, and managed as clinically appropriate. Suspected wound infection was diagnosed via wound swabs, and appropriate systemic antibiotics were prescribed. Topical antibiotics were contraindicated per protocol.

2.8 | Sample size and statistical analysis

According to *a priori* power analysis, using an effect size of 0.45 and a power of 0.8, the sample size for each arm required 20 patients. Power calculations for the primary endpoint were based on a two-sided Z-test with pooled variance. The primary endpoint was evaluated using an intent-to-treat (ITT) analysis of all randomised patients. A Fisher exact test was used for the primary outcome while time to heal within 6 and 12 weeks was analysed using Kaplan-Meier log-rank test. The primary and secondary endpoints were tested hierarchically in a confirmatory manner while a logistic regression was performed as exploratory analysis if the primary endpoint was significant. Other endpoints assessed in an exploratory manner included: 12-week percent area reduction (PAR), Wound-QoL, pain score changes from baseline to 12 weeks, and total cost of treatment until closure. Statistical tests were two-sided and performed at a significance threshold of .05. Statistical analysis was performed using SPSS Statistics 27 (IBM, Armonk, NY).

3 | RESULTS

Forty-six patients were screened, with 40 randomised to treatment with either PRBM or SOC (Figure 2). One patient in the PRBM arm was withdrawn at week 11 and excluded from PP (per protocol) analysis because of an SAE requiring hospitalisation, while two others were also excluded from PP analysis because of missed scheduled treatment visits. In the SOC Arm, 10 subjects exhibited poor wound healing trajectories (<50% area reduction

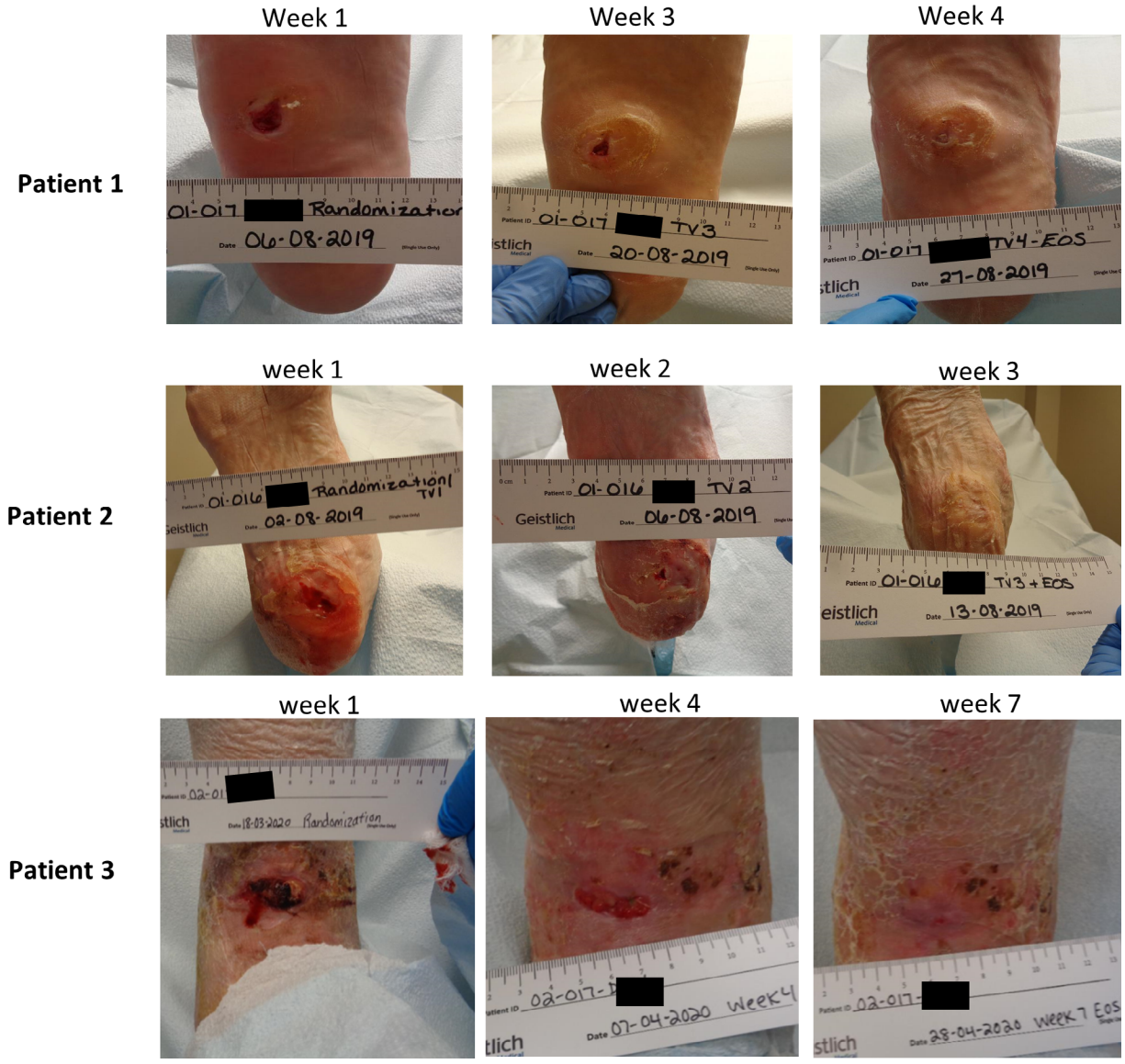

FIGURE 5 Photos depicting representative PRBM wound healing course. Representative cases depicting the time progression of wound healing following treatment with PRBM. Patient 1: 76-year-old female BMI 33.7 presented with 1.4 cm^2 DFU present for 12 weeks. After two PRBM treatments the wound area decreased over 90%, and, following the third treatment, the ulcer was confirmed to be fully healed (4-week visit). Patient 2: 65-year-old female BMI 27.4 presented with a 2-cm^2 DFU present for 8 weeks. After the initial PRBM treatment the wound area had decreased by over 90%, and after two treatments was confirmed to be fully healed (3-week visit). Patient 3: 73-year-old male BMI 32.5 presented with a 5.12-cm^2 DFU present for 20 weeks. After three PRBM treatments, the wound area had decreased by over 54%, and after six treatments, the wound area was confirmed to be fully healed (7-week visit)

after six treatments) and were, therefore, designated per protocol as treatment failure. One SOC patient with a healed wound at 6 weeks presented at the confirmation visit (week 8) with evidence of wound reopening and was designated as a treatment failure.

The study cohort was representative of the diabetic population at the investigational sites, with the typical range of comorbidities. Patient demographics and wound characteristics were well balanced between the two arms (Tables 3 and 4). The only statistical difference between the groups was that patients randomised to PRBM reported a lower age at first DFU occurrence.

Wound closure rate was significantly higher in the PRBM arm than the SOC arm.

Using an ITT approach, after 12 weeks of treatment, the PRBM arm had 85% (17/20) of ulcers healed compared with 30% (6/20) in the SOC arm ($P < .001$) with all patients analysed. When evaluated per protocol (PP), the PRBM arm demonstrated 94% (16/17) wound closure compared with 30% (6/20) in the SOC Arm ($P < .001$). In

TABLE 5 Results of RCTs evaluating performance of advanced biomaterial for chronic DFUs

Description	6-wk healing	12-wk healing	Mean cost to closure ($US)	Refs
Purified refined bilayer matrix (PRBM); purified porcine ECM	65% PRBM vs 20% SOC	ITT: 85% PRBM vs 30% SOC	$1731	Current study
		PP: 94% PRBM vs 30% SOC		
Acellular single layer—dehydrated human amnion-chorion membrane (dHACM)	Not assessed	ITT: 70% dHACM vs 50% SOC	$ NA	27
		PP: 81% dHACM vs 55% SOC		
		ITT: 97% dHACM vs 51% SOC	$2798	29
Aseptically processed dehydrated human amnion and chorion allograft (dHACA)	70% dHACA vs 15% SOC	ITT: 85% dHACA vs 25% SOC	$1400	21
		ITT: 85% dHACA vs 33% SOC	$1771	22,23
Aseptically processed human reticular dermal tissue (HR-ADM)	65% HR-ADM vs 5% SOC	ITT: 80% HR-ADM vs 20% SOC	$1475	28
	68% HR-ADM vs 15% SOC	ITT: 80% HR-ADM vs 30% SOC	$1200	30
Dehydrated human umbilical cord allograft (dHUC)	Not assessed	ITT: 70% dHUC vs 48% SOC	$3251	31
		PP: 81% dHUC vs 54% SOC		
Tri-layer porcine, small intestinal-submucosa collagen scaffold (SIS)	Not assessed	ITT: 54% SIS vs 32% SOC	$3019	20,32

Note: Summary of similarly designed RCTs evaluating advanced biomaterials vs standard of care (SOC) for treatment of chronic diabetic foot ulcers (DFUs).
Abbreviations: ITT, intent-to-treat analysis; PP, per-protocol analysis.

addition to the main effect variable, several additional variables were evaluated in regression models using partial factorial approach, including the variables, initial wound area and depth, offloading duration at screening, and wound area at randomisation. All components except treatment were not significant. Accordingly, adjustment for other covariates was unnecessary. A Kaplan-Meier plot of healing probability (Figure 3) illustrates early divergence after 1 week, with PRBM showing higher likelihood of closure. An odds ratio (OR) is defined as the relative ratio of a successful outcome for one treatment modality compared with another. At 12 weeks, the calculated OR for PRBM treatment compared with SOC alone was 13 (95% CI: 2.8-63).

Ulcers healed significantly faster when treated with PRBM. On average, PRBM-treated wounds healed completely in 37 days (95% CI: 26-48, median 21 days) vs complete healing in the SOC group averaging 67 days ($P = .002$; 95% CI: 55-78, median inestimable). A Kaplan-Meier plot of healing probability within 12 weeks illustrates early and maintained divergence in healing probability between groups (Figure 2), with PRBM showing higher probability of closure. Analysis of time to heal within 6 weeks showed a significant difference between study arms, with the PRBM-treated wounds healing in a mean of 28 days (95% CI: 22-35) compared with a mean of 39.9 days (95% CI: 38-42) for wounds in the SOC arm ($P = .002$). Healing rate in the PRBM arm at the 6-week mid-study point was 65% compared with 20% in the SOC arm.

The mean percent area reduction (PAR) at 6 and 12 weeks for wounds treated with PRBM was 95% (SD: 8%) and 96% (SD: 10%), respectively, compared with 24% (SD: 82) and 9.8% (SD: 89%) for wounds in the SOC group. Conditional power testing shows this difference to be statistically significant. As depicted in Figure 4, the PAR values demonstrate considerable divergence in healing trajectories at approximately 1 week, with PRBM-treated wounds experiencing more rapid area reduction. Figure 5 depicts representative healing courses of wounds treated with PRBM.

The investigators evaluated the wound quality of life (Wound-QoL) and patients in the PRBM arm reported a

47% improvement in mean Wound-QoL scores from baseline compared with a 23% improvement in the SOC arm. The difference, however, between the two arms did not reach the level of statistical significance. Similarly, patients in both groups reported generally decreasing VAS pain scores over time, with the PRBM arm reporting a mean reduction of 0.4 and the SOC group a mean reduction of 0.6 over the 12-week study, but the difference also was not statistically significant.

There were no AEs deemed to be related to the PRBM. Ten AEs were reported in four patients in the PRBM arm, three of these were characterised as serious (SAEs): fractured left ankle, necrotizing fasciitis to venous ulcer in contralateral leg, and septic shock. In the SOC Arm, there were nine AEs reported, of which one was an SAE where pulmonary hypertension occurred in one patient.

A mean of 5.2 (SD: 3.5; median 4; range 1-12) PRBM grafts was applied to achieve wound healing. Mean per-patient PRBM cost to closure was $1731 (SD: $1308; median $1050). Smaller grafts were applied as wound area decreased, minimising cost and product waste. To address effectiveness of a treatment, the number needed to treat (NNT) and absolute risk reduction (ARR) were calculated. ARR interprets absolute risk reduction between PRBM treatment and SOC control. NNT represents number of patients who need to be treated by one treatment compared with another to achieve good outcome for one additional patient. ARR for PRBM was 0.55, thus PRBM reduces the absolute risk of unhealed DFU by 55% compared with SOC. NNT for PRBM vs SOC at 12 weeks was 1.82 (95% CI: 1.2, 3.4), suggesting that approximately one in two subjects will benefit from PRBM treatment rather than SOC alone.

4 | DISCUSSION

Diabetic patients with lower limb ulcers are common in podiatric practice. Unfortunately, even with strict adherence to standard treatment protocols, approximately 30% of these wounds will not completely heal, putting patients at increased risk for invasive wound complications, amputation, and premature death.[14]

Effective treatment requires clinicians to consider biologically active therapies capable of stimulating, supporting, and advancing the natural wound healing cascade. Over the past decade, reports in the literature have described advanced biomaterials with these inherent properties. [15-19] Existing clinical studies and subsequent meta-analyses of published RCTs evaluating the use of advanced biomaterials as treatment for DFUs suggest that the use of these therapies, regardless of their diverse origin and preparation, offers benefit without untoward complications.[20-31]

Most recently, a novel porcine-derived PRBM with a uniquely designed ECM structure was evaluated in vitro and in vivo[9,10] and found to have favourable characteristics necessary for successful wound healing. The present study is the first randomised, controlled clinical investigation of PRBM for treatment of chronic DFUs. Wounds treated with PRBM showed superior outcomes compared with a comparable study arm treated with an SOC protocol, including collagen alginate dressing.[29] The 85% complete closure rate over a 12-week period in the PRBM arm was consistent with the success rate reported in the PRBM pilot study.[9] Furthermore, the 85% wound closure rate observed with PRBM is comparable to wound closure rates of 70% to 97% at 12 weeks reported in similar RCTs evaluating other advanced biomaterials, including human amnion/chorion membranes and acellular dermal matrices.[21-23,27,29] Table 5 summarises the primary outcomes of these comparable RCTs, including 6- and 12-week healing rates and cost to closure. Direct comparative prospective randomised studies will be required to confirm these observations.

The economic impact of diabetic wounds is significant, with the cost to treat a patient with one or more DFUs ranging from $11 700 to $16 883.[33] When selecting a course of care, substantial thought is placed on not just the therapeutic benefits and risks but also on cost-effectiveness. The $1731 mean product cost of closure for PRBM in this trial was somewhat higher than the $1203 reported in the pilot study,[9] yet remained lower than the published cost to closure for amniotic/placental tissue products, which ranged from $1771 to $2252[21-23,27] and also lower than processed porcine grafts with reported mean cost of closure between $1901 and $3019.[32,34] The added cost of grafting has to be placed in context with the cost of non-healed wounds, which is significant and does not take into account the cost of time away from work as well as the cost associated with limb loss.

Non-healing wounds critically impact patient quality of life and carry significant morbidity and mortality,[2,14] yet quantitative assessment of quality of life has not typically been reported. The current study incorporated a patient-centric approach including patient-reported outcome measures.

Wound-specific pain is frequently underestimated in diabetics, with up to 75% of patients reporting DFU-related pain, because of an assumption that these patients are insensate secondary to underlying neuropathy.[35] Pain and the anticipation of pain can induce stress, which may further delay proper wound treatment and healing.[36,37] In this study, patients in the PRBM arm reported a mean reduction in VAS pain score of 0.4 and

also 47% improvement in average Wound QoL. VAS pain and QoL score improved in both arms of this study, presumably related to healing progress and successful DFU closure; however, the differences between the two groups were not statically significant in our study. In general, however, we would expect that wound treatment modalities that reduce pain and improve QoL during the course of treatment would be expected to additionally contribute to overall treatment success by reducing patient anxiety and increasing the likelihood of participation in regular clinic visits and compliance with a treatment plan.

The findings of this study are encouraging, but as with all studies certain limitations are recognised. These include: a small cohort of only 40 patients as well as a relatively small number of sites compared with large premarket trials; the inclusion of only full-thickness, non-infected, non-ischaemic wounds; lack of longer-term follow-up.

A comprehensive assessment of advanced skin substitutes by the Agency for Healthcare Research and Quality[8] suggests a need for studies evaluating patients with more serious comorbidities. Therefore, future trials should consider a 'real-world' patient population with more complex wounds, including deeper wounds. Additionally, longer-term studies reporting recurrence, hospitalizations, amputation, and mortality are recommended.[8] Furthermore, it should be recognised that in many countries treatment options such as PRBM are not available and therefore this may influence rate of adoption of such approaches, and as clinicians we should work for avenues to allow for more broad access. .

Based on the positive performance and economic profile associated with PRBM in this study, the authors recommend further investigation of its use in a larger, more heterogeneous population.

5 | CONCLUSIONS

Application of a PRBM (Geistlich Derma-Gide) significantly accelerated chronic wound healing with a favourable cost to closure. The product was safe and the bilayer construct made it easy to handle for the investigators. Weekly applications of PRBM were well tolerated, and PRBM-treated patients reported improved quality-of-life scores. This study validates and extends the outcomes observed in our pilot evaluation of PRBM.[9]

CONFLICT OF INTEREST

David G. Armstrong, DPM, MD, PhD received research funds from PERI to design and administrate the trial and also assist with the writing and review of the manuscript. Dennis P. Orgill, MD, PhD received research funds to serve as a validating/adjudicating plastic surgeon to review study photos and assist with the writing and review of the manuscript. Robert D. Galiano, MD received research funds to serve as a validating/adjudicating plastic surgeon to review study photos and assist with the writing and review of the manuscript. Paul M. Glat, MD received research funds to serve as a validating/adjudicating plastic surgeon to review study photos and assist with the writing and review of the manuscript. Jarrod P. Kaufman MD received research funds to assist in study design and manuscript preparation. Marissa J. Carter, PhD received research funds to provide the statistical analysis plan, and provide the statistical analysis for this trial and assist with writing of the result section of the manuscript. Lawrence A. Didomenico, DPM is the medical director of the LEIRT and his company received research funds for enrolment in the clinical trial and write the paper for publication. Charles M. Zelen, DPM is the medical director of the PERI and his company received research funds to administrate the clinical trial and write the paper for publication. There are no other conflict of interests with any of the authors in relationship to this study, or with regard to Geistlich Pharma. IRB conflict of interest statements are on file with PERI.

FINANCIAL DISCLOSURE

This study was funded through a research grant from Geistlich Pharma AG; provided to the Professional Education and Research Institute (PERI), which Charles M. Zelen, DPM is medical director.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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