

# Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomized, double-blind, controlled, multicenter study.

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William J. Ennis, DO; Phil Formann, DPM; Neal Mozen, DPM; Joi Massey, PT; Teresa Conner-Kerr, PhD, PT; Patricio Meneses, PhD; and the MIST Ultrasound Diabetic Foot Study Group

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Diabetes is increasing in the US. An estimated 15% of patients with diabetes will develop a foot ulcer sometime in their life.<sup>1</sup>

This fact, coupled with the myriad of treatment options available, ensures that managing diabetic foot ulcers will continue to be a major clinical problem for years to come. Patients with diabetes are 30 to 40 times more likely to have an amputation compared to non-diabetic patients.<sup>2</sup> Overall, people with diabetes account for 60% of all amputations performed in the US annually.<sup>3</sup> The majority of amputations performed on patients with diabetes occurs from complications secondary to a non-healing foot ulcer.<sup>4</sup> Although no single treatment regimen for diabetic neuropathic foot ulcers has been universally adopted, several aspects of care have been accepted as standard. Identification and aggressive treatment of infection, offloading, debridement, optimal glucose control, providing a moist wound environment, and the use of adjunctive therapies such as cell and/or cytokine therapy are all components of quality care.<sup>5</sup>

Recently within the wound healing community, interest in both diagnostic and therapeutic ultrasound has increased. Ultrasound is defined as a mechanical vibration transmitted at a frequency above the upper limit of human hearing (>20 KHz).<sup>6</sup> High frequency ultrasound (20 to 40 MHz) devices are able to assess the periwound skin, wound bed, and underlying soft tissue components.<sup>7,8</sup> Therapeutic ultrasound has been employed in sports medicine, physical therapy, and physiatry for years but wound care clinicians are only recently becoming aware of its potential benefits for treating recalcitrant wounds.

Information concerning the bio-acoustical effects of ultrasound continues to evolve from animal, plant, human, cellular, and epidemiological studies.<sup>9</sup> One of the main mechanisms of action for ultrasound is achieved through the process of cavitation.<sup>10</sup> Cavitation involves the production and vibration of micron-sized bubbles within the coupling medium and fluids within the tissues. As the bubbles collect and condense, they are compressed before moving on to the next area. The movement and compression of the bubbles can cause changes in the cellular activities of the tissues subjected to ultrasound.<sup>7</sup> Microstreaming (the movement of fluids along the acoustical boundaries as a result of the mechanical pressure wave associated with the ultrasound beam) refers to the development of microscopic cavities created by the formation of micro-bubbles.<sup>7,11</sup> The combination of cavitation and microstreaming, which are more likely to occur with kilohertz ultrasound, provides a mechanical energy capable of altering cell membrane activity.<sup>12</sup>

A new hypothesis known as the *frequency resonance theory* has been proposed, which carries the above concepts to the protein and genetic level.<sup>13</sup> Mechanical energy from an ultrasound wave is absorbed by individual protein molecules, causing conformational changes. Signal-transduction pathways also are stimulated from the ultrasound-generated mechanical energy, which result in a broad range of cellular effects, some of which have direct implications for wound healing. Leukocyte adhesion, growth factor production, collagen production, increased angiogenesis, increased macrophage responsiveness, increased fibrinolysis, and increases in nitric oxide are all examples of ultrasound-induced cellular effects.<sup>14-20</sup>

Historically, megahertz-range ultrasound has been studied in the clinical treatment of periwound tissue. Recently, a shift has occurred toward the use of low-frequency ultrasound in the kilohertz range to achieve vascular vasodilatation and bone healing, as well as with the use of cytotoxic chemicals as sonosensitizers, including the treatment of malignant cells.<sup>21-23</sup> This study was conducted to evaluate the safety and efficacy of a new, novel technology using non-contact, kilohertz-range ultrasound therapy for the treatment of recalcitrant diabetic foot ulcers.

## Materials and Methods

The MIST™ therapy system (Celleration Inc., Eden Prairie, Minn.) is a non-contact ultrasound device. The generator converts voltage to high frequency electrical energy. The electrical energy is transmitted to a piezoelectric transducer (lead zirconate titanate PZT) where it is changed to mechanical energy. The transducer operates at 40 KHz with a distal displacement of 60 to 70 microns. The mechanical energy is transferred to the transducer horn (titanium alloy), which vibrates longitudinally, creating an acoustic pressure output. The maximum transducer intensity at a distal displacement of 65 microns when the leading edge of the applicator tip touches tissue (10 mm) is 1.25W/cm<sup>2</sup>. The treatment intensity within the therapeutic range is 0.1 W/cm<sup>2</sup> to 0.5 W/cm<sup>2</sup>.

**Study design.** This prospective, randomized, double-blinded, controlled, multicenter study was designed to evaluate the safety and efficacy of the ultrasound system compared to a sham device. Of the 23 participating centers, 17 were outpatient wound clinics/private practice settings (which contributed 113 of the initial 133 patients) and six were university hospital clinics (contributing 20 patients). The clinical sites were distributed across the US and one was in Canada. Each facility applied for and received Institutional Review Board (IRB) approval to conduct the study, which was considered a non-significant risk study in accordance with the Code of Federal Regulations 21CFR 812.3. This study designation was

verified by all participating IRBs. An interim data analysis and evaluation by a data safety monitoring board was planned after enrollment of 50 patients.

**Study eligibility.** Patients with diabetes (either Type 1 or Type 2) and a chronic diabetic foot ulcer (>30 days in duration) were eligible to participate if they met the additional inclusion criteria. Eligible patients had to be at least 18 years of age and have a recorded glycosylated hemoglobin value of  $\leq 12$  within 30 days of the study start date. Only Wagner grade 1 or 2 ulcers on the plantar surface of the foot without exposure of bone, muscle, ligaments or tendons were considered.<sup>24</sup> In order to provide a homogeneous population, the investigator had to ensure the patient had no clinical signs of infection and was not taking antibiotics at the time of enrollment. (Ultrasound therapy is not contraindicated for infected wounds but because investigator consensus on the clinical signs and symptoms that would define an infection in this patient population was found to be sufficiently difficult to ascertain, it was decided to exclude infected wounds from the study.) The patients were informed of the three-times-per-week treatment protocol and follow-up schedule in order to increase their chance of successful study completion.

**Screening.** All potential study candidates were screened. An ankle brachial index (ABI) was calculated for each potential participant with a study target value between 0.65 and 1.2. The lower value allowed for exclusion of a significant ischemic component to the wound etiology. If the ABI was  $\geq 1.2$ , a toe/brachial index was obtained because toe-brachial index studies are not affected by falsely elevated values that are often seen in standard ankle-brachial measurements taken from diabetic patients.<sup>25</sup> In order to qualify for study participation, the toe/brachial index had to be  $\geq 0.7$ .

All wounds in this study by definition were required to be  $>1 \text{ cm}^2$  and  $<16 \text{ cm}^2$  in size. If the patient had multiple wounds on the foot, the largest wound, with no other wound within 2 cm, which still met all study enrollment criteria, served as the index wound. Patients were required to be ambulatory at least 75% of the time with weight bearing on the index foot. Pre-study consultations with the investigators determined that a “real world” approach would be more useful for practicing clinicians; therefore, weight bearing was a requirement during the study. Women of childbearing age had to demonstrate proof of non-pregnancy and use of an acceptable form of birth control. Exclusion criteria are listed in Table 1.

A baseline debridement was performed followed by a post-debridement quantitative culture biopsy at the screening visit. The results of these biopsies were not made available to the participating clinicians during the trial. The baseline debridement included the sharp/surgical removal of all callus/necrotic tissue, tunneling, and sinus tracts. A complete history, physical exam, and Semmes Weinstein filament testing was completed on all patients. All patients received a standard fixed ankle-foot orthotic, instructions on using saline moistened gauze, and standard pre-packaged dressing packets for twice daily dressing changes during the 7-day washout period. On day 7, any patient whose wound demonstrated an area reduction of  $>30\%$  was not enrolled in the study; these wounds were thought to have established a healing trajectory and, therefore, were not truly recalcitrant.

**Randomization and enrollment.** Following the 7-day washout period, patients with  $<30\%$  reduction in wound area were enrolled in the study and randomized using a computer-generated randomization table provided by the study sponsor to the active ultrasound (device) or control (sham) group. Patients in both groups were treated three times per week for 4-minute treatment intervals. A full clinical assessment including wound photography, tracing, and a limited physical exam was performed once per week at each assessment visit. Patients

were asked about their level of activity and their ability to complete the dressing regimen. Debridement was performed if considered clinically necessary by the investigator at each weekly assessment. The level of debridement was recorded using current procedural terminology (CPT; 2005 American Medical Association Press) codes: selective debridement without anesthesia (97601) and partial-thickness, full-thickness, and subcutaneous level debridements (11040,11041,11042, respectively). Debridement levels were recorded by the investigators following each debridement procedure. This information was collected with the intent to determine whether any correlation was noted between the ultimate healing rates and the level or depth of debridement.

Patients remained in the study until the wound healed or 12 weeks of therapy was completed, whichever came first. Due to the rigorous protocol of three visits per week, patients were allowed up to seven missed visits. If these visits were consecutive, the patient would have received a total of 10 weeks of therapy, which was determined to be the lowest evaluable treatment time. Patients were required to return to the clinic 1 week following the visit at which wound closure was first noted in order to confirm the diagnosis and ensure an adequate healing response. Patients whose wounds were confirmed healed were followed monthly for 3 months to monitor their healing status and record recurrences.

**Standard of care treatment.** Care was standardized for all patients regardless of their randomization assignment. Dressing packets included a contact layer to protect the wound. The contact layer extended onto the surrounding intact skin and was held in place with hypoallergenic tape and covered by a saline-moistened gauze dressing cut to fit the wound. The moistened gauze was covered by a layer of dry gauze, an optional layer of Vaseline (Tyco/Kendall Health Care, Mansfield, Mass. Vaseline is a registered trademark of Chesebrough-Pond's, Inc., and is used under license) gauze, and a roll gauze wrap. The need to apply impregnated gauze underneath the roll gauze wrap was determined by the clinician and based on moisture level, exudation, and maceration. Saline-moistened gauze was selected for use during this study because it has been considered standard of care by the American Diabetes Association.<sup>26</sup> Complete dressing changes occurred three times a week at the clinic treatment site and on alternate days; the patient or family member changed the secondary dressing(s) twice per day. The contact layer remained in place until the next clinic visit to minimize any damage to the wound bed that might occur if this layer was changed by the patient or a family member. All patients were expected to use a fixed ankle-foot walker. To ensure consistency, all sites used the same fixed ankle-foot walker. Appropriate diabetes management, as determined by the investigator, included diet and medications to achieve a stable glycemic state. Standard foot care education using consistent procedures was provided to each patient at the time of enrollment. Routine diabetic care procedures and nutrition guidelines were included in the investigator manual.

**Wound evaluations.** Weekly wound evaluations included wound and skin assessments. Numerous wound variables were assessed at each weekly visit, including wound exudation, quantity and quality of granulation tissue, eschar, fibrin, and slough. Exudation was assessed and recorded by quantity as "none," "mild," or "moderate" and by quality (serous, sero-sanguineous). Granulation, fibrin, and eschar were assessed as a grouped percentage of overall wound area (0% to 25%, 25% to 50%, 51% to 75%, and >75%). Peri wound skin maceration and wound edge undermining also were recorded. Callus formation and undermining of the wound edge were recorded ("no"/"yes") and maceration was assessed using a descriptive scale ("none," "mild," "moderate," "intense"). Adverse events were recorded and debridement procedures were described using the CPT coding criteria (see enrollment procedures).

Compliance was assessed and compared to the last visit, including the use of the offloading device, activity level, and the dressing changes at each weekly evaluation visit.

**Ultrasound treatment.** After removing the dressing and irrigating the wound with saline, the ultrasound device was prepared and a new sterile saline bottle was attached to the transducer. A 4-minute treatment was conducted holding the device perpendicular to the wound bed and moving the device in an up-and-down pattern across the wound bed. Treatment times had been calculated as 4 minutes in duration for wounds measuring  $<15\text{ cm}^2$ ; therefore, a 4-minute treatment time was selected as standard for the trial. After the treatment was completed, the dressings were applied as described.

**Sham device.** No commercially available device currently exists that could achieve the identical performance parameters of the ultrasound unit in this study; therefore, a sham device was designed, developed, and manufactured by the sponsor. The sham delivered an equivalent volume, flow rate, and pressure of saline mist to the wound bed as the study device. However, in order to reproduce identical energy (pressure) delivery to the wound bed, the sham device needed to be held 4 to 6 inches from the wound bed as compared to the ultrasound device, which was 5 mm to 15 mm away. The treatment time and the application technique were the same as described for the ultrasound system. Biocompatibility testing was performed on the sham device and no negative effects were detected with an *in vitro* assay using L-929 mouse fibroblasts conducted under Good Laboratory Practice conditions. Lastly, pressure delivered was analyzed using the measured displacement angle of a standard sheet of cellophane. The only difference between the two systems was the distance the devices were held from the wound bed and the absence of ultrasound in the sham device.

**Blinding protocol.** Patients and investigators evaluating the wounds were blinded to the treatment randomization. Only the clinician who opened the randomization envelopes and subsequently performed the treatments knew the actual treatment group status of the patient. Because the sham device generated a slightly louder noise than the study unit, a modified double dummy blinding technique was used. A drape was placed between the patient and the equipment and both the sham and ultrasound devices were turned on during the ultrasound treatments so all patients heard similar sounds. Although the sham device was turned on, it did not direct saline toward the wound bed or interfere with the ultrasound unit.

**Efficacy assessment.** Efficacy was evaluated at each weekly visit throughout the trial. Wound closure was defined as complete epithelialization without drainage. Patients with wounds found to be open at the 1-week follow-up confirmation visit were continued in the study and removed from the “closed” data group if closure was not achieved within the defined 12-week treatment period.

**Safety assessments.** Adverse events were monitored for ultrasound and sham patients at the weekly evaluation visits. The degree and distribution of adverse events were analyzed and divided into “mild” (a transient event easily tolerated by the patient); “moderate” (causes discomfort and interrupts participant’s normal activities); and “severe” (an adverse event that causes considerable interference with participant’s normal activities has occurred and/or an event that may be incapacitating or life-threatening). These adverse events also were evaluated according to whether they were probably, possibly, unlikely, or not considered to be related to the study procedures.

**Data treatment and analysis.** All data were recorded on case report forms maintained by the investigator. Clinical monitors from the sponsoring company ensured completeness and

accuracy in reporting through site visits and phone consultation. All completed forms were forwarded to a central data processing center. All statistical analyses were performed using SAS software (Cary, NC).

## Results

A total of 133 patients were enrolled at 23 clinical study sites. All patients were screened and received at least one ultrasound or sham treatment and included in the intent-to-treat population. Review of the records revealed eight patients with wounds beyond the size limits for the study. Four of the remaining 125 patients were found to have wounds <4 weeks in duration. An additional 24 patients were lost to follow-up before completing the required 10-week course of therapy, leaving 97 patients considered evaluable according to the study protocol criteria. A planned interim analysis in October 2003 revealed no significant difference between the treatment regimens, which was in conflict with prior clinical experience using the ultrasound device. In addition, two centers reported 100% healing using the sham. These findings prompted a study-wide clinical site audit. During the audit process, five centers (42 enrolled patients) were found to be inverting the treatment distances described in the protocol. These protocol violations resulted in a final evaluable population of 55 patients for the efficacy analysis group. All patients treated more than once were included in the overall safety analysis (see Figure 1). Using an intent-to-treat model (all 133 patients who received >1 treatment), no statistically significant difference was found between the ultrasound and the sham device ( $P = 0.69$ , Fisher's exact).

**Efficacy.** Study participant gender, age, body mass index, and race did not differ between the two treatment groups (see Table 2). The initial mean wound area was larger in the sham treatment group than in the ultrasound group ( $P < 0.05$ ), prompting a Cox proportional hazards regression analysis (see Table 3). To determine whether the significant effect of the ultrasound treatment was due to the possibly confounding effect of important covariates, various multiparameter analyses were performed. Cox proportional hazards regression analyses were conducted using the following covariates to determine whether they mediated the treatment effect: age, gender, baseline mean area, use of offloading, percentage of visits where debridement was performed, intensity of debridement (depth), chronicity of ulcer at baseline, investigational center. A proportional hazards regression model was constructed using a step-wise process to identify the best overall model as well as the forced incorporation of all of the above covariates. For the step-wise approach, all of the above covariates were included, along with the treatment group. The criteria for variable entry was  $\alpha = 0.25$  and the criteria for final inclusion was  $\alpha = 0.15$ . The overall best model ultimately contained only treatment group, age, and two of the investigational sites. The effect of the treatment variable was found to be statistically significant ( $P = 0.0061$ ) even with the inclusion of the important effects of the other variables. Likewise, treatment was found to be statistically significant when all of the above variables were forced into the model ( $P = 0.0287$ ). Even though the control group presented with significantly larger index ulcers at screening, this difference was not found to have a deleterious effect on the significant influence of the ultrasound therapy in closing the diabetic foot ulcers in either of these regression models. The curves for the two groups support the proportional hazards assumption of the Cox model used to determine a significant benefit of ultrasound therapy. Although many wound parameters were collected, according to the protocol, only the secondary endpoints of wound exudation, granulation tissue, and debridement were analyzed statistically. Granulation tissue amount and quality were not significantly different between the two groups at baseline or the completion of the study (see Table 4). The amount of exudation was similar for the two groups at baseline but by week 5, a statistically significant reduction in the exudation from

wounds treated with ultrasound was noted. The overall amount and quality of exudation was significantly different at the end of the study; patients treated with ultrasound demonstrated smaller amounts of exudation that was more serous (see Figure 2 and Table 4).

Overall, 40.7% of wounds in the ultrasound therapy, compared to 14.3% in the sham treatment group, healed ( $P = 0.0366$ , Fisher's exact test) (see Table 5). Time to healing differed significantly between the two treatment groups. Kaplan Meier survival analysis results found a mean time to healing of 9.12 (SD 0.58) weeks and a median of 11 weeks (SD 0) for the ultrasound compared to a mean of 11.74 (SD 0.22) and a median of 12 weeks (SD 0.82) for sham treatment (log rank  $P < 0.0144$ ). Wound recidivism follow-up 3 months after healing showed that only one of the 15 closed wounds reopened (one of 14 in the ultrasound and zero of four in the control group). This difference was not significant. No significant differences in the amount or frequency of debridement were noted between the two groups; therefore, sharp debridement, in and of itself, was not responsible for the ultimate healing results seen in this study (see Table 6). The results of the initial, post-debridement quantitative culture biopsies taken at enrollment showed that 86% of wound cultures in the group randomized to ultrasound treatment had  $>100,000$  colonies/g of tissue compared to 93% in the sham group. These differences were not statistically significant (see Table 7). However, the results are surprising because the investigators were asked to enroll only patients they felt were clinically non-infected and the cultures were taken after an initial debridement.

**Safety: intent-to-treat population.** One-hundred, ninety-three (193) adverse events were reported for the 133-patient study population (see Table 8 and Table 9). The adverse events included cellulitis, development of additional wounds on the index foot, pain, wound drainage, and erythema. No statistically significant difference in the number or severity of adverse events was found between the two treatment groups. Of the 193 reported adverse events, 160 (83%) were not related to the study or sham treatment devices. Pain was reported in four cases — three in the sham group and one in the ultrasound group. Wound infection was reported in two cases in the ultrasound group (see Table 10).

## Discussion

The ultrasound therapy described in this study employs a recently FDA-cleared device for the cleansing and debridement of wounds with an expanded indication (promotes healing). Used as directed, this device delivers an energy of  $0.1 \text{ W/cm}^2$  to  $0.5 \text{ W/cm}^2$  within the defined therapeutic range. A recent study<sup>27</sup> using an induced diabetic rat, acute excisional wound model noted a statistically significant increase in blood vessel growth and collagen deposition in the ultrasound-treated wounds compared to sham control, validating that the bio-acoustical effects generated by a non-contact, kilohertz ultrasound device are similar to prior results obtained with megahertz ultrasound devices.<sup>17</sup>

The current report is the first randomized human clinical trial describing the clinical effectiveness of this new approach of delivering kilohertz ultrasound therapy directly to the wound bed employing a non-contact delivery model. Prior ultrasound therapy for the treatment of chronic wounds has focused on periwound tissue and primarily has utilized ultrasound in the megahertz range. The results of this double-blinded, randomized, sham-controlled trial demonstrate a positive effect on the healing of diabetic foot ulcers.

An attempt was made to design a trial that addressed many of the previous shortcomings of both ultrasound and diabetic foot ulcer studies. The methodological filters of Sackett et al, described in Robertson and Baker's 2001 review,<sup>28</sup> were examined and each question/concern

was addressed in the design of this trial. An attempt was made to standardize the vascular status of the patient population with extensive, well-defined, reproducible non-invasive vascular parameters. Offloading was controlled with a uniform requirement that only fixed ankle-foot walkers be used during the study. Standard diabetic socks were supplied to all centers for use during the trial. Patients were required to ambulate at least 75% of the time to simulate the potential clinical results that can be expected when this technology is implemented in a real-world clinical environment. Ulcer severity was controlled by limiting enrollment to patients with ulcers that were either Wagner grade one or two

Clinicians were asked to exclude patients with wounds they believed to be clinically infected as well as patients who were receiving antibiotic therapy. Although the results of quantitative culture biopsies taken on all patients enrolled were not revealed to investigators, the post study analysis of the results is intriguing. Despite the absence of clinical signs of infection as determined by the investigator, 86% of the ultrasound-treated patients and 93% of the sham-treated patients demonstrated  $>10^5$  aerobic bacteria per gram of tissue (55 patient evaluable cohort). Recent work by Cutting and White<sup>29</sup> recommends that clinical criteria for wound infections be created for each specific wound etiology. These and other authors have previously described the inherent problems with accurately determining wound infections using either clinical findings or culture results.<sup>30,31</sup> Furthermore, whether any particular quantitative value is, in and of itself, indicative of infection remains a matter for debate. Much has been written about the concept of a bioburden continuum and it has been suggested that factors such as the total quantity of bacteria, their virulence, and host factors all contribute to an individual patient's risk of developing infection.<sup>32</sup> At a minimum, clinicians accept that reducing the bioburden in the wound bed leads to a healthier physiological state with a reduced competition for oxygen and nutrients, diminished exudate, and lowered inflammatory cytokines, all of which allow for healing to proceed. This raises the question: Should all wound healing clinical trials begin with a quantitative biopsy to stratify patients and subsequent outcomes when investigational therapies are studied? If the bioburden continuum is truly clinically linked to healing, the answer is likely "yes." Browne et al<sup>33</sup> have shown that wound healing rates were related to quantitative biopsy values in a study of patients with diabetic foot ulcers receiving bioengineered dermal substitutes.

The addition of ultrasound in this study is the only true treatment variable between the two study groups, leading investigators to postulate that an antimicrobial function of the ultrasound device could, in part, explain the positive outcomes despite a lower than planned for total evaluable cohort. Further support for this theory includes the unpublished animal studies conducted by the sponsor, demonstrating bacterial disruption after ultrasound therapy confirmed by scanning electron microscopy.<sup>34</sup> Further clinical trials specifically designed to answer these questions are needed. Additional support for the potential antimicrobial effects of ultrasound therapy is the fact that exudation levels decreased over time as the number of ultrasound treatments were performed (see Figure 2). Also, attention should be drawn to the small increase in exudation noted with the initiation of ultrasound therapy. This transient increase is thought to coincide with the re-establishment of an inflammatory response in a previously chronic, recalcitrant wound.

Another question posed by this trial design was whether the depth or level of debridement had an impact on overall healing rates. A large multicenter, randomized controlled trial<sup>35</sup> found a positive correlation between healing in centers frequently performing debridement. However, whether the extent of debridement has an impact on healing rates is not known. In this study, frequency of debridement and debridement CPT codes were recorded to determine the extent of debridement. No statistically significant differences were noted between the two

groups. One potential limitation of this method of analyzing debridement depth is the potential for over- or undercoding. Future study designs should explore this phenomenon because the small patient population in this study may have precluded finding any significant effects. The importance of differentiating maintenance debridement from surgical/sharp debridement also has been noted. The use of ultrasound therapy did not decrease the number of sharp/surgical debridements performed.

Prior ultrasound studies either did not include a control device or did not describe the control device or its physical parameters. Although the sham device in this study delivered equivalent saline volumes and pressure when used at the appropriate distance from the wound bed, the need to treat the two study groups at different distances from the wound bed with the two therapies caused confusion and resultant protocol violations. Despite hands-on training sessions, an instructional video, and frequent clinical monitor site visits, multiple protocol violations occurred. Notwithstanding the smaller-than-planned-for remaining efficacy cohort, the ultrasound therapy-managed group had a significantly higher proportion of healed ulcers than the sham treatment group. The impact of treatment on bioburden could explain these findings. Another postulate is that sham therapy may have had a negative effect on healing. The overall sham intent-to-treat group (133 patients) experienced a 22% healing rate at 12 weeks, compared to a 14.3% healing rate at 12 weeks of the efficacy group (55 patients). These values are in reasonable agreement with Margolis'<sup>36</sup> published meta-analysis that examines control group outcomes of recently published diabetic foot ulcer trials. Current results also suggest that the sham device did not significantly impede healing. The discrepancy between the intent-to-treat and the evaluable sham healing rates may be related to the increased debridement effects secondary to holding the sham device too close to the wound bed as observed at clinical sites where protocol violations occurred.

## Conclusion

Ultrasound therapy has been shown to be a useful adjunct to standard of care for the treatment of diabetic foot ulcers. When used appropriately, 40.7% of treated wounds were healed after 12 weeks of care compared to 14.3% of wounds healed in the sham treatment group. The device was found to be safe, well-tolerated by patients, and easy to administer. When used in clinical practice, confusion about the distance of the device from the wound, which occurred during the study, is not a factor because clinicians only have access to an active unit. Despite the decrease in the total evaluable population, statistically significant differences were observed. The proportion of ulcers healed in this study compares favorably with prior randomized controlled diabetic foot ulcer studies.<sup>37,38</sup> Specifically, after 12 weeks, 30% of diabetic foot ulcers treated with bio-engineered tissue (Dermagraft\*; Smith & Nephew, Largo, Fla.) were healed compared to 18.3% control-treated ulcers and 56% of ulcers treated with Apligraf® (Organogenesis, Canton, Mass.) were healed compared to 38% of control ulcers. A healing rate meta-analysis of patients receiving control treatments in randomized controlled trials for diabetic foot ulcers found that at 12 weeks the mean healing rate was 24.2%.<sup>35</sup>

The results of this study suggest the need for further research, including assessing the impact of quantitative biopsy results at enrollment, debridement depth and impact on healing, as well as the potential antimicrobial action of this ultrasound device. Better methods of quantifying the debridement process must be evaluated in order to accurately compare study results. In general, designing clinical studies for wound healing is difficult and surrogate endpoints might enable trials to be constructed with valid outcomes measures other than total

closure. Many randomized controlled clinical wound care studies have failed to deliver the outcomes anticipated by pre-clinical work, an observation that warrants further study.<sup>39</sup>

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