Diabetic foot ulcer treatment with focused shockwave therapy: two multicentre, prospective, controlled, double-blinded, randomised phase III clinical trials

Objective: To investigate the efficacy of focused extracorporeal shockwave therapy (ESWT) as an adjunctive treatment for neuropathic diabetic foot ulcers (DFU) (1A or 2A on the University of Texas grading scheme), compared with sham treatment.
Method: We performed two multicentre, randomised, sham-controlled, double-blinded, phase III clinical trials using focused ESWT compared with sham examining DFUs that did not reduce in volume by ≥50% over 2 weeks' standard treatment immediately prior to randomisation. Patients were enrolled into the trials and randomised for either standard care and focused ESWT (pulsed acoustic cellular expression. dermaPACE System, SANUWAVE Health Inc.) active therapy, or standard care and sham therapy. Both active and sham therapy were administered four times in 2 weeks in study 1 and a maximum of eight times over 12 weeks in study 2. Standard care continued in both studies throughout the 12-week treatment phase. The proportion of DFUs that closed completely by 12, 20 and 24 weeks was measured.
Results: The two studies evaluated 336 patients; 172 patients treated with active therapy and 164 managed with a sham device. The demographic characteristics of patients in the two arms of both studies were balanced and statistical comparison of the two studies justified pooling datasets for analysis. Statistically significantly more DFU healed at 20 (35.5% versus 24.4%; p=0.027) and 24 weeks (37.8% versus 26.2%; p=0.023) in the active treatment arm compared with the sham-controlled arm. At 12 weeks the active therapy arm trended to significance (22.7% versus 18.3%).
Conclusion: The outcome of these two trials suggests that ESWT is an effective therapeutic modality in combination with standard care for neuropathic DFU that do not respond to standard care alone.
Declaration of interest: PM is a member of the SANUWAVE Scientific Advisory Board. Both studies were funded by SANUWAVE. SANUWAVE provided the basic outline and supporting clinical basis; hired consultants (medical, statistical, regulatory); and wrote the protocol with medical advisory consultants, adding review and comment. Independent, external statisticians and regulatory consultants analysed the data.

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Despite the use of recognised standards of care to manage chronic wounds such as diabetic foot ulcers (DFU), venous leg ulcers (VLU) and pressure ulcers (PU), a significant proportion of these wounds do not heal quickly. Healing rates are variable and more advanced therapies to stimulate wound closure are often required.[1,2] Non-healing wounds are a significant burden on clinical resources and place a large economic burden on health-care providers.[3–7] Average in-hospital costs are ~$10,800 per DFU episode. Primary healed DFUs cost on average ~$4800, single minor amputations ~$13,600 and major amputations ~$73,800 per episode with median duration of in-hospital care in the US of 17 weeks.[8] The time to achieve closure of a chronic DFU varies widely, but in routine clinical practice averages at least 6 months.[9] DFUs arise in patients where the foot has been rendered insensate and anatomically altered by peripheral neuropathy. The patient cannot detect when the foot is subject to pressure or trauma, and tissue breakdown caused by repeated insults that stimulate hyper-inflammation leads to ulceration.[10–12] The challenges presented by DFUs are expected to increase as the population expands, poor lifestyle leads to increased diabetes and obesity and the population ages.[14–16] Interventions to accelerate closure may therefore be cost-effective and will minimise the potential for complications.

The current standard of care for neuropathic DFU includes glycaemic control, infection management, debridement, local wound care using moist wound healing, and offloading.[17] A number of advanced technologies have been developed to enhance healing in the DFU and yet full closure remains challenging. Shockwave is a non-invasive means to re-initiate the chronic wound by activating the body's own healing pathways. Shockwave energy increases angiogenesis and growth factor production, and decreases inflammation within the wound bed and the surrounding tissues.[18]

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Table 1. Inclusion criteria for studies 1 and 2

Inclusion criteria	
Trial 1	**Trial 2**
Male or female ≥18 years of age	Male or female ≥22 years of age at visit 1
Female subjects of child-bearing potential must practice contraception continued through the duration of the study and have a negative urine qualitative pregnancy test within 2 weeks of visit 2	Female subjects of child-bearing potential must practice contraception continued through the duration of the study and have a negative urine qualitative pregnancy test within 2 weeks of visit 2
Female and post-menopausal incapable of pregnancy, or be postmenopausal for at least one year	Female and post-menopausal incapable of pregnancy, or be postmenopausal for at least one year
At least one diabetic foot ulcer in the ankle area or below that has persisted a minimum of 30 days prior to the screening visit. Subjects may have more than one diabetic foot ulcer, but only one will be treated in this study. *For a target ulcer located on the toe(s), the tip of the ESWT applicator must be able to be held perpendicular to the target ulcer **and** must be able to be applied to the entire surface of the target ulcer including the area 1cm beyond the surface of the ulcer in each direction at visit 2*	At least one diabetic foot ulcer in the ankle area or below that has persisted a minimum of 30 days prior to visit 1. Subjects may have more than one diabetic foot ulcer, but only one, the target ulcer, will be treated in this study. *For a target ulcer located on the toe(s), the tip of the PACE applicator must be able to be held perpendicular to the target ulcer **and** must be able to be applied to the entire surface of the target ulcer including the area 1cm beyond the surface of the ulcer in each direction at visit 2*
Diabetic (diabetes mellitus: DM) with a HbA_{1c} ≤12%	Type I or type II DM with a HbA_{1c} ≤12% at visit 1
Capable of wound care at home	Capable of wound care at home
Target ulcer ≥1.0cm^2 and ≤16cm^2	Target ulcer ≥1.0cm^2 and ≤16cm^2 at visits 1 and 2
Target ulcer which is an ulcer grade 1 or 2, stage A according to the University of Texas Diabetic Wound Classification system	Target ulcer that is grade 1 or 2, stage A according to the University of Texas Diabetic Wound Classification system, at visits 1 and 2
Ankle brachial index (ABI) ≥0.7 and ≤1.2, or toe pressure >50 mmHg, or $tcPo_2$ >40 mmHg	The leg with the target ulcer has an ABI ≥0.7 and ≤1.2, or if the ABI is >1.20 has a toe pressure > 50 mmHg, or $tcpO_2$ >40 mmHg at Visit 1
Subject, or the subject's legal representative, agrees for the subject to participate in the study, including all study-related procedures and evaluations, and signs the IRB/EC-approved informed consent form	Subject, or the subject's legal representative, agrees for the subject to participate in the study, including all study-related procedures and evaluations, and signs the IRB/EC-approved informed consent form at visit 1

Extracorporeal shockwave technology (ESWT) medical devices have been used for over 30 years in urology for lithotripsy (breaking up kidney stones). In the last decade, the US Food and Drug Administration (FDA) has approved ESWT for chronic plantar fasciitis and lateral epicondylitis for patients that do not respond to conservative treatments. ESWT has been shown to promote healing in several wound-healing applications. Experimental studies have demonstrated in both animal models and in case series that shockwave energy can enhance healing in burns, traumatic wounds, DFUs and VLUs, and enhance survival of reconstructive skin flaps.[19,20]

Against this background, the objective of the two prospective, randomised, controlled trials described here is to examine the safety and effectiveness of a focused shockwave device in combination with standard treatment for the treatment of DFUs. Similar protocols were followed in both trials; the key difference was the number of ESWT therapy sessions used per DFU. The second trial was designed to build on the outcomes of the first trial using an informative prior via Bayesian analysis. This paper reports the primary outcome data and briefly summarises the secondary outcome data. Secondary outcomes will be fully reported in a follow-up paper.

Method

The two trials were undertaken sequentially. Both were prospective, randomised, double-blind, parallel-group, sham-controlled, multicentre, interventional, clinical studies with 24 weeks' follow up in DFU. Active ESWT therapy (dermaPACE System, SANUWAVE Health Inc., Suwanee, US) used adjunctively with standard care was compared with sham treatment and standard care. Both studies required ethics committee approval and written and informed patient consent was sought and obtained for both studies. The studies were authorised under IDE G070103 and satisfied the requirements of the International Conference on Harmonisation Good Clinical Practices (ICH GCP) Guidelines with ethical principles based on the Declaration of Helsinki, ISO 14155:2003 (Parts 1 and 2), the EC Council directive on medical devices 93/42/EEC, and the European Standard EN 540.

Study 1 (ClinicalTrials.gov Identifier: NCT00536744): setting and study locations

The study was conducted in 21 trial sites, 19 in the US and one each in Germany and the UK. Centres included a mix of hospital or university research facilities (38%), Veterans Administration Hospitals (14%) and wound clinics, centres, and physicians' offices (48%). Randomisation took place from 15 October 2007 to 24 March 2010.

Participants

Inclusion and exclusion criteria (Tables 1 and 2) were designed to ensure a high degree of study population homogeneity. Subjects were screened up to 14 days before enrolment and included if they met all of the inclusion and none of the exclusion criteria at screening and/or baseline visits.

Enrolment, randomisation and blinding

Each randomised patient was followed up for 24 weeks and the last patient completed on 10 September 2010. Screened patients considered eligible for the study were enrolled into a run-in period of 2 weeks ±2 days before randomisation to determine eligibility based on the chronicity and clinical responsiveness of the index ulcer. Patients self-administered standard care and changed dressings every three days. Adherence was documented in diaries reviewed at the randomisation visit. All wounds were traced for area measurement at

Table 1. Exclusion criteria for studies 1 and 2

Exclusion criteria	
Trial 1	**Trial 2**
Female subjects currently pregnant or planning to become pregnant during the study; female subjects nursing/actively lactating	Female subjects currently pregnant or planning to become pregnant during the study; nursing/actively lactating
Morbidly obese: body mass index (BMI)≥40	Morbidly obese: BMI≥40 at the study screening visit (visit 1)
On dialysis	Clinically significant renal disease and/or impaired renal function
Foot ulcer which involves osteomyelitis or has osteomyelitis	Osteomyelitis in foot or ankle on which target ulcer is located at visit 1 or 2. Previous treatment of osteomyelitis must have completed ≥60 days before visit 1
Prior ulcer in the same area as the target ulcer	Prior ulcer in the same location as target ulcer, healed and re-opened ≤60 days
Target ulcer that decreased in volume by 50% or more at the end of the 2-week, run-in period	Target ulcer that decreased 50% or more at visit 2 compared with the volume at visit 1
Multiple foot ulcers connected by fistulas, or ulcer(s) within 5cm of the target ulcer	Multiple foot ulcers connected by fistulas, or ulcer(s) within 5cm of the target ulcer at visit 1 or 2
Target ulcer tunnels into wound tracks which cannot be fully visualised from the wound surface	Target ulcer tunnels into wound tracks which cannot be fully visualised from wound surface at visit 1 or 2
Active cellulitis at the site of, or in the surrounding area of, the target ulcer	Active cellulitis at the site of, or in the surrounding area of, the target ulcer at visit 1 or 2
Target ulcer has visually purulent or malodorous exudates	Target ulcer has visually purulent or malodorous exudates at visit 1 or 2
Peripheral vascular disease (PVD) requiring vascular surgery intervention	PVD requiring vascular surgery intervention at visit 1 or 2
Offloading for a reason other than the target ulcer	Offloading diabetic walker device for a reason other than the target ulcer at visit 1 or 2
Lower extremity revascularisation procedure within 8 weeks of the study screening visit	Lower extremity revascularisation procedure of the index lower extremity within 8 weeks before visit 1
Active Charcot foot	Active Charcot foot of the index foot at visit 1 or 2
Surgical procedure to correct biomechanical abnormities ≤8 weeks of visit 1	Surgical procedure to correct biomechanical abnormities of index foot ≤8 weeks before visit 1
Deep vein thrombosis (DVT) within 6 months of visit 1	DVT of the index lower extremity within 6 months before visit 1
Lymphoedema	Lymphoedema of the index lower extremity at visit 1
Chemotherapy within 60 days prior to screening visit	Chemotherapy within 60 days before visit 1
Life expectancy ≤2 years	Life expectancy ≤2 years
–	Previously participated in an extracorporeal shockwave technology (ESWT) DFU study
Target ulcer treated with growth factors, prostaglandin therapy, negative pressure or vasodilator therapy within 2 weeks of visit 1	Target ulcer treated with growth factors, prostaglandin therapy, negative pressure or vasodilator therapy within 2 weeks of visit 1
Receiving ≥10mg of steroid therapy per day	Receiving ≥10mg/day of steroid therapy
Sickle cell anemia	Sickle cell anemia
Immunodeficiency disorder	Immunodeficiency disorder at visit 1 or 2
Radiation treatment within 120 days of visit 1	Radiation treatment within 120 days before visit 1
Treatment with immunosuppressants, or biologically active cellular products within 60 days of visit 1	Treatment with immunosuppressants within 60 days before visit 1
Treatment with acellular (collagen-based) products, within 30 days of visit 1	Treatment with biologically active cellular products on the target ulcer within 60 days before visit 1; treatment with acellular (collagen-based) products on the target ulcer within 30 days before visit 1
Current history of substance abuse	Current history of substance abuse before visit 1
History of major systemic infections requiring hospitalisation within 3 months of visit 1	Has a history of major systemic infections requiring hospitalisation within 3 months before visit 1
Current or history of malignancy within the past 5 years	Current or history of malignancy within the past 5 years of visit 1
Physical/mental disability or geographical concerns that inhibit adherence with required study visits	Physical/mental disability or geographical concerns that inhibit compliance with required study visits
Planned exclusionary treatment/procedure during the study	Planned exclusionary treatment/procedure during the study
Participated in another clinical investigation within 30 days before study visit 1	Participated in another clinical investigation within 30 days of visit 1
Subject believed by the Investigator to be unwilling or unable to comply with study protocol requirements	Subject believed by the investigator to be unwilling or unable to comply with study protocol requirements

enrolment and managed using documented standard care. Standard care included, but was not limited to, sharp debridement according to local practice, sterile saline-moistened gauze, adherent or non-adherent secondary dressings including foams and hydrocolloids, and pressure-reducing footwear. The use of antibacterial products was not permitted. Patients whose ulcers reduced in volume >50% as determined by Canfield's web-based system were removed from the intention-to-treat (ITT) population. Patients who met the enrolment criteria were randomised to receive either standard care and sham ESWT or standard care and active therapy.

Randomisation was stratified by diabetes type (type 1 or type 2). Subjects were allocated to treatment groups by sealed envelopes prepared before the study started and labelled according to diabetes type. Randomisation envelopes were opened sequentially after removal from a locked box kept in a secure location. For subjects with two qualifying ulcers, the oldest, largest volume, or depth of ulcer was chosen (in that order). For subjects with three or more qualifying ulcers, the ulcer that was the median in age, volume and depth was chosen. All patients randomised and who received at least one active or sham shockwave therapy were considered part of the ITT population for data analysis. The per-protocol (PP) population was defined as randomised subjects who followed the protocol without significant deviation. All randomised patients were included in the safety population. The subjects, evaluating investigators, investigators who traced ulcers and conducted planimetry, and study coordinators were all blinded to treatment groups. Each site designated one or two members of the study staff as unblinded application administrators whose role was to administer the study application and to maintain the sealed/re-sealed randomisation envelopes and randomisation/treatment log securely.

Interventions

All subjects received standard care with adjunctive active therapy or sham ESWT according to the randomisation schedule. The active therapy device consists of two components, a procedure console and an applicator (Fig 1). All treatments were administered by an unblinded operator. The principal investigator (PI) was excluded from the treatment room during treatment. Subjects in the active therapy cohort received the first application of 500 impulses (shocks) lasting between 2 and 5 minutes using an energy flux density of 0.23mJ/mm^2 at a rate of four impulses per second and delivered at a power setting of E2. The shockwave dose was derived from ischaemic flap studies in a rat model.[21] The shockwave applicator was covered with a sterile sleeve, and sterile ultrasound gel was applied to the wound surface as a coupling medium. Shockwaves were applied directly to the wound surface. Subjects in the sham-control cohort were treated identically to subjects in the active therapy except a dummy applicator (non-energised applicator not connected to the generator) was applied to the patient's wound area. All subjects were positioned such that the application could not be observed. While the non-energised applicator was passed across the wound area in a simulated therapy application, 500 impulses were discharged on a second active therapy applicator connected to the generator, which did not make contact with the patient and provided the sound effect of active therapy energy delivery.

Fig 1. Extracorporeal shockwave therapy device

Thereafter, subjects received standard of care and three additional adjunctive active or sham device applications every 3±1 days over 2 weeks. Standard care continued for both groups until the target ulcer healed or the follow-up period ended. Follow-up visits took place every 14±2 days. The full treatment period was 12 weeks after initial application; the follow-up period continued for 12 additional weeks after the treatment period for a total of 24 weeks, to confirm continued wound closure and for safety assessment.

At each treatment period visit and post-treatment period follow-up visit, basic physiological parameters and concomitant mediations and procedures were assessed; wounds were assessed, measured for area and depth, traced, and photographed; the visual analogue scale (VAS) was used to assess pain; standard care was delivered; and adverse events (AEs) assessment was conducted. Where the target wound had healed, a Healed Ulcer Appearance Questionnaire was completed at the first visit at which full wound closure was recorded. The patient diary was collected, analysed and returned to the patient.

If at any time a wound closed at an application visit, the subject was no longer to receive study device treatment, but other procedures per the requirements of schedule of events were performed.

Outcomes

The primary efficacy endpoint for all subjects who received at least one episode of treatment was the incidence of complete wound closure within 12 weeks. Wound closure, determined by the blinded evaluating investigators, was defined as skin re-epithelialisation without drainage or dressing requirements, confirmed

over two consecutive visits within 12 weeks. If the wound was considered closed for the first time at the 12-week visit, then the next visit was used to confirm closure. The primary efficacy endpoint was measured using serial photography (Canon PowerShot G7 Digital 10MP Camera, Canon, US) at each visit, and wound area measurements using wound tracings were analysed (Canfield Scientific Central Imaging Laboratory, US). Wound depth was measured using the VISITRAK Depth Probe (Smith & Nephew, UK). Sensation was assessed using a Semmes-Weinstein 5.01 monofilaments (Touch-Test Sensory Evaluators, Stoelting, US).

The primary safety endpoint was the rate of AEs of the active therapy and sham control at 24 weeks after initial application, including serious adverse events (SAEs), device-related adverse events, and active therapy malfunctions throughout the application, treatment, and follow-up periods.

Secondary endpoints were: target ulcer area, volume, depth and perimeter; rate of wound closure; mean wound area reduction; percentage of patients with an increase in wound area; rate of treatment emergent AEs, treatment emergent SAEs and device-related treatment emergent AEs; recurrence and amputation rate; rate of ESWT malfunctions; and changes in baseline values in wound pain assessed by VAS. Infection occurrence was diagnosed by the blinded evaluating investigators.

Statistical methods

The enrolment target was 200 subjects randomised 1:1 into the two treatment groups accounting for a dropout rate of 25%. The sample size was determined based on the primary efficacy endpoint of wound healing, defined as the proportion of subjects who have wound closure by the end of 12 weeks following the initial application. Calculations were based on a Pearson chi-square test assuming a 1:1 randomisation ratio and a type I error rate (α-level) of 0.05. It was estimated that 55% of the subjects in the active therapy group would have complete wound closure by week 12.[22] If 29% of the subjects in the sham group have complete wound closure,[23] then 75 subjects per group would provide 90% power to detect this difference of 26% between the two treatment arms.

Comparison between groups, including time points to 24 weeks, was made using a Cochran-Mantel-Haenszel chi-square test stratified by type of diabetes. A 95% confidence interval (CI) around the difference between treatment groups was calculated. As a sensitivity analysis, a logistic regression analysis was performed to confirm the results of the primary analysis. Factors included in the model were treatment group, investigative site, type of diabetes, baseline variables unbalanced between treatment groups, and other clinically important baseline variables. Time-to-event analyses were estimated by using the Kaplan-Meier analysis. Multivariate logistic regression analyses were used to assess the contribution of the active and sham-control devices relative to complete wound closure. An α of 0.1 for was used for interaction terms. Safety variables were summarised descriptively. For secondary endpoints, time to wound closure was assessed using life-tables analysis, and wound area, volume, depth and perimeter were summarised descriptively. Subgroup analysis was performed on week 24 for data on height, weight, body mass index (BMI) and HbA1c, gender, age and smoking status.

Study 2 (ClinicalTrials.gov Identifier: NCT01824407)

Study 2 was conducted in 18 sites (17 in the US and one in Canada). Centres included a mix of hospital or university research facilities (17%), Veterans Administration Hospitals (11%) and wound clinics, centres, and physicians' offices (72%). The first patient was randomised in June 2013 and the last patient completed in May 2015.

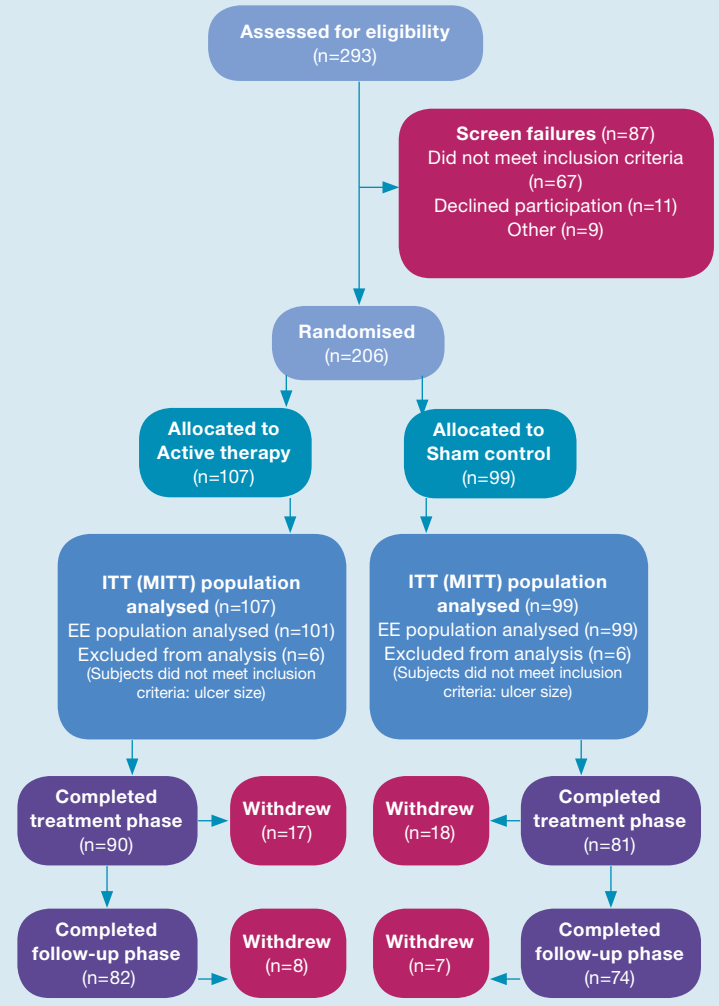
The design was largely identical to that for study 1 with some important variations as follows. Healing efficacy endpoints were measured using the Aranz SilhouetteStar (ARANZ Medical Ltd., Christchurch, New Zealand) at each study visit. Photographs were taken as soon as the subject arrived at every study visit once the dressing and any dressing residue had been removed, and uploaded to the Aranz central database. If the target ulcer had not closed, photographs were taken both before and after cleaning and/or debridement. Wound closure was determined both by the investigator and an external third party that assessed photographs. Discrepancies were resolved by discussion between the investigator and the external third party. The secondary safety endpoint variable was the rate of adverse events by 24 weeks post-initial device application.

Inclusion and exclusion criteria were identical to those for study 1 but with a slightly higher minimum age for subjects (≥22 years) and additional specifications for renal disease (Tables 1 and 2). The age limit was increased to exclude patients meeting the FDA's definition of a paediatric patient (21 years). Patients who participated in study 1 were ineligible. Randomisation was balanced by using randomly permuted blocks stratified by study site and target ulcer duration (<1 year, >1 year).

Dosing for study 2 was based on clinical outcomes in DFU[24] and reported effects of active therapy on growth factor expression in laboratory studies.[25,26] Patients in study 2 could receive up to eight active therapy or sham treatments. The first four were administered every 3±2 days during treatment visits, and thereafter every 2 weeks over the 10-week treatment period. Active therapy was delivered using the same settings and durations as for study 1. Treatment was terminated if the target ulcer healed before 10 weeks.

Study 2 was designed using Bayesian clinical trial simulation where study 1 was the informative prior by an independent Data Monitoring Committee (DMC) which also conducted data reviews. There were three interim assessments for effectiveness (superiority) planned. The first look would occur when 90 subjects had completed their 12-week follow-up, the second

Fig 2. Patient enrolment, randomisation and data analysis flow chart: study 1



when 130 subjects completed their 12-week follow-up, and the final look when 172 subjects were complete. The posterior probability thresholds for stopping the study for superiority at the three looks were 0.965, 0.98, and 0.985, respectively. At each look, there was also the possibility to stop for futility.

Sample size and statistical analysis

In study 2 the randomised enrolment target was 200. The null and alternative hypotheses were:

- H0: HR<1
- H1: HR>1,

where HR was the hazard ratio of complete closures (active therapy /control) by 12 weeks. The study would be declared successful if the hazard ratio was >1. In order to further confirm study success and that the expected benefit size associated with the hazard ratio is clinically meaningful, the between-group difference in complete closures by 12 weeks were calculated, but not tested for statistical significance. Statistical analysis of primary efficacy outcomes used frequentist methods in a multiple regression model analysis on the modified ITT group (MITT) population. The HR (active therapy versus sham-control) and 95% CI were estimated. The HR of the two treatments was compared using a Wald chi-square test in the context of a Cox Proportional Hazards regression model. The regression model included the following covariates and subgroups, with subgroup-by-treatment interactions: gender, age (<65 versus ≥65 years), race, ethnicity, target ulcer duration and study site as subgroups, and baseline wound area and number of treatment received as continuous covariates. Covariates and subgroups were included in the full model, and any found to be not statistically significant at α=0.10 level were removed in a step-wise elimination method. The reduced model was used for the primary efficacy analysis. The analysis of the MITT population was supported by analysis repeated using the PP population.

Quantitative secondary efficacy endpoints in study 2 were summarised descriptively (n, mean, standard deviation, minimum, maximum) by treatment at each time point for the percent change-from-baseline for the target ulcer area, perimeter, depth and volume. For each of these metrics, the difference between the means of the two treatment groups was tested by time point by ANCOVA, accounting for correlations among the repeated measurements upon subjects, visit-specific effects accounting for the non-linear progression of the endpoint, and used the above-specified covariates, if statistically significant at the α=0.10 level. Amputation rates were compared between the two groups by logistic regression using the covariates above. Subgroup analysis was performed on week 24 for data on height, weight, BMI and HbA1c, gender, age and smoking status.

Definitions of patient populations for analysis

In both studies the ITT population was defined as all subjects who were randomised into the treatment phase of the studies. A MITT was defined as all eligible, randomised subjects who received at least one device application and provided at least one post-randomisation efficacy evaluation. In practice the number of patients in the ITT and MITT populations was the same because all ITT patients received at least one treatment application and one post-randomisation efficacy evaluation. The PP population included all available data from eligible, randomised subjects in the MITT population who followed the protocol without significant protocol deviation. All efficacy endpoints analyses were conducted using the MITT population. The safety population included all patients in the MITT population.

Poolability of datasets

Study 2 did not produce outcomes in line with expectations based on study 1. Additional evidence was therefore required to satisfy the requirements for a *de novo* pathway submission to the FDA. Statistical analyses were performed in order to provide evidence supporting simple pooling of patients from study 1 and study 2 when evaluating the

Table 3. Baseline characteristics, studies 1 and 2

	Study 1		Study 2		All participants	
Demographic	**Active n=107**	**Sham n=99**	**Active n=65**	**Sham n=65**	**Active n=172**	**Sham n=164**
Age (mean, years)	60.4±10.4	56.2±9.4	59.1±9.4	56.8±10.7	59.9±10.0	56.4±9.9
Gender (% male)	77.6%	83.8%	83.1%	75.4%	79.7%	80.5%
Height (inches)	70.0±4.1	70.0±3.8	69.6±3.9	70.7±4.8	69.9±3.0	70.3±4.2
Race						
American Indian or Alaska Native	2 (1.9%)	4 (4.0%)	0 (0.0%)	2 (3.1%)	2 (1.1%)	6 (3.7%)
Asian	1 (0.9%)	1 (1.0%)	0 (0.0%)	1 (1.5%)	1 (0.6%)	2 (1.2%)
African American	19 (17.8%)	20 (20.2%)	11 (16.9%)	14 (21.5%)	30 (17.4%)	34 (20.7%)
Caucasian	82 (76.6%)	66 (66.7%)	50 (76.9%)	47 (72.3%)	132 (76.7%)	113 (68.9%)
Multiple race	1 (0.9%)	0 (0.0%)			1 (0.6%)	0 (0.0%)
Native Hawaiian/other Pacific Islander			2 (3.1%)	0 (0.0%)	2 (1.2%)	0 (0.0%)
Other	2 (1.9%)	8 (8.1%)	2 (3.1%)	1 (1.5%)	4 (2.3%)	9 (5.5%)
Health						
Weight (pounds)	222.0±42.2	221.5±44.7	217.2±45.0	225.5±49.0	220.2±43.2	223.1±46.3
Body mass index (kg/m^2)	31.8±5.1	31.6±5.2	31.4±5.6	31.6±5.5	31.6±5.3	31.6±5.3
Smokers	13.1%	22.2%	18.5%	13.9%	15.1%	18.9%
Target ulcer size (cm^2)	3.5±3.2	2.8±2.4	3.71±2.8	3.73±2.8	3.55±3.1	3.16±2.5
Target ulcer age (weeks)	48.7±66.6	69.5±107.5	44.6±53.4	49.7±59.2	47.2±61.8	61.7±91.7
HbA1c<7	30.8%	33.3%	34.9%	20.6%	32.6%	28%
HbA1c ≥7	69.2%	66.7%	65.1%	79.4%	67.4%	72%
Diabetes type 1	6	10	4 (6.2%)	10 (15.4%)	10 (5.8%)	20 (12.2%)
Diabetes type 2	101	89	61 (93.8%)	55 (84.6%)	162 (94.2%)	144 (87.8%)
Ankle brachial pressure index	1.01±0.13	1.04±0.13	N/A	N/A		
Toe pressure (mmHg)	101.6±24.1	89.9±16.9	N/A	N/A		
Duration of diabetes (years)						
Mean standard deviation	18.0±10.0	15.7±11.1	15.44 ±11.4	17.45±13.3		
Median			14.4	15.3		
Tobacco use status						
Never			30 (46.2%)	38 (58.5%)		
Former			23 (35.4%)	18 (27.7%)		
Current			12 (18.5%)	9 (13.8%)		

wound closure endpoints at week 12 and out to week 24. These analyses examined similarity in results and patient characteristics across studies and the influence of degree to which sampling variability affected heterogeneity of treatment group differences between studies. The additional evidence consisted of a comprehensive evaluation of clinical effectiveness across a wide range of relevant clinical endpoints, combining the results from study 1 and study 2.

Analyses conducted to justify data pooling showed that study was not a factor in statistical models and that valid estimates of treatment effect size could be obtained through pooling of patients from the two studies. The observed heterogeneity of treatment group differences between studies was consistent with sampling variability. Baseline characteristics were comparable between studies. These conclusions were based on comparisons of odds ratios and p-values with and without controlling for a study factor, tests for study by treatment interaction, and baseline comparisons between studies. Frequentist analyses were used to evaluate treatment group differences based on the pooled analysis dataset. However, because of the difference between studies in the maximum number of treatment applications and some baseline patient characteristics such as target ulcer age (see baseline characteristics section), some results are presented separately by study. Subgroup analysis was performed using data from week 24 on height, weight, BMI and HbA1c, gender, age and smoking status. This analysis acceptably supported pooling data from the perspective of regulators.

Results

Patient flow and baseline characteristics: study 1

Fig 2 shows the flow diagram for patient enrolment, randomisation and data analysis. During the study, 293

subjects were screened. Of these, 87 patients were excluded because they did not meet inclusion criteria (n=67), declined to participate (n=11) or other reasons (n=9). There were 206 patients randomised, all of who underwent at least one active therapy or sham-control treatment. The efficacy evaluable group (EE group) represented the 194 subjects who had a DFU at baseline equal to or between 1cm^2 and 16cm^2 and that did not decrease in volume by more than 50% during the 2-week, run-in period. Of the 206 patients who were randomised, 164 patients remained enrolled in the trial at the 12-week time point, and 149 patients at the 24-week time point.

There were 42 subjects who withdrew in the treatment phase of study 1, 19 subjects from the active therapy group (nine for AEs, one died, five withdrew consent, three were lost to follow-up and one was withdrawn by the investigator). From the sham group 23 withdrew, six for AEs, one died, seven withdrew consent, four were lost to follow-up, one was withdrawn by the investigator and four withdrew for other reasons. There were 15 withdrawals during the post-treatment follow-up phase, 10 from the active therapy group (four for AEs, one died, two withdrew consent, two were withdrawn by the investigator and one withdrew for other reasons). Five subjects withdrew from the sham group (four for AEs, and one subject withdrew consent).

Fig 3. Patient enrolment, randomisation and data analysis flow chart: **study 2**

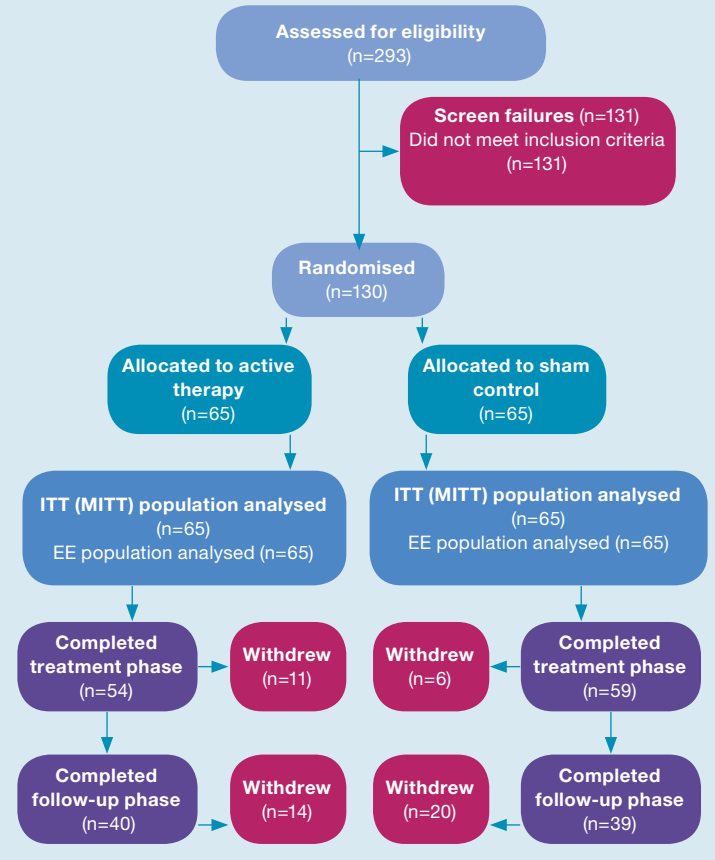


Table 3 shows the baseline characteristics for both studies and the combined datasets. In general, in study 1, baseline characteristics for the active therapy subjects did not differ significantly compared with sham-control subjects. However, the mean age of subjects and duration of diabetes was significantly higher in the active therapy group versus the sham-control group: 60.4±10.4 versus 56.2±9.4 years (p=0.005) and 18.0±10.0 versus 15.7±11.1 years (p=0.005), respectively.

Patient flow and baseline characteristics: study 2

Fig 3 shows the flow diagram for patient enrolment, randomisation and data analysis. A total of 261 subjects were screened. There were 131 patients excluded because they did not meet inclusion criteria, and 130 patients were randomised. All randomised patients underwent at least one active therapy or sham-control treatment and were included in the MITT population. The EE group represented the 261 subjects. Of the 130 patients who were randomised, 113 remained enrolled in the trial at the 12-week time point, and 79 remained at the 24-week time point.

There were 25 subjects who withdrew in the treatment phase in study 2, 15 from the active therapy group (six for AEs, four withdrew consent, three were lost to follow-up and two were withdrawn by the investigator). There were 10 withdrawals in the sham group (four for AEs, three withdrew consent, two were lost to follow-up and one was withdrawn for other reasons). During the post-treatment, follow-up phase 12 subjects withdrew, seven from the active therapy group (four for AEs, one was lost to follow-up, and two were withdrawn by the investigator). From the sham group, five subjects withdrew (two for AEs, one withdrew consent, one was lost to follow-up and one withdrew for other reasons). Study 2 baseline characteristics for the active therapy subjects did not differ significantly compared with sham-control subjects (Table 3).

Patient flow and baseline characteristics: pooled dataset

The two studies evaluated 336 patients; 172 patients treated with active therapy and 164 managed with a sham device. A statistically significant difference in age was found between the two groups; the active therapy group was on average approximately 3 years older than the control group. However, there were no notable differences in the outcomes of the groups when stratified by age. Additionally, although the difference was not statistically significant, the sham group had higher target ulcer age by 14+ weeks in the pooled dataset. There were also no notable differences between study groups in numbers of subjects whose HbA1c levels were ≥7 versus patients whose HbA1c was <7. Data analysis by diabetes mellitus (DM) type could not be conducted because too few type 1 DM subjects were enrolled.

Table 4. Primary efficacy outcomes for studies 1 and 2 and pooled study data

Complete wound closure								
Study	Visit (week)	Active therapy			Sham control			$\chi 2$ p-value
		Total enrolled N[1]	Actual N[2]	n (%)3	Total enrolled N[1]	Actual N[2]	n (%)[3]	
Study 1	12	107	90	22 (20.6%)	99	81	15 (15.2%)	0.363
	20	107		39 (36/4%)	99		23 (23/2%)	0.047
	24	107	82	42 (39.3%)	99	74	26 (26.3%)	0.054
Study 2	12	65	54	17 (26.15%)	65	59	15 (23.08%)	0.684
	20	65		22 (33.84%)	65		17 (26.15%)	0.444
	24	65	40	23 (35.38%)	65	39	17 (26.15%)	0.254
Study 3	12	172	144	39 (22.67%)	164	140	30 (18.29%)	0.320
	20	172		61 (35/47%)	164		40 (24.39%)	0.027
	24	172	122	65 (37.79%)	164	113	43 (26.22%)	0.023

[1] Total number of randomised subjects per study and pooled; [2] Total number of subjects who completed the 12 or 24 weeks in each study;[3] Wound closure percentage and $\chi 2$ p-value calculated using all enrolled subjects

The outcomes for the active therapy groups in both studies demonstrate that the increase in the number of treatment applications from 4 to 8 did not significantly impact the safety or effectiveness of the device. The successful results (attainment of the primary outcome of complete wound closure at the time point) at 24 weeks for study 1 were 39.3% in the active therapy group compared with 35.4% in study 2. Additionally, the percentage of patients with at least one SAE in study 1 was 31.8% in the active therapy group compared with 32.3% in study 2, indicating that no additional safety risks were introduced with the increase in the number of applications.

Primary outcomes: complete wound closure (study 1)

There was a trend towards greater complete wound closure in the ITT group during the first 12 weeks of the study that achieved statistical significance at the 20-week time point. At 24 weeks, the differences in wound closure approached statistical significance (p=0.054). Of 107 active therapy subjects, 22 (20.6%) achieved complete wound closure at 12 weeks, whereas 15/99 (15.2%) sham-control subjects achieved complete wound closure at the same point (p=0.363) (Table 4). Over time, these early differences in the incidence of complete wound closure achieved statistical significance. The primary efficacy endpoint achieved statistical

Table 5. Complete wound closure rates by subject characteristics for pooled dataset at weeks 12 and 24

Complete wound closure							
Demographic		Active therapy			Sham control		
		n	%12 weeks	% 24 weeks	n	%12 weeks	% 24 weeks
Age (years)	<65	120	21.7	37.5	129	17.1	31.3
	≥65	52	25.0	38.5	35	22.9	26.3
Gender	Male	137	24.8	40.1	132	16.7	25.8
	Female	35	14.3	28.6	32	25.0	25.3
Smoking status	Non-users	146	21.9	37.0	133	19.5	27.3
	Users	26	26.9	42.3	31	12.9	26.9
Body mass index (kg/m^2)	<32	84	29.8	45.2	87	18.4	25.3
	≥32	88	15.9	30.7	77	18.2	27.3
Weight (pounds)	<220	86	25.6	40.7	78	19.2	26.9
	≥220	86	19.8	34.9	86	17.4	25.6
Height (inches)	<70	72	12.5	27.8	72	23.6	43.7
	≥70	100	30.0	45	92	14.1	19.6
Ulcer age (months)	<12	125	27.2	48.4	110	24.5	36.0
	≥12	47	10.6	25.9	56	5.4	18.0
HbA1c*	<7	55	20.0	36.4	46	17.4	30.4
	≥7	115	24.3	39.1	116	19.0	25.0

* HbA1c values were not recorded for two subjects

Table 6. Complete wound closure in relation to BMI, ulcer age and HbA1c in study 1 and 2 at 12 and 24 weeks

Complete wound closure													
Demographic		Active study 1 4 treatments			Sham study 1 4 treatments			Active study 2 >4 treatments			Sham study 2 >4 treatments		
		n	12 wks	24 wks	n	12 wks	24 wks	n	12 wks	24 wks	n	12 wks	24 wks
			%	%		%	%		%	%		%	%
BMI (kg/m^2)	< 32	53	26.42	41.51	50	16.0	28.0	31	35.48	51.61	37	21.62	21.62
	≥ 32	54	14.81	37.04	49	14.29	24.49	34	17.65	20.59	28	25.0	32.14
Ulcer age (months)	< 12	19	23.8	43.8	66	21.2	33.3	45	33.3	46.7	44	29.5	31.8
	≥ 12	27	11.1	25.9	33	3.0	12.1	20	10.0	10.0	21	9.5	14.3
HbA1c	<7	33	24.2	42.4	33	15.1	27.3	22	13.6	27.3	13	23.1	38.5
	≥7	74	18.9	37.8	66	15.1	28.8	41	34.1	41.5	50	24.0	24.0

BMI—body mass index; Wks—weeks

significance at 20 weeks in the ITT population with 39/107 (36.4%) active therapy subjects compared with 23/99 (23.2%) sham-control subjects achieving complete wound closure (p=0.047). The EE population also achieved statistically significant complete wound closure at 20 weeks, with 38/101 (37.6%) active therapy treated subjects and 20/93 (21.5%) sham-control subjects achieving complete wound closure (p=0.018).

Primary outcomes: complete wound closure (study 2)

At the 12, 20 and 24-week time points there were no significant differences between the primary efficacy outcomes for active therapy and sham-treated subjects (Table 4). However, at every time point, the rate of complete wound closure trended towards greater closure in the active therapy group. At week 20 in the active therapy and sham groups respectively 33.8% and 26.2% of wounds had closed, and at the 24-week time point the corresponding figures were 35.4% and 26.2%. In order to produce information required for submission to FDA, the data from study 2 were pooled with those from study 1 and further analyses conducted on the pooled dataset.

Table 7. Safety endpoints for pooled data from studies 1 and 2

Safety endpoints	Active (n=172)	Sham (n=164)	p-value[1]
	n (%)	n (%)	
Primary endpoint			
All adverse events (24 weeks)	126 (73.2%)	112 (68.9%)	0.338
Secondary endpoints			
Treatment-emergent AEs	96 (55.8%)	84 (51.2%)	0.444
Serious AEs	55 (32.0%)	71 (43.3%)	0.042
Treatment-emergent serious AEs	33 (19.2%)	34 (20.7%)	0.785
Device-related, treatment-emergent AEs	9 (5.2%)	4 (2.4%)	0.259
Additional safety analyses			
Recurrence rate[2]	5 (7.7%)	5 (11.6%)	0.49
Partial amputation rate	4 (2.3%)	5 (3.0%)	0.745
Target foot amputation rate	4 (2.3%)	11 (6.4%)	0.065

[1] Fisher's Exact test (2-sided); [2] Recurrence rates determined as 5/65 (7.7%) and 5/43 (11.6), respectively; Serious AEs were defined as adverse events which required medical intervention and were disruptive to the daily activities of the patient; Device-related, treatment-emergent AEs were AEs determined by the investigators to be possibly or probably related to the treatment

Primary outcomes: complete wound closure pooled dataset

The rate of complete closure in the pooled dataset was not significantly different at 12 weeks (22.7% and 18.3% for active therapy and sham respectively) whereas at week 20 the difference, 35.5% and 24.4%, reached statistical significance (p=0.027) (Table 4). The difference (37.8% and 26.2%) was also statistically significant for active therapy and sham respectively at 24 weeks (p=0.023). The relationships between complete wound closure and the characteristics of subsets of patients in the pooled dataset are shown in Table 5. Notable differences were found in patient BMI, gender, and target ulcer age. Although the study was not designed to detect an interaction across BMI, the data appear to indicate that wound closure rates were lower at 12 weeks for subjects with BMI≥32 compared with subjects with BMI<32. However, this finding is reversed by week 24 of active therapy with the exception of patients who received more than three treatments. Complete wound closure was higher in male subjects managed with active therapy than in female subjects. There were notable differences in complete wound closure when stratified by BMI and target ulcer age (Table 6). Patients with BMI>32 seemed to have lower rates of wound closure when they received more than four treatments. The same trend was noted for ulcers greater than one year old. Slightly better wound closure outcomes were reported in the patients treated with active therapy with HbA1c≥7 compared with sham treatment and compared with patients with HbA1c<7. This finding may suggest, counterintuitively, that the subjects with uncontrolled diabetes experienced improved wound healing results with the active therapy compared with subjects with controlled diabetes.

Safety endpoints: pooled dataset

Safety endpoint analysis was conducted on the pooled dataset (Table 7). Despite the occurrence of high rates

of AEs in relation to the primary efficacy endpoint of 126 in 172 subjects (73.2%) and 112 in 164 subjects (68.9%) in the active therapy and sham groups respectively, there were no statistical differences between them at 24 weeks. AEs led to withdrawals in only a small number of patients; 23 in study 1 and 15 in study 2, suggesting that AEs did not generally deter involvement. AEs related to secondary endpoints generally showed no statistically significant difference between active therapy and sham groups except for serious AEs which were reported more frequently in the sham group (55/172 [32%] versus 71/164 [43.3%]). There were more amputations in the foot with the target (treated) DFU in the sham group (2.3% versus 6.4%). The incidence trended towards significance.

Device-related emergent AEs were analysed. Of subjects who used active therapy 18% experienced increased wound size compared with 31.1% in the sham cohort at 12 weeks. At week 24, the incidence of increase in wound area in the active therapy cohort was 25.6% compared with 34.2% for the sham group. Active therapy emergent treatment AEs (TESAE) at 24 weeks in the pooled dataset included burning sensation (n=2), pain (n=2) and headache (n=2) or infection. In the sham cohort, TESAE included increased burning sensation, cardiac disorder and DFU infection (n=1 each). Similar numbers of subjects experienced at least one AE in both treatment groups in both studies.

Secondary outcomes

A brief summary of the secondary outcomes is presented here. In the pooled dataset, wound area reduction was statistically significantly different in favour of active therapy from week 6 to week 24. By week 4, more subjects in the active therapy group had achieved 50% wound closure than in the control group although this did not reach statistical significance. More subjects in the active therapy group achieved 80% wound area reduction than in the control group from week 6 on, achieving significance at week 14.

Discussion

The patient population selected for randomisation into this study was by definition hard-to-heal. The selection process enrolled subjects into a 2-week, run-in period during which standard care alone was delivered. Patients who achieved >50% wound volume reduction were ineligible for randomisation. This process ensured that only patients whose wounds were unresponsive to standard care were randomised. The population may therefore be considered more challenging than one chosen without the run-in period. The inclusion and exclusion criteria selected a homogeneous population of patients, controlling variables as far as possible consistent with running a timely trial. In this regard, the study was similar to other DFU randomised controlled trials and the outcomes may therefore be comparable.

The enrolment targets for these studies were determined by statistical powering analyses with inputs for study 1 derived from published data.[22,23] The treatment difference derived from the published studies was estimated to be 26% leading to a randomisation target of 200 subjects to account for a 25% withdrawal rate and to allow for the power of the study to be maintained. The second study was designed using Bayesian methods, in which the first study was the informative prior. Together the pooled dataset contained 336 subjects, one of the largest randomised trials of healing outcomes for DFU clinical research.[27–30]

The active therapy is a medical device capable of conducting non-invasive acoustic pressure wave procedures. The focused, acoustic pressure waves are true shockwaves, characterised by a high-peak pressure wave followed by an area of negative pressure.[31] The shockwave impulses are delivered rapidly, within nanoseconds of one another. The impulses are created by an electrohydraulic mechanism that creates a shockwave by igniting a spark in a fluid medium. The fluid medium vaporises forming a plasma bubble that collapses on itself, creating a shockwave.[31] Active therapy with the test device has been reported to cause an immediate increase in wound perfusion,[32] and an up-regulation in angiogenic and pro-inflammatory responses that directly contribute to wound healing.[26] In bone, tendon and bone/tendon interface, shockwave therapy has been shown to increase expression of endothelial nitric oxide synthase, vascular endothelial growth factor, and proliferation cell nuclear antigen.[18] Ischaemic flap survival is enhanced by ESWT by increasing perfusion[33] and fibroblast and leukocyte recruitment.[34] Shockwave therapy may enhance the susceptibility of staphylococcal biofilm to antimicrobial agents[35] and facilitate biofilm removal.[35]

Previous clinical studies with ESWT have reported outcomes similar to those reported here in DFU. Two systematic reviews and meta-analyses of randomised studies of ESWT in chronic wounds reported clinical benefit when ESWT was used adjunctively with standard of care,[37,38] a finding closely aligned with the outcome of the two studies reported here. Healing in chronic VLUs and DFUs is enhanced by ESWT as evidenced by a number of clinical trials.[19,39,40] Increased transcutaneous oxygen levels have been observed with ESWT treatment[19] supporting the proposed mechanism of action. DFU may be managed using a variety of advanced technologies[41] including hyperbaric oxygen therapy (HBOT), although few of these technologies have been endorsed by experts.[42] However, ESWT has been shown to be significantly more clinically effective than HBOT in DFU.[43]

A trial of Integra Template versus standard care in DFU reported a higher rate of complete wound closure at 12 and 16 weeks for Integra Template compared with outcomes reported here.[29] However, the inclusion criteria were less stringent in selecting non-healing DFU, requiring only 30% wound closure at 2-weeks, run-in period[29] compared with 50% in the trials reported here. A trial of placental membrane in DFU[30]

used only a 1-week, run-in period and no requirement for a threshold healing rate for randomisation, reporting significantly better healing in the placental membrane cohort than the standard care cohort, an outcome that exceeds that reported here for ESWT. The lack of selection of non-healing DFU in the placental membrane study may underpin the better healing rates achieved by increasing the responsiveness to care of the patient population. Clinical outcomes may have been associated with increases in growth factor expression, which were statistically significantly greater than those with HBOT.[44] Taken together, these findings for ESWT devices strongly suggest that their use in DFU would be clinically beneficial.

Limitations

The inclusion and exclusion criteria for the studies reported here selected a specific population of patients. The outcomes in patients who were not eligible for enrolment for randomisation are therefore unknown, including DFU patients under 18 years of age, patients with HbA1c ≥12%, DFUs larger than 16cm^2, DFUs classified under the University of Texas system in groups other than 1A and 2A, DFUs with significant ischaemia, and DFUs that are not classified as hard-to-heal following standard of care.

The run-in period required the patient to self-manage for 2 weeks and record the care in a diary. Patients are known to report their own behaviours and care inaccurately, and this may have happened in the run-in period in these studies leading to inaccurate classification of a DFU as non-responsive when in fact it may have been a responder. A reduction in wound size of >50% in 4 weeks is an indicator of healing potential.[45] The run-in criterion that the wound cannot reduce in area greater than 50% is unusually high compared with similar studies that used a maximum reduction area of 30%.[29] Allowing subjects whose wounds reduced in size between 30% and 50% to remain in the study may have served as a confounder. The protocol detailed the standard of care to be used in the studies.

Although the two studies were conducted ~8 and ~4 years before this report, the authors consider that the standard of care remains consistent with current practice. There was variation permitted in the specific products allowed, for example dressings. This may be mitigated by the reported outcomes of meta-analyses of dressings that have found no compelling effect of dressings on healing outcomes. Offloading was also used according to local practice. Adherence with removable offloading is variable and may have affected the outcome. However, this should have been balanced by the randomisation process.

Conclusion

The studies presented here support the use of the active therapy as an adjunct to standard care in patients with HbA1c <12%, uninfected, non-ischaemic, hard-to-heal DFUs, University of Texas Ulcer grade 1 or 2, stage A, no larger than 16cm^2. The outcomes compare favourably with those using negative pressure wound therapy (NPWT) and HBOT.[43, 46] The multicentre design supports the use of the active therapy across multiple settings including specialist centres, hospitals and clinics. The active therapy is recommended to manage DFUs that do not reduce by >50% following treatment for 4 weeks with standard care. The extent of healing at 4 weeks is generally taken to be a marker for the likelihood of future healing potential in DFUs.[45–50] The increased wound closure rates suggest that the active therapy may reduce the risk of infection and/or amputation. The reduced rate of increase in wound size may suggest that the active therapy is associated with stabilising the wound.

Despite the pre-existing findings from clinical and laboratory studies on the effects of the active therapy being used to support the increased dosing regimen in study 2, and the increase in dosing from 4 to 8 active treatments per patient in study 2, the clinical outcomes did not match expectations. A smaller proportion of patients in the active therapy group achieved complete wound closure at 24 weeks compared with study 1 (35.4% versus 39.3%) whereas complete closure in the sham control groups was the same in both studies (26.2% versus 26.3%). This difference may be explained by small differences (smokers, target ulcer size, HbA1c) in the patient characteristics or natural variation. However, these differences were not deemed to be material following analysis to justify pooling datasets. The lack of apparent effect of the increased dose may be explained by the use of the 8 doses in study 2 irrespective of wound size. Unpublished investigations conducted with the active therapy using a larger number of shocks and treatments per wound since the completion of study 2 suggest that clinical outcomes may be improved when dosing is proportional to the size of the wound. Early signs suggest that larger wounds respond better to higher doses. Further studies are required to confirm this. **JWC**

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