

Extracorporeal Shockwave Therapy Versus Placebo for the Treatment of Chronic Proximal Plantar Fasciitis: Results of a Randomized, Placebo-Controlled, Double-Blinded, Multicenter Intervention Trial

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Extracorporeal shockwave therapy (ESWT) has demonstrated efficacy in the treatment of recalcitrant proximal plantar fasciitis. The objective of this investigation was to compare the outcomes of participants treated with a new ESWT device with those treated with placebo. A total of 172 volunteer participants were randomized in a 2:1 active-to-placebo ratio in this prospective, double-blind, multicenter trial conducted between October 2003 and December 2004. ESWT (n = 115) or placebo control (n = 57) was administered on a single occasion without local or systemic anesthesia or sedation, after which follow-up was undertaken. The primary outcomes were the blind assessor's objective, and the participant's subjective assessments of heel pain during the first 3 months of follow-up. Participants were also followed up to 1 year to identify any adverse outcomes that may have been related to the shockwave device. On the visual analog scale, the blind assessor's objective assessment of heel pain displayed a mean reduction of 2.51 in the shockwave group and 1.57 in the placebo group; this difference was statistically significant (P = .045). On the visual analog scale, the participant's self-assessment of heel pain displayed a mean reduction of 3.39 in the shockwave group and 1.78 in the placebo group; this difference was statistically significant (P < .001). No serious adverse events were observed at any time. It was concluded that ESWT was both efficacious and safe for participants with chronic proximal plantar fasciitis that had been unresponsive to exhaustive conservative treatment. (The Journal of Foot & Ankle Surgery 45(4):196–210, 2006)

Key words: extracorporeal shockwave therapy (ESWT), heel pain, Orthospec, proximal plantar fasciitis

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Proximal plantar fasciitis is a common complaint that confronts physicians treating the foot (1–6). Conservative therapies for this condition include various combinations of padding, strapping, nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, night splints, and corticosteroid injections, and these therapies, for the majority of participants, prove to be beneficial (7–13). Nonetheless, approximately 10% of participants fail to respond satisfactorily to these conservative treatment strategies, and, for these participants, treatment options have traditionally evolved around surgical intervention for release of the plantar fascia at its attachment to the tuberosity of the calcaneus, with or without concomitant removal of a portion of the plantar calcaneus when there is radiographic evidence of a plantar calcaneal spur (14, 15). Moreover, postoperative complications such as recurrent pain, nerve injury, infection, and tarsal instability detract from the usefulness of surgical intervention.

Since the mid-1990s, extracorporeal shockwave therapy (ESWT) has been successfully used in the treatment of chronic plantar fasciitis (16). Shockwaves are sound waves that are generated by a source that creates vibrations which are then transported through tissues via fluid and solid particle interaction. Proponents of shockwave therapy suggest that ESWT creates controlled local tissue injury that causes neovascularization, and is associated with increased amounts of tissue growth factors within the locally injured structures. It is therefore hypothesized that ESWT stimulates healing by creating a wound environment at the site of shockwave delivery (17–19). Other hypothesized mechanisms of action include the physical alteration of small axons, thereby inhibiting pain impulse conduction; chemical alteration of pain receptor neurotransmitter, thereby preventing pain perception; and hyperstimulation activation of the gate control mechanism, thereby affecting analgesia (20, 21). Although shockwaves used for lithotripsy are of higher energy than those used for the treatment of plantar fasciitis, animal studies have shown the development of an inflammatory response in tissues, ranging from tendon to physal plate to trabecular bone, with energy levels ranging from 0.28 to 1.5 mJ/mm² (22–28). It is generally understood that energy levels ranging from 0.22 to 0.36 mJ/mm² are high enough to induce a therapeutic response in the plantar fascia by 3 to 6 weeks. However, randomized controlled trials of different shockwave delivery systems have yielded varying results (29–39). Currently, shockwave delivery systems delivering energy levels more than 0.34 to 0.36 mJ/mm² require the recipient to undergo regional nerve blocks combined with either intravenous sedation or general anesthesia, and the therapeutic guidelines for these devices call for one or more additional applications of ESWT should the participant not experience satisfactory resolution of his or her heel pain. Devices that do not deliver energy levels of at

least 0.26 mJ/mm² generally do not require local anesthesia at the site of delivery; however, they have been criticized as not being as efficacious as devices delivering shockwaves of higher energy (40).

The Orthospec ESWT (Medispec LTD, Germantown, MD) device is an extracorporeal shockwave delivery system that is approved for distribution and use in the United States by the Food and Drug Administration (FDA). Although shockwave therapy has been available for the treatment of plantar fasciitis for about a decade in this country, the device under investigation in this clinical trial conveys unique features that distinguish it from other ESWT devices used for this condition. This device produces shockwaves electrohydraulically and delivers the energy to the treatment area through a rubber contact membrane (Fig 1). The energy is dispersed over a treatment area that is large enough that the intensity of the shockwaves reaches therapeutic levels while remaining generally well tolerated by recipient patients without the need for anesthesia or sedation. Moreover, the effective distribution of the shockwaves is over a broad enough anatomical area that there is no need for ultrasonic or radiographic targeting. The hypothesis of this industry-sponsored FDA phase-3 investigation is that the Orthospec (active ESWT) device would provide greater relief of pain in comparison with a placebo control, after a one-time application for the treatment of recalcitrant proximal plantar fasciitis.

Materials and Methods

An FDA-approved, randomized, placebo-controlled, double-blinded, multicentered clinical trial to compare the efficacy and safety of the Orthospec device was designed and undertaken at clinical centers in Pennsylvania, Connecticut, and Maryland. Figure 2 schematically depicts the organization and flow of the investigation.

Sample Size and Power

Using 2.2 as the standard deviation for the change from baseline heel pain to postintervention heel pain, in accordance with previous experience, and allowing for a 5% loss to follow-up, a total of 183 participants, randomized 2:1 (122 active and 61 placebo), was required to provide 80% power to detect a difference of 1.0 at the 5% level of significance. Only one foot per participant was to be enrolled and treated in this study.

Study Population

To be included as a participant in the investigation, potential candidates had to be a man or woman older than 18 years of age; if female, not pregnant; diagnosed with prox-



FIGURE 1 (A) The ESWT device. (B) The Orthospec device positioned against the plantar heel.

imal plantar fasciitis on the basis of history and physical examination with symptoms present for more than 6 months; have been treated by a licensed healthcare professional for at least 4 months; have a pain intensity score of ≥ 5 cm on the visual analog scale (VAS) in the investigator's heel pain assessment and the participant's self-assessment of pain on the first few minutes of walking in the morning; and have a single site of tenderness with local pressure over the plantar calcaneal tuberosity on passive dorsiflexion of the foot. Potential participants with chronic

conditions such as osteoarthritis, diabetes mellitus, or peripheral vascular disease were considered eligible for participation only if the condition did not overtly or acutely affect their foot pain. Moreover, potential participants must have previously failed two pharmacologic (analgesic, anti-inflammatory, or other) and two nonpharmacologic treatment modalities for relief of heel pain, and agree to avoid such treatments within the following time windows before the intervention visit: 6 weeks for local corticosteroid injections, 48 hours for NSAIDs or analgesic medications, and 2 weeks for physical therapy. Furthermore, potential participants had to agree to avoid the use of NSAIDs or analgesic medications for at least 48 hours before any follow-up visit.

Potential participants were excluded if they had a recent history of significant cardiac, neurological, hepatic, renal, metabolic, or hematological disease or impairment as determined by pre-admission testing, medical history (recent and previous), and specialist evaluations. Potential participants with a history of previous surgery for plantar fasciitis or heel spur; those who chose to continue physical therapy or other conservative treatments for their heel pain during the time that they would be enrolled in the study; those having undergone a corticosteroid injection in the heel within 6 weeks of study treatment; those with neuropathic, malignant, or infectious causes of pain; those with a known coagulation disorder or those taking anticoagulant medications for either acute or chronic anticoagulant therapy; those with suspected tears of the plantar fascia, bilateral plantar fasciitis, an infection or malignancy at the area to be subjected to intervention; those who had any condition in which the exposure to radiation was not advisable (that is, pregnancy); those who were unable to provide informed consent themselves or who required a guardian to provide consent to be a volunteer participant in the study; and those simultaneously participating in another device or drug study or who had participated in any clinical trial involving an experimental device or drug within 30 days of entry into this study were also excluded. The investigators made the final determination of whether candidates were eligible to enroll in the study.

Data Collection

Consent forms were reviewed and signed and demographic data were collected for all of the participants who met the inclusion criteria, in accordance with the institutional review board–approved investigational protocol. Participants were randomized into two groups, either ESWT active or placebo, in a ratio of 2:1, as determined by computer-generated random numbers separately for each study center. A minimum of two investigators participated at each site. Because it was a double-blind study, both the participating patients and blinded investigator(s) were unaware of

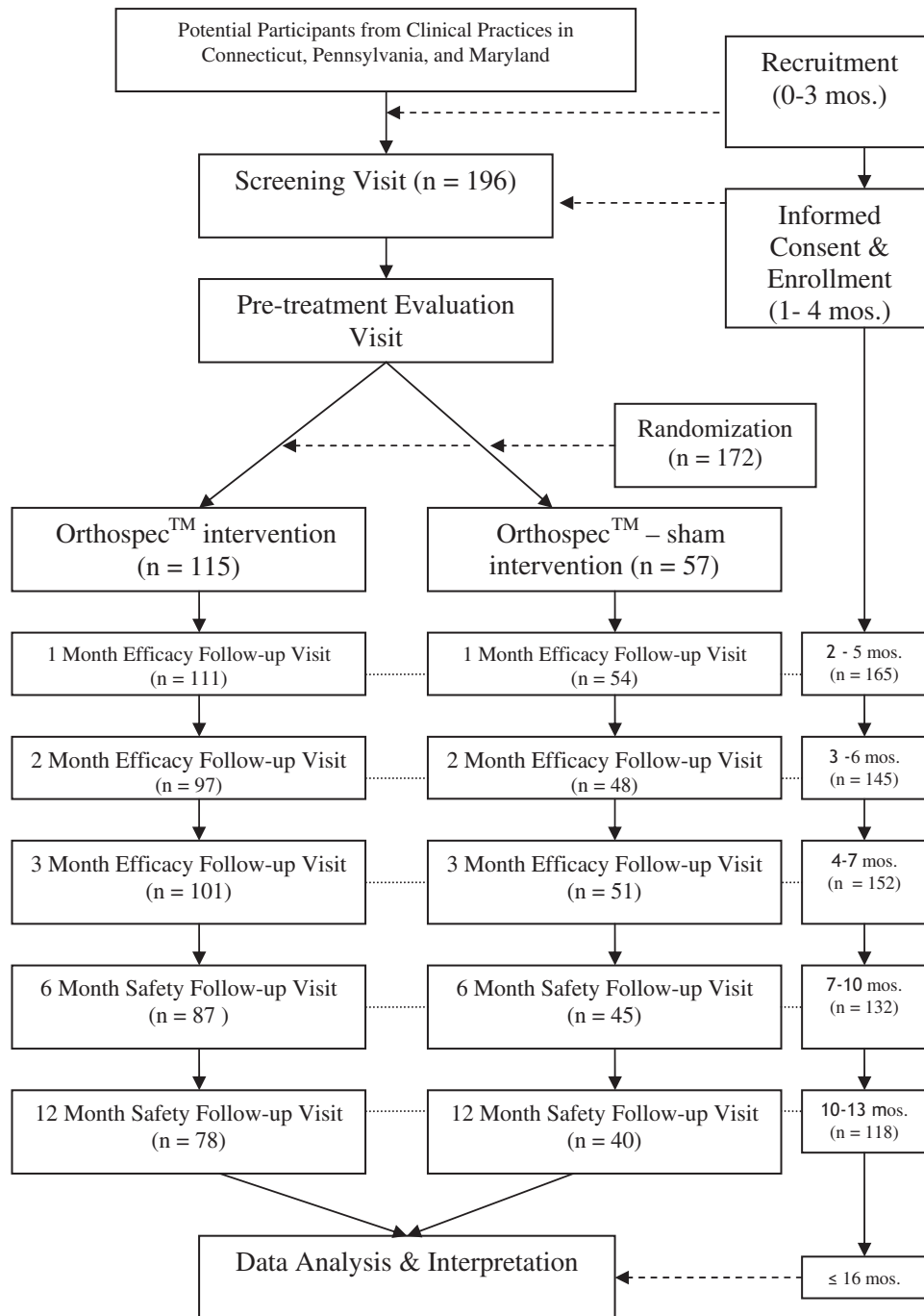


FIGURE 2 Protocol flow chart.

treatment allocation. All evaluations, before and after the intervention, were carried out by blinded investigators who were responsible for performing the initial screening and history as well as all of the preintervention and postintervention assessments of heel pain. Investigators who were not blinded were responsible for administering the treatment and collecting data during the intervention. Data collected during the intervention included the amount of ESWT ac-

tive or placebo intervention administered and whether any adverse events occurred during the intervention. Data collected preintervention and postintervention (blind assessors) included the participant's self-assessment and the investigator's assessment of heel pain, self-assessment of activity and function level, use of analgesics, radiographic and integument assessments, blinding assessment, and adverse event and complication data.



FIGURE 3 (A) The PressureSpec calibrated pressure applicator. (B) PressureSpec device used to apply and standardize plantar pressure.

Investigator's pain assessments were accomplished with the PressureSpec (Medispec LTD) device (Fig 3), a calibrated handheld instrument that allowed standardized quantification of heel pain when it was applied to the symptomatic area. A 10-point VAS was used by the participants for the investigator's assessment and the participant's self-assessment of heel pain. The continuous nature of the data obtained with this scale was upheld by means of measuring the distance (centimeters) from the origin to the participant's mark on the scale. Participants were also provided with a diary so that they could record their heel pain on initial weight bearing in the morning. Activity and function were measured by the distance the patient was able to walk without heel pain. The diary was also used to record the participants' use of anti-inflammatory and/or analgesic medications. Blind investigators assessed participant activity and function by means of a prescribed interview and examination, as well as review of the diary at 1, 2, and 3 months after the intervention visit.

Intervention Protocol

One Orthospec device and two different contact membranes were placed at each clinical site, and investigators

who were not blinded administered either the active or sham shockwave intervention. During the intervention, all participants were positioned comfortably in front of the contact membrane of the device, and ultrasound gel was applied to both the membrane and the target heel. For participants randomized to the active intervention group, an unlined (noninsulated) contact membrane was used. For those participants randomized to the placebo group, a foam-insulated membrane was used to absorb the shockwaves and inhibit transmission of most of the energy. The visible appearance of both the sham and active contact membranes was identical, and the procedures for the intervention proceeded in an identical fashion for both treatment groups.

Each patient, in both the ESWT active and placebo groups, underwent continuous shockwave transmission that started at the lowest energy level (level 1) and increased at 3-minute and 35-second intervals until the highest energy level (level 7) was achieved. The creation of shockwaves resulted in a sharp, audible sound, and participants and operators were provided with ear protection that they could use if desired. The intervention session lasted 25 minutes, during which 3800 shockwaves were administered at a rate of 150 shocks per minute. No form of systemic or local anesthesia, or sedation, was provided before, during, or after the intervention. If a participant was unable to tolerate a particular energy level, the unblinded investigator administering the intervention would decrease the energy level. Afterwards, the unblinded investigator recorded the highest energy level sustained and the number of shockwaves administered, and any adverse events or device malfunctions noted. At the end of the intervention session, in an effort to assess blinding, participants were asked whether they thought they had received the active or the placebo intervention.

Outcomes

The primary efficacy endpoint for this study was the change from baseline to 3 months postintervention in the investigator's assessment of heel pain. All randomized participants who had at least one follow-up evaluation for this outcome were included in the primary analysis of efficacy. If a participant did not have an assessment at 3 months postintervention, for whatever reason, then the last available assessment data were carried forward (last observation carried forward [LOCF] method). Secondary efficacy endpoints for this investigation included:

1. The investigator's heel pain assessment responder analysis, whereby participants who had a decrease from baseline to the third postintervention visit of 50% or more with a VAS score ≤ 4 cm were to be considered a success, whereas all others were to be considered a

- failure. The last observation was carried forward for all participants who were missing a value at the third visit.
2. Change from baseline to 3 months posttreatment (third visit) in the participant's self-assessment of heel pain. If a participant did not have an assessment at the third visit, then the last available assessment was carried forward.
 3. Participant's self-assessment of pain analyzed as a dichotomous variable, wherein participants who had a decrease from baseline to the third visit of 50% or more with a VAS score ≤ 4 cm were to be considered a success, whereas all others were to be considered a failure. The last observation was carried forward for all participants who were missing a value at the third visit.
 4. Participant's self-assessment of activity level and function was treated as a dichotomous variable, where an improvement of 1 point or more over baseline, or maintaining a baseline score of 0 or 1 was considered a success. All other responses were to be considered a failure.
 5. Change in use of pain medications from study enrollment was analyzed as a 3-point categorical variable representing increased, no change, or decreased use of analgesic medication.

Reassessment of heel pain was performed with the PressureSpec device and the VAS at 1, 2, and 3 months postintervention. Prescribed questions regarding activity and function were also asked at these visits, in terms of the number of blocks walked before experiencing heel pain, and participant diaries were checked to assess and record the participant's use of pain medications. At the 1-, 2-, 3-, 6-, and 12-month follow-up visits, blinded investigators interviewed participants and examined the study heel for any signs of adverse events such as swelling, bruising, or paresthesia. Safety endpoints were recorded as the first occurrence of any adverse event or complication.

Statistical Plan

The protocol-defined primary endpoint was the change from baseline to 3 months posttreatment in the investigator's heel pain assessment. This endpoint was analyzed by an analysis of covariance that included the effects of treatment group, study center, and the baseline investigator's heel pain assessment. Continuous secondary endpoints were analyzed in the same way as the primary endpoint, and categorical secondary endpoints (responder analyses) were analyzed by a logistic regression that included the effects of treatment group, study center, and the corresponding baseline assessment. The change in the use of pain medication was analyzed by the Cochran-Mantel-Haenszel procedure, stratified by study center. Scores of 1, 0, and -1 were assigned to the response categories of increased, remained

the same, and decreased, to create a test of the mean scores. Device safety was assessed by the first occurrence of all adverse events and all device-related adverse events. Each adverse event was presented as the rate per treatment group and tested using the Fisher's exact test. All analyses were based on randomized treatment and all statistical tests were 2-sided at the 5% level of significance. All of the analyses were performed with SAS Version 8.2 (SAS Institute, Cary, NC).

Results

A total of 196 participants were screened, 172 were randomized to treatment, and 152 completed the 12-week efficacy trial. A total of 168 participants had at least 1 follow-up visit and were included in analyses of efficacy. Inspection of the distributions of the data confirmed that our statistical assumptions were met. The 172 participants had a mean age of 51 years, 33% were men, the mean weight was 184 pounds, 87% were white, and the mean duration of foot pain was 30 months. Baseline demographic and clinical data are summarized in [Table 1](#) by treatment group. Nineteen of the 172 participants (11.0%) had not used any oral medication to treat their foot pain.

Primary Efficacy Results

The mean change in the investigator's assessment of heel pain is summarized in [Table 2](#), and these data indicate that the mean change from baseline in the ESWT group was significantly greater than that in the placebo group (difference = -0.94; $P = .045$; 95% confidence interval, -1.87 to -0.02). Moreover, the difference also achieved statistical significance at month 2.

To assess the effect of the absence or presence of a radiographically evident plantar calcaneal spur, the mean changes from baseline by radiographic finding are summarized in [Table 3](#). These data show that in the absence of a radiographically evident plantar calcaneal spur, the reduction in heel pain was statistically significantly greater for the ESWT group than for the placebo group, whereas in the presence of a plantar calcaneal spur, the reduction in heel pain was not statistically significantly different between the groups.

To assess the dose-response relationship with respect to the primary endpoint, all placebo participants were pooled, and the mean changes from baseline in the investigator's assessment of heel pain, adjusted for study center and baseline assessment, are presented in [Figure 4](#) by maximum shockwave energy applied. One participant was randomized to ESWT but received placebo by mistake and was included in the placebo group in this table. Of the 115 participants receiving active ESWT, 89 (77%) tolerated shockwave en-

TABLE 1 Baseline and demographic summary

	ESWT (N = 115)	Placebo (N = 57)
Age (y)		
Mean ± SD	50.8 ± 10.1	52.1 ± 11.1
Range	28–75	30–79
Sex		
Men: n (%)	36 (31.3%)	21 (36.8%)
Women: n (%)	79 (68.7%)	36 (63.2%)
Race		
Black: n (%)	8 (7.1%)	5 (8.8%)
White: n (%)	102 (90.3%)	48 (84.2%)
Asian: n (%)	0 (0%)	3 (5.3%)
Hispanic: n (%)	3 (2.7%)	1 (1.8%)
Duration of foot pain (mo)		
Mean ± SD	31.6 ± 36.3	26.0 ± 24.4
Range	6–240	6–120
Weight (lb)		
Mean ± SD	187.3 ± 42.3	177.0 ± 36.4
Range	112–290	114–280
Calcaneal radiographs		
Plantar spur present	46 (40.0%)	21 (37.5%)
Activity: blocks walked without pain		
No/Minor limitation: n (%)	12 (10.4%)	9 (15.8%)
6–10 Blocks: n (%)	14 (12.2%)	0 (0%)
4–6 Blocks: n (%)	6 (5.2%)	6 (10.5%)
1–3 Blocks: n (%)	18 (15.7%)	9 (15.8%)
<1 Block: n (%)	65 (56.5%)	33 (57.9%)
Preintervention analgesic use for heel pain		
No analgesic used	12 (10.4%)	7 (12.3%)
Aspirin	4 (3.5%)	5 (8.8%)
Celecoxib	9 (7.8%)	6 (10.5%)
Flurbiprofen	1 (0.9%)	0 (0%)
Ibuprofen	23 (20.0%)	17 (29.8%)
Indomethacin	0 (0%)	1 (1.8%)
Meloxicam	3 (2.6%)	0 (0%)
Nambunetone	1 (0.9%)	0 (0%)
Naproxen sodium	10 (8.7%)	5 (8.8%)
Rofecoxib	9 (7.8%)	7 (12.3%)
Other	59 (51.3%)	25 (43.9%)

ergy levels ≥ 6 without any form of anesthesia, analgesia, or sedation (Table 4).

A number of baseline factors were assessed to see if they had an effect on the investigator's assessment of heel pain. The only one found to be significant ($P < .05$) was the baseline assessment, indicating that none of the baseline demographic factors influenced the investigator's assessment of heel pain.

Table 5 summarizes the number and percent of responders (decrease from baseline of 50% or more with a VAS score ≤ 4 cm) at each visit with the last value carried forward for all missing values. These results show that the differences achieved statistical significance at months 2 and 3 of follow-up.

Secondary efficacy endpoints included the participant's assessment of heel pain, the participant's assessment of

TABLE 2 Mean change from baseline in investigator's assessment of heel pain (LOCF)

	ESWT	Placebo	P value
Month 1			
N	111	54	
Mean*	-1.61	-1.27	.34
Difference (95% CI)	-0.34 (-1.06, 0.37)		
Month 2			
N	111	54	
Mean*	-2.30	-1.31	.026
Difference (95% CI)	-0.99 (-1.86, -0.12)		
Month 3			
N	112	56	
Mean*	-2.51	-1.57	.045
Difference (95% CI)	-0.94 (-1.87, -0.02)		

Abbreviations: LOCF, last observation carried forward; ESWT, extracorporeal shockwave therapy; CI, confidence interval.

*Estimated from an analysis of variance and adjusted for baseline assessment and clinical site.

TABLE 3 Mean change from baseline to month 3 in investigator's assessment of heel pain by the radiographic absence or presence of a plantar calcaneal spur (LOCF)

	ESWT	Placebo	P value
Plantar spur absent			
N	68	36	
Mean*	-3.67	-2.19	.012
Difference (95% CI)	-1.48 (-2.63, -0.33)		
Plantar spur present			
N	45	20	
Mean*	-2.06	-1.99	.96
Difference (95% CI)	-0.07 (-1.66, 1.52)		

Abbreviations: LOCF, last observation carried forward; ESWT, extracorporeal shockwave therapy; CI, confidence interval.

*Estimated from an analysis of variance and adjusted for baseline assessment and clinical site.

activity and function, and the change in use of pain medication. The participant's assessment of heel pain was handled both as a continuous variable and as a dichotomous variable, as was done for the primary endpoint. These data were analyzed by the same model that was used for the primary endpoint with the LOCF for all missing visits and are reported in Table 6. As with the primary endpoint, the difference at 3 months achieved statistical significance ($P < .001$). Table 7 summarizes the results of the responder analyses for the participants' assessment of heel pain. As with the continuous analysis, the results at 3 months achieved statistical significance ($P = .003$).

The protocol defined a responder, relative to the participant's self-assessment of activity and function, as a participant displaying an improvement of at least one category from baseline or a participant displaying maintenance of a baseline score of 0 or 1. These data were analyzed by a logistic regression that included the effects of treatment

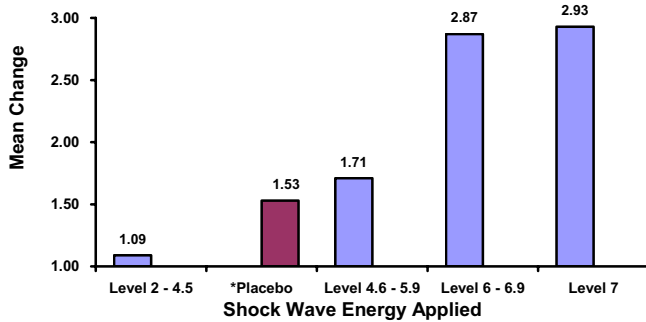


FIGURE 4 Mean change from baseline to month 3 in investigator's assessment of heel pain by maximum shock wave energy applied (LOCF). *The placebo intervention did provide some degree of therapeutic effect. As demonstrated in this figure, the placebo mean decrease was equivalent to treatment levels <4.5.

TABLE 4 Maximum shockwave energy level applied (N = 115)

Energy Level	n (%)
2-4.5	14 (12.2)
4.6-5.9	12 (10.4)
6-6.9	54 (47.0)
≥7	35 (30.9)

TABLE 5 Investigator's assessment of heel pain—responder's analysis* (LOCF)

	ESWT	Placebo	P value
Month 1			
Responders: n/N (%)	22/111 (19.8%)	9/54 (16.7%)	.58
Odds ratio (95% CI)	1.30 (0.52, 3.27)		
Month 2			
Responders: n/N (%)	38/111 (34.2%)	9/54 (16.7%)	.019
Odds ratio (95% CI)	2.69 (1.17, 6.16)		
Month 3			
Responders: n/N (%)	48/112 (42.9%)	11/56 (19.6%)	.003
Odds ratio (95% CI)	3.13 (1.46, 6.73)		

Abbreviations: LOCF, last observation carried forward; ESWT, extracorporeal shockwave therapy; CI, confidence interval; VAS, visual analog score.

*A responder is a participant with a ≥50% decrease from baseline and a VAS score ≤4 cm. Analysis was performed by a logistic regression including baseline assessment and clinical site as covariates.

group, clinical site, and baseline category; the results of which are presented in Table 8. The results indicated that participants in the ESWT group had a higher response rate than those in the placebo group at months 2 and 3. However, at neither month did the difference achieve statistical significance.

At each posttreatment follow-up visit, investigators were asked to assess whether the participant had changed his or her use of pain medication in comparison with when he or

TABLE 6 Mean change from baseline in participant's assessment of heel pain (LOCF)

	ESWT	Placebo	P value
Month 1			
N	110	54	
Mean*	-2.23	-2.12	.79
Difference (95% CI)	-0.11 (-0.95, 0.72)		
Month 2			
N	111	54	
Mean*	-2.67	-1.94	.102
Difference (95% CI)	-0.73 (-1.60, 0.15)		
Month 3			
N	112	56	
Mean*	-3.39	-1.78	<.001
Difference (95% CI)	-1.61 (-2.55, -0.67)		

Abbreviations: LOCF, last observation carried forward; ESWT, extracorporeal shockwave therapy; CI, confidence interval.

*Estimated from an analysis of variance and adjusted for baseline assessment and clinical site.

TABLE 7 Participant's assessment of heel pain—responder's analysis* (LOCF)

	ESWT	Placebo	P value
Month 1			
Responders: n/N (%)	39/110 (35.5%)	17/54 (31.5%)	.61
Odds ratio (95% CI)	1.20 (0.60, 2.41)		
Month 2			
Responders: n/N (%)	48/111 (43.2%)	17/54 (31.5%)	.14
Odds ratio (95% CI)	1.67 (0.84, 3.32)		
Month 3			
Responders: n/N (%)	59/112 (52.7%)	16/56 (28.6%)	.003
Odds ratio (95% CI)	2.85 (1.42, 5.69)		

Abbreviations: LOCF, last observation carried forward; ESWT, extracorporeal shockwave therapy; CI, confidence interval.

*A responder is a participant with a ≥50% decrease from baseline and a score ≤4. Analysis was performed by a logistic regression including baseline assessment and clinical site as covariates.

she enrolled in the study. The numbers of participants who increased, had no change, or decreased their use of pain medication are summarized in Table 9. These data were analyzed by the Cochran-Mantel-Haenszel procedure, stratified by clinical site. Scores of 1, 0, and -1 were assigned to the 3 response categories to create tests of the mean scores. As seen, participants in the ESWT group had significantly greater decreases in the use of pain medication than participants in the placebo group at months 2 ($P = .028$) and 3 ($P < .001$).

As seen in Figure 4, participants treated with an energy level of ≤4.5 appeared to have less pain relief than those treated with higher energy levels. To demonstrate the efficacy among participants receiving energy level >4.5, the primary analysis and each of the secondary analyses were repeated excluding ESWT participants who received an energy level of ≤4.5. Specifically, the mean change from

TABLE 8 Participant's self-assessment of activity and function—responder's analysis* (LOCF)

	ESWT	Placebo	P value
Month 1			
Responders: n/N (%)	60/111 (54.1%)	31/54 (57.4%)	.58
Odds ratio (95% CI)	0.82 (0.41, 1.66)		
Month 2			
Responders: n/N (%)	64/111 (57.7%)	27/54 (50.0%)	.43
Odds ratio (95% CI)	1.32 (0.66, 2.65)		
Month 3			
Responders: n/N (%)	72/112 (64.3%)	32/56 (57.1%)	.33
Odds ratio (95% CI)	1.42 (0.70, 2.85)		

Abbreviations: LOCF, last observation carried forward; ESWT, extracorporeal shockwave therapy; CI, confidence interval.

*Improvement of ≥ 1 point or maintenance of a baseline score of 0 or 1. Analysis was performed by a logistic regression including clinical site and baseline category as covariates.

TABLE 9 Change in use of pain medication from study enrollment*

	ESWT	Placebo	P value
Month 1			
Increase: n/N (%)	7/111 (6.3%)	5/54 (9.3%)	.083
Decrease: n/N (%)	35/111 (31.5%)	10/54 (18.5%)	
Month 2			
Increase: n/N (%)	1/95 (1.1%)	5/47 (10.6%)	.028
Decrease: n/N (%)	28/95 (29.5%)	9/47 (19.2%)	
Month 3			
Increase: n/N (%)	1/100 (1.0%)	6/51 (11.8%)	<.001
Decrease: n/N (%)	34/100 (34.0%)	7/51 (13.7%)	

Abbreviation: ESWT, extracorporeal shockwave therapy.

*Analyzed with the Cochran-Mantel-Haenszel procedure stratified by clinical site and assigning scores of 1, 0, and -1 to the 3 response categories.

baseline in the investigator's assessment of heel pain, overall, and responder's analysis; the mean change from baseline in the participant's assessment of heel pain, overall, and responder's analysis; and the change in the participant's activity and function and his or her change in analgesic use were reanalyzed (data not shown) for those participants receiving energy levels >4.5 . As previously stated in regard to Figure 4, the participant who was randomized to ESWT but received placebo by mistake was included in the placebo group for these analyses. For each of these analyses, there was a higher level of improvement in pain relief, activity, and function when participants were administered a shockwave energy level >4.5 . Figure 5 graphically depicts the mean change from baseline in the investigator's assessment of heel pain (LOCF, analysis of variance adjusted for baseline assessment and clinical site) for ESWT participants sustaining energy level >4.5 . Similarly, Figure 6 graphically depicts the mean change from baseline in the participant's assessment of heel pain (LOCF, analysis of variance adjusted for baseline assessment and clinical site) for ESWT

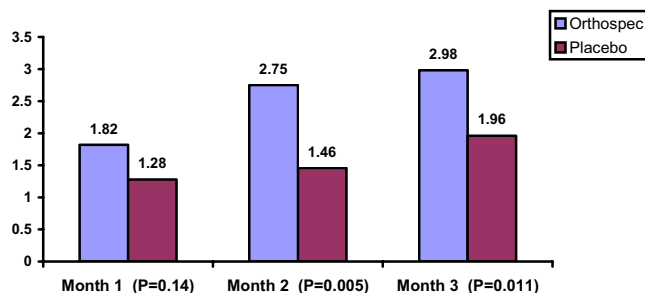


FIGURE 5 Mean change from baseline in investigator's assessment of heel pain for ESWT >4.5 .

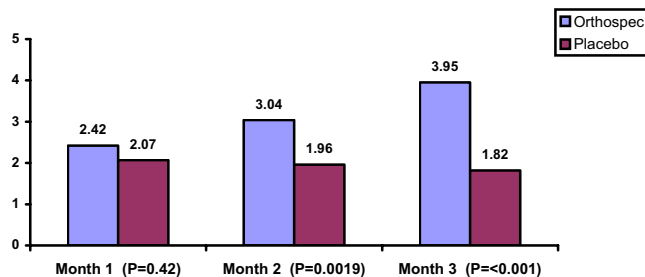


FIGURE 6 Mean change from baseline in participant's assessment of heel pain for ESWT level >4.5 .

participants sustaining energy level >4.5 . The results of each of the efficacy endpoints, and the method of analysis, are summarized in Table 10.

We also considered it of interest to combine the 4 protocol-defined success criteria at 3 months (investigator's assessment of pain, participant's assessment of pain, participant's assessment of activity and function, and change in use of pain medication), and Figure 7 summarizes the numbers of participants by the number of efficacy endpoints for which they responded. As seen, the difference achieved statistical significance for each of the endpoints measured.

Safety Results

There were no serious adverse events encountered in this clinical trial. None of the participants in the placebo group (N = 57) experienced an adverse event. Three participants in the active ESWT group (N = 115) reported 1 adverse event each, all of which were either mild or moderate and were reported as being definitely, probably, or possibly related to the device. Two participants (1.7%) experienced bruising at the site of shockwave application on the heel, and these incidents were considered by the participant and the investigator to be device-related; one participant (0.9%) experienced local swelling that was determined to be unrelated to the device. The energy levels reached for these participants were reported to range from 4.5 to 7.

TABLE 10 Summary of efficacy results at 3 months for ESWT participants receiving energy level >4.5 versus placebo

Measurement	ESWT (N = 88)	Placebo (N = 52)	P value
Investigator's assessment of pain (VAS)*			
Mean change from baseline	-2.98	-1.69	.011
Response rate	50.0%	21.2%	<.001
Participant's self-assessment of pain (VAS)*			
Mean change from baseline	-3.95	-1.82	<.001
Response rate	62.1%	28.9%	<.001
Participant's self-assessment of activity and function (diary)†			
Response rate	67.0%	56.1%	.16
Change in use of analgesic medications (diary)‡			
Increased	1.0%	11.80%	<.001
No change	65.0%	74.50%	
Decreased	34.0%	13.70%	

Abbreviations: ESWT, extracorporeal shockwave therapy; VAS, visual analog scale.

*Analysis of variance adjusted for baseline assessment and clinical site.

†Improvement of ≥1 point or maintenance of a baseline score of 0 or 1; analysis via a logistic regression including clinical site and baseline category as covariates.

‡Cochran-Mantel-Haenszel procedure stratified by clinical site and assigning scores of 1, 0, and -1 to the 3 response categories.

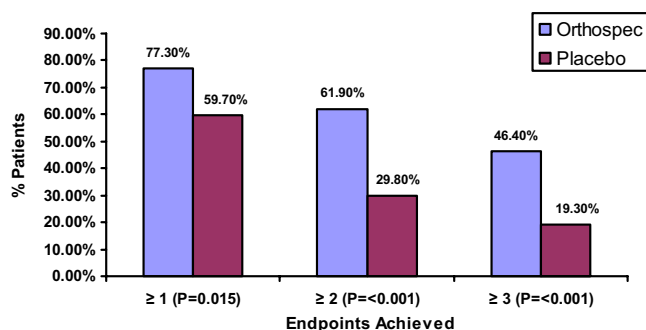


FIGURE 7 Percentage of patients by the number of efficacy endpoints for which they responded for Orthospec levels >4.5.

TABLE 11 Mean change from baseline to month 3 in investigator's assessment of heel pain by sex (LOCF)

	ESWT	Placebo	Difference	Interaction P value
Men				
N	35	21		
Mean*	-3.50	-1.59	-1.91	.15
Women				
N	77	35		
Mean*	-2.10	-1.59	-0.51	

Abbreviations: LOCF, last observation carried forward; ESWT, extracorporeal shockwave therapy.

*Adjusted for clinical site and baseline assessment.

Subgroup Analyses

Subgroup analyses were done for sex, age group (<45 years, 46-64 years, ≥65 years), and body weight (<160 lb, 161-192 lb, ≥193 lb). Table 11 presents a subgroup analysis based on sex, while Table 12 is based on age and Table 13 is based on body weight tertiles (weight categories that encompass approximately 3 equal groups of

TABLE 12 Mean change from baseline to month 3 in investigator's assessment of heel pain by age group (LOCF)

	ESWT	Placebo	Difference	Interaction P value
<45 Years				
N	36	16		
Mean*	-2.54	-1.65	-0.89	
46-64 Years				.89
N	64	33		
Mean*	-2.43	-1.33	-1.10	
≥65 Years				
N	12	7		
Mean*	-2.87	-2.51	-0.36	

Abbreviations: LOCF, last observation carried forward; ESWT, extracorporeal shockwave therapy.

*Adjusted for clinical site and baseline assessment.

participants). Included in these tables are the tests of treatment group-by-subgroup interaction, which assess the homogeneity of the differences between ESWT and placebo among subgroups. These data indicate that the differences between ESWT and placebo were consistent across the different subgroups.

Discussion

The Orthospec ESWT device used in this study uses an electrohydraulic, or “spark-gap”, method of creating therapeutic shockwaves. In this system, an electrode ignites an electrical charge within a water-filled, stainless-steel, semi-ellipsoid chamber, evaporating a small portion of the water contained in the chamber and creating a shockwave that is reflected outward. The portable shockwave generator used in this study targets the shockwaves to a 35-mm diameter therapy zone that enables shockwaves of sufficient energy to be delivered to the tissues in a single therapeutic session,

TABLE 13 Mean change from baseline to month 3 in investigator's assessment of heel pain by body weight (LOCF)

	ESWT	Placebo	Difference	Interaction <i>P</i> value
≤160 lb				
N	36	18		
Mean*	-2.05	-1.28	-0.77	
161–192 lb				.35
N	33	24		
Mean*	-2.29	-2.08	-0.21	
≥193 lb				
N	41	14		
Mean*	-2.93	-1.02	-1.91	

Abbreviations: LOCF, last observation carried forward; ESWT, extracorporeal shockwave therapy.

*Adjusted for clinical site and baseline assessment.

without the need for directional imaging, anesthesia, or sedation.

The indications for ESWT include a wide range of conditions including plantar fasciitis, tendinosis calcarea (shoulder), lateral epicondylitis (tennis elbow), medial epicondylitis (golf elbow), chronic subcutaneous calcifications, patellar tendinitis, nonunion/pseudarthrosis, and nephrolithiasis, as well as uses related to the treatment of nervous system disorders. In this investigation, ESWT was used specifically for proximal plantar fasciitis, and was shown to be efficacious relative to the reduction of pain (Tables 2, 5, 6, and 10, and Figs 4, 5, and 6) and the reduction in use of analgesic medications for heel pain relief (Table 9). Moreover, the ESWT device was shown to be consistently effective at decreasing plantar heel pain regardless of the participant's sex, age, or body weight (Tables 11, 12, and 13). It is also interesting to note that the mean average weight of those participating in the active ESWT group was approximately 10 lb heavier in comparison with those in the placebo group (Table 1); however, this difference in weight was not statistically significant. Furthermore, although our data revealed greater qualitative improvements in activity and function in those participants in the ESWT group when compared with the placebo group, these differences were not statistically significant (Table 8). We also observed a difference in the effect of ESWT intervention on the change in heel pain for participants with and without a plantar spur (Table 3). For those participants with a plantar spur, the change from baseline to the month 3 follow-up for the investigator's assessment of heel pain was greater (a greater reduction in heel pain) in the ESWT group than in the placebo control group, although this difference did not meet statistical significance ($P = .96$). For those participants without a plantar spur, the change from baseline to the month 3 follow-up for the investigator's assessment of heel pain was statistically significantly ($P = .012$) greater (a greater reduction in heel pain) in the ESWT group than in

the placebo control group. Despite noting a greater reduction in heel pain in the active ESWT group, for those with and without a plantar spur, the lack of a statistically significant reduction in pain when a spur was present prohibits us from saying that the efficacy was not diminished by the presence of the spur. Therefore, these results only suggest that the presence of a plantar spur did not alter the efficacy of ESWT and, perhaps, a greater sample size would enable a more definitive statement in this regard. Our data also indicated that those participants in the ESWT group responded to a greater number of efficacy endpoints (pain relief, improved activity and function, and reduced use of analgesics) than did those in the placebo group (Fig 7).

The exclusion criteria for this investigation took into consideration the general contraindications to the use of ESWT, including pregnancy, children, nerve damage, tarsal tunnel syndrome, osteoporosis, rheumatoid arthritis, peripheral vascular disease, infection, tumor, bleeding diathesis, cardiac pacemaker, and healing fracture. And, although the known adverse local effects of ESWT include subcutaneous hematoma, skin erosion, swelling, petechial hemorrhage, pain/paresthesia, and the systemic response of vasovagal syncope, we observed no serious adverse effects with the use of the ESWT device. During the course of this study, the ESWT device was still categorized as an investigational device under the scrutiny of the FDA and, therefore, safety was a key issue throughout our investigation. The shockwave energy used in this study was observed to be safe and not related to any significant adverse effects.

This study also made clear the importance of administering shockwaves at sufficiently high energy levels, those being \geq level 4 for the device tested in this trial. The relationship of the amount of energy administered to the amount of heel pain relief can be seen in Figure 4, which displays the mean change from baseline to the third month postintervention in the investigator's assessment of heel pain by the maximum amount of shockwave energy applied. These data depict the dose-response effect of the ESWT used in this investigation. Moreover, Tables 5, 7, and 10 and Figures 5, 6, and 7 show that the statistically significant difference changed from $P = .045$ to $P = .003$ (statistically significant to highly statistically significant) when the mean change from baseline in the investigator's assessment of heel pain was considered for all of the energy levels combined versus energy levels >4.5 . In fact, the data in Table 10, as well as in Figures 5, 6, and 7, all support the finding that relief of heel pain was most efficacious among participants receiving shockwaves at levels >4.5 . These data further reinforce the relationship of the amount of shockwave energy to pain reduction and suggest that a maximum energy level of 4.5 or less may be subtherapeutic. Inspection of Tables 2, 5, 6, and 7 also reveals a greater response to ESWT at 2 months versus 1 month, and again at 3 months versus 2 months. This finding is in keeping with the com-

mon understanding that the maximum benefit of ESWT is usually not observed until at least 6 to 8 weeks after administration of the acoustic energy. This investigation also showed that 89 of 115 participants (77%) in the active ESWT group were able to safely tolerate shockwave energy levels ≥ 4.5 without the use of anesthesia, analgesia, or sedation (Table 4). To our knowledge, this is the first report of shockwave energy levels of this magnitude being safely tolerated without concomitant administration of anesthesia, analgesia, sedation, or combinations thereof by a large proportion of patients with proximal plantar fasciitis.

Although the randomized controlled trial is generally considered the highest form of clinical investigation of a therapeutic intervention or a diagnostic test, and is therefore accepted as the most likely study design to yield valid results, we understand that every trial conveys certain limitations that are specific to the individual investigation. We would like to mention limitations that we have considered in relationship to this study. First, we did not use a health-related quality-of-life measurement, such as the short-form health survey (36 items) (41), the Bristol Foot Score (42), or the Foot Function Index (43), all of which have become generally accepted as reliable instruments that can produce valid information. Our emphasis was on measuring pain before and after shockwave therapy and observing whether alteration of pain affected each participant's function. Therefore, we combined pain measurement on the VAS with a number of functional measurements, namely ambulatory ability and the use of analgesic medication. Despite their wide acceptance and use, VASs have been criticized for a number of biases, including end-digit aversion and spacing-out partiality (44, 45). Key to our decision to use the VAS, however, was its ease of application and traditionally high levels of participant acceptance, understanding, and high rates of completion, and wide acceptance as a useful tool for measuring a variety of health states, including pain. Furthermore, the FDA commonly accepts the use of the VAS as a means of measuring pain in clinical trials related to musculoskeletal disorders (46). Our use of the participant diary to record walking activity and analgesic use could have been biased by inaccuracies, either purposeful or inadvertent. However, we took particular care at the time of enrollment to explain the use of the diary, and, at each follow-up visit, the diary was reviewed with the participant and its purpose and usage, again, reiterated and clarified.

Second, we only measured efficacy outcomes up to 3 months after the intervention. This is in keeping with many phase-3 device trials conducted under the auspices of the FDA. The goal of this trial was to establish whether the shockwave device was efficacious and safe within the confines of the investigation. As with any one-time intervention, the longer the period between administration of the intervention and the follow-up evaluation, the more likely it

is that other interventions, including time itself, could contaminate the results. Moreover, in patients who have already failed typical conservative strategies, diminished or alleviated pain within 3 months after shockwave administration seems to be a clinically reasonable amount of time by which one could expect to identify an alteration of plantar heel pain. Further, previous experience has indicated that the usual time required before shockwave therapy affects an alteration in pain is about 6 weeks. Therefore, measuring efficacy outcomes at 12 weeks would reasonably be expected to be a sufficient period of time in which to identify pain relief, without unduly increasing the risk of contaminating the intervention. Our efforts to combine efficacy endpoints and to report the number of endpoints achieved depending on the intervention received (Table 10) was undertaken in an effort to qualitatively get a sense of the number of symptoms affected by ESWT. We consider this information with the understanding that we are, in this investigation, weighing all of the endpoints evenly and that it is likely that these endpoints should probably be weighted differently.

Several methodological techniques used in this investigation biased toward the null and imparted a conservative tone to our results. These methods pertained to the way in which the placebo was applied and to the data analysis. By design, it was understood that some degree of shockwave energy, possibly even a therapeutic dose, could be experienced in the placebo group despite the use of the energy-absorbing foam insert in the contact membrane. In essence, the sham intervention was not a pure placebo. This biased the results toward the null when comparing the active intervention with the sham therapy. Similarly, use of the LOCF method of analysis also biased toward the null in that participants who did not have an assessment at 3 months postintervention, for whatever reason, had their last available data carried forward for use in the computation of efficacy. Understanding that ESWT typically does not result in notable clinical improvement until at least 3 to 6 weeks postintervention, missing the third month follow-up visit would likely result in carrying forward a pain measurement that would be higher than a measurement actually taken at the 3-month follow-up visit, and would therefore minimize the apparent effect of the intervention relative to the reduction of heel pain. Furthermore, we performed a responder analysis wherein a responder was defined as a participant who had a decrease from baseline to follow-up at 3 months of 50% or more with a VAS score ≤ 4.0 cm. Participants meeting this definition were considered a therapeutic success, whereas all others were considered a failure. Here, again, handling the outcomes in this fashion imparted a conservative influence on the results in that the definition of a responder was linked to pain relief, and the responder analysis only considered the dichotomous variable, success or failure. Understanding that success required a minimum

of a 50% reduction in pain, with a score of 4.0 cm or less on the VAS, participants who noted reductions in pain that did not reach a magnitude consistent with being a responder were counted as therapeutic failures regardless of whether they had clinically improved. Moreover, the LOCF method of analysis was also used in the responder analysis, and, as previously noted, this further biased toward the null.

In regard to external validity, our protocol excluded patients with bilateral proximal plantar fasciitis despite the fact that patients commonly have bilateral plantar heel pain when they present to the clinic, and this may have diminished the generalizability of our findings. We focused on patients with just one painful heel, because this was an investigational new device study and we did not want to put any volunteer participants at undue risk. We also wanted to avoid analytical issues that may have obscured interpretation of the results or diminished the statistical power to determine a significant difference. Moreover, we believe that collecting data from 3 different clinical centers, having minimal loss to follow-up, and controlling for center effects in the analysis increased the generalizability of our findings. For all of these reasons, we believe that the methods used to measure the primary and secondary outcomes in this clinical trial were acceptable, and, along with the bias-reducing methods of randomization and blinding of participants and outcomes assessors, as well as the multicenter nature of this study, contributed to the generation of valid results that convey external validity.

Summary and Conclusions

The results of this clinical investigation demonstrate the safety and efficacy of the Orthospec Extracorporeal Shock-wave Therapy device for treatment of recalcitrant proximal plantar fasciitis. The study achieved statistical significance in its protocol-defined primary endpoint ($P = .045$), change from baseline in the investigator's assessment of heel pain at 3 months. When participants were assessed by whether they achieved a clinical response in the primary endpoint, the number of responders was statistically significantly greater ($P = .003$) in the ESWT group (42.9%) than in the placebo group (19.6%). These results were further confirmed in each of the secondary measures of heel pain, the participant's assessment of pain, and the change in use of pain medication. The mean decrease from baseline in the participant's assessment of pain was statistically significantly greater ($P < .001$) in the ESWT group (-3.39) than in the placebo group (-1.78), and the proportion of participants who achieved a clinical response in this endpoint was also statistically significantly greater ($P = .003$) in the ESWT group (52.7%) than in the placebo group (28.6%). When we assessed the change from study enrollment in the use of pain medication to treat heel pain, participants in the

ESWT group had a smaller proportion with an increase (1.0% vs 11.8%) and a larger proportion with a decrease (34.0% vs 13.7%), and these differences were highly statistically significant ($P < .001$). Participants in the ESWT group also had a higher response rate at 3 months than those in the placebo group in the participant's assessment of activity and function; however, this endpoint did not achieve statistical significance. Although the placebo intervention did provide some degree of therapeutic effect, the ESWT group demonstrated a stronger effect in comparison with the placebo.

These results indicate that ESWT remains an encouraging alternative to surgical intervention for treating pain caused by proximal plantar fasciitis. This randomized, double-blinded, placebo-controlled, multicenter trial demonstrated clinical success in an unbiased fashion. All assessments of the reduction of heel pain were found to be statistically significant when compared with placebo in participants who had already failed standard conservative treatments. Moreover, significant pain relief was achieved with a single treatment session without the use of local anesthetics or systemic analgesics or sedatives, or combinations of these agents. Furthermore, in this study, there were no participant deaths or other serious adverse events observed in the follow-up period (an important aspect of the investigation of any new therapeutic device), and only 3 transient adverse events were reported: 2 cases of bruising (relatedness code: definitely and probably related) and 1 case of mild local swelling (relatedness code: not related). All 3 cases were considered mild and displayed complete resolution of symptomatology after several days. The FDA-approved Orthospec ESWT device used in this clinical trial is considered an alternative treatment intervention in the management of recalcitrant proximal plantar fasciitis with or without a plantar calcaneal spur.

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References

1. McCarthy DJ, Gorecki GE. The anatomical basis of inferior calcaneal lesions. *J Am Podiatr Med Assoc* 69:527-533, 1979.
2. Sherer PR. Heel pain syndrome: pathomechanics and nonsurgical treatment. *J Am Podiatr Med Assoc* 81:68-72, 1991.
3. Malay DS. Plantar fasciitis and heel spur syndrome: a retrospective

- analysis. In *Reconstructive Surgery of the Foot and Leg: Update 1996*, pp 133–135, edited by NS Vickers, Podiatry Institute, Tucker, GA, 1996.
4. Pfeiffer G, Bacchetti P, Deland J, Lewis A, Anderson R, Davis W, Alvarez R, Brodsky J, Cooper P, Frey C, Herrick R, Myerson M, Sammarco J, Janecki C, Ross S, Bowman M, Smith R. Comparison of custom and prefabricated orthoses in the initial treatment of proximal plantar fasciitis. *Foot Ankle Int* 20:214–221, 1999.
 5. Riddle DL, Pulisic M, Pidcoe P, Johnson RE. Risk factors for plantar fasciitis: a matched case-control study. *J Bone Joint Surg Am* 85-A: 872–877, 2003.
 6. Riddle DL, Schappert SM. Volume of ambulatory care visits and patterns of care for patients diagnosed with plantar fasciitis: a national study of medical doctors. *Foot Ankle Int* 25:303–310, 2004.
 7. Govindarajan R, Bakalova T, Doss NW, Splain SH, Michael R, Abadir AR. Posterior tibial nerve block in the therapeutic management of painful calcaneal spur (plantar fasciitis): a preliminary experience. *Can J Anaesth* 50:862–863, 2003.
 8. DiGiovanni BF, Nawoczenski DA, Lintal ME, Moore EA, Murray JC, Wilding GE, Baumhauer JF. Tissue-specific plantar fascia-stretching exercise enhances outcomes in patients with chronic heel pain. A prospective, randomized study. *J Bone Joint Surg Am* 85-A:1270–1277, 2003.
 9. Martin JE, Hosch JC, Goforth WP, Murff RT, Lynch DM, Odom RD. Mechanical treatment of plantar fasciitis. A prospective study. *J Am Podiatr Med Assoc* 91:55–62, 2001.
 10. Probe RA, Baca M, Adams R, Preece C. Night splint treatment for plantar fasciitis. A prospective randomized study. *Clin Orthop* 368: 190–195, 1999.
 11. Crawford F, Atkins D, Young P, Edwards J. Steroid injection for heel pain: evidence of short-term effectiveness. A randomized controlled trial. *Rheumatology (Oxford)* 38:974–977, 1999.
 12. Lynch DM, Goforth WP, Martin JE, Odom RD, Preece CK, Kotter MW. Conservative treatment of plantar fasciitis. A prospective study. *J Am Podiatr Med Assoc* 88:375–380, 1998.
 13. Gudeman SD, Eisele SA, Heidt RS Jr, Colosimo AJ, Stroupe AL. Treatment of plantar fasciitis by iontophoresis of 0.4% dexamethasone. A randomized, double-blind, placebo-controlled study. *Am J Sports Med* 25:312–316, 1997.
 14. Tomczak RL, Haverstock BD. A retrospective comparison of endoscopic plantar fasciotomy to open plantar fasciotomy with heel spur resection for chronic plantar fasciitis/heel spur syndrome. *J Foot Ankle Surg* 34:400–407, 1995.
 15. Kinley S, Frascone S, Calderone D, Wertheimer SJ, Squire MA, Wiseman FA. Endoscopic plantar fasciotomy versus traditional open heel spur surgery: a prospective study. *J Foot Ankle Surg* 32:595–603, 1993.
 16. Rompe JD, Hopf C, Nafe B, Burger R. Low-energy extracorporeal shockwave therapy for painful heel: a prospective controlled single-blind study. *Arch Orthop Trauma Surg* 115:75–79, 1996.
 17. Perez M, Weiner R, Gilley JC. Extracorporeal shockwave therapy for plantar fasciitis. *Clin Podiatr Med Surg* 20:323–334, 2003.
 18. Daecke W, Kusnierczak D, Loew M. Long-term effects of extracorporeal shockwave therapy in chronic calcific tendinitis of the shoulder. *J Shoulder Elbow Surg* 11:476–480, 2002.
 19. Haake M, Wessel C, Wilke A. [Effects of extracorporeal shockwaves (ESW) on human bone marrow cell cultures]. *Biomed Tech (Berl)* 44:278–282, 1999.
 20. Plaisier PW, van der Hul RL, Terpstra OT, Bruining HA. Current role of extracorporeal shockwave therapy in surgery. *Br J Surg* 81:174–181, 1994.
 21. Wilner JM, Strash WW. Extracorporeal shockwave therapy for plantar fasciitis and other musculoskeletal conditions utilizing the Ossonator—an update. *Clin Podiatr Med Surg* 21:441–447, 2004.
 22. Delius M, Draenert K, Al Diek Y, Draenert Y. Biological effects of shockwaves: in vivo effect of high energy pulses on rabbit bone. *Ultrasound Med Biol* 21:1219–1225, 1995.
 23. McCormack D, Lane H, McElwain J. The osteogenic potential of extracorporeal shockwave therapy: an in-vivo study. *Ir J Med Sci* 165:20–22, 1996.
 24. Rompe JD, Eysel P, Hopf C, Vogel J, Kullmer K. [Extracorporeal shockwave treatment of delayed bone healing. A critical assessment]. *Unfallchirurg* 100:845–849, 1997.
 25. Orhan Z, Alper M, Akman Y, Yavuz O, Yalciner A. An experimental study on the application of extracorporeal shockwaves in the treatment of tendon injuries: preliminary report. *J Orthop Sci* 6:566–570, 2001.
 26. Perlick L, Schifffmann R, Kraft CN, Walny T, Diedrich O. [Extracorporeal shockwave treatment of the achilles tendinitis: experimental and preliminary clinical results]. [Article in German]. *Z Orthop Ihre Grenzgeb* 140:275–280, 2002.
 27. Martini L, Fini M, Giavaresi G, Torricelli P, de Pretto M, Rimondini L, Giardino R. Primary osteoblasts response to shockwave therapy using different parameters. *Artif Cells Blood Substit Immobil Biotechnol* 31:449–466, 2003.
 28. Orhan Z, Ozturan K, Guven A, Cam K. The effect of extracorporeal shockwaves on a rat model of injury to tendoAchillis. A histological and biomechanical study. *J Bone Joint Surg Br* 86:613–618, 2004.
 29. Hyer CF, VanCourt R, Block A. Evaluation of ultrasound-guided extracorporeal shockwave therapy (ESWT) in the treatment of chronic plantar fasciitis. *J Foot Ankle Surg* 44:137–143, 2005.
 30. Alvarez RG, Ogden JA, Jaakkola J, Cross GL. Symptom duration of plantar fasciitis and the effectiveness of Orthotripsy. *Foot Ankle Int* 24:916–921, 2003.
 31. Haake M, Buch M, Schoellner C, Goebel F, Vogel M, Mueller I, Hausdorf J, Zamzow K, Schade-Brittinger C, Mueller HH. Extracorporeal shockwave therapy for plantar fasciitis: randomized controlled multicentre trial. *BMJ* 327:870–875, 2003.
 32. Speed CA, Nichols D, Wies J, Humphreys H, Richards C, Burnet S, Hazleman BL. Extracorporeal shockwave therapy for plantar fasciitis. A double blind randomized controlled trial. *J Orthop Res* 21:937–940, 2003.
 33. Hammer DS, Adam F, Kreutz A, Kohn D, Seil R. Extracorporeal shockwave therapy (ESWT) in patients with chronic proximal plantar fasciitis: a 2-year follow-up. *Foot Ankle Int* 24:823–828, 2003.
 34. Speed CA, Nichols D, Wies J, Humphreys H, Richards C, Burnet S, Hazleman BL. Extracorporeal shockwave therapy for plantar fasciitis. A double blind randomized controlled trial. *J Orthop Res* 21:937–940, 2003.
 35. Rompe JD, Decking J, Schoellner C, Nafe B. Shockwave application for chronic plantar fasciitis in running athletes. A prospective, randomized, placebo-controlled trial. *Am J Sports Med* 31:268–275, 2003.
 36. Buchbinder R, Ptasznik R, Gordon J, Buchanan J, Prabaharan V, Forbes A. Ultrasound-guided extracorporeal shockwave therapy for plantar fasciitis: a randomized controlled trial. *JAMA* 288:1364–1372, 2002.
 37. Hammer DS, Rupp S, Kreutz A, Pape D, Kohn D, Seil R. Extracorporeal shockwave therapy (ESWT) in patients with chronic proximal plantar fasciitis. *Foot Ankle Int* 23:309–313, 2002.
 38. Rompe JD, Schoellner C, Nafe B. Evaluation of low-energy extracorporeal shock-wave application for treatment of chronic plantar fasciitis. *J Bone Joint Surg Am* 84-A:335–341, 2002.
 39. Ogden JA, Alvarez R, Levitt R, Cross GL, Marlow M. Shockwave therapy for chronic proximal plantar fasciitis. *Clin Orthop* 387:47–59, 2001.
 40. Haake M, Buch M, Schoellner C, Goebel F, Vogel M, Mueller I,

- Hausdorf J, Zamzow K, Schade-Brittinger C, Mueller HH. Extracorporeal shockwave therapy for plantar fasciitis: randomised controlled multicentre trial. *BMJ* 327:75–79, 2003.
41. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ* 306: 1437–1440, 1993.
 42. Barnett S, Campbell R, Harvey I. The Bristol Foot Score: developing a patient-based foot-health measure. *J Am Podiatr Med Assoc* 95:264–272, 2005.
 43. Bennett PJ, Patterson C, Wearing S, Baglioni T. Development and validation of a questionnaire designed to measure foot-health status. *J Am Podiatr Med Assoc* 88:419–428, 1998.
 44. Shmueli A. The visual analog rating scale of health-related quality of life: an examination of end-digit preferences. *Health Qual Life Outcomes* 3:71, 2005.
 45. Paul-Dauphin A, Guillemin F, Vuruib JM, Briancon S. Bias and precision in visual analogue scales: a randomized controlled trial. *Am J Epidemiol* 150:1117–1127, 1999.
 46. Guidance for industry: clinical development programs for drugs, devices, and biological products intended for the treatment of osteoarthritis (OA). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health (CDRH), July 1999, p. 3. (Available at <http://www.fda.gov/ohrms/dockets/98fr/980077g2.pdf>/ last accessed May 23, 2006).