Focused shockwave therapy in diabetic foot ulcers: secondary endpoints of two multicentre randomised controlled trials

Objective: The objective of this paper is to present the secondary safety and efficacy outcomes from two studies of focused extracorporeal shockwave therapy (ESWT) used adjunctively with standard care in the treatment of neuropathic diabetic foot ulcers (DFU) (1A or 2A on the University of Texas grading scheme), compared with sham treatment and standard care.

Method: We carried out two multicentre, multinational, randomised, sham-controlled, double-blinded, phase III clinical studies using standard care with adjunctive focused ESWT compared with sham treatment and standard care in patients with a DFU. DFUs that did not reduce in volume by at least 50% over two weeks' standard treatment were included. DFUs were randomised and managed with standard care and focused ESWT (pulsed acoustic cellular expression; dermaPACE System, SANUWAVE Health, Inc.) active therapy, or with standard care and sham treatment, four times over a two-week treatment phase in study 1 and up to eight times over 12 weeks in study 2. Standard care continued in both studies throughout the 12-week treatment phase. Secondary outcomes were indicators of wound closure and progression, pain, infection, amputation and recurrence, and device reliability. Efficacy-related secondary endpoints were measured at 12, 20 and 24 weeks. The studies were analysed separately and following statistical comparison to justify the method, as a pooled data set.

Results: Wound area reduction (48.6% versus 10.7%, p=0.015, intention to treat (ITT) population with last observation carried forward (LOCF)) and perimeter reduction (46.4% versus 25.0%, p=0.022, ITT population with LOCF) were significantly greater in the active therapy group compared with the sham-treated group, respectively. The difference in time to wound closure in the pooled ITT population was significantly in favour of the active therapy group (84 days versus 112 days for 25% of subjects to reach wound closure in the active and sham-treated groups, respectively; p=0.0346). The proportion of subjects who achieved wound area reduction (WAR) from baseline at week 12 of ≥90% was significantly higher in the active therapy group. The incidence and nature of infection were consistent with previously published studies, and pain was not increased in the active therapy group. Amputation was insignificantly higher in the sham-treated group and recurrence did not differ. The ESWT device was found to be reliable.

Conclusion: The outcomes for the primary and secondary endpoints from these studies show that ESWT administered adjunctively with standard care is an effective advanced therapy for neuropathic DFUs (grade 1A and 2A) that do not respond to two weeks' standard care alone by reducing wound volume by at least 50%.

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chronic wound • diabetic foot ulcer • extracorporeal shockwave therapy • PACE technology • randomised controlled trial

Diabetic foot ulcers (DFU) arise in patients as a result of ischaemia, neuropathy or a combination of the two.[1] Peripheral neuropathy leads to loss of protective sensation and deformity in the foot, and patients so affected are more likely to ulcerate. Repeat undetected insult stimulates chronically disturbed inflammation and tissue destruction.[1–5] Recalcitrant healing in neuropathic DFUs managed with standard care, including glycaemic control, debridement, infection management and offloading, is attributable to the underlying pathophysiology.

New therapies that target the underlying biological disturbances in DFUs are required to tip the balance in favour of healing. With the projected demographic changes, the clinical and economic burden is set to increase,[6] placing greater emphasis on the implementation of clinically-proven effective therapies.

Although a number of advanced technologies are available to enhance healing in DFUs, the need for effective wound closure for the majority of patients remains unsatisfied. Shockwave therapy is a non-invasive modality to reinvigorate the chronic wound by activating the body's healing mechanism. Shockwave energy increases angiogenesis and growth factor production, and decreases inflammation within the wound bed and surrounding tissues.[7] Research has improved our understanding of the tissue repair mechanisms of shockwave energy at the tissue and cellular levels,[8–10] and

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with clinical findings these understandings have justified CE marking in Europe and FDA clearance in the US for extracorporeal shockwave therapy (ESWT) for wound healing.

Two prospective, randomised, controlled trials—the primary endpoints for which were described previously—[10] were conducted to investigate the safety and effectiveness of a focused ESWT device in combination with standard treatment for the treatment of foot ulcers in patients with diabetes. The second study was designed via Bayesian analysis based on the outcome of the first study, which was an informative prior. Similar protocols were followed in both studies; the key difference was the greater number of shockwave therapies used per DFU. The previous paper from these studies reported a significant difference in favour of ESWT as an adjunct to standard care compared with standard care and sham ESWT for the primary efficacy endpoint of complete wound closure by 24 weeks.[10] Safety endpoints were also reported. The current paper reports on the secondary outcomes from the same studies.

Method

Study design and ethics

The methods used in the two studies were described fully in a previous publication.[10] Briefly, the studies, which ran sequentially, were prospective, randomised, double-blind, parallel-group, sham-controlled, interventional, and multicentre, with 24 weeks follow-up in DFUs. Active ESWT therapy (dermaPACE System, SANWUAVE Health, Inc., Suwanee GA, US) used adjunctively with standard care was compared with sham treatment and standard care. Both studies were approved by ethics, authorised under IDE G070103 and complied with 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. Written and informed patient consent was obtained for both studies.

Setting, study locations participants and randomisation

Study 1 was run in 21 sites and study 2 in 18 sites in the US, Germany and the UK (study 1) and the US and Canada (study 2) in hospital or university research facilities, Veterans Administration Hospitals and wound clinics, centres, and physicians' offices. Inclusion and exclusion criteria were described in full previously.[10] Enrolled subjects had non-ischaemic, grade 1 or 2, stage A (University of Texas Diabetic Wound Classification) DFUs of more than 30 days' duration and between 1–16cm^2 surface area. Subjects were randomised to active therapy adjunctive to standard care or standard care with sham ESWT treatment arms after a 2-week, run-in period if the index ulcer had closed by <50%. Subjects were followed up for 24 weeks.

Subjects were allocated to treatment groups by sealed envelopes prepared before the study. Randomisation was managed as described previously.[10] All patients randomised and who received at least one active or sham shockwave therapy were considered part of the intention to treat (ITT) population. Randomised subjects who followed the protocols without significant deviation formed the per-protocol (PP) population, and 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. The clinician who delivered treatments was not blinded.

Interventions

All randomised subjects received standard care with adjunctive active therapy or sham ESWT administered by an unblinded operator in the absence of the principal investigator (PI). The patient flow for both studies was as described previously.[10] Patients in the active therapy arm in each study received shockwave therapy.[10]

Sample size

The enrolment target for study 1 and study 2 was 200 subjects randomised 1:1 into the two treatment groups, accounting for a dropout rate of 25% in study 1 and 18% in study 2. The sample size for both studies was determined based on the primary efficacy endpoint of wound healing.[20]

Poolability of data sets

The justification that supported analysis of pooled data from the two studies was as described previously.[10] Briefly, heterogeneity of treatment group differences between studies was consistent with sampling variability and baseline characteristics were comparable between studies. The data sets were therefore pooled. Results from both studies are presented individually and as a pooled data set.

Outcomes

The prospectively-defined secondary efficacy endpoints for all subjects who received at least one episode of treatment were:

- Change in target ulcer (TU) area, volume, depth and perimeter
- Time to wound closure
- Rate of wound closure
- Mean wound area reduction
- Percentage of patients with an increase in wound area
- Frequency of recurrence and amputation at 24 weeks
- Frequency of ESWT malfunctions.

Secondary endpoints related to healing and wound closure were determined as for the primary endpoint by photography and wound tracings[10] for study 1 and the Aranz SilhouetteStar (ARANZ Medical Ltd., Christchurch, New Zealand) in study 2. Wound depth was determined using the VISITRAK depth probe (Smith & Nephew) in study 1 and the Aranz SilhouetteStar device in study 2.

The prospectively-defined secondary safety endpoints were rate of treatment emergent AEs, treatment emergent

serious AEs (SAEs) and device-related treatment emergent AEs at 24 weeks; infection occurrence diagnosed by the blinded evaluating investigators; incidence of amputation and recurrence; changes in baseline values in wound pain in study 1 and procedural pain and application site pain in study 2.

TU pain was assessed throughout the study using a visual analog scale (VAS) with a 10cm line, where 0cm represented no pain and 10cm represented worst pain. The VAS was used to assess TU pain but not neuropathic pain, and was completed at all study visits for all subjects. Pain was assessed prior to TU debridement if debridement was performed. During the application period (visits 2–5), the VAS was completed both pre- and post-device application.

Statistical methods

Outcomes in the active therapy and sham-controlled groups were compared and differences were declared significant when $\alpha \leq 0.05$. Two-tailed tests were used for all statistical testing. The distribution of continuous variables was summarised using means, standard deviations (SD), medians, minima and maxima, and the number of observations with non-missing data. Statistics were calculated with and without last observation carried forward (LOCF) for continuous variables. Categorical variables were summarised using frequency counts. Life table analysis was used for time to wound closure. Statistical trend analyses were not conducted.

Results

Study participants

No deviations from the pre-specified plan and protocol were reported. Secondary endpoints for the subjects reported here are derived from the same patient population as for the primary endpoints reported previously.[10] In brief, in study 1, a total of 293 patients were screened. Of those, 206 were randomised and underwent at least one application of active or sham therapy. The efficacy evaluable (EE) population comprised 194 subjects. A total of 42 subjects withdrew during the treatment phase; 19 from the active therapy group and 23 from the sham-treated group. There were 15 who withdrew during the post-treatment phase, 10 from the active therapy group and 5 from the sham-treated group. There were no significant differences in the characteristics of the subjects in active and sham groups except for mean age of subjects, 60.4±10.4 years versus 56.2±9.4 years, respectively; (p=0.005) and duration of diabetes subjects (18.0±10.0 years versus 17.7±11.1 years, respectively; p=0.005).

In study 2, 261 patients were screened and 130 randomised. Of these, 25 withdrew consent during the treatment phase of the study (15 from the active therapy group and 10 from the sham-treated group). A total of 12 subjects withdrew during the post-treatment phase (7 and 5 from the two groups, respectively). Baseline characteristics for the two groups did not differ significantly.

The pooled patient population comprised 336 subjects, 172 in the active therapy group and 164 in the sham-treated group. The active therapy group was statistically older than the sham-treated group by approximately three years. There were no other statistically significant differences.

Outcomes: wound closure-related secondary endpoints

At both 12 and 24 weeks the proportion of DFUs that increased in size was greater in the sham-treated cohort than in the active therapy cohort, suggesting that management with ESWT avoided a proportion of cases of wound size increase. This parameter was reported previously.[10]

Ulcer area, volume, depth and perimeter

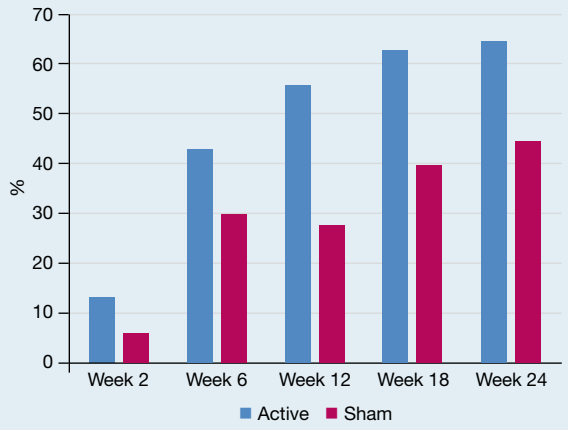
In study 1 the average wound area reduction at week 12 was significantly greater in subjects managed in the active therapy group compared with the sham-treated group in both the ITT (p=0.015) and EE (p=0.022) populations

Table 1. Wound area change from baseline at 12 weeks. ITT/MITT and EE population, study 1

Treatment group	Total number of paired subjects at 12 weeks	Baseline average wound area (cm^2)	Average wound area at 12 weeks (cm^2)	Average wound area reduction (cm^2)	p-value
ESWT (ITT/MITT with LOCF)	107	3.5	1.8	–1.7 (48.6%)	0.015
Sham–control (ITT/MITT with LOCF)	99	2.8	2.6	–0.3 (10.7%)	
ESWT (ITT/MITT without LOCF)	85	3.5	1.6	–1.9 (54.3%)	0.004
Sham–control (ITT/MITT without LOCF)	71	2.9	2.7	–0.2 (6.9%)	
ESWT (EE with LOCF)	101	3.5	1.7	–1.8 (51.4%)	0.022
Sham–control (EE with LOCF)	93	2.9	2.6	–0.3 (10.3%)	
ESWT (EE without LOCF)	71	3.6	1.5	–2.1 (58.3%)	0.096
Sham–control (EE without LOCF)	62	2.8	2.2	–0.5 (17.9%)	

ESWT—extracorporeal shockwave therapy; EE—efficacy evaluable; LOCF—last observation carried forward; ITT—intention to treat; MITT—modified intention to treat

Fig 1. Mean wound area reduction from baseline (cm^2)



with LOCF (Table 1). The difference in the ITT population was also significant without LOCF (p=0.004) but not in the EE population (p=0.096). In the EE population without LOCF, although not statistically significant, the numerical difference in wound area trended in favour of the active therapy group. At 24 weeks all wound area differences between treatment groups in both the ITT and EE populations trended in favour of the active therapy group, although the difference was significant only for the ITT population without LOCF. Fig 1 shows the wound area reduction (WAR; cm^2) over 24 weeks for study 1. At every time point from week six to week 24, WAR was statistically greater in the active therapy group. The difference in the proportion of DFUs either fully closed or at least 90% closed at 12 weeks was statistically significant at 47.7% in the active therapy group and 31.3% in the sham-treated group (p=0.016).

Consistent with the change in wound area, the difference in the change in wound perimeter between the two treatment groups was significant for the ITT population with (p=0.022) and without (p=0.011) LOCF and in the EE population with (p=0.024) but not without LOCF (p=0.23; Table 2). Wound perimeter differences between the treatment groups at 24 weeks were not significant although absolute differences trended in favour of active therapy (data not shown). No significant differences between the active and sham-treated groups with respect to wound volume or depth were observed at either 12 or 24 weeks, although differences between absolute values trended in favour of active therapy (data not shown).

In study 2, no significant differences were observed in any of the wound closure-related endpoints for the ITT population over the 24 weeks of the study. However absolute WAR, wound perimeter reduction, mean depth reduction and wound volume reduction outcomes trended in favour of the active therapy group at 24 weeks. (data not presented). The outcomes for the EE population were not analysed for study 2. Furthermore, the secondary endpoints related to wound closure in the pooled data set described above were not analysed.

Complete wound closure and wound area reduction after run-in period

The amount of wound closure at the end of the 2-week, run-in period was analysed for the ITT population, stratified by closure ≤30% and >30% in each study and the pooled data set. The relationship between the DFUs that closed completely after randomisation and the amount of wound reduction at randomisation stratified by reduction ≤30% and >30% for studies 1 and 2 and for the pooled data was analysed (Table 3). The distribution of patients in the active therapy and sham-treated arms was broadly balanced and comparable. In all cases those that reduced in size ≤30% outnumbered those that reduced >30%. The numbers of patients who had reduced in size >30% at randomisation was low in comparison with those that reduced ≤30%. In the patients who achieved 100% closure, in both studies, a greater proportion of the population with WAR >30% at

Table 2. Wound perimeter change from baseline at 12 weeks. ITT/MITT and EE population, study 1

Treatment	Total number of paired subjects at 12 weeks	Baseline average wound perimeter (cm)	Average wound perimeter at 12 weeks (cm)	Average wound perimeter reduction (cm)	p-value
ESWT (ITT/MITT with LOCF)	107	6.9	3.8	–3.2 (46.4%)	0.022
Sham-control (ITT/MITT with LOCF)	99	6.4	4.7	–1.6 (25.0%)	
ESWT (ITT/MITT without LOCF)	85	7.1	3.4	–3.7 (52.1%)	0.011
Sham-control (ITT/MITT without LOCF)	71	6.6	4.7	–1.9 (28.8%)	
ESWT (EE with LOCF)	101	7.0	3.8	–3.2 (45.7%)	0.024
Sham-control (EE with LOCF)	93	6.5	4.8	–1.7 (26.2%)	
ESWT (EE without LOCF)	71	7.3	3.3	–4.0 (54.8%)	0.230
Sham-ontrol (EE without LOCF)	62	6.6	4.3	–2.3 (34.9%)	

ESWT—extracorporeal shockwave therapy; EE—efficacy evaluable; LOCF—last observation carried forward; ITT—intention to treat; MITT—modified intention to treat

Table 3. Relationship between wound closure at randomisation and complete wound closure

		Patients achieving <30% and >30% closure at randomisation ITT—full population		Patients achieving 100% closure stratified by percent closure at randomisation	
Study	**Cohort**	**WAR after 2-week run-in**		**WAR after 2-week run-in**	
		< 30 %	>30 %	< 30 %	>30 %
S1	ESWT	87 (81.3%, n=107)	20 (18.7%, n=107)	33 (37.9%, n=87)	9 (45%, n=20)
S1	Sham-control	83 (83.8%, n=99)	16 (16.2%, n=99)	19 (22.9%, n=83)	7 (43.8%, n=16)
Significance				p=0.045	
S2	ESWT	51 (78.5%, n=65)	14 (21.5%, n=65)	16 (31.4%, n=51)	7 (50%, n=14)
S2	Sham-control	46 (70.8%, n=65)	19 (29.2%, n=65)	9 (19.7%, n=46)	8 (42.1%, n=19)
Significance				p=0.245	
Combined	ESWT	138 (80.2%, n=172)	34 (19.8%, n=172)	49 (35.5%, n=138)	16 (47.1%, n=34)
Combined	Sham-control	129 (78.7%, n=164)	35 (21.3%, n=164)	28 (21.7%, n=129)	15 (42.9%, n=35)
Significance				p=0.015	

ESWT—extracorporeal shockwave therapy; ITT—intention to treat; Number—patients meeting the stratified subset criteria; n—total population in a specified subset; WAR—wound area reduction. Percentages were calculated as ((Number/n) x 100); significance was calculated using Fisher's Exact test

randomisation achieved complete closure in both the active and sham-treated groups compared with patients with ≤30% WAR at randomisation. For those whose WAR at randomisation was ≤30% and who achieved complete wound closure during the study (in study 1 and the pooled population) the difference between the two treatment arms was significant (p=0.045 and p=0.015 respectively; Fisher's Exact test). The difference was not significant in study 2.

Time to wound closure

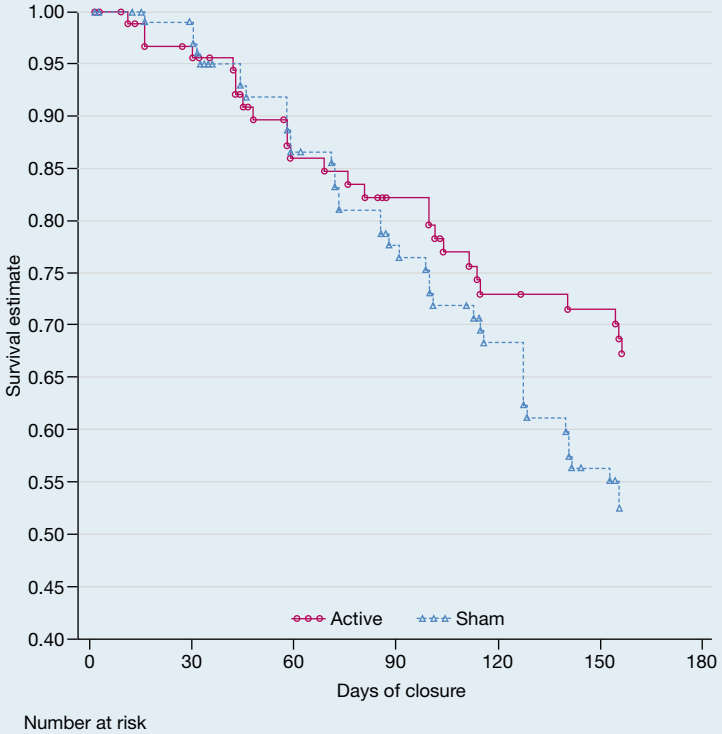
Fig 2 shows the Kaplan-Meier estimates for time to wound closure over 24 weeks' follow-up of the modified ITT (MITT) population—this is, the group in the ITT population who received at least one ESWT or sham treatment and provided at least one post-randomisation efficacy evaluation—in study 1. The difference in time to wound closure between the active therapy and sham-treated groups was not significant (p=0.102). However, after approximately 70 days, the healing trend was in favour of the active therapy group.

Fig 3 shows the Kaplan-Meier estimates for time to wound closure over 24 weeks' follow-up of the MITT population in study 2. The difference in time to wound closure between the active therapy and sham-treated groups was not significant (p=0.1878). However, after approximately 28 days, the healing trend favoured the active therapy group.

Pooled data

Kaplan-Meier estimates for time to wound closure over 24 weeks' follow-up of the ITT population in the pooled data sets from studies 1 and 2 were conducted (Fig 4). The difference in time to wound closure between the active therapy and sham-treated groups was statistically significantly in favour of the active therapy group (p=0.0346). Approximately 25% of subjects undergoing active therapy reached wound closure, according to the

Fig 2. Kaplan-Meier curve of complete wound closure for the intention to treat (ITT) population in study 1

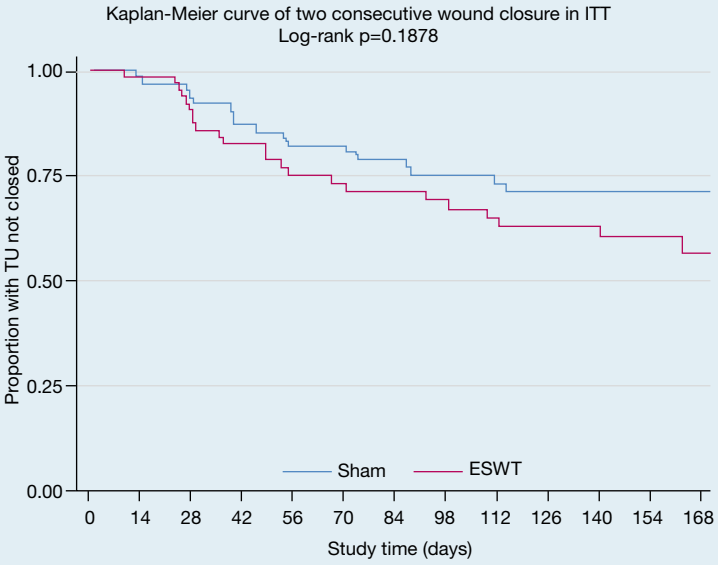


Number at risk

Sham-control	99	93	90	86	83	81	80	76	75	73	72	72	72
ESWT	107	105	104	97	96	92	89	88	87	85	85	82	79

ESWT—extracorporeal shockwave therapy

Fig 3. Kaplan-Meier curve of complete wound closure for the intention to treat (ITT) population in study 2

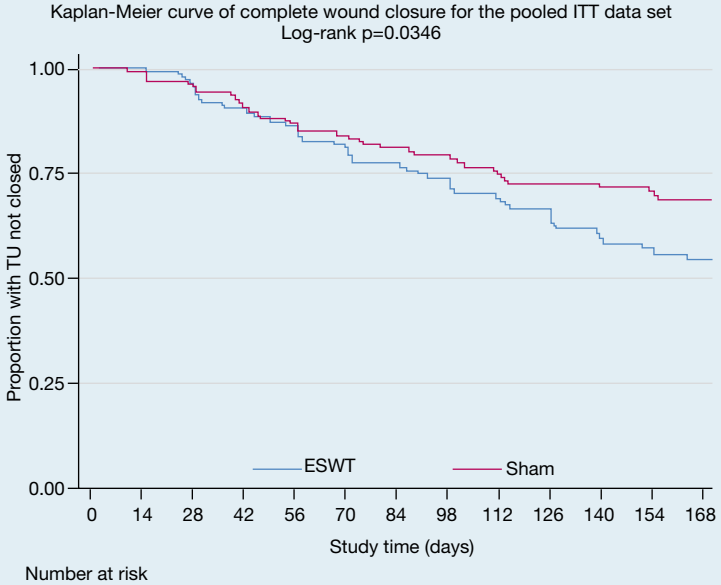


Number at risk

Sham	65	59	57	52	49	48	45	40	38	35	34	31	18
ESWT	65	61	57	48	40	39	37	32	30	28	28	25	9

ESWT—extracorporeal shockwave therapy; TU—target ulcer

Fig 4. Kaplan-Meier curve of complete wound closure for the pooled intention to reat (ITT) data set



Number at risk

Sham	164	152	147	138	132	129	125	116	113	108	106	103	90
ESWT	172	166	161	145	136	131	126	120	117	113	113	107	81

ESWT—extracorporeal shockwave therapy; TU—target ulcer

study definition by day 84 (week 12). By comparison, the same percentage in the control group (25%) reached wound closure by day 112 (week 16), a difference of 28 days in favour of active therapy. These data indicate that, in addition to the proportion of subjects reaching wound closure being higher in the subjects undergoing active therapy, subjects also reached wound closure earlier when undergoing active therapy.

Rate of wound closure

The proportion of subjects in the ITT population who achieved WAR from baseline at week 12 of ≥50% and ≥90% was analysed. In study 1 the difference in the proportion of DFUs that achieved at least 90% WAR in the active therapy group was significantly higher from week 12 to week 24 than in the sham-treated group (p=0.0064 to 0.026). There was no significant difference in WAR between the active therapy and sham-treated DFUs in study 2. WAR of ≥50% in studies 1 and 2 was not analysed separately.

The difference between the active therapy and sham-treated groups was not significant for WAR of ≥50% (Fig 5) but WAR was greater in the active therapy group. The proportion of wounds that achieved ≥90% WAR between weeks 14 and 22 was significantly greater in the active therapy group (Fig 6).

Frequency of ESWT malfunctions

Malfunctions with the ESWT device were reported 12 times in nine centres in study 1. The number of treatments delivered using active therapy in study 1 was 416, giving a frequency of malfunctions of 2.88% over 24 weeks of the studies. There was no effect on patients for 10 of the malfunctions; malfunctions were detected by the device, which was not then used on patients. In two instances, malfunction resulted in under-treatment of the subject because the number of pulses delivered was lower than the specified 500 per treatment. In these instances there was no safety issue for the subjects involved. There were no device malfunctions in study 2. In the pooled population malfunctions occurred in 1.4% (12/846) of treatments.

Infection

Table 4 presents the frequency of infection-related outcomes for studies 1 and 2 and for the pooled data set. Infection was reported at least once in 28% of active subjects and 25.3% of sham-treated subjects in study 1. The corresponding figures in study 2 were 36.9% and 35.4% respectively, and in the pooled data set, 31.4% and 29.3% respectively. The specified categories of infection reported most often in both treatment arms, at similar levels and in descending order of frequency, were application site infection or cellulitis, cellulitis and osteomyelitis. Osteomyelitis was reported more frequently in the active group than the sham-treated group in study 2 (13.8% versus 7.7%). Patients with diabetes are at higher risk of infection than non-diabetic patients. Infection is a common event in DFUs[11–13] and these study outcomes are consistent with this.

The general category 'other infections' was also reported frequently (Table 4). These infections, which were not associated with the DFU, were reported more

frequently for the active therapy group in both studies and the pooled data set. The 'other infections' category included urinary tract infection, nasopharyngitis, non-TU infection, pneumonia, gastroenteritis and other less-frequent infections.

Amputation and recurrence

There was no difference in the partial amputation rate at 24 weeks in the active and sham treatment groups (2.3%, 4/172 versus 3.0%, 5/164 respectively; p=0.745). No significant difference was noted in recurrence rates at 24 weeks in the active and sham treatment groups (7.7%, 5/65 versus 11.6%, 5/43 respectively; p=0.49).

Pain

In the ITT population in study 1 there was no significant change in TU pain from baseline for the active and sham-control groups and no significant difference in TU pain between the active therapy and sham-control groups throughout the study. Although there was no significant difference in pain between the active therapy and sham-control groups, 70% of the subjects in the active group showed a 30% decrease in pain at visit 16. At visit 17, 76% of the active therapy subjects showed a 30% decrease in pain, a difference that trended towards significance (p=0.053). In study 2 procedural and application site pain were assessed. Procedural pain was reported in 1.2% (2/65) in the active therapy cohort and in no subjects in the sham-treated cohort after 24 weeks' follow-up. Application site pain was not reported by subjects in the active therapy cohort and by 1.8% (3/65) in the sham-treated cohort (not significant).

Discussion

We previously reported that the proportion of DFUs that closed during the course of the 24-week follow-up period when treated with active therapy and standard care was significantly higher than for DFUs treated with sham control and standard care. The endpoints reported previously demonstrated the safety of ESWT.[10] There were no statistically significant differences in the rate of safety-related endpoints observed in the active therapy and sham-controlled cohorts after 24 weeks' follow-up for the pooled data set, except in the case of serious AEs which occurred more frequently in the sham group (43.3%, 71/164) than in the active therapy group. Treatment-emergent adverse events were infrequent in both cohorts.

The protocols for those two studies detailed secondary endpoints to be measured, including additional efficacy-related and safety endpoints, and device malfunction endpoints. The efficacy-related secondary endpoints reported here are consistent with the primary endpoints.[10] For all endpoints wound closure outcomes numerically favoured the active therapy group. The differences in reduction in wound perimeter for the active therapy and sham groups were not significant at 24 weeks. Wound depth and volume outcomes were not significantly different between the two groups, but at 12 and 24 weeks the changes favoured the active therapy. The proportion of subjects who reached ≥90% WAR significantly favoured the active therapy group, and time to wound closure was faster in the active therapy group although not significantly. A large proportion of wounds achieved ≥50% WAR at two weeks in the active therapy group, and although the difference between this outcome and that for the sham-treated group was not significant, WAR was less in the sham-treated group.

These studies randomised subjects in whom the target DFU had not closed by at least 50% after two weeks of standard care. Randomisation appears to be followed by increased healing in both treatment arms, suggesting that a continued high standard of care activated healing. However, the effect of active therapy was incremental (Fig 5), lending further support to the proposition that ESWT stimulates healing. Time to healing did not differ significantly but was shorter in the active therapy group than in sham-treated wounds. In study 2 the differences in wound healing endpoints did not reach statistical significance, but DFUs in the active therapy group healed faster than sham-treated DFUs did. Time to wound closure in the pooled data set was significantly shorter in the active therapy group.

There was a difference in initial DFU size between the

Fig 5. Proportion of subjects achieving ≥50% wound area reduction

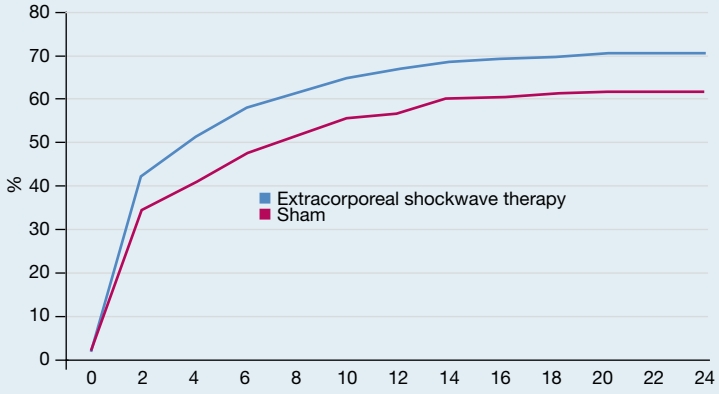


Fig 6. Percent subjects achieving 90% wound area reduction

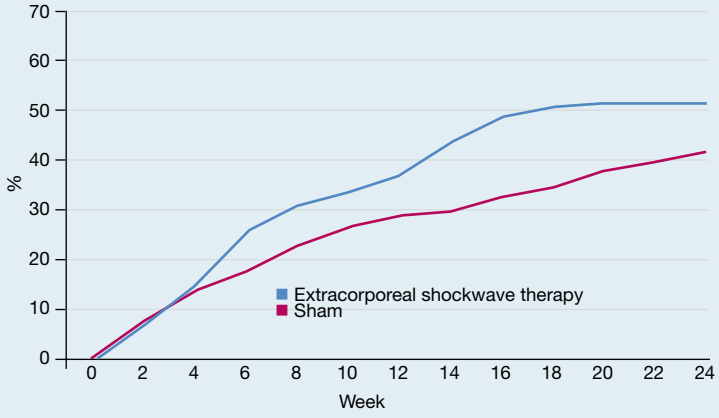


Table 4. Incidence of infection in study 1 and study 2, and the pooled data set

		Study 1		Study 2		Pooled	
Safety endpoints		**ESWT**	**Control**	**ESWT**	**Control**	**ESWT**	**Control**
Identified safety risk	**Related adverse event**	**(N=107) n (%)**	**(N=99) n (%)**	**(N=65) n (%)**	**(N=65) n (%)**	**(N=172) n (%)**	**(N=164) n (%)**
Infection	Bacterial infection	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0%)
	Infected skin ulcer	0 (0.0%)	0 (0.0%)	5 (7.7%)	6 (9.2%)	5 (2.9%)	6 (3.7%)
	Localised infection	0 (0.0%)	0 (0%)	3 (4.6%)	2 (3.1%)	3 (1.7%)	2(1.2%)
	Osteomyelitis	5(4.7%)	5 (5.1%)	9 (13.8%)	5 (7.7%)	14 (8.1%)	10 (6.1%)
	Paronychia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0%)	1 (0.6%)
	Any abscess bacterial	0 (0.0%)	2 (2.0%)	0 (0.0%)	3 (4.6%)	0 (0%)	5 (3.0%)
	Cellulitis	10 (9.4%)	7 (7.0%)	5 (7.7%)	5 (7.7%)	15 (8.7%)	12 (7.3%)
	Application site infection/cellulitis	14 (13.1%)	15 (15.1%)	5 (7.7%)	5 (7.7%)	19 (11.0%)	20 (12.2%)
	Any wound infection	2 (1.9%)	4 (4.04%)	1 (1.5%)	1 (1.5%)	3 (1.7%)	5 (3.0%)
	Sepsis	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.6%)	0 (0%)
	Septic shock	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	1 (0.6%)	0 (0%)
	Tinea pedis	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0%)	1 (0.6%)
	Gangrene	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0%)	1 (0.6%)
	Other	16 (15%)	4 (4.0%)	5 (7.7%)	3 (4.6%)	21 (12.2%)	7 (4.3%)
		Study 1		**Study 2**		**Pooled**	
Safety endpoints		**ESWT**	**Control**	**ESWT**	**Control**	**ESWT**	**Control**
	Percentage of subjects with at least one infection	30 (28%)	25 (25.3%)	24 (36.9%)	23 (35.4%)	54 (31.4%)	48 (29.3%)

Table 5. Relationship between number of debridement procedures and incidence of complete healing at 12 and 24 weeks

	12-week closure rate, pooled data					**24-week closure rate, pooled data**				
	ESWT		**Control**			**ESWT**		**Control**		
No. debridement procedures	**N**	**n (%)**	**N**	**n (%)**	**p-value (Fisher's Exact test)**	**N**	**n (%)**	**N**	**n (%)**	**p-value (Fisher's Exact test)**
< 4	33	13 (39.4%)	32	9 (28.1%)	0.434	33	14 (42.4%)	32	10 (31.3%)	0.443
>4	139	26 (18.7%)	132	19 (14.4%)	0.415	139	51 (36.7%)	132	33 (25%)	0.048

N—total number of patients in the subset; n—number of patients with complete closure

active therapy and sham-treated groups in these studies. Patients in the active therapy group had wounds 25% larger. There is a relationship between wound size and time to healing where larger DFUs take longer to heal than smaller DFUs.[14] Despite this, ESWT led to a higher proportion of completely healed DFUs and wound area reduction in these studies. Furthermore, the studies randomised predominantly hard-to-heal DFUs as indicated by the distribution of patients whose wounds had reduced in size by <30% and >30% during the run-in period. The number of patients in the two treatment groups whose WAR was <30% at randomisation was comparable, as were the numbers whose WAR was >30%.

For the hard-to-heal subset defined by WAR at randomisation, the difference in complete closure between the active therapy and sham-treated groups was significant in study 1 (p=0.045) and in the pooled population (p=0.015), but not in study 2. Where WAR was >30% at randomisation, the differences between treatment groups for patients who achieved complete

closure were not significant. This analysis further supports the proposition that ESWT delivered with the test device accelerates healing in hard-to-heal DFUs.

Infection is a major concern which delays DFU healing,[15] increases morbidity, precedes amputation in many cases and is costly to manage.[12] Approximately 50% of DFUs will become infected or are clinically infected at presentation.[13,16–18] The protocols used for the two studies reported here enrolled subjects with grade 1A or 2A defined as uninfected superficial ulcers without involvement of underlying structures or ischaemia. Subjects with cellulitis in the wound or its surrounding area were specifically excluded. Infections reported in the ITT population therefore arose during the course of the studies, a finding consistent with the literature.[13,15–17] The frequencies of different categories of infection between the two groups were low and the infections reported were characteristic of patients with DFUs. The only infection category which differed between the groups was osteomyelitis, which was higher in the active therapy group than the sham-treated group in study 2; however, in the pooled data set, there was only a small non-significant difference between the groups. The frequency of osteomyelitis is similar to that reported in other studies in DFU.[19] In these studies X-ray was used to screen for osteomyelitis, which is less able than other diagnostic methods to detect early changes associated with osteomyelitis, and which may subsequently develop from undiagnosed foci of infection. It is likely, therefore, that the four patients in these studies who were diagnosed with osteomyelitis within two weeks of randomisation had unrecognised foci of early osteomyelitis when randomised. In our study three cases of osteomyelitis developed at least 12 weeks after the last ESWT treatment. The effects of ESWT treatment subside after two weeks;[20] it is therefore unlikely that these late-appearing cases were device-related.

The proportion of subjects who experienced at least one infection varied very little between treatment groups in the two studies between 25.3–36.9%. These are consistent with infection frequency reported in other DFU papers.[21,22] In these studies the device applicator was covered with a sterile single-use sleeve, and sterile gel was applied to the covered applicator for each intervention. These were discarded after each treatment in order to minimise the possibility that use of the device increased the risk of infection. These use patterns and data suggest that ESWT is not associated with additional risk of infection.

The frequency of device malfunctions in these studies was low across both studies, all in study 1 (12 in 336 subjects). Of these, two led to potentially reduced efficacy as a result of fewer pulses of shockwave energy being delivered to the wounds. All other malfunctions were detected by the integrated device monitoring systems, which alerted the investigators to use a different device. In clinical use the integrated monitoring system ensures that a fully functional device is used in routine patient management to optimise the efficacy and effectiveness of the treatment.

The pathophysiology of DFUs is complex, involving chronically-upregulated inflammation caused by repeated trauma to the affected site on the foot. Chronic inflammation in human chronic wounds leads to tissue breakdown by endogenous mechanisms, including overexpressed proteinases and reactive oxygen species (ROS) produced by inflammatory cells that impair healing.[2,3] The biological signalling in chronic wounds[23–25] is thought to be maintained by the repeated inflammatory stimulation.[26] Endothelial cells explanted from DFUs into *in vitro* sponge models of healing demonstrated impaired angiogenesis and expression of ROS, senescence-associated proteins and thrombospondin, an angiogenesis inhibitor.[27]

In order to encourage DFUs to heal, the repeated stimulation must be managed and the optimum environment for healing created. This is the objective of standard care as recommended by a number of organisations. Advanced therapies such as ESWT are indicated for compromised DFUs to enhance healing. The acceleration of healing by ESWT is related to the effects of shockwave therapy on the biological processes. The dose of shockwaves delivered by the device used penetrates tissue to a depth of 10mm, and was selected based on preclinical studies in an ischaemic flap survival model. In the model, flap survival was optimal when the number of shockwaves at the power settings used was between 500 and 2500;[28] 500 was selected as the smallest number of shockwaves that was shown to be effective and least likely to expose the patients to potential harm. These studies have demonstrated efficacy. The precise mechanism for the effectiveness at different numbers of shocks with different devices is currently not known. However, shockwaves delivered by ESWT are associated with rapidly increased tissue perfusion;[29] increased angiogenic and pro-inflammatory responses;[30] fibroblast and leukocyte recruitment[31] and in bone, tendon and bone/tendon interface; increased expression of endothelial nitric oxide synthase; vascular endothelial growth factor, and proliferation cell nuclear antigen.[32] A further mechanism for enhancing healing is its effect on biofilm organisms, in which susceptibility to antimicrobial agents and removal of biofilm may be enhanced by ESWT.[33]

The primary outcomes reported previously[10] were in line with other published findings for ESWT, and our secondary outcomes further strengthen those findings. A small study in 2009 reported 53.3% of DFUs healed completely compared with 33.3% in the comparator group.[34] The present study and the previously-reported primary endpoints[10] demonstrate that ESWT enhances healing in hard-to-heal DFUs. ESWT has also previously shown clinical benefit in a variety of chronic wound indications.[35–38]

Clinical investigations in DFUs with a number of advanced technologies have been reported and generally all show clinical benefit. Such technologies include tissue equivalent or tissue-engineered products, hyperbaric oxygen therapy (HBOT) delivered in hyperbaric chambers, and other modalities.[26,39] The quality of research that

underpins advanced technologies in DFU management is generally poor.[40] A number of randomised controlled trials have shown efficacy in DFU healing for HBOT.[39,41] However, the effectiveness and health economics of HBOT are the subject of debate following cohort studies in a large number of non-ischaemic plantar DFUs.[42–45] The effectiveness of topical oxygen in DFUs remains equivocal; one clinical study on DFUs was too small to draw reliable conclusions[46] and other topical oxygen products are supported by only small studies.[47]

A meta-analysis of low-level laser therapy (LLLT) concluded that LLLT is beneficial in DFUs. LLLT was investigated in a small study in DFUs with similar characteristics to those in this study.[48] Overall, healing rates were lower than those for ESWT in these studies but the study was too small for firm conclusions to be drawn.[48]

LeucoPatch (now known as 3C Patch System; Reapplix), a device that isolates autologous leucocytes, platelets and fibrin from the patient's blood and manufactures a disc to be applied to the wound, is indicated for exuding wounds including DFUs. LeucoPatch was evaluated in hard-to-heal DFUs that did not respond to standard care over four weeks by closing at least 50%. Over 20 weeks' follow-up with LeucoPatch adjunctive to standard care, 34% of 132 DFUs healed compared with 22% in the standard care arm.[49] The proportion of DFUs that closed completely with LeucoPatch is lower than the proportion that healed when managed with ESWT in these studies.

Sucrose octasulfate dressing (Urgo) showed clinical benefit over control dressing in non-ischaemic, grade 1C or 2C (University of Texas Diabetic Wound Classification) DFUs.[50] Healing was reported in 48% of test dressing-treated DFUs and patients were randomised following a screening period if their wounds healed by less than 30%, a more stringent requirement than was used in these study. This is likely to have randomised subjects with more severe DFUs than those in the present studies.

Tissue equivalent products, with or without cells, have been evaluated over a number of years for the management of DFUs. These include Integra Dermal Regeneration Template (Integra),[51] NeoPatch (CryoLife, Inc.),[19] Grafix (Osiris),[52,53] AlloPatch (MTF Biologics Wound Care)[54] and EpiFix (MiMedx).[55] In many of these studies the overall healing rates were higher than those reported here for ESWT. A common randomisation criterion in these studies was healing of less than 20% or 30% following a period of management with standard care of 1 or 2 weeks. A common randomisation criterion in these studies was healing of less than 20% or 30% following a period of management with standard care of 1 or 2 weeks, a more demanding requirement than those for other published studies. The present study is likely to have randomised less severe DFUs, which may have healed better. The subset of DFUs that had reduced in size >30% at randomisation in the ESWT studies reported here may have been easier to heal than those randomised in other published studies. However, the subset of DFUs that reduced in size ≤30% were likely to have been as recalcitrant as those in other studies. This cohort formed the larger subset in the present study.

Both these studies used the same 'dose' of shockwave therapy per treatment episode, although the second study allowed up to eight treatment episodes over the course of the active therapy phase in comparison with the first study that allowed four. The per-treatment dose did not take account of the wound size. There is therefore a gap in understanding the possible effect of per-treatment dose modulated in proportion to wound area, whereby a large wound would receive a greater shockwave therapy dose than a small wound would. Studies currently in progress are designed to address this question.

Limitations

These studies enrolled patients with specified clinical characteristics that represent a subset of the full spectrum of DFUs. The outcomes reported for these two studies should not be extrapolated to DFUs with clinical characteristics more severe than those enrolled.

Subjects were randomised after following a self-administered run-in period of two weeks, recorded in a diary. Self-reporting of behaviours and care is likely to be inaccurate, which may have occurred in this study. The implication is that DFUs enrolled may have been inaccurately identified as non-responsive; some may have been responders. However, subjects were randomised to treatment arms only after the run-in period, and so inaccuracies are likely to have been distributed equally in both treatment arms. A reduction in wound size of >50% in four weeks is an indicator of healing potential.[56] These studies required wounds to reduce <50% to be eligible for randomisation. This is an unusually high area reduction compared with similar studies that used a maximum reduction area of 30%. An ulcer that heals by up to 50% within a defined period has greater healing potential than a wound required to heal by less than 30% in the same period. This implies that DFUs enrolled in these studies may have been more likely to heal. Nevertheless, those managed using standard care and ESWT healed better than those managed with standard care alone.

The standard of care used in the studies, conducted ~8 and ~4 years before the present paper, was specified by the protocol. Study centres were permitted to use certain products according to local practice. However, little evidence exists from meta-analyses that the dressing regimen exerts an influence over healing in DFUs.

The operator who delivered the ESWT therapy was not blinded to the treatment because of the method used to deliver treatment while concurrently ensuring that the patient was blinded to the treatment group to which they had been randomised. This may have led to unconscious bias on the part of the operator. Despite the difference in study dates and the practice variations allowed, we consider that the standard of care for both studies was consistent with current practice.

Offloading was used according to local practice. Removable offloading, adherence with which is variable, was allowed in the studies and may have affected the outcome. However, randomisation should have balanced

the effects of non-adherence. Outcomes achievable with ESWT adjunctive to standard care in which antimicrobial agents are used cannot be extrapolated from these findings.

Conclusion

These studies show that ESWT used adjunctively with standard care leads to more effective closure of wounds with no increase in wound or procedural pain, infection rates consistent with infection in patients with DFUs, and a high level of reliability of the device. These findings imply that, clinically, DFUs with the same characteristics as those enrolled in these studies—and managed with standard care that includes offloading, sharp debridement, saline-moistened gauze primary dressings and adherent or non-adherent secondary dressings supplemented by ESWT therapy—are likely to heal more effectively than those managed with standard care alone. Standard care did not include the use of antimicrobial agents. JWC

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